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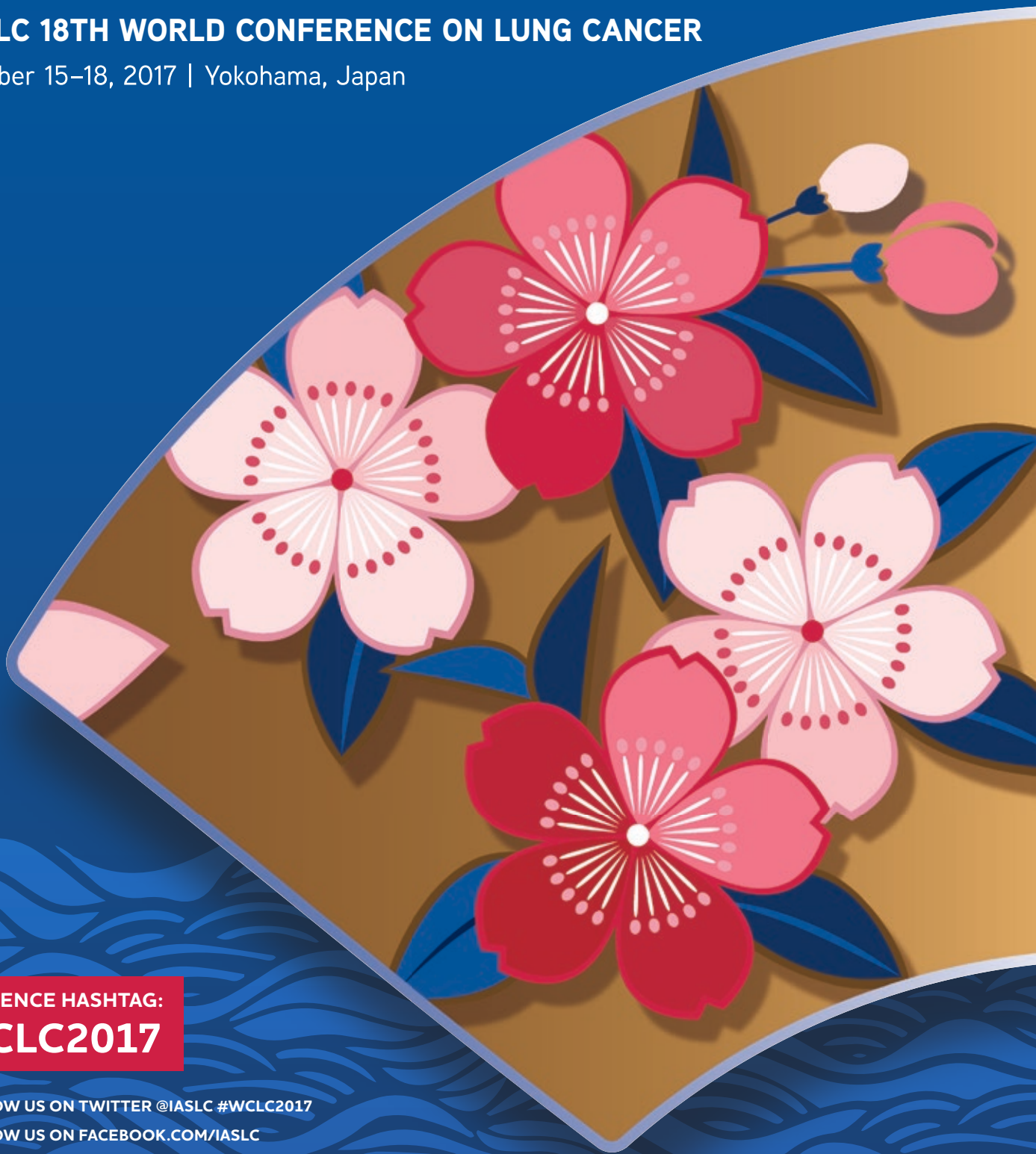
Abstracts

IASLC 18TH WORLD CONFERENCE ON LUNG CANCER

October 15–18, 2017 | Yokohama, Japan



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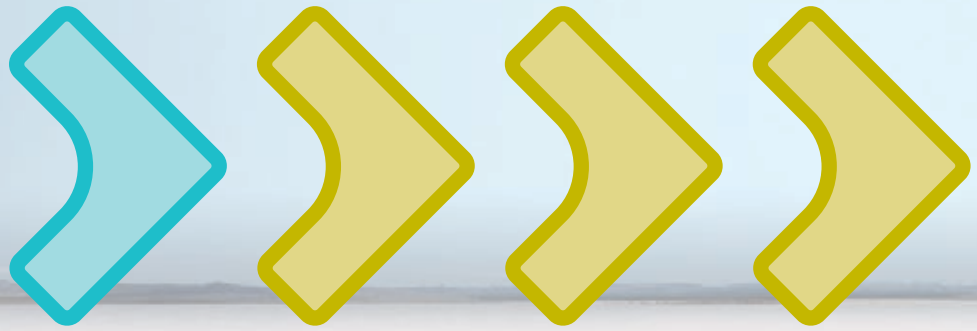

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PLENARY SESSIONS

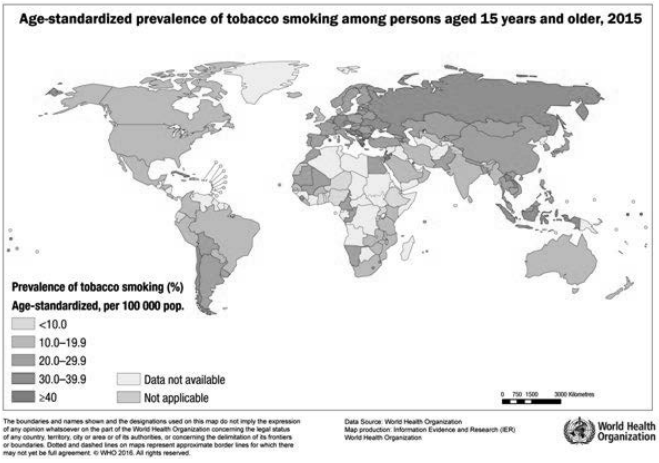
PL 01 PREVENTION, SCREENING, AND MANAGEMENT OF SCREEN-DETECTED LUNG CANCER
MONDAY, OCTOBER 16, 2017 - 08:15-09:45

PL 01.01 CURRENT STATUS OF SMOKING CESESSION PROGRAM (TOBACCO CONTROL)

C. Dresler

Human Rights and Tobacco Control Network, Rockville/US

Smoking Cessation - What will it look like in the near future Perspective of the smoking epidemic by global map of smoking prevalence:



What is 'smoking cessation' and what does it get us? Why should we care what is happening to the tobacco products that people are smoking? California led the tobacco control efforts in the USA and within 3-5 years saw a drop in lung cancer deaths. The tobacco control efforts in California began in the late 1980's and the drop in lung cancer quickly was evident from people stopping smoking. (Barnoya & Glantz. Cancer Causes Control 2004;15(7): 689-95) With better tobacco control, with resultant smoking cessation, many other countries have similarly seen a decline in the deaths from lung cancer, mostly in western, high income countries. Most people who smoke want to quit, and wish they had never started and most people started smoking before they were 18 years of age. Smoking cigarettes, with its pulmonary delivery, is a very good delivery system for nicotine. It is the nicotine that addicts people and creates one of the most difficult to quit drugs in our societies. So, it is known that smoking cigarettes is addictive, that most people who smoke want to quit and smoking them causes the number one cause of cancer death in the world - lung cancer. And, it is well-established that quitting smoking decreases the incidence and mortality from lung cancer. There are three major transnational tobacco companies in the world: Phillip Morris International (PMI), based in Lausanne, Switzerland; British American Tobacco (BAT) based in London, UK; and Japan Tobacco International (JTI) based in Tokyo, Japan. The largest tobacco company is the Chinese National Tobacco Corporation - and they are not quite yet international in their marketing scope. There are rumors of a financial bonus if PMI mergers with Altria in the USA - following their split in 2008; BAT has purchased Reynold Tobacco - the second-largest tobacco company in the USA. Thus, selling the product that causes a third of all cancers, including the number one, lung cancer, is an outcome of successful marketing by 4 major companies: PMI, BAT, JTI and China (largely overseen by the government). Marlboro cigarettes are one of the largest brand in the world - sold by PMI and Altria. Why does all of this matter to us? Because, where Marlboro goes, so goes the market. PMI has started to market its replacement of the Marlboro cigarette and they call i iQOS - or, 'I quit ordinary smoking'. It is a 'heat-not-burn' product that they claim does not combust the tobacco and therefore is a less deadly product. At the time of this writing, PMI is in 30 countries and will be expanding globally in the near future. They have an application for the ability to claim a 'reduced-harm' product in the USA. (https://www.fda.gov/downloads/TobaccoProducts/Labeling/MarketingandAdvertising/UCM560044.pdf). Japan was one of the early markets for iQOS and it has taken the country by storm. One must make a reservation to purchase the product, as their specially designed stores are not able to keep them in stock. The iQOS product is steadily gaining prevalence in Japan - to the dismay for JTI who previously overwhelming had the largest market share. PMI has launched in South Korea, in hopes to capture the same success as they have found in Japan. As was stated earlier, most people want to quit smoking cigarettes - both for their health and the impact of secondhand smoke on others. iQOS claims to provide them with the nicotine that will continue to support their addiction, but removes the 'harm' from smoking. Of course, this is not known if this is true until changes are seen in the incidence of tobacco induced diseases, including of lung cancer. BUT - if there is a dramatic change from what people have smoked in the past and what they change to smoke in the future - there may be dramatic differences in lung cancer incidences and probably, of the type of lung cancer. Electronic cigarettes have also significantly impacted the marketplace and also claim to cause significantly less tobacco related disease. Uptake of electronic cigarettes has been variable around the world due to differences in regulatory environments and availability of marketing acumen. However, none of electronic cigarettes have the marketing strength of the largest trans-national tobacco company, PMI, and their heat-not-burn product. The CEO of PMI Andre Calantzopoulos has stated: "if you extrapolate the figures, then logically we could reach the tipping point in five years. That is when we could start talking to governments about phasing out combustible cigarettes entirely." {in interview with Nikkei Asian Review} Of course, he only means for the countries that can afford their heat-not-burn product - for the rest of the world, they can still have their combusted cigarettes. For us in IALSC, we can hope that electronic cigarettes and heat-not-burn products do cause less lung cancer - as people who smoke cigarettes quit - even if they transition to heat-not-burn cigarettes or electronic cigarettes. What is unknown is whether people who use either a heat-not-burn or electronic cigarettes - who quit smoking cigarettes - will have fewer lung cancers - in the very near future.

Keywords: new tobacco products, Smoking Cessation

PL 01 PREVENTION, SCREENING, AND MANAGEMENT OF SCREEN-DETECTED LUNG CANCER
MONDAY, OCTOBER 16, 2017 - 08:15-09:45

PL 01.02 MAJOR ADVANCES IN CT SCREENING: A RADIOLOGIST'S PERSPECTIVE

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Advances in CT scanners. CT screening was first introduced when helical CT scanners became available in the early 1990's (1-4). Since then, there have been remarkable advances in CT scanner technology with concurrent increase in the number of CT examinations per year by approximately 10% annually. More powerful hardware and image reconstruction algorithms have allowed faster scanning at lower radiation doses in today's multidetector CT (MDCT) scanners. Ultra low-dose techniques are gaining acceptance. With respect to lung cancer screening, thinner collimation now possible has led to the detection of many more small pulmonary nodules. Also, there have been evolutions in diagnostic techniques such as percutaneous biopsies, navigational bronchoscopy, and PET scans and these advances have been integrated into the regimen of screening with a resulting decrease in the frequency of surgical resection of benign nodules (5). **Definition of Positive Results.** Updates in the definition of positive results have continued to be developed that allow for improvements in the efficiency of workups. One of the major changes has been to update the size thresholds for positive results from 4 to 6 mm and also to avoid rounding errors (6, 7). The NELSON trial introduced the concept that a positive result should be based on the initial CT scan and a follow-up CT scan for small nodules, rather than solely on the initial CT scan and this has been adopted by I-ELCAP (6). The I-ELCAP and NLST databases have been used to provide follow-up strategies for nonsolid and part-solid nodules (6). Considerations as to screening frequency may substantially reduce costs for lower risk individuals. There is increasing recognition that different approaches are needed for baseline and repeat scans where even when nodules might have the same characteristics as they should be managed differently. The management of both nonsolid and part-solid nodules has dramatically changed. For the first time, imaging as a biomarker for aggressiveness has been used to monitor whether a cancer is progressing. Growing nonsolid nodules can be followed on an annual basis and only the emergence of a solid component triggers more aggressive intervention. For the part-solid nodule it has now been recognized that the important component from a prognostic perspective is the solid portion not the overall size. **Quantitative assessments.** Quantitative assessment of many findings on chest CT scans have been developed (6). In particular, assessment of nodule size and growth as to the probability of malignancy and lung cancer aggressiveness has progressed. Most guideline organizations have moved from a single measurement of length to an average diameter (average of length and width) (6) and to three measurements of volume (7). The errors involved in any of these measurements are influenced by multiple factors including the intrinsic properties of the nodule and the software used to make the measurement (8, 9). Additionally, they are impacted by the variability of CT scanners and their adjustable scan parameters. Advances in incorporating measurement errors into growth assessment by RSNA's Quantitative Imaging Biomarkers Alliance (QIBA) has led to a web-based calculator. The American College of Radiology (ACR) specifies that growth for a nodule of any size requires "an increase of 1.5 mm or more." Both approaches allow for large measurement errors for the wide range of CT scanners and the protocols. The I-ELCAP guidelines for solid and the solid component of part-solid nodules is given explicitly in I-ELCAP protocol (6). Each of these approaches has specific technical requirements as measurement error is influenced by both the scanner itself, the choice of various adjustable parameters on the scanner (slice thickness, slice spacing, dose, FOV, pitch, recon kernel etc.) as well as characteristics of the nodule itself. Additional considerations for computer-assisted volume change assessment requires: 1) inspecting the computer scans and the segmentation for image quality (e.g. motion artifacts) and for the quality of the segmentation; 2) the radiologist visually inspecting both nodule image sets side-by-side to verify the quality of the computer segmentation for each image that contains a portion of the nodule; 3) examination of the segmentations for errors such as when a vessel is segmented as part of a nodule in one scan but not in the other; 4) that the scan slice thickness for the purpose of volumetric analysis should be 1.25 mm or less. When using any computer-assisted software, the radiologist must be satisfied with the CT image quality and the computer segmentation results, further substantiating the notion that the decision of whether growth has occurred is ultimately based on clinical judgment. **Innovations in use of imaging and genetic information.** Radiomics is an emerging field of study on the quantitative processing and analysis of radiologic images and metadata to extract information on tumor behavior and patient survival (10). The hypothesis is that data analysis through automated or semi-automated software can provide more information than that of a physician. Its use has shown improved diagnostic accuracy

in discriminating lung cancer from benign nodules. It has been used successfully in breast imaging, with 2017 FDA approval of a computer-aided diagnosis tool which utilizes advanced machine learning analytics. Furthermore, radiomics has been linked with the field of genomics, inferring that imaging features are closely linked to gene signatures such as EGFR expression, a known therapeutic target. In the future, as larger data sets emerge and inter-institutional sharing of images becomes more commonplace, radiomics will become more tightly integrated with lung cancer diagnosis, treatment planning, and patient survival prognostication. **References** 1. Henschke C, McCauley D, Yankelevitz D, Naidich D, McGuinness G, Miettinen O, Libby D, Pasmantier M, Koizumi J, Altorki N, and Smith J. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354:99-105. 2. The International Early Lung Cancer Action Program Investigators. Survival of Patients with Stage I lung cancer detected on CT screening. NEJM 2006; 355:1763-71 3. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, and Moriyama N. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996; 201: 798-802. 4. Sone S, Nakayama T, Honda T, Tsushima K, Li F, Haniuda M, et al. Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. Lung Cancer. 2007; 58:329-41. 5. Linek HC, Flores RM, Yip R, Hu M, Yankelevitz DF, Powell CA. Non-malignant resection rate is lower in patients who undergo pre-operative fine needle aspiration for diagnosis of suspected early-stage lung cancer. Am J Respir and Crit Care Med 2015; 191: A3561 6. International Early Lung Cancer Action Program protocol. http://www.ielcap.org/sites/default/files/I-ELCAP%20protocol-v21-3-1-14.pdf Accessed March 27, 2015 7. Van Klaveren RJ et al. Management of Lung Nodules Detected by Volume CT Scanning. N Engl J of Medicine 2009; 361: 2221-9 8. Henschke CI, Yankelevitz DF, Yip R, Archer V, Zahlmann G, Krishnan K, Helba B, Avila R. Tumor volume measurement error using computed tomography (CT) imaging in a Phase II clinical trial in lung cancer. Journal of Medical Imaging 2016; 3:035505 9. Avila RS, Jirapatnakul A, Subramaniam R, Yankelevitz D. A new method for predicting CT lung nodule volume measurement performance. SPIE Medical Imaging 2017: 101343Y 10. Lee G, Lee HY, Park H, et al. Radiomics and its emerging role in lung cancer research, imaging biomarkers and clinical management: State of the art. Eur J Radiol. 2017; 86:297-307.

Keywords: Radiomics, quantitative, positive results

PL 01 PREVENTION, SCREENING, AND MANAGEMENT OF SCREEN-DETECTED LUNG CANCER
MONDAY, OCTOBER 16, 2017 - 08:15-09:45

PL 01.04 WHAT IS THE OPTIMAL MANAGEMENT OF SCREEN-DETECTED LUNG CANCERS

S. Watanabe

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Introduction With the recent development of the CT scanner, the number of CT screen-detected early-stage lung cancer showing ground-grass opacity (GGO) is rising. Therefore a new optimal therapeutic strategy for pulmonary resection for screen-detected lung cancer has been required. History of standard surgical procedure for lung cancer Cahan (1960) reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, which was called "radical lobectomy." Since then, this procedure was universally accepted and has remained a standard surgery for lung cancer. As for sublobar resection, segmentectomy was initially used for the resection of localized bronchiectasis as reported by Churchill and Belsey (1939). Jensik (1973) reported their 15-year successful experience of segmentectomy for lung cancer patients. However, the use of sublobar resection as definitive management of NSCLC has been a controversial issue. Lung Cancer Study Group (LCSG) (1995) conducted the only randomized trial comparing sublobar resection with lobectomy for stage IA NSCLC patients. They observed a 75% increase in recurrence and a 50% increase in cancer death in the patients undergoing sublobar resection, compared to those in the patients undergoing lobectomy. This is the reason why lobectomy has remained a standard lung cancer surgery for a half century since Cahn's successful report in 1960. Controversies in sublobar resection for patients with small-sized NSCLC Sublobar resection is a lung parenchyma-preserving surgery with limited nodal dissection. However, even small-sized lung cancer less than 2 cm in size shows hilar and mediastinal nodal disease with an incidence of more than 20%. Although PET is considered to be the most sensitive and accurate investigation for screening of lymph node involvement, with a sensitivity of 79 to 85% and specificity of 90 to 91% in a meta-analysis, the assessment of nodal status by PET is not reliable in patients with microscopic nodal metastasis. Riquet (1989) reported that lung cancer metastasizes so easily to the mediastinum that selection of the patients for limited surgery should be discussed carefully. Furthermore, lung cancer has a phenomenon termed "skip metastasis" consisting of N2 disease without N1 involvement with the incidence of 20-38% in N2 patients. Therefore, lobectomy with hilar and mediastinal lymph node dissection is considered to be a basic standard procedure for lung cancer. Differences in survival between sublobar resection and lobectomy Proposals of sublobar resection for clinical stage IA small-sized lung cancer less than 2 cm have been undertaken in some previous reports. Although these were non-randomized study, Okada (2001) and Koike (2003) conducted the comparative study between intentional sublobar resection and standard lobectomy in patients with tumors 20 mm or less in diameter. They showed no significant difference in survival between two groups and suggested that sublobar resection was acceptable operation for small-sized lung cancer. The significance and role of sublobar resection for subsolid tumor have become important so far. Clinical trials regarding sublobar resection vs. lobectomy Japan Clinical Oncology Group (JCOG) has conducted a cohort study (JCOG0201) evaluating correlation between radiological and pathological findings in stage I adenocarcinomas. With pathologic non-invasive adenocarcinoma defined as those with no lymph node metastasis or vessel invasion, radiological non-invasive lung adenocarcinoma was defined as those with a consolidated maximum tumor diameter to tumor diameter ratio (C/T ratio) of less than 0.5 (9). Currently, a prospective, randomized, multi-institutional phase III trial for small-sized (<=2 cm) lung cancer patients is being conducted by Cancer and Leukemia Group B (CALGB140503) to determine the effectiveness of an intentional sublobar resection for small-sized peripheral tumors. Similar phase III study (JCOG0802) is also being conducted, comparing lobectomy vs. segmentectomy for small-sized tumor with more than 0.5 C/T ratio. JCOG has already accumulated planned number of patients and now following the patients. JCOG is also conducting other two prospective multi-institutional phase II trials regarding the sublobar resection for GGO-dominant type tumors. One is JCOG0804, wide wedge resection for non-solid GGO lesion less than 2cm, and the other is JCOG1211, segmentectomy for part-solid GGO lesion with less than 0.5 C/T ratio and 2.1-3.0 cm in tumor diameter. Sublobar resection: anatomic or non-anatomic? No large-scale randomized trial comparing AS with non-anatomic WR, which is technically much easier than AS, for small-sized NSCLC has been conducted so far. Despite the fact that patients undergoing AS were more likely to have nodal sampling/dissection, and more LNs retrieved than patients undergoing WR in the present study, Altoki (2017) suggested that it did not lead to an improvement in survival. This is consistent with the results of the ACOSOG Z0030 trial comparing lymph node sampling with systematic nodal dissection in patients with T1-2 N0-1 NSCLC with no difference in survival between the two groups. These findings are of interest since data from the LCSG randomized trial showed that locoregional recurrence after WR was two-fold higher than that after AS. The results that AS should be the preferred option for SR were supported by recent large population-based studies suggesting. Smith (2013) reported the results of evaluating a large population Surveillance, Epidemiology and End Result-Medicare registry (SEER) database. They found that WR were associated with inferior survival compared to AS. However, advantage of AS over WR in the SEER database is probably due to different patient selection criteria as well as inadequate wedge resections with sub-optimal resection margins and insufficient or no nodal assessment. Whether WR and AS were comparable oncologic procedures for cT1N0M0 NSCLC patients or not has been still controversial issue so far. Conclusions Since the clear evidence regarding the survival benefit of sublobar resection for lung cancer patient is lacking so far, lobectomy should be an appropriate therapy for medically operable lung cancer patient at the moment. Abovementioned randomized trials will clearly define the role of sublobar resection in patients with stage I patients. As the number of early-stage peripheral lung cancers is increasing, and a certain number of patients are with multifocal small lesion, the choice of surgical procedure, that is, lobectomy, AS or WR, should be tailored to each case in the future.

Keywords: sublobar resection, lobectomy, CT screening

PL 02 PRESIDENTIAL SYMPOSIUM
TUESDAY, OCTOBER 17, 2017 - 08:15-09:45

PL 02.02 PATIENT-REPORTED OUTCOMES WITH DURVALUMAB AFTER CHEMORADIATION IN LOCALLY ADVANCED, UNRESECTABLE NSCLC: DATA FROM PACIFIC

R. Hui[1], M. Özgüroğlu[2], D. Daniel[3], D. Baz[4], S. Murakami[5], T. Yokoi[6], A. Chiappori[7], K.H. Lee[8], M. De Wit[9], B. Chul Cho[10], J. Gray[7], A. Rydén[11], L. Viviers[12], L. Poole[13], P. Dennis[14], S. Antonia[7]

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PL 02 PRESIDENTIAL SYMPOSIUM
TUESDAY, OCTOBER 17, 2017 - 08:15-09:45

PL 02.04 SCAT PH III TRIAL: ADJUVANT CT BASED ON BRCA1 LEVELS IN NSCLC N+ RESECTED PATIENTS. FINAL SURVIVAL RESULTS A SPANISH LUNG CANCER GROUP TRIAL

Bartomeu Massuti1, Manuel Cobo[2], Manuel Rodriguez-Paniagua[1], Isabel Ballesteros[3], Teresa Moran[4], Ricardo Arrabal[2], Jose Luis Gonzalez Larriba[5], Isidoro Barneto[6], Yat Wah Pun[3], Javier de Castro Carpeño[7], Santiago Ponce-Aix[8], Carlos Baamonde[6], Miguel Angel Muñoz[9], Guillermo Lopez-Vivanco[10], JJ Rivas de Andres[11], Dolores Isla[12], Rafael Lopez[13], Jose Miguel Sanchez[14], José Sánchez-Payá[1], Rafael Rosell[15];

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PL 02 PRESIDENTIAL SYMPOSIUM
TUESDAY, OCTOBER 17, 2017 - 08:15-09:45

PL 02.06 THE IASLC LUNG CANCER STAGING PROJECT: ANALYSIS OF RESECTION MARGIN STATUS AND PROPOSALS FOR R STATUS DESCRIPTORS FOR NON-SMALL CELL LUNG CANCER

J. Edwards[1], K. Chansky[2], L. Shemanski[2], P. Van Schil[3], H. Asamura[4], R. Rami-Porta[5]

[1]Department of Cardiothoracic Surgery, University of Sheffield, Sheffield/GB, [2]Biostatistics, Cancer Research and Biostatistics, Seattle/US, [3]Department of Thoracic and Vascular Surgery, Antwerp University Hospital and University of Antwerp, Edegem/BE, [4]Division of Thoracic Surgery, Keio University School of Medicine, Tokyo/JP, [5]Thoracic Surgery, Hospital Universitari Mutua Terrassa, and Ciberes Lung Cancer Group, Terrassa/ES

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PL 03 IMMUNOLOGY IN LUNG CANCER UPDATE 2017
WEDNESDAY, OCTOBER 18, 2017 - 08:15-09:45

PL 03.01 SERENDIPITIES OF ACQUIRED IMMUNITY

T. Honjo

Department of Immunology and Genomic Medicine, Graduate School of Medicine Kyoto University, Kyoto/JP

Summary of the Lecture In 1992, we started working on PD-1 and found that this acts as a brake in the immune system. Then, in 2002, we discovered that PD-1 inhibition could be effective in treating cancer in animal models. After 22 years of study, this idea has borne fruit in a new, breakthrough immunotherapy that is being hailed as a 'penicillin moment' in cancer treatment. I believe that, just as a number of antibiotics developed in the wake of the discovery of penicillin now protect humans against threats of infectious diseases, this discovery will play a leading role in advancement of cancer immunotherapy so that in the future the fear of dying from cancer will cease to exist. Through evolution, vertebrate animals have developed immunity against infection by microorganisms. In the process, they incidentally acquired a sophisticated system for diversifying genomic information by combining gene fragments. It was doubly fortunate that the success in cancer treatment via PD-1 inhibition brought the realization that immunity, a "weapon" against infectious diseases, could also serve as a "shield" against cancer. It has been said that, whereas humankind's greatest enemies in the 20th century were infectious diseases; cancer is the major foe in the 21st century. It is a pleasant surprise to discover that the acquired immunity system holds the keys to overcoming both of these difficult medical challenges.

Keywords: Immunotherapy, PD-1

PL 03 IMMUNOLOGY IN LUNG CANCER UPDATE 2017
WEDNESDAY, OCTOBER 18, 2017 - 08:15-09:45

PL 03.03 BLUEPRINT 2: PD-L1 IMMUNOHISTOCHEMISTRY COMPARABILITY STUDY IN REAL-LIFE, CLINICAL SAMPLES

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PD-L1 immunohistochemistry (IHC) has been established as companion or complementary diagnostic assays, each having been developed as a predictive biomarker for specific anti-PD-1/PD-L1 immunotherapies.[1] The Blueprint phase 1 was conducted as a feasibility study to assess the staining (analytical) comparability of four PD-L1 IHC assays (22C3, 28-8, SP142, and SP263) that were developed for their respective immune checkpoint inhibitor therapies.[2] Without correlation with treatment outcome, the study also assessed the putative diagnostic performance of these assays through comparisons of PD-L1 status classification above and below selected expression cutoffs associated with the clinical use of various assays. Serial sections from paraffin blocks of 39 resected non-small cell lung cancers (NSCLC) were stained using assays that were used in the clinical trials, and three experts in interpreting the four respective assays independently assessed the percentages of tumor and immune cells staining positive at any intensity. The results 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 less tumor cells compared to the other assays.[2] In contrast, all assays stained tumor infiltrating immune cells, but with poor concordance between assays. The phase 1 study had several limitations: (1) samples were obtained from a commercial source and did not necessarily reflect the real-world samples tested clinically, and (2) the number of pathologists involved in the scoring was small. In addition, a fifth PD-L1 assay (73-10) has since been developed as a potential biomarker for avelumab (EMD Serono/Merck KGaA/Pfizer). The goals of Blueprint phase 2 are: (1) to validate the assay comparability results obtained in Blueprint phase 1 study using real world clinical lung cancer samples and all five clinically used PD-L1 assays (28-8, 22C3, SP142, SP263, and 73-10), (2) to assess the comparability and heterogeneity of PD-L1 assay results in surgical tumor resection, core needle and FNA samples prepared from same tumor, and (3) to assess the concordance of PD-L1 scoring by pathologists from around the world using standard light microscopy vs. digital images accessed by a web-based system. In blueprint phase 2A, 18 participating pathologists, with respective institutional research ethics board approval, contributed unstained serial sections from altogether 81 lung cancer cases that came through routine clinical practice. These included 40 adenocarcinomas, 25 squamous cell carcinomas, 5 poorly differentiated non-small cell carcinoma and 11 small cell carcinomas. The cases included resected tumor (n=20), core/bronchial biopsies (n=20), tumor positive lymph node biopsy/resection (n=20) and cytology cell block (n=21) samples. In blueprint phase 2B, 9 pathologists prepared from 30 freshly resected NSCLC specimens, paraffin blocks of matched resection, core needle and fine needle aspiration samples. Each slide set of 81 cases from phase 2A were stained with the FDA-cleared (28-8, 22C3, SP142) or clinical trial (SP263 and 73-10) PD-L1 assays, in a CLIA-approved immunohistochemistry laboratory. The slides were scored by 24 experienced pulmonary pathologists (IASLC Pathology committee Blueprint phase 2 members),[4] all having received group training on scoring the PD-L1 IHC on tumor and immune cells. PD-L1 stained tumor cells were scored as continuous number (0% to 100%), and placed into 1 of 7 categories (<1%, 1-4%, 5-9%, 10-24%, 25-49%, 50-79%, 80-100%). These categories represent cut-offs that have been used in various immune checkpoint inhibitor trials. All assays were also scored for immune cell PD-L1 staining based on the scoring system developed for the SP-142 assay. As only one set of glass slides is available for each assay, each pathologist was randomly assigned to conduct the scoring using microscope (2 glass assays) or by web-based digital images (3 digital assays). The inter-assay concordance of PD-L1 staining on tumor cells and tumor infiltrating immune cells will be assessed using the mean scores from all pathologists. The large sample size scores should provide more reliable data on their analytical comparability. Inter-pathologist concordance results should provide evidence on reliability of scoring with different cut-points. Importantly, the above concordance results across different sample types should also provide insights on potential variability and feasibility in PD-L1 scoring across different sample types, especially cytology samples. This may then allow for a broad implementation strategy on PD-L1 testing in clinical practice. The results of phase 2A will be presented at the meeting.

IASLC Pathology Committee Blueprint phase 2 members: Mary-Beth Beasley, Alain Borczuk, Johan Botling, Lukas Bubendorf, Gang Chen, Lucian Chirieac, Teh-Ying Chou, Jin-Haeng Chung, Sanja Dacic, Fred R. Hirsch, Keith M. Kerr, Mari Mino-Kenudson, Sylvie Lantuejoul, Andre Moreira, Andrew Nicholson, Masayuki Noguchi, Guiseppe Pelosi, Claudia Poleri, Prudence Russell, Jennifer Sauter, Erik Thunnissen, William D. Travis, Ming S. Tsao, Ignacio Wistuba, Murry Wynes, Yasushi Yatabe, Hui Yu. **References:** IASLC ATLAS of PD-L1 Immunohistochemistry Testing in Lung Cancer. M.S.Tsao, K.M. Kerr, Y. Yatabe, S. Dacic, F.R. Hirsch (Editors), International Association for Study of Lung Cancer (IASLC) Press, 2017 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.* 2017 Feb;12(2):208-222. Feng Z, Schlichting M, Helwig C, et al. Comparative study of two PD-L1 expression assays in patients with non-small cell lung cancer (NSCLC). J Clin Oncol 35, 2017 (suppl; abstr e20581)

Keywords: complementary diagnostics, companion diagnostics, PD-L1 immunohistochemistry

PL 03 IMMUNOLOGY IN LUNG CANCER UPDATE 2017
WEDNESDAY, OCTOBER 18, 2017 - 08:15-09:45

PL 03.04 CURRENT STATUS AND FUTURE OF IMMUNOTHERAPY IN LUNG CANCER

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The therapeutic approach to overcome Tumor-induced suppression of specific T-cell activation by using specific antibodies, which are interacting with regulating pathways, the immune check-points has substantially changed treatment of patients with advanced NSCLC. In particular the development of antibodies inhibiting cytotoxic T-lymphocyte-associated antigen 4 (anti CTL4), programmed death receptor 1 (anti PD-1) or programmed death receptor ligand 1 (anti PDL-1) have shown efficacy in NSCLC. In five randomized trials anti PD-1/anti PD-L1 antibodies have shown significant improvement in overall survival (OS) compared to chemotherapy and an improved safety profile. Efficacy was correlated to PD-L1 expression on tumor cells. However confirmed activity has also been documented in patients with PD-L1 negative tumors. Besides harmonization of different existing tests for assessment of PD-L1 expression identification of novel markers like tumor mutational burden (TMB) might help to identify best benefitting patients. In selected patients with high PD-L1 expression on tumor cells (TPS =/> 50%) monotherapy with the anti PD1 antibody pembrolizumab has demonstrated superiority in response, progression free

survival and OS compared to platinum based chemotherapy in first-line treatment. Current randomized trials evaluate the activity of combinations of chemotherapy with checkpoint inhibitors or of immunotherapy combinations compared to chemotherapy and will provide important information about the next steps in the development of immunotherapy in lung cancer. For the future the development of novel immunotherapeutic agents either as monotherapy or in combination with checkpoint inhibitors as well as the understanding of resistance mechanisms and strategies to overcome resistance will be of paramount importance.

PL 04 CLOSING PLENARY: WHERE WE ARE NOW, AND WHERE WE WILL BE IN 10 YEARS
WEDNESDAY, OCTOBER 18, 2017 - 16:30-17:45

PL 04.01 WHERE WE ARE NOW, AND WHERE WE WILL BE IN 10 YEARS: FROM NORTH AMERICAN PERSPECTIVE

P. Bunn, Jr.

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Stage 4 NSCLC 1st line Rx: In addition to complete staging, all patients with any histology should have PD-L1 testing of their tumor. In addition patients with an adenocarcinoma histology and never smokers should have molecular testing that would include at least EGFR, ALK, ROS1 and BRAF. If NGS testing is selected that additional genes can be tested including MET,RET, HER2,and NTRK. Patients with a PD-L1 tumor proportion score (TPS) >49% who do not have a molecular driver can be treated with pembrolizumab as their first therapy. This therapy is continued for 2 years or until progression or unacceptable toxicity. For those with a TPS score of 1-49, concurrent chemotherapy plus pembrolizumab may be considered based on the results of a small phase II trial. However, larger phase III trials are in progress and may alter this choice. Patients with a molecular alteration in EGFR, ALK, ROS1, or BRAF are treated with the appropriate TKI or TKI combination in the case of v600E BRAF. Although all of the randomized trials comparing these new therapies to chemotherapy included only PS 0-1 patients, there is clear evidence that patients with PS 2 and even PS 3 and elderly patients may benefit from these therapies and should thus be tested. For patients with a lower TPS score or no molecular abnormality and PS0-1, the standard therapy is a platinum doublet chemotherapy with or without bevacizumab. For patients with adenocarcinoma, the most frequently used regimen is pemetrexed with platinum. In North America the platinum is most often carboplatin because of its preferred toxicity profile. PS 0-1 adenocarcinoma patients may also receive bevacizumab if there are no comorbid conditions that would increase toxicity. A taxane doublet with or without bevacizumab is also acceptable. For patients with squamous carcinoma the platinum doublet usually contains gemcitabine or a taxane with carboplatin with or without bevacizumab. Patients receiving chemotherapy are restaged after 2 cycles. Those with progressive disease are offered second line therapy. Patients with stable disease or response receive 2 additional cycles and are then restaged again. Those with acceptable toxicity and continued response are offered 2 additional cycles for a total of 6. Those without further response or additional toxicity are offered maintenance therapy after the 4 cycles. Patients receiving 6 cycles are also offered maintenance therapy. Maintenance therapy may consist of continued pemetrexed or continued bevacizumab for those responding to these. Switch therapy to pemetrexed or to erlotinib or gemcitabine may be considered. 2nd Line Rx. For patients receiving 1st line pembrolizumab, 2nd line rx is first line chemotherapy as discussed above. For patients progressing on a 1st line TKI, the 2nd line therapy is most often a 2nd or 3rd generation TKI. When therapy with a TKI is exhausted, the next line of therapy is standard first line chemotherapy as described above. For patients who receive 1st line chemotherapy, the second line therapy is most often immunotherapy which can be any of the 3 approved agents for patients with a TPS score of >1 or nivolumab or atezolizumab for patients with a TPS score of 0. 3rd Line Rx: Patients who receive 1st line I/O followed by chemo or who receive gene specific TKIs followed by 1st line chemotherapy, the 3rd line treatment would be what was previously considered 2nl line chemo such as docetaxel +/- ramicirumab. Other chemotherapy agents can also be considered such as gemcitabline, other taxanes or irinotecan. Clinical trials may be substituted for any of these treatments in any lines of therapy. Unresectable Stage III. The standard approach is currently concurrent chemotherapy with chest radiotherapy. This is likely to change as positive results of a trial comparing CT/RT alone to CT/RT followed by immunotherapy with durvalumab were announced in mid-2017. The chest RT is generally about 60 Gy given over 6 weeks. The chemotherapy is generally a platinum doublet with etoposide, paclitaxel or pemetrexed. At the time of progression the algorhythm described for stage 4 above can be instituted. Resectable stage I-IIIA. For stage 1A standard therapy is lobectomy alone or stereotactic body radiotherapy (SBRT) for those who are medically inoperable. Patients with stage IB, especially with poor prognostic features such as large size or vascular invasion may receive neoadjuvant or adjuvant chemotherapy with a cisplatin doublet and surgery is standard while other smaller stage IB tumors are treated with lobectomy alone. Stage II and IIIA patients may be treated with neoadjuvant chemotherapy or neoadjuvant CT/RT followed by surgery. They may also receive surgical resection first followed by adjuvant CT or CT/RT. The future: It is highly likely that immunotherapy combinations will prove to be superior to single checkpoint inhibitors so that the majority of sage IV patients without a molecular driver are likely to receive an immunotherapy combination, likely irrespective of TPS score. For stage IV patients with a molecular driver, it is likely that initial therapy will consist of the TKI plus another agent that can affect the cells that persist after initial TKI therapy. It is likely that immunotherapy combinations and molecular combinations will be used in unresectable stage III disease before, after or during CT/RT and will improve cure rates. I believe that a large change in approach to early stage patients will occur with the development of neoadjuvant immunotherapy and molecular therapy. In these approaches we have the opportunity to improve cure rates as well as to more rapidly develop new therapies based on pathologic complete response rates as we now do in breast cancer. The future is also likely to see new ways to define risk in both smokers and non-smokers so that we can detect patients early and so that we can develop new prevention strategies for those at high risk.

2017 Treatment Algorithm

Determine Performance Status, Histology, PD-L1 status and Presence of Driver Mutations

	Adenoca with Driver PS 0-3	Adeno,squamous, opr LC with PD-L1>49 PS 0-3	Adenoca No Driver PD-L1<50% PS 0-2	Squamous PD-L1<50 PS 0-2	LCNE PD-L1 PS 0-2
1st Line	EGFR + Gefitinib, Erlotinib, Afatinib,osimertinib ALK/ROS1+ Crizotinib,Alectinib BRAF+ Debrafenib/Trametinib RET, MET, HER2, NTRK+ specific TKI	Pembrolizumab	Platinum doublet (Pem,Taxane) ± Bevacizumab	Platinum doublet (Gem, Taxane) ± Necitumumab	Etop+ Platinum
Maintenance	Continue TKI	Pembrolizumab	Bev, Pem, Erlotinib or none	None? Doce, Gem, Erlotinib	None
2nd/3rd Line	2nd/3rd-generation TKI then chemo,then I/O	Platinum Doublet +/-bev Doce+/-ram	Nivo,Pembro,Atezo Doce ± Ramucirumab	Nivo,pembro ,atezo, Doce ± Ram	I/O, CAV, Irinotecan, Taxane, Gem

Keywords: Lung Cancer Therapy

PL 04 CLOSING PLENARY: WHERE WE ARE NOW, AND WHERE WE WILL BE IN 10 YEARS
WEDNESDAY, OCTOBER 18, 2017 - 16:30-17:45

PL 04.02 WHERE WE ARE NOW, AND WHERE WE WILL BE IN 10 YEARS: FROM ASIAN PERSPECTIVE

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Compared with 30 years ago non-small cell carcinoma (NSCLC) became a vast dominant type of lung cancer and majority of clinical trials focus on it. At the end of 20th century, effect of platinum doublet containing third generation cytotoxic drugs reached a plateau and thoracic oncologists felt skepticism to achieve the goal in lung cancer treatment. Development of EGFR-TKIs (Gefitinib and Erlotinib) was one of the biggest breakthroughs for rollback of chemotherapy in lung cancer. The EGFR mutation was discovered in 2004 but it took 5 years until there was general agreement that it was an important driver mutation which could predict for response to EGFR-TKI. Evolution of EGFR-TKI proceeds to irreversible 2nd (Afatinib and Dacomitinib) and mutation specific 3rd generation (Osimertinib) TKIs which can combat the issues of resistance. In Asia more than 50% of adenocarcinoma are EGFR-Mt+ and physicians experienced many long term survivors like surgical treatment in early stage lung cancer. In addition CTONG trial demonstrated that adjuvant EGFR-TKI (Gefitinib) delays recurrence in EGFR-positive surgically resected EGFR-Mt+ NSCLC. WJOG in Japan is conducting exactly the same schedules of trial. There will be a possibility to conduct study of EGFR-TKI combined with chemoradiotherapy in EGFR-M + stage III NSCLC in Asian countries although this strategy was not successful in unselected population. Many driver mutations have been identified and its molecular classification made rapid progress in lung cancer, especially adenocarcinoma. The identification ALK and ROS rearrangement quickly followed by the development of active drugs (Crizotinib, Alectinib, Brigotinib, Lorlatinib). J-ALEX and ALEX trials clearly showed that Alectinib was extremely active drug against ALK rearranged NSCLC. The Nation Wide Genomic Screening Project (LC-Scrum-Japan) leaded by K Goto has been started on February 2013 in Japan. Under this project many driver mutations have been identified not only in non-squamous cell carcinoma but also in squamous and small cell lung cancer. Many clinical trials are ongoing targeting genomic alterations screened in LC-SCRUM-Japan. Among them LURET trial demonstrated that Vandetanib could show 53% response rate (9/17) in RET+ lung cancer and Crizotinib produced 69% response rate (89/129) in ROS-1+ patients in OxOnc12-01 Asian Global trial. Driver mutation targeted drugs showed dramatic effect compared with standard cytotoxic chemotherapy, however, there is so far no positive data of their combination in spite of clear preclinical synergistic or additive effect. Human RAS oncogenes are the most commonly mutated gene family in Caucasian. About 35% (15% in Asian) of lung cancer are driven by activating mutations of KRAS. RAS is really an oncogenic driver and numerous preclinical studies suggest that KRAS is an excellent and well validated target. However, unlike EGFR, ALK, ROS, there is no effective drugs against KRAS. It will be extremely an important issue to develop KRAS targeting drugs. Robust negative data accumulate in immunotherapy for lung cancer including peptide vaccine therapy. Based on unique idea of Allison J. first immune checkpoint inhibitor, anti-CTLA4 antibody (ipillimumab) produced survival benefit in melanoma. PD-1 was cloned by Honjo T (Japan) on 1992 and antitumor activity of anti-PD-1 antibody was reported on 2002. During past 7 years, immune checkpoint inhibitors have been an exciting new addition to the armamentarium fort lung cancer. Two anti-PD-1 antibodies such as Nivolumab and Pemblolizumab has become a standard for second line treatment of lung cancer based on durable response and marked increase in overall survival. In first line treatment Pemblolizumab prolonged OS and PFS compared with standard chemotherapy in NSCLC with high PD-L1 expression >50% (Keynote024). On the other hand, Nivolumab failed to show PFS benefit compared with cytotoxic agents because of poor patient selection. The most important issue will be how to concentrate responsive population and how to eliminate ineffective patients. Although there is a tendency of correlation between PD-L1 expression and objective response/ PFS/OS, responders are experienced even in PD-L1 negative patients. Microsatellite instability has related with response to anti-PD-1 antibody in colorectal cancer. Mutation burden may influence on antigenicity of tumor cells. Infiltration of CD8+ lymphocytes is also considered to be a predictive biomarker but it is too objective

for precise quantification. The successful patient selection for immune checkpoint inhibitors may depend on the development of methods for quantitative measurement of tumor specific cytotoxic activity of CD8+ lymphocytes. Can cytotoxic drugs survive as one of the modalities for lung cancer treatment? Combination of cytotoxic drugs and immune checkpoint inhibitors shows promising antitumor activity in lung cancer and gastric cancer. Antibody-drug conjugate (ADC) is a very interesting strategy for effective chemotherapy. DS-8201 targeting HER2, developed by Daiichi-Sankyo showed high response rate and favorable toxicity profile in previously treated HER2 positive gastric and breast cancer. ADC will be a potent strategy in future cytotoxic chemotherapy for lung cancer. Progress in the treatment of small cell lung cancer is very behind because of decrease in absolute number of SCLC patients and no discovery of driver mutations. JCOG conducted serial randomized clinical trials in SCLC. However, treatment result reached a plateau in both of limited and extensive diseases. Discovery of druggable targets in near future may have a significant impact in small cell lung cancer.

EDUCATION SESSIONS

ES 01 NEW TNM AND WHO CLASSIFICATION
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

ES 01.01 NEW TNM CLASSIFICATION

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Introduction The new tumor, node and metastasis (TNM) classification of lung cancer –the 8th edition– has already been discussed in the two previous World Conferences of Lung Cancer. (J Thorac Oncol 2015; 10 (Supp 2): s69; J Thorac Oncol 2017; 12 (Supp 1): s2-s3.) The purpose of this educational session is to revise the innovations of the 8th edition, to point out its lights and shadows, and to highlight how they can affect our clinical practice. The innovations introduced in the 8th edition were based on sound statistical analyses of 70,189 patients with non-small cell lung cancer and 6,189 with small cell lung cancer diagnosed from 1999 to 2010. (1) Although a large number of patients was registered in the International Association for the Study of Lung Cancer database, data originated mainly from Asia and Europe and the other geographic regions of the world were scarcely represented. The innovations are applicable to both types of carcinomas (2) and also to bronchopulmonary carcinoids. (3) Rules to classify lung cancers with multiple lesions were provided based on data where data were available or on multidisciplinary consensus. (4) **Primary tumor (T component)** New T categories were introduced based on tumor size: T1a </= 1cm, T1b >1-2cm, T1c >2-3cm, T2a >3-4cm, T2b >4-5cm, T3 >5-7cm and T4 >7cm. In addition, endobronchial location less than 2 cm from the carina and total atelectasis / pneumonitis were reclassified as T2, while invasion of the diaphragm was reclassified as T4 and invasion of the mediastinal pleural was deleted as a T descriptor. The definition of visceral pleural invasion proposed for the 7th edition, i.e., the invasion of its elastic layer, was confirmed for the 8th edition and the recommendation to use elastic stains was reinforced. (5, 6) Codes for adenocarcinoma in situ –Tis(AIS) – and minimally invasive adenocarcinoma –T1mi– were defined, too. (7) Because tumor size has more prognostic relevance, its measurement must be as accurate as possible. The recommendation is to measure it on computed tomography with the lung window, because the mediastinal window may underestimate it. The registered size should be the greatest dimension in any of the available projections: axial, coronal or saggital. For part-solid non-mucinous adenocarcinomas, only does the size of the solid part on computed tomography at clinical staging or the size of the invasive part at pathologic examination count to assign a T category based on tumor size. (7) **Nodal involvement (N component)** The present N categories (NX, N0, N1, N2 and N3) and their descriptors remain unchanged. An important confirmation in the analyses of survival was that quantification of nodal disease at pathologic staging impacts prognosis: the more involved nodal stations, the worse the prognosis. (8) Therefore, identifying the number of involved nodal stations is important both at clinical and pathologic staging, although it is difficult to determine them accurately at clinical staging unless a lymphadenectomy is performed at the time of mediastinoscopy. The proposed subclassification of the N categories for prospective testing are: N1a – involvement of a single N1 station; N1b – involvement of multiple N1 stations; N2a1 – involvement of a single N2 station without N1; N2a2 – involvement of a single N2 station with N1; and N2b – involvement of multiple N2 stations. N1b and N2a1 have similar prognosis. **Metastatic disease (M component)** Intrathoracic metastases (M1a: malignant pleural and pericardial effusions and/or nodules, and contralateral separate tumor nodules) remain the same. Extrathoracic metastases were divided into single extrathoracic metastasis (the redefined M1b category) and multiple extrathoracic metastases in one or in several organs (the new M1c category). (9) These innovations imply that counting the number of metastases is important, at least from the prognostic point of view, but also from the therapeutic, because single extrathoracic metastasis can be the base to define oligometastatic disease, the treatment of which is aimed to be radical, with whatever therapeutic means are available, instead of palliative, as it usually is the case with polymetastatic disease. **Stage grouping** More stages have been created to accommodate the new T1 (T1a N0 M0 is stage IA1, T1b N0 M0 is stage IA2 and T1c N0 M0 is stage IA3) categories; to isolate locally advanced tumors (T3-T4 N3 M0 are now stage IIIC); or to separate metastatic disease (M1a and M1b are stage IVA and M1c is stage IVB). (10) Some tumors have shifted their positions. Tumors that are stage shifters should be treated according to evidence and not according to the treatment for those stages in which they now are based on prognosis, because a mere change in taxonomy does not imply a change in treatment. Clinical judgment in the multidisciplinary team discussions should led to the best therapeutic option for these patients whose tumors have moved from one stage to another. **Conclusion** The 8th edition facilitates the indication of prognosis and the stratification of tumors in future clinical trial, but requires more discipline from us when measuring tumor size, quantifying nodal disease and determining the number of extrathoracic metastasis. **References** 1. Rami-Porta R, Bolejack V, Giroux DJ et al. J Thorac Oncol 2014; 9: 1618-1624. 2. Nicholson AG, Chansky K, Crowley J et al. J Thorac Oncol 2016; 11: 300-311. 3. Travis WD, Giroux DJ, Chansky K, et al. J Thorac Oncol 2008; 3: 1213-1223. 4. Detterbeck FC, Nicholson AG, Franklin WA et al. 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Keywords: lung cancer, Staging, TNM classification

ES 01 NEW TNM AND WHO CLASSIFICATION
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

ES 01.02 NEW HISTOLOGICAL CLASSIFICATION

W. Travis

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The 2015 WHO Classification had a major impact on the new 8th Edition TNM Classification. Compared to the 2004 Classification, major changes include: 1) use of immunohistochemistry throughout; 2) New emphasis on genetic studies and personalized therapeutic strategies; 3) A new classification of lung cancer in small biopsy and cytology samples; 4) adoption of the 2011 IASLC/ATS/ERS lung adenocarcinoma classification; 5) reclassification of large cell carcinoma based upon immunohistochemistry and genetics. Since publication of the 2015 WHO Classification new advances include recognition of ciliated muconodular papillary tumors, SMARCA4 and SMARCB1 deficient neoplasms and digital image analysis as a novel way to assess lung cancer morphology. This presentation will primarily focus on the impact of the new WHO Classification on the 8th Edition TNM classification. First the new TNM classification incorporates the introduction of the concepts of adenocarcinoma *in situ* (AIS) which should be staged as Tis (AIS) and minimally invasive adenocarcinoma (MIA) which should be staged as T1mi. AIS is defined as a lung adenocarcinoma with pure lepidic growth measuring ≤3 cm. MIA is defined as a ≤3 cm lepidic predominant adenocarcinoma with an invasive component measuring 0.5 cm or less. Both AIS and MIA should lack stromal, vascular, or pleural invasion and spread through alveolar space invasion (STAS). Lepidic predominant adenocarcinomas are lung adenocarcinomas with a predominant lepidic component that measure > 3 cm in total size or that have an invasive component measuring >0.5 cm. It is recommended to use invasive size for T-descriptor size in nonmucinous adenocarcinomas with a lepidic component. This is in keeping with a recommendation made in three editions of the UICC TNM Supplement since 2003. It is also supported by a growing amount of evidence showing that invasive size is a better predictor of survival than total size in nonmucinous adenocarcinomas with a lepidic component. Both radiologists and pathologists should report the greatest dimension for tumor size for both clinical and pathologic staging. In addition for nonmucinous lung adenocarcinomas, both the total size and invasive size should be reported with invasive size used for T-factor size determination. By computed tomography (CT) in nonmucinous lung adenocarcinomas, the presence of ground glass versus solid opacities generally correspond to lepidic versus invasive patterns respectively seen pathologically. Since, this is not an absolute correlation, when CT features suggest nonmucinous AIS, MIA and LPA, reporting of the suspected diagnosis and clinical staging, should be made as a preliminary assessment that may need to be revised after evaluation of resected specimens pathologically. Since the mucinous variants of AIS, MIA and invasive mucinous adenocarcinomas usually present by CT as a solid or consolidated nodule, and due to the lack of proven correlation between ground glass/solid CT appearance with lepidic/invasive growth pathologically it is not recommended to apply the total vs solid size assessment by CT in suspected invasive mucinous adenocarcinomas. Furthermore there is insufficient data in invasive mucinous adenocarcinomas that invasive size is a better predictor of survival than total size. Pathologic assessment of total vs invasive tumor size in resected nonmucinous lung adenocarcinomas with a lepidic component can be improved by reviewing CT scans because the lepidic component is often poorly appreciated pathologically on gross exam and size is underestimated. In addition, tumor size can be more accurately assessed after radiologic pathologic correlation in the following settings: 1) Lepidic nonmucinous adenocarcinomas that do not fit onto a single slide, 2) Sausage or bilobed shaped tumors where the maximum single diameter may be better assessed using all three CT views (axial, coronal and sagittal) rather than just axial alone, 3) Tumors removed in multiple parts, 4) Intraoperative defects in tumors, 5) Marked non-neoplastic reactions, 6) Mistaken pathologic assessment. In neoadjuvant tumors, it can be difficult to measure tumor size because tumors that show considerable treatment effect often do not have a uniform response allowing a single focus of viable tumor to be measured. It has been shown that 90% or more treatment effect is the most important prognostic finding instead of tumor size in surgically resected nonsmall cell lung cancer patients following induction therapy. One way to estimate viable tumor size is to multiply the percent of viable tumor cells times the size of the total tumor bed. This can be utilized in the setting of a single focus or multiple foci of viable tumor. Recording the percentage of treatment effect is important in addition to estimating tumor size for T-factor determination. **REFERENCES** 1. Travis WD, et al The New IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. JThoracic Oncol 2011;6:244-85. 2. Travis WD, et al WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer; 2015. 3. Travis WD, et al The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2016;11:1204-23. 4. 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Keywords: Pathology, WHO Classification, TNM classification

ES 01 NEW TNM AND WHO CLASSIFICATION
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

ES 01.04 STAGING AND PATHOLOGY OF MULTIPLE NODULES PRESENTING IN THE LUNGS

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Multiple tumor nodules arising in the lungs can be due either to separate primary lung cancers (SPLCs) or intrapulmonary metastases (IPM) (separate tumor nodules). The recently revised Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) staging manuals (8th editions), based on proposals from work undertaken by the IASLC Staging and Prognostic Factors Committee (SPFC), include updates in T, N and M components, that reflect increased interest in staging of patients with multiple tumor nodules (1-4) due to increased frequency of presentation (1) and advances in classification of tumor subtypes (5). T categories for multiple tumor nodules are unchanged when compared to the 7th edition, with SPLCs continuing to be staged individually, with the recommendation that multiple lesions be grouped with the number of lesions in brackets (e.g. (2)), or (m) for multiple. Patients with IPM are staged as T3 (same lobe), T4 (different lobe in ipsilateral lung) and M1a (contralateral lung). However, although unchanged, these categories have been impacted by changes in the histologic classification of lung cancer (6), in particular adenocarcinomas (7). For the current edition, those tumors that present with multiple areas of pneumonic consolidation, these frequently corresponding to invasive mucinous adenocarcinomas, are viewed as a potential subgroup of IPM. There is also increased interest in those patients who present with multiple ground glass lesions, these typically corresponding to patients with non-mucinous adenocarcinomas with a lepidic component. These types of multiple tumor nodules are currently viewed as a potential subgroup of SPLCs. It is hoped that the next decade will see further research from within the lung cancer community that informs the 9th edition in relation to the staging of these types of tumor (3). In relation to pathologic staging, from 1975 until recently, distinction between SPLC and IPM was undertaken using criteria proposed by Martini and Melamed: tumors occurring in different lobes, having different major histologic types or being separated by a time interval of more than two years were to be classified as SPLCs (8). Recently, these criteria have been supplanted by the process of comprehensive histologic assessment (CHA) (9). CHA involves determination of major histologic type, assessment of predominant and minor histologic patterns according to histologic subtyping and evaluation of cytological features. CHA has been shown to significantly improve the pathologic distinction between SPLC and IPM to a level comparable to molecular analysis (9). Recent work undertaken by the IASLC Pathology Committee has also shown that usage of this methodology has good reproducibility amongst diagnostic pathologists. Furthermore, p staging status strongly correlated with nuclear pleomorphism, cell size, acinar formation, nucleolar size, and mitotic rate. In addition to the above, immunohistochemistry already has a role in refining the distinction between SPLC and IPM, and molecular techniques are also likely to be used increasingly in the situation. Studies have been published showing that comprehensive genotypic and morphological assessment is feasible, though they are not yet sufficient to establish clonal relationships between multiple tumour nodules (10). Ultimately, a multidisciplinary approach is likely to be the best methodology for distinction between SPLC and IPM, in particular the assessment of imaging data alongside histologic, immunohistochemical and molecular profiles, both in the context of biopsies and resections. 1. Detterbeck FC, Franklin WA, Nicholson AG, Girard N, Arenberg DA, Travis WD, et al. 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ES 02 DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY IN LUNG CANCER: UPDATE 2017
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

ES 02.01 THE DUTCH-BELGIAN LUNG CANCER SCREENING TRIAL (NELSON)

H. De Koning

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Background Lung cancer is the most important tobacco-related health problem worldwide, accounting for an estimated 1.3 million deaths each year, representing 28% of all deaths from cancer. Lung cancer screening aims to reduce lung cancer-related mortality with relatively limited harm through early detection and treatment. The US National Lung Screening Trial showed that individuals randomly assigned to screening with low-dose CT scans had 20% lower lung cancer mortality than did those screened with conventional chest radiography. On the basis of a review of the literature and a modelling study, the US Preventive Services Task Force (USPSTF) recommends annual screening for lung cancer for high-risk individuals. However, the balance between benefits and harms of lung cancer screening is still greatly debated. Some investigators suggest the ratio between benefits and harms could be improved through various means. Nevertheless, many questions remain with regard to the implementation of lung cancer screening. Whether nationally implemented programmes can provide similar levels of quality as achieved in these trials remains unclear. The NELSON trial is Europe's largest running lung cancer screening trial. The main purposes of this trial are; (1) to see if screening for lung cancer by multi-slice low-dose CT in high risk subjects will lead to a 25% decrease in lung cancer mortality or more; (2) to estimate the impact of lung cancer screening on health related quality of life and smoking cessation; (3) to estimate cost-effectiveness of lung cancer screening. The NELSON trial was set up in 2003 in which subjects with high risk for lung cancer were selected from the general population. After informed consent, 15,792 participants were randomised (1:1) to the screen arm (n=7,900) or the control arm (n=7,892). Screen arm participants received CT-screening at baseline, after 1 year, after 2 years and after 2,5 years. Control arm participants received usual care (no screening). In the NELSON trial a unique nodule management protocol was used. According to the size and volume doubling time of the nodules, initially three screen results were possible: negative (an invitation for the next round), indeterminate (an invitation for a follow-up scan) or positive (referred to the pulmonologist because of suspected lung cancer). Those with an indeterminate scan result received a follow-up scan in order to classify the final result as positive or negative. All scans were accomplished at the end of 2012. The lung cancer detection rate across the four rounds were, respectively: 0.9%, 0.8%, 1.1% and 0.8%. The cumulative lung cancer detection rate is 3.2% which is comparable with the Danish Lung Cancer Screening Trial (DLCST). Relative to the National Lung Screening Trial (NLST), more lung cancers were found in the NELSON: 3.2% vs. 2.4%. However, the NLST had less screening rounds and a different nodule management protocol and a different study population. False-positive rate after a positive screen result of the NELSON is 59.4%. The overall false-positive (over four rounds) is 1.2% in the NELSON study, which is lower compared to other lung cancer screening studies. A 2-year interval did not lead to significantly more advanced stage lung cancers compared with a 1-year interval (p=0.09). However, a 2.5-year interval led to a stage shift in screening-detected cancers that was significantly less favourable than after a 1-year screening interval (e.g. more stage IIIb/IV cancers). It also led to significantly higher proportions of squamous-cell carcinoma, boncho-alveolar carcinoma, and small-cell carcinoma ($p<0.001$). Compared with a 2-year screening interval, there was a similar tendency towards unfavourable change in stage distribution for a 2.5-year screening interval although this did not reach statistical significance. Also, the interval cancer rate was 1.47(28/19) times higher in the 2.5-year interval compared with the 2-year interval. Moreover, in the last six months before the final fourth screening round the interval rate was 1.3(16/12) times higher than in the first 24 months after the third round, suggesting that a 2.5-year interval may be too long. On average, 69.4% of the screening-detected lung cancers across the four screening rounds in the NELSON trial were diagnosed in stage I and 9.8% in stage IIIb/IV. This cumulative stage distribution of the screening-detected lung cancers in the NELSON trial appears to be favourable compared to those of the DLCST and the NLST (68.1% and 61.6% of cancers at stage I, and 15.9% and 20.0% at stage IIIb/IV, respectively).However, this finding should be interpreted with caution because 1) the NLST used the 6th edition of the TNM staging system, while the NELSON trial used the 7th edition, 2) the NLST and DLCST applied different eligibility criteria than the NELSON trial, and 3) the proportion of over-diagnosed lung cancers in the screening group is yet unknown. The lung cancers found in the NELSON control group have yet to be investigated.

Keywords: Lung cancer; screening; Europe's largest running trial

ES 02.02 THE FLEISCHNER GUIDELINE / LUNG-RADS

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The Fleischner Society guidelines (most recently revised in 2017) [1,2] are the most referenced guidelines for management of pulmonary nodules detected incidentally on CT images. In 2014, the American College of Radiology produced the Lung-RADS assessment categories specifically to guide management of nodules detected by Low Dose CT screening for lung cancer [3]. Nodule management guidelines have also been published by the American College of Chest Physicians (ACCP) in 2013 [4] and the British Thoracic Society (BTS) in 2015 [5]. Whilst the Fleisher guidelines and Lung-RADS predominantly offer specific recommendations for interpretation of CT images and guidance for surveillance imaging, the ACCP and BTS guidelines in addition offer more proscriptive recommendations for ongoing investigation or treatment of larger nodules with PET-CT, biopsy techniques, and surgical/ non-surgical treatment. There is much common ground between the four proposals. Most of the high quality evidence for nodule management comes from screening studies that only included patients at high risk of lung cancer, and there is an acknowledged paucity of evidence for guiding nodule management in patients with a lower background risk of cancer. There is agreement about the need to minimise radiation dose for CT surveillance for nodules, and an acknowledgement of the low likelihood of malignancy in small nodules detected through any route. All guidelines recognise that sub-solid nodules require a different management algorithm which incorporates a less interventional approach (acknowledging the more indolent nature of the tumours that these may represent) but by implication the need for longer follow-up before nodules can be deemed benign or harmless. Differences between the recommendations are summarised in Table 1. The size below which nodules can be ignored differs slightly between the guidelines. Lung-RADS recommends no intervention for nodules <6mm (or <4mm for new nodules) on the assumption that the patient continues with annual LDCT screening. Determining a threshold for discharge of small nodules detected out a screening program is of potentially greater significance, as a patient with a small malignant nodule discharged in this context is likely to have a poor outcome if that nodule subsequently presents as a symptomatic lung cancer. The Fleischner Society guidelines select a threshold of 1% lung cancer risk (roughly equating to 6mm diameter) below which surveillance is not routinely recommended (although is an option if the patient is high risk). The BTS guidelines base their discharge threshold of 80mm^3 (5mm) on data from the NELSON screening trial which demonstrated this to be the threshold below which the presence of a nodule did not appear to increase the likelihood of subsequently diagnosed lung cancer above that seen in screening participants with no nodules [6]. More recent data from NELSON has suggested a different size threshold for nodules newly appearing during the screening process. New incident nodules above 27mm^3 appeared to confer an increased risk of cancer [7], and this is reflected in the Lung-RADS category 3 which suggests a 6 month surveillance scan for new incident nodules ≥4mm. When an incidentally detected nodule can be shown to be new compared to recent CT imaging, a lower threshold for ongoing surveillance is probably merited, although not currently recommended in the three relevant guidelines. The use of composite risk-prediction scores in guiding nodule management differs between the various guidelines. The Fleischner guidelines highlight the various risk factors to be considered when deciding management but do not recommend use of a risk prediction score. The ACCP guidelines recommend either qualitative assessment of the probability of malignancy, or quantitative assessment using a validated model (referencing the Mayo model [8]). The BTS guideline recommend use of the Pancan lung cancer risk calculator [9] to decide which nodules should be evaluated with PET-CT on the basis of a validation study in a UK population [10]. Subsequent studies from Australia and Denmark have also demonstrated the utility of the Pancan model in screening studies. The guidelines also differ in the extent to which they promote use of semi-automated volumetry. No reference to volumetry is made in Lung-RADS assessment categories. Both the Fleischner and BTS guidelines acknowledge the better reproducibility of volumetry over diameter measurements and the superior sensitivity in detecting growth. Both however highlight the need to use identical software versions if comparing nodule volumes between scans due to clearly demonstrated variability between different software programs/versions. The Fleischner guidelines comment that robust validated volumetry is not currently widely used hence continuing to base recommendations predominantly on caliper long and short-axis diameter measurements, whereas the BTS guidelines have strongly recommended volumetry in an attempt to drive uptake of this technology. The definition of what constitutes nodule growth also differs between the guidelines. Lung-RADS and the Fleischner guidelines define growth as an increase is diameter of >1.5mm and ≥2mm respectively, reflecting possible inaccuracy in smaller increments in size according to caliper measurements. The threshold of 25% change in volume recommended in the BTS guideline is based on the nodule management stategy used in both NELSON and UKLS. By way of comparison, nodule growth from 7mm to 9mm represents a 113% increase in volume (from 180mm^3 to 381mm^3). All four guidelines/ assessment categories have been published within the last 5 years, and there have been few validation studies published to date. Lung-RADS was compared to the National Comprehensive Care Network guidelines for lung cancer screening and was shown to increase the positive predictive value without increasing false-negative results. Prospective comparisons between these guidelines/approaches are needed to guide future practice. Table 1: Summary of significant differences between nodule management strategies recommended by various guidelines/assessment categories Fleischner [1,2] Lung-RADS [3] BTS [4] ACCP [5] Remit Incidentally detected nodules Screen-detected nodules Incidentally and screen-detected nodules Incidentally and screen-detected nodules Assessment of size Average of long & short axis diameter Average diameter Semi-automated volumetry where possible As per Fleischner guidelines Threshold for discharge <6mm - optional follow-up below this size if high risk <6mm (revert to annual screen) <80mm3 <5mm - optional follow-up below this size if high risk Selection of further investigation for larger nodules >8mm - consider PET, PET-CT or biopsy ≥8mm - PET-CT, biopsy or assess with Brock/ Pancan score ≥8mm - Brock/ Pancan score to guide PET-CT/other tests ≥8mm - clinical judgement or validated model (e.g. Mayo) Assessment of growth Increase in size of ≥2mm Increase in size of >1.5mm Increase in volume of >25% Not specified Pure Ground Glass Nodules Surveillance only for 5 years duration Revert to annual screen (unless >20mm) Risk assess, but surveillance preferred (for 4 years) CT surveillance for 3 years **References** [1] MacMahon H, Naidich DP, Goo JM, et al. 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Keywords: Low dose CT screening for lung cancer, pulmonary nodule

ES 02.03 RADIOLOGIC IMPLICATIONS OF THE WHO CLASSIFICATION FOR LUNG CANCER

K. Garg

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Invited Lecture: Marked heterogeneity exists in clinical, radiologic, molecular, and pathologic features among adenocarcinoma cases. Therefore, a new Classification of Lung Adenocarcinoma was proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society in 2011 (1). The 2011 classification addressed three important weaknesses in the previous classification. First, it eliminated the term bronchioloalveolar carcinoma (BAC). Second, it added new terminologies of carcinoma-in-situ (CIS), and minimally invasive adenocarcinoma (MIA) to recognize that minimal invasion (< 5mm) had nearly similar clinical outcome as noninvasive nodules. Third, it replaced the terminology of mixed subtype of adenocarcinoma. In this revised classification, invasive lung ADCs were divided into the five subtypes; lepidic, acinar, solid, papillary, and micropapillary patterns primarily based on histologic features. The term predominant is appended to all categories of invasive ADC, as most of these tumors consist of mixtures of the subtypes (1). The widespread availability of MDCT and abundance of new information obtained especially from low-dose CT lung cancer screening programs, have increased our understanding of the types and management of small peripheral lung nodules encountered in daily clinical practice, in particular, the importance and prevalence of subsolid pulmonary nodules (atypical adenomatous hyperplasia (AAH), ground glass nodules (GGN) and part-solid nodules). Thin-section CT has emerged as a new biomarker for lung adenocarcinoma subtypes. The approval of CT as a screening tool for lung cancer was based primarily on National Lung Screening Trial (NLST) results. The NLST recently found that Low Dose Helical Computed Tomography (LDCT) reduces lung cancer specific mortality by 20% relative to chest x-ray screening in a cohort at high risk of lung cancer (2). However, significant concerns remain regarding its high false positive rate, overdiagnosis, cost effectiveness and concerns related to radiation burden from repeat CT screens. There is a trade-of between early detection of lung cancer vs unnecessary work-up of indeterminate nodules resulting in many side effects including anxiety, radiation exposure from CT follow-up to assess for growth, cost and morbidity and mortality related to biopsy or resection of a benign nodule. It is expected that false positive rate would decrease by 50% using more accurate phenotyping of a nodule using the lung CT reporting and data system (Lung-RADS) appropriately (3). One of the major changes proposed in Lung-RADS is the size threshold for positive screen, from 4 mm in NLST to 6 mm for solid nodules and 20 mm for nonsolid nodules. Tissue sampling would be used primarily for larger than 15 mm solid nodules or PET positive nodules with larger than 8 mm solid component. False positive rate would still be likely not acceptable for an individual using this approach. There is need for more accurate nodule assessment and risk stratification as given our current understanding that genetic make-up of a nodule is the ultimate determinant of clinical outcome (4).

Further improvements in stage discrimination and management of lung nodules could be expected in the future, as more robust data related to texture analyses of tumors, their genetic profiles and impact of those on clinical outcome becomes available (5-8). Simple measuring the tumor size with one-dimentional (Response Evaluation Criteria in Solid Tumors (or RECIST) long-axis measurements do not reflect the complexity of tumor morphology or behavior. Also, it may not be predictive of therapeutic benefit. In contrast, the emerging field of radiomics is a high-throughput process in which a large number of shape, edge, and texture imaging features are extracted, quantified, and stored in databases in an objective, reproducible, and mineable form. Once transformed into a quantifiable form, radiologic tumor properties can be linked to underlying genetic alterations and to medical outcomes. Marked heterogeneity in genetic properties of different cells in the same tumor is typical and reflects ongoing intratumoral evolution. Clinical imaging is well suited to measure temporal and spatial heterogeneity. Subjective imaging descriptors of cancers are inadequate to capture this heterogeneity and must be replaced by quantitative metrics that enable statistical comparisons between features describing intratumoral heterogeneity and clinical outcomes and molecular properties. A recent study adds further support toward taking a conservative approach in the management and treatment of patients with part-solid nodules especially when the solid component is small. This strategy is already reflected in the Lung-RADS guidelines, which recommend focusing on the size of the solid component in the part-solid nodule instead of on the overall nodule size. For the future, the critical issue will be further refinements for the follow-up of nonsolid and part-solid nodules based on the size or volume that allow a process of shared decision making in selecting appropriate management and treatment (9-10). This lecture will address the radiologic implications of this new lung adenocarcinoma classification. References: Travis W, Brambilla E, Noguchi M, et al. IASLC/ATS/ERS International multidisciplinary classification of lung adenocarcinoma. J Thoracic Oncol 2011;6:244-285 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 American College of Radiology: Lung-RADS Version 1.0 Assessment Categories Release date: April 28, 2014. Accessed at . Accessed January 11, 2016

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ES 02.04 INTERVENTIONAL RADIOLOGY ON PERSONALIZED MEDICINE FOR LUNG CANCER

T.J. Kim

Radiology, Samsung Medical Center, Seoul/KR

Recent advances molecular target therapies have provided a remarkable benefit to patients harboring specific genetic alterations. Most patients treated against molecular targets eventually develop resistance even after initial dramatic response. T790M mutation is a major mechanism for clinical failure in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy. Osimertinib has been recently approved and demonstrated dramatic response in NSCLC patients with T790M mutation. In tumors with anaplastic lymphoma kinase (ALK) or ROS-1 rearrangement, cereitinib has been approved and recommended in case of crizotinib resistance. Therefore, clinical demand for rebiopsy to identify these druggable mutations has been increasing, and rebiopsy plays an important role in clinical application for exploring resistant mechanisms and determining further therapeutic strategies. This session will focus on rebiopsy issues in relapsed NSCLCs. We will describe the growing need for rebiopsy and review the current data about rebiopsy, both published and unpublished. We will discuss the technical aspects of interventional radiology-guided rebiopsy; patient selection, guiding-modalities, lesion targeting, and tissue sampling. Hurdles and solutions for rebiopsy will be discussed with appropriate examples. Current role of liquid biopsy in comparison with conventional tissue biopsy will be briefly covered. Finally, we will discuss how to collaborate more effectively as a lung cancer multidisciplinary team from radiologists' perspective.

Keywords: Target therapy, interventional radiology, rebiopsy

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ES 02.05 MRI AND ADVANCED APPLICATIONS FOR LUNG CANCER

Y. Ohno

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Since magnetic resonance imaging (MRI) was introduced for the assessment of thoracic and lung diseases, various limitations. However, from 2000, various techniques have been demonstrated their utility for lung cancer evaluations, and is now covered by health insurance in many countries including North America, Eastern Asia and Europe. In this lecture, I will show you these recent advances in lung MRI focusing on its application in lung cancer evaluation, especially with regard to 1) pulmonary nodule detection, 2) pulmonary nodule and mass assessment, and 3) lung cancer stage and recurrence evaluations.

ES 03 CURRENT TOPICS FOR NURSES & ALLIED HEALTH
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

ES 03.01 IASLC IMMUNOTHERAPY GUIDELINES

K. Rohan

Medical Oncology, Edward Cancer Center, Naperville/IL/US

Immunotherapy has become a large part of care for patients with lung cancer and has a very different side effect profile than what Allied Health Care Professionals are use to managing. To that end, the nursing and allied health care research committee of IASLC has developed Immunotherapy Side Effect Guidelines to assist the AHCP in assessing and managing their patients on immunotherapy. This presentation will review these guidelines and discuss implementation in the treatment setting.

ES 03 CURRENT TOPICS FOR NURSES & ALLIED HEALTH
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ES 03.02 PULMONARY REHABILITATION

C. Granger

Department of Physiotherapy, The University of Melbourne, Melbourne/VIC/AU

This presentation will outline the rationale, role and evidence supporting pulmonary rehabilitation for people with lung cancer. Lung cancer is associated with high disease burden and physical hardship. Individuals with lung cancer experience complex symptoms, which can include dyspnoea, fatigue and pain. These frequently lead to a cycle of inactivity and functional decline. Individuals with lung cancer are less physically active than similar aged healthy peers at time of diagnosis, with less than 40% meeting the physical activity guidelines [1]. Following diagnosis, physical activity levels are lowest whilst patients undergo treatment and do not recover back to pre-treatment levels within six months [1]. Progressive functional decline occurs over this time, with reduction in exercise capacity and muscle strength [1]. In lung cancer, reduced exercise performance is associated with poorer functional independence, worse cancer treatment tolerability and higher all-cause mortality [2]. People with lung cancer, who are less physically active, have worse symptoms, and poorer exercise capacity and health-related quality of life (HRQoL) compared to those who are more active [1]. There is a strong need for pulmonary rehabilitation for this patient group [3]. There are well-established guidelines regarding exercise for people with cancer [4]. The guidelines state that people with cancer should engage in 30 minutes of moderate intensity physical activity on five or more days of the week and muscle strengthening exercises at least twice a week. This is supported by research which demonstrates that exercise is associated with improved exercise capacity, physical function, muscle strength, HRQoL, symptoms and depression in many cancer types [4]. The evidence for pulmonary rehabilitation specifically in non-small cell lung cancer (NSCLC) is growing rapidly [3, 5, 6]. Studies consistently demonstrate that pulmonary rehabilitation and exercise training is safe in lung cancer [3]. Pulmonary rehabilitation can be applied at any stage along the disease spectrum. The majority of evidence currently exists in the pre- and post-operative settings, however there is now growing evidence for pulmonary rehabilitation in advanced stage disease [3]. Prehabilitation is exercise training delivered before treatment. This is a relatively new concept in lung cancer. A recent Cochrane review [5] of exercise training for patients before surgery for NSCLC, included five randomised controlled trials (RCTs), and found pre-operative exercise training compared to usual care (no exercise) was associated with a 67% reduced risk of patients developing a postoperative pulmonary complication, fewer days that patients needed an intercostal catheter (mean difference MD -3.33 days, 95%CI -5.35 to -1.30); shorter post-operative hospital stay (MD -4.24 days, 95%CI -5.43 to -3.06) and improvement in exercise capacity (6-minute walk test MD 18.23m, 95%CI 8.50 to 27.96 m). Recently Licker and colleagues found that preoperative high-intensity interval training and resistance training improved exercise performance, as compared with an exercise and lifestyle advice group who experienced deterioration in exercise capacity while waiting for surgery [7]. The Cochrane review concluded the overall quality of evidence is low and more high-quality trials are needed [5]. Pulmonary rehabilitation following treatment with curative intent is associated with improvements in exercise capacity, muscle function and fatigue [3]. The Cochrane review of exercise training after lung resection included three RCTs, and found significant improvements in exercise capacity in favour of the intervention compared to usual care (no exercise) (6-minute walk test MD 50m, 95% CI 15 to 85) [6]. More recently, Edvardsen and colleagues found a 20-week high intensity endurance and resistance training program compared to usual care, commencing 5-7 weeks post-operatively, was associated with improved exercise capacity, quadriceps muscle strength and mass, and physical function [8]. There is less evidence published to date on pulmonary rehabilitation in advanced disease, however the early evidence suggests that exercise may be effective at increasing exercise capacity, function and HRQoL, and reducing symptoms [3] There are a number of current RCTs in progress at the moment specifically investigating exercise in inoperable or advanced lung cancer. The specific exercise training prescription in lung cancer has varied in the studies completed to date. It is likely that a combination of aerobic and resistance training is required for maximum effect to target both skeletal muscle function and cardiorespiratory fitness; both of which contribute to poor exercise performance in lung cancer [9]. Similarly, the duration of programs (weeks to months) and delivery (inpatient, outpatient, home based) has varied. Further research is required to confirm the optimal timing, prescription and delivery of pulmonary rehabilitation for people with lung cancer. In most countries, pulmonary rehabilitation is not currently part of routine clinical practice for people with lung cancer. As the evidence base grows our next challenge is to translate findings into clinical practice [10]. 1. Granger, C., et al., Low physical activity levels

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Keywords: pulmonary rehabilitation, exercise, physiotherapy

ES 03 CURRENT TOPICS FOR NURSES & ALLIED HEALTH
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

ES 03.03 ALLIED HEALTH: THE MISSING LINK IN COMPREHENSIVE CANCER CARE

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While lung cancer care internationally is spoken about in terms of being multidisciplinary, how far does this go in practice, to having comprehensive multidisciplinary involvement of all appropriate medical, nursing and allied health professionals as part of standard lung cancer care? There are an increasing number of allied health professionals internationally who specialise in oncology, with an increase in the evidence base for interventions. I propose that the involvement of allied health professionals as part of standard lung cancer care will lead to improved comprehensive multidisciplinary care, with improved quality of life and function for people living with a lung cancer diagnosis. The core allied health professions include occupational therapy, physiotherapy, exercise physiology, dietetics, speech pathology, social work and psychology. Some countries have other professions that fit into the allied health disciplines, such as physician's assistant and respiratory therapist. This presentation will focus on the disciplines found primarily in Australia and the UK. Occupational Therapy focuses on enabling ongoing participation in chosen everyday activities. In curative treatment, the occupational therapist has a key role in pre-habilitation, assisting the individual to reach optimum function prior to treatment, and rehabilitation following treatment, to facilitate the persons return to previous chosen and meaningful roles. In metastatic disease, the occupational therapist focuses on enabling continued participation in chosen and meaningful roles. In the acute hospital setting the focus is often on what functional level the individual needs to be at to be able to safely manage the tasks of personal care, meal preparation and other personal and community activities of daily living at home following discharge. While these aspects of function are important, it is key to allow the person living with lung cancer to identify the roles and tasks that they find meaningful and important to participate in. A person may choose to have community assistance with personal care and meal preparation, as this ensures they have the energy to participate in activities that lead to improved engagement and quality of life. Physiotherapy is concerned with identifying and maximising quality of life and movement potential in the areas of promotion, prevention, treatment/intervention, habilitation and rehabilitation[1]. Physiotherapists have a key role in working with people living with lung cancer prior to and following their treatment for lung cancer. There is a growing body of evidence that suggests exercise following treatment for lung cancer is associated with improvements in physical and psychological outcomes[2]. Exercise physiologists are newer members of the lung cancer multidisciplinary team. In Australia, we are seeing as increasing use of exercise physiologists in the private hospital and pulmonary rehabilitation setting. Their role is of smaller scope than physiotherapists, focusing on prescribing and supervising exercise programs to improve exercise capacity, with the aim of improving function and quality of life. Dieticians are key members of the lung cancer team, however they are often not embedded within the multidisciplinary team. Given that cancer cachexia is a common symptom in lung cancer, affecting functional status, treatment tolerance and survival[3] we should be seeing an increase of dieticians within the lung cancer multidisciplinary team internationally. Speech pathologists provide expert assessment and treatment of swallowing and communication disorders. There is a growing body of evidence in the treatment for head and neck cancer, however there is currently no published speech pathology research in the lung cancer space. People living with lung cancer may require the specialist input of a speech pathologist due to dysphagia, as a result of treatment or disease, or speech difficulties caused by brain metastasis. Social Work and Psychology are key members of the lung cancer multidisciplinary team, as studies have demonstrated the prevalence of distress in lung cancer patients to be high[4,5]. All lung cancer patients should have their psychosocial needs regularly screened, with appropriate referrals for support made to ensure these needs are met. Psychologists and social workers need to be embedded within the lung cancer multidisciplinary team to ensure appropriate screening and intervention of patients. Lung cancer multidisciplinary teams need to utilise their allied health professionals to ensure comprehensive care is offered, and received, by patients who are living with a lung cancer diagnosis. There is a paucity of evidence and research into allied health interventions that may benefit people living with lung cancer. It is critical that allied health professionals build on the evidence and continue to research the efficacy of interventions used to optimise quality of life and function for people living with lung cancer. References: WORLD CONFEDERATION OF PHYSICAL THERAPY 2011. Policy statement: Description of physical therapy. World Federation of Physical Therapy. GRANGER CL 2016. Physiotherapy management of lung cancer. *Journal of Physiotherapy,* 62**,** 60-67. PERCIVAL C, HUSSAIN A, ZADORA-CHRZASTOWSKA S, WHITE G, MADDOCKS M & WILCOCK A 2013. Providing nutritional support to patients with thoracic cancer: Findings of a dedicated rehabilitation service. *Respiratory Medicine,* 107**,** 753-761. STEINBERG T, ROSEMAN M, KASYMJANOVA G, DOBSON S, LAJEUNESSE L, DAJCZMAN E, KREISMAN H, MACDONALD N, AGULNIK J, COHEN V, ROSBERGER Z, CHASEN M & SMALL D 2009. 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Keywords: Allied Health, Multidisciplinary Care, comprehensive lung cancer care

ES 03 CURRENT TOPICS FOR NURSES & ALLIED HEALTH
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

ES 03.04 MESOTHELIOMA: BEYOND THE BASICS

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Background: While prognostic factors for pleural and peritoneal mesothelioma have been investigated over the last decade, the characterization of molecular alterations in pleural mesothelioma may lead to a better understanding of tumorigenesis and targeted chemotherapeutic treatments for these tumors. In a recent study examining mutation burden outcome of non-small cell lung cancer, Rizvi et al. found that smokers had more mutations, correlated higher mutation load, and better clinical outcome to immune-targeted therapies than non-smokers. This has yet to been fully elucidated for MPM. Method: A systematic review of literature published from October 2009 – July 2017 was done using PubMed. **Discussion:** Various studies have shown patients with a history of smoking and asbestos exposure have a greater mutation burden than non-smokers. Despite non-small cell lung cancer studies suggesting that patients with greater mutational burden have better clinical outcomes to immune-targeted therapies, this population of MPM patients typically is excluded from these trials. To date there has not been a study showing that MPM patients with multiple malignancies should be precluded from participating in immunotherapy trials. Participatory groups in immunotherapy must be reshaped to include this subset of MPM patients to better grasp the role that multiple malignancies play with regards to appropriate treatment measures. It is notable that several large mesothelioma trials have not successfully made it pass Phase 2. This suggests that the correct population has not been identified. Perhaps early data showing promising results are merely a synergistic effect between study agents and tumor burden and should be reconsidered. Rather than potentiating study agents effects, increased tumor burden may be an independent factor in patient response. **Conclusion:** Elucidation of the role of tumor burden may improve the effectiveness and utility of novel MPM which retains its attractiveness despite the current sparse and narrow body of supporting data. Instead of observing treatment by individual case, there must be a shift in treatment observation to account for populations of similar characteristics (i.e. multiple malignancies). With no cure for mesothelioma on the horizon, evaluating the study populations will be imperative to understanding the effectiveness of these new treatments.

Keywords: Mesothelioma, tumor burden, immunotherapy

ES 04 BIOLOGY OF LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

ES 04.01 NOVEL TARGETABLE ONCOGENES IN LUNG CANCER

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Aberrations of oncogenes, such as EGFR mutation; and ALK and ROS1 fusions, function as a driver in the development of lung adenocarcinoma (LADC) and are established therapeutic targets. We previously identified RET fusion present in 1-2% of LADC (Kohno, Ichikawa, Nat Med, 2012). Its activity as an oncogenic driver in lung carcinogenesis was validated by a study of transgenic mice expressing KIF5B-RET cDNA in their lungs (Saito, Carcinogenesis, 2014). RET fusion is likely to be another target of therapy using tyrosine kinase inhibitors, as represented by a high response rate of RET-fusion positive LADC to vandetanib (LURET study, Yoh et al., Lancet Resp Med, 2016). Our genome-wide sequencing study revealed that ALK, RET and ROS1 oncogene fusion-positive LADCs carry less numbers of mutations in cancer-related genes than others (Saito, Cancer Res, 2015), indicating a small mutation burden in the development of the formers. On the other hand, >30% of LADC and most of other types of lung cancers are negative for the oncogene aberrations above, therefore, other therapeutic targets are needed for precision lung cancer medicine. We have revealed frequent inactivation of chromatin-regulating genes, such as SMARCA4/BRG1 and CREBBP, in lung cancers negative for oncogene aberrations (Ogiwara et al, Cancer Discovery, 2016). We propose a synthetic lethal therapeutic method for

chromatin regulator-deficient lung cancers based on inhibition of paralog proteins. LADC driven by somatic EGFR mutations is more prevalent in East Asians (30-50%) than in European/Americans (10-20%). We recently revealed that variations in HLA-class II loci underlie the risk of the disease, by conducting a genome-wide association study of 3,173 EGFR-LADC patients and 15,158 controls (Shiraishi et al., *Nature Comm*, 2016). The result indicates that LADC develops *in vivo* through interaction between somatic oncogene mutations and germline variations that modulate immune reaction. We would like to discuss here precision lung cancer medicine based on information on cancer and the host genomes.

Keywords: RET fusion, synthetic lethal therapy, lung cancer risk

ES 04 BIOLOGY OF LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

ES 04.02 RESISTANCE MECHANISM IN TKI

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The implementation of mutation-directed therapy has revolutionized systemic treatment of non-small cell lung cancer (NSCLC). In particular in lung adenocarcinoma targetable driver mutations can be found in a substantial proportion of patients allowing therapy with specific tyrosine kinase inhibitors (TKI) with higher efficacy and better tolerability compared to chemotherapy. Such personalized treatment approaches partly have already become first line standard therapy (EGFR, ALK, ROS1, BRAF V600), other driver mutations are currently evaluated in clinical trials (MET, RET, HER2, NTRK). Also with these new treatment options, however, we are still far away from cure and, mostly after a median progression free survival (PFS) of 10 – 12 months, resistance develops and the patients suffer from relapse. Different mechanisms may underlie primary as well as secondary resistance, which can be subdivided in two major groups: (I) pharmacological resistance, caused by reduced absorption or increased metabolism of the drug or, as a particular challenge in patients with CNS-metastases, by inadequate CNS penetration; (II) biological resistance by molecular changes in the target molecule (resistance mutations or gene copy number gain) or by activation of oncogenic bypass pathways (1). Impressive progress in treating NSCLC patients resistant to TKI therapy has been achieved by a deep understanding of the molecular mechanisms underlying biological resistance, in particular in EGFR mutated and ALK positive NSCLC. In about 60% of patients with acquired resistance (AR) to first- or second generation EGFR-TKIs resistance is caused by the secondary EGFR point mutation T790M leading to reduced TKI binding affinity and conferring growth advantage to the cancer cells. The resistance mechanisms include activation of bypass pathways e.g. by amplification of CMET or HER2 and transition to small cell carcinoma (2). Osimertimib, a third-generation EGFR-TKI, can overcome resistance caused by the T790M mutation and, based on its high clinical activity and favorable tolerability, now has become standard treatment for patients with T790M positive AR to EGFR-TKIs (3). However, resistance also occurs under osimertinib therapy and the molecular mechanisms, which are partly different to those conferring reistance to first generation EGFR inhibitors, are increasingly understood on the molecular level. They include occurrence of the EGFR C797S mutation, activation of the RAS/RAF/MEK/ERK pathway, CMET amplification and HER2 amplification (4,5). Dependent on the molecular mechanism underlying resistance to third generation EGFR inhibitors treatment strategies include the development of next generation inhibitors with activity against C797S positive cancer cells (6) as well as the evaluation of combination therapy approaches e.g. EGFR-TKI plus MET- or MET-inhibitors. These combination approaches are evaluated in the clinical setting of manifest relapse (to overcome resistance) but also as first line treatment (to prevent or postpone relapse). Similarly, also osimertinib is being evaluated in the first line setting and a substantial higher PFS has been reported in this clinical situation. A particular challenge for molecular diagnostics as well as for the development of resistance-overcoming therapeutic strategies is clonal heterogeneity, i.e. the occurrence of different driver mutations within the same patient (7). Also in ALK positive patients substantial progress has been achieved in understanding and overcoming the molecular mechanisms underlying resistance to therapy with ALK-directed TKIs. Similarly to AR to EGFR-TKIs also in AR to ALK-TKIs resistance can be caused by resistance mutations in the ALK receptor itself or by the activation of transforming bypass pathways. A series of resistance mutations has been identified and several next-generation ALK-inhibitors are either already approved or in clinical evaluation. These ALK inhibitors differ in their activity against distinct ALK mutations providing a basis for moleculary guided sequential therapy (8). Already now, impressive prolongation of survival has been reported by the sequential use of the first generation ALK inhibitor crizotinib and the next generation ALK inhibitors alectinib and ceritinib (9,10). Also for other driver mutations like ROS1, BRAF V600 or CMET resistance to TKI therapy is increasingly understood on the molecular level enabling the development of resistance-overcoming treatment strategies for these patients. The development of molecularly guided treatment strategies in AR to TKIs also poses a challenge to molecular diagnostics. In view of the numerous mechanisms which might underly resistance, the implementation of rebiopsies and molecular multiplex diagnostics using next-generation-sequencing (NGS) technologies in clinical routine becomes increasingly important. In addition, the particular challenge of clonal heterogeneity might be addressed already in the near future by the development of highly sensitive NGS-based liquid biopsy diagnostics. References Camidge R et al. Nat Rev Clin Oncol 11, 473-481 (2014) Yu HA et al. Clin Cancer Res 8, 2240-2247 (2013) Mok TS et al. NEJM 7, 629-640 (2017) Thress KS et al. Nat Med 6, 560-562 (2015). Ortiz-Cuaran et al. 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Keywords: acquired resistance, resistance mutation, next-generation kinase inhibitors

ES 04 BIOLOGY OF LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

ES 04.03 TUMOR HETEROGENEITY

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Heterogeneity is a universal phenotype across different cancer types, including non-small cell lung cancer (NSCLC). Tumor heterogeneity is present not only between different tumors from different patients or within the same patients (inter-tumor heterogeneity), but also between different cells within the same tumor (intra-tumor heterogeneity, ITH). ITH results from tumor evolution and in the meanwhile servers as a substrate for tumor evolution. ITH may be influenced by the host antitumor immune surveillance as well as anticancer therapies. Delineating cancer evolution and ITH may provide pivotal insight to our understanding of cancer development, progression and therapeutic resistance, and may eventually help us design more effective preventive and therapeutic strategies. Pioneering studies by multi-region profiling and by comparing paired primary and relapsed tumors have shed light on cancer genomic evolution and suggested the potential impact of genomic ITH on cancer biology and patient outcome. Tracking Non-Small Cell Lung Cancer Evolution through Therapy (TRACERx) is by far the largest study on genomic ITH of NSCLC using multi-region sequencing approach. The results from the first 100 patients enrolled in TRACERx were recently published in the *New England Journal of Medicine*. In this elegant study, 327 tumor regions from 100 tumors were subjected to high-depth whole exome sequencing (WES). Extensive genomic ITH was demonstrated at both nucleotide and chromosomal levels: a median of 30% of somatic mutations and 48% of copy number alterations (CNAs) were subclonal. Early clonal mutations were associated with smoking signatures in the majority of tumors, while subclonal mutations were significantly enriched for genomic signatures related to spontaneous deamination of methylated cytosines and APOBEC suggesting different mutational mechanisms in play at different times during cancer progression. A high proportion of subclonal CNAs was associated with an increased risk of recurrence and shorter disease free survival (DFS). However, no significant association with DFS was observed between the groups when stratified by proportion of subclonal mutations. The rich data from TRACERx and previous studies are provocative for the future translational and clinical research. Herein, we outline some of the concepts. First, TRACERx provided another piece of evidence that genomic heterogeneity is associated with survival of patients with localized NSCLC. However, it is somewhat surprising that more commonly regarded ITH in point mutations was not found to be associated with survival in this patient cohort, which is in contrast with previous reports in NSCLC and other malignancies. Given the relative small sample size, short postsurgical follow up (median follow up of approximately 18 months with 80% patients less than 2 years) and only 20 relapses, any imbalance in major prognostic factors such as stage, age, histology, smoking, and adjuvant therapy may have masked an actual association between mutational ITH and survival. Our group has recently completed multi-region deep WES on 30 stage IA NSCLC -15 patients relapsed within 3 years post-surgery (cases) and 15 patients have not relapsed with a minimum of 5-year postsurgical follow up (controls). Cases and controls are matched for stage, tumor size, gender, age, histology, smoking history etc. and none of the patients received neoadjuvant or adjuvant therapy. In this well-balanced case-control study, higher degree of point mutation ITH was found to be associated with shorter overall survival and shorter DFS. Nevertheless, the association between CNA ITH and DFS reported in the TRACERx study remained significant after adjusting for known prognostic factors suggests that chromosomal ITH may have greater impact on patient outcome than somatic mutations. This is probably because gain or loss of chromosomal segments or even whole chromosomes could affect hundreds or thousands of genes that may thus disrupt multiple key molecular processes, while point mutations usually affect single genes or pathways. Second, subclonal driver mutations are often detected by multi-region sequencing, which introduces a challenge to our current personalized oncology approach based on sequencing driver genes from single biopsies. Multi-region sequencing is not practical for patients with metastatic diseases or unresectable tumors. However, ctDNA is not spatially limited to certain tumor regions and may have the advantage in detecting subclonal mutations compared to single biopsies. With the rapid progress being made in liquid biopsy and sequencing technologies, sequencing ctDNA could become a practical alternative for multi-region tumor sequencing. Third, majority of studies on NSCLC ITH are based on primarily resected tumors. How chemotherapy, targeted therapy, radiation or immune therapy would impact ITH architectures remains unknown. One can hypothesize that residual tumor cells that survive neoadjuvant therapies could represent the subclones resistant to the these therapies. Therefore, investigating the residual tumors post-neoadjuvant treatment may provide valuable information on mechanisms of drug resistance. As such, well-designed window-of-opportunity neoadjuvant clinical trials would be invaluable for studying drug resistance. Forth, in addition to serving as a potential prognostic biomarker, ITH itself could become a potential therapeutic target. Given the important role of genomic instability in tumor evolution, modulating genomic stability such as targeting APOBEC family, a common cause of subclonal diversification of NSCLC, or inhibiting DNA repair pathways could become a novel therapeutic strategy. This strategy has been recently highlighted by the efficacy of PARP inhibitors in homologous recombination-deficient tumors. Last but not least,

the majority of studies on ITH have mainly focused on the genomic ITH. However, ITH can be present at different molecular levels (genetic, epigenetic, gene expression etc.) of cancer cells and also of tumor microenvironment constituting of epithelial cells, blood and lymphatic vessels, cytokines, infiltrating immune cells etc. ITH of any of these components may impact tumor evolution and patient outcome. Our pilot study has demonstrated that a higher level of methylation ITH was associated with larger tumor size, advanced patient age and increased risk of postsurgical recurrence in NSCLC patients. Furthermore, we recently reported substantial T cell repertoire ITH in NSCLC with the majority of T cell clones restricted to individual tumor regions and that a higher degree of T cell repertoire ITH was associated with an increased risk of postsurgical recurrence and shorter DFS. Tumor evolution is a complex process, during which cancer cells accumulate molecular alterations that change their phenotypic features by interacting with the tumor microenvironment. In order to systematically understand the tumor ITH and evolution, future studies are required to depict the overall molecular (genetic, epigenetic, gene and protein expression) ITH of cancer cells as well as the tumor microenvironment components, ideally from longitudinally collected samples with or without treatments to dissect the evolutionary history of NSCLC and other malignancies leading to novel diagnostic, preventive and therapeutic strategies.

Keywords: Molecular evolution, Tumor heterogeneity, non-small cell lung cancer

ES 05 SURGICAL SKILLS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 05.01 STRATEGY FOR N2 NSCLC

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The clinical stage is the clinician's best and final estimate of the extent of the disease prior to the initiation of definitive therapy. As such, the clinical stage creates the foundation for all cancer treatment recommendations. Patients with lung cancer and metastasis to the ipsilateral mediastinal and/or subcarinal lymph node(s) (LN) have a nodal descriptor of N2. Such N2 metastasis reflects a biologically advanced disease with spread beyond the primary tumor in the lung itself. In the forthcoming eighth addition of the TNM classification for lung cancer, the current (7th edition) nodal descriptors and location for both clinical and pathological nodal status (N0 to N3) adequately predict prognosis. Although for lung cancer, nodal status is based on the anatomic location of the involved node, and not on the number of metastatic lymph nodes, future staging models could assess the number of involved nodes and location.(1) Determination of metastases to mediastinal lymph nodes constitutes a critical point in staging and treatment recommendations. Computed tomography and FDG-PET + CT scans are helpful to guide treatment decisions; invasive staging is still recommended to confirm mediastinal nodal involvement. (2) (3) (4) Invasive staging for diagnosis of N2 LN includes cervical mediastinoscopy (CME) or mediastinotomy (Chamberlain's procedure), endoscopic bronchial ultrasound (EBUS), or esophageal ultrasound (EUS). The use of CME regardless of radiographic evidence of nodal involvement ("routine mediastinoscopy") is not a cost effective approach, and adds little to the accuracy of staging in patients with an adequate noninvasive preoperative evaluation. (5) Endobronchial ultrasound combined with mediastinoscopy (2;4) can be effective. VATS techniques can evaluate enlarged level 5 or 6 lymph nodes, and as well, enlarged level 8 or 9 or low level 7 lymph nodes. Esophageal ultrasound (EUS) guided aspiration can be used for level 7 and AP window LN Patients with clinically early stage NSCLC (cStage I or II), who have complete resection (R0) and subsequently identified microscopic or occult N2 metastases, represent a biologically favorable subset with improved survival following adjuvant therapy. Surgery alone for cStage IIIA (N2) lung cancer is infrequently performed however, selected patients may benefit from a multidisciplinary approach to treatment which include local and systemic components. (6). Definitive concurrent chemoradiotherapy is commonly recommended for N2 disease given the identifiable locally advanced NSCLC and likely occult systemic metastases. . Induction chemoradiotherapy has been evaluated for treatment of clinical stage IIIA (N2) NSCLC. (7;8) In these two phase III trials, surgery did not provide an overall survival benefit; however, in an exploratory analysis, induction therapy followed by lobectomy had improved survival. Multidisciplinary team discussions for individual patients are essential to optimize benefits of treatment. In selected resectable IIIA NSCLC patients, induction chemoradiotherapy followed by resection is an alternative treatment to chemoradiotherapy alone. (6) The Society of Thoracic Surgery National General Thoracic Surgery Database evaluated identified only 3319 patient with cStage IIIA (N2) NSCLC who underwent resection between 2002 and 2012. (9) Patients were >65 years of age and only 46% were treated with induction therapy. 93% had FDG PET scans, and 51% were coded as having undergone invasive mediastinal staging. Nodal over-staging occurred in 43% of patients. Lobectomy was the most common procedure (69%). The unadjusted 5 year survival following induction therapy was 35%. Selection of patients for resection may depend on the number of ipsilateral LN stations involved, and the ability of induction therapy to create a clinical post-induction yN0 nodal status. Endobronchial ultrasound (EBUS) is used initially to diagnosis ipsilateral LN metastasis and exclude contralateral metastasis. Following induction therapy, repeat EBUS may confirm yN0 status of the previously involved LN, and be validated by cervical mediastinoscopy. The surgeon must answer this question for each patient with N2 disease: When does resection following induction therapy consistently provide better survival than definitive C+RT? Large pragmatic clinical trials may facilitate new knowledge in this area. Regardless of approach (open or minimally invasive techniques), a mediastinal lymph node dissection is recommended. A recent study utilizing the National Cancer Database from the American College of Surgeons Commission on Cancer, demonstrated that with Stage I NSCLC better survival was associated with resecting 10 or more lymph nodes to optimally confirm stage I status.(10) Although this is not a therapeutic intervention, it emphasizes the need for mediastinal lymph node dissection to ensure accuracy by decreasing variability in the mediastinal dissection, and optimizing the accuracy of the pathologic staging. Reference List (1) Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015 Dec;10(12):1675-84. (2) Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. 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Keywords: N2, induction therapy, invasive staging,

ES 05 SURGICAL SKILLS
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ES 05.02 SUPERIOR SULCUS TUMOR

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The unique location of Pancoast tumors makes complete resection challenging and usually includes the upper lobe, involved chest wall with or without the subclavian vessels, portions of the vertebral column and T1 nerve root, and dorsal sympathetic chain. Several approaches are used depending on tumor location. **Posterior Approach** The patient is positioned in the lateral decubitus position, rotated slightly anteriorly to expose the paravertebral region. The chest is explored via a posterolateral thoracotomy in the 5th intercostal space. If the tumor appears resectable, the incision is extended to the base of the neck posteriorly and around the anterior border of the scapula anteriorly. The scapula is elevated with an internal mammary retractor. The scalene muscles are detached from the first and second ribs. Involved ribs are divided anteriorly. Dissection is carried along the superior border of the first rib in the subperiosteal plane. The erector spinae muscles are retracted off the thoracic spine to expose the costovertebral gutter. The transverse processes and rib heads are resected en-bloc at the lateral border of the facet joint. The chest wall is retracted anteriorly, and the intercostal nerves ligated before division to prevent cerebrospinal fluid leak. Thoracic nerve roots below T1 are transected without neurologic sequelae. Since the T1 nerve root provides motor innervation to the hand, it is ligated only in cases of tumor invasion. Division of the C8 nerve root will result in permanent arm/hand paralysis. The detached chest wall is allowed to fall into the chest cavity and an upper lobectomy and lymph node dissection is completed. Reconstruction of the chest wall is necessary when the defect is larger than the first three ribs and can be performed with a 2 mm thick PTFE patch. **Tumors Involving the Vertebral Bodies and Epidural Region** Vertebral body invasion by Pancoast tumors no longer a contraindication to surgical resection because of contemporary spine instrumentation. With multimodality therapy, T4 lesions with vertebral body or epidural extension can be resected with curative intent. We use spine MRI to divide tumors into four classes, A-D, based on the degree of spinal column and neural tube involvement. Class A and B tumors are T3 lesions amenable to complete R0 resection. Class C and D tumors are T4 lesions not amenable to en-bloc resection but can still be completely resected. Class C tumors extend into the neural foramina with limited or no vertebral body involvement but have unilateral epidural compression. Class D tumors involve the vertebral column, either the vertebral body and/or lamina with or without epidural compression. Class A, B and some class C tumors are approached through a posterolateral thoracotomy. A high-speed drill is used to remove involved vertebral bodies. The posterior longitudinal ligament is removed and provides a margin on the anterior dura. The disc spaces adjacent to the tumor are exenterated in order to aid in spinal fixation. Anterior reconstruction alone is sufficient for resections of 1-2 vertebral bodies. Autologous bone from the iliac crest or non-diseased rib, allograft fibula, methymethacrylate with Steinman pins, or corpectomy cages can all be used for reconstruction. Patients requiring any degree of epidural decompression

in the upper thoracic spine undergo combined posterior and anterior approach. Long segment posterolateral spinal instrumentation and fusion avoids the development of debilitating deformity. Class D tumors involving the posterior elements (spinous process, laminae, and pedicles) are also resected through a combined posterior/anterior approach. Patients are first positioned prone and a posterior midline incision made. The involved areas of the spinous process, laminae, and pedicles are resected. Epidural tumor is dissected off the dura and a multilevel resection of affected nerve roots done. Posterior fixation is accomplished in order to maintain coronal and sagittal stability. Muscle flap rotation by a plastic surgeon can be done to reduce the risk of skin breakdown and infection of the spine hardware. The incision is then closed, the patient turned to the lateral decubitus position, a posterolateral thoracotomy performed, and the lung and chest wall resection completed. **Anterior Approaches** Pancoast tumors involving the subclavian vessels are best approached anteriorly, using the anterior transcervical approach originally described by Dartevelle and modified by others. The patient is positioned supine with the neck hyperextended and the head turned to the opposite side of the lesion. An inverted L-shaped incision is carried down the anterior border of the sternocleidomastoid muscle and extended below the clavicle to the level of the second intercostal space, then turned horizontally following a parallel line below the clavicle to the deltopectoral groove. The sternal attachment of the sternocleidomastoid is divided along with the insertion of the pectoralis major. The scalene fat pad and lymph nodes are excised. If the tumor is resectable, the upper part of the manubrium is divided and the incision carried into the second intercostal space via an L-shaped incision. The involved section of the subclavian vein is resected but not reconstructed. The anterior scalene muscle is divided at its insertion onto the first rib. The phrenic nerve is preserved. The subclavian artery is resected and reconstructed with a 8 or 10 mm PTFE graft. The middle scalene muscle is detached from the first rib to expose the C8 and T1 nerve roots. The ipsilateral prevertebral muscles and paravertebral sympathetic chain and stellate ganglion are resected off the anterior aspect of the vertebral bodies of C7 and T1. TheT1 nerve root is commonly divided just lateral to the T1 intervertebral foramen. The anterolateral arch of the first rib is divided at the costochondral junction and the second rib is divided at its midpoint. The third rib is dissected on its superior border in a posterior direction toward the costovertebral angle and the first two through three ribs are disarticulated from the transverse processes. From this cavity, an upper lobectomy is completed. If exposure for the lobectomy and chest wall resection is inadequate, the anterior incision is closed, the patient turned into the lateral decubitus position and the rest of the resection performed via a posterolateral thoracotomy

ES 05 SURGICAL SKILLS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 05.03 MANAGEMENT OF EARLY STAGE LUNG CANCER

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In recent years, the number of early stage lung cancers has enormously increased mainly due to frequent use of chest CT in routine practice or screening purpose. Both curability and non-inavasiveness are required especially for such early disease. Increased number of VATS lobectomy and sublobar resection for selected patients is the international trend in such situation. Diagnosis: Retrospective data revealed that the sensitivity of conventional bronchoscopic examination for peripheral cancer < 2cm is only 34%. The combination of Virtual bronchoscopic navigation and EBUS guide-sheath has demonstrated the improved sensitivity, thus this new combination strategy should be necessary for differential diagnosis of small cancers detected by chest CT[1]. Surgical procedure: A total of 38000 lung cancers were resected in Japan in 2013 and 70% of surgeries were video-assisted[2]. Segmentectomy has been performed intentionally mainly for lung cancer 2cm or less in diameter. Several comparative studies between lobectomy and segmentectomy for tumors < 2cm showed no significant difference in survival[3]. Recently, segmentectomy is selected based on the size and high resolution CT (HRCT) findings of the tumor. The proportion of consolidation diameter to tumor diameter correlates with biological malignancy and the establishment of robust image criteria predicting non-invasive cancer is desirable to find candidates for segmentectomy. The Japan Clinical Oncology Group (JCOG) conducted a prospective study to recognize the relationship between HRCT finding and pathological non-invasiveness in clicical stage IA cancer (JCOG0201)[4]. This study revealed that adenocarcinoma <2.0 cm with <0.25 consolidation to the maximum tumor diameter showed pathological non-invasiveness in 98.7% and this criterion could be used to predict early lung cancer preoperatively[5]. Based on the result of JCOG0201, two prospective studies were performed and finished recruitment, phase II trial of wide wedge resection for radiological non-invasive adenocarcinoma (tumor diameter 2cm or less and consolidationratio<0.25) (JCOG0804) and randomised phase III trial for radiological invasive adenocarcinoma (tumor diameter 2cm or less and consolidation ratio>0.25) to evaluate non-inferiority in OS of segmentectomy compared to lobectomy (JCOG0802)[6]. The indication of segmentectomy will be demonstrated by the results of these studies. Clinical research: PET-CT has been routinely used for clinical staging and the standardized uptake value (SUV) of the main tumor is recognized to be as a predictor of the clinicopathological characteristics and prognosis. Analyses of 610 resected stage IA adecocarcinoma showed that maxSUV and GGO ratio cutoffs to predict recurrence were 2.9 and 25%, respectively. They were also related to nodal metastasis, histological tumor invasiveness and recurrence. The 5-year RFS of cases with maxSUV <2.9 (n=456) was 95%, while cases with maxSUV>2.9 (n=154), 72% (p<0.001)[7]. Our result showed that maxSUV cutoff of possibility for recurrence was 2.6 in adenocarcinoma, which was also related to nodal metastasis and histological tumor invasiveness. The 3-year relapse-free survival was 99%/78% (maxSUV lower/higher than 2.6) and following multivariate analysis, pathological nodal status and SUVmax were found to be independent predictive factors for relapse-free survival. Surgical management of early stage lung cancer should be selected based on the tumor size and consolidation ratio on HRCT. The results of RCTs will demonstrate the indication of sublobar resection in near future. Further analysis is encouraged for the evaluation of biological aggressiveness in each case[8]. References Asano F, Shinagawa N, Ishida T, et al. 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Keywords: lobectomy, segmentectomy, early stage lung cancer

ES 05 SURGICAL SKILLS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 05.04 MINIMALLY INVASIVE SURGERY FOR LUNG CANCER, INCLUDING ROBOTICS

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During the last two-three decades the surgical approach for the treatment of lung cancer had significantly changed. Compared to the traditional posterolateral thoracothomy the introduction and diffusion of a more conservative muscle sparing lateral thoracothomy has shown a first change to lesser trauma for patients, but only with the advent of mininvasive surgery we have witnessed the real change in terms of improving the quality of life and reducing perioperative pain (1). According to some review articles (2) not only perioperative outcome was improved with MIS compared to thoracotomy but also advantages in terms of oncological outcome have been reported even if it is possible that some selection bias could have played a role in the review results. Many studies have confirmed the benefits for the patients treated with MIS compared to open including reduced pain, complications, blood trasfusions and postoperative stay, and improved quality of life, ahestetic and functional results (3). Different technique have been described with different number of small incisions but all have in common that no rib spreading is performed and the dissection is done looking at the monitor. The most common videothoracoscopic techniques are: a. the Cophenaghen approach with an anterior incision of 4-6 cm in the IV intercostal space and 2 more trocars is characterised by an anterior to posterior approach to the mediastinum. This technique has been described by Heine Hansen and by Mc Kenna (4); b. the posterior approach of the Edinburgh school has been described by William Walker and reproduces the posterior approach to the hylum similar to that of the posterolateral thoracothomy (5). In this technique the utility incision is posterior, in the auscultatory triangle and usually two or three additional ports are used; c. the single port described by Gaetano Rocco and Diego Gonzales Riva with a single incision of 4-8 cm usually in the V intercostal space through which the tools and the camera are inserted (6). More recently new approaches has been described including the microlobectomy and the subxhifoid approach. Both techniques are aimed to reduce the pain of the intercostal nerve injury by avoiding the utility incision in the intercostal space. Despite all these advantages for the patients the manual vats has been embraced by a minority of thoracic surgeons and the diffusion has been very slow mainly due to technical difficulties, like the limited visual information, limited freedom of movement, unstable camera platform and poor ergonomics, and doubts on oncological radicality. To overcome videothoracoscopic technical limitations, the micromechanic and robotic sophisticated technology has been introduced with the robotic surgical systems. Natural movements of the surgeon's hands are translated into precise instrument movements inside the patient with tremor filtration. Three dimensional view offers a visual magnification that compensate the absence of haptic feedback. The robotic surgical system is the result of a long process of development aimed at producing a natural extension of the surgeon's eyes and hands via the intermediation of a computer. In this way, the ease of movement obtained with open surgery is summated with the advantages of the minimally invasive technique. Since 2002, when the first robotic system for surgery was introduced, robot-assisted thoracic surgery (RATS) has been adopted by an increasing number of centres around the world, and today is used in ~10% of lobectomies in the US (7, 8). Two different techniques have been described in robotic thoracic surgery, the complete portal robotic lobectomy or segmentectomy (CPRL or CPRS) maynly used by surgeons of North American, characterised by 3-4 arms technique, CO2 insufflation, posterior to anterior hilar dissection and a specimen extraction incision at the end of the procedure (9); and the Robotic Assisted Thoracoscopic Surgery (RATS), characterized by a 4-arms approach, a utility incision since the beginning, no routine CO2 insufflation and anterior to posterior hilar dissection (10). To date, no

randomized trials have reported comparative data on RATS vs. VATS or thoracotomy for lung cancer. Retrospective analysis comparing RATS vs. thoracotomy have revealed advantages for the RATS approach, especially shorter hospital stays and a lower complication rate but when compared to VATS, RATS produces similar or only slightly better results, the two being minimally invasive techniques with no need for rib separation. A few studies have reported RATS to be safer than VATS, with less conversions for bleeding, less complications and lengths of stay; in others, it was associated with lower postoperative consumption of pain killers and quicker return of patients to normal activity. In addition, lymph-node upstaging has been shown to be higher with RATS than with VATS, with a similar rate as thoracotomy. The main disadvantage of RATS is the higher costs of instrumentation and surgical kits. Nevertheless, the future will probably see reductions in the costs of robotics and improvements in the instrumentation, integration with 3D imaging to improve virtual reality, and more patients benefitting from minimally invasive procedures for lung malignancies. **References** 1. Demmy TL, Curtis JJ. Minimally invasive lobectomy directed toward frail and high-risk patients a case-control study. Ann Thorac Surg 1999;68:194-200. 2. Whitson BA, et al. Thoracoscopic versus thoracotomy approaches to lobectomy: differential impairment of cellular immunity. Ann Thorac Surg 2008;86:1735-44. 3. Bendixen M, et al. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol. 2016;17:836-44. 4. Hansen HJ, et al. Video-assisted thoracoscopic surgery (VATS) lobectomy using a standardized anterior approach. Surg Endosc. 2011;25:1263-9. 5. Walker WS, et al. Thoracoscopic pulmonary lobectomy. Early operative experience and preliminary clinical results. J Thorac Cardiovasc Surg. 1993;106:1111-7. 6. Gonzalez-Rivas D, et al. Uniportal video-assisted thoracoscopic bronchovascular, tracheal and carinal sleeve resections†. Eur J Cardiothorac Surg 2016;49 Suppl 1:i6-16. 7. Park BJ, et al. Robotic assistance for video-assisted thoracic surgical lobectomy: technique and initial results. J Thorac Cardiovasc Surg 2006;131:54-9. 8. Cerfolio RJ, et al. Initial consecutive experience of completely portal robotic pulmonary resection with 4 arms. J Thorac Cardiovasc Surg 2011;142:740-6. 9. Dylewski MR, et al. Pulmonary resection using a total endoscopic robotic video-assisted approach. Semin Thorac Cardiovasc Surg 2011;23:36-42. 10. Veronesi G, et al. Four-arm robotic lobectomy for the treatment of early-stage lung cancer. J Thorac Cardiovasc Surg 2010;140:19-25.

Keywords: Videothoracoscopy, Surgery, robotic

ES 05 SURGICAL SKILLS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 05.05 LUNG CANCER SURGERY FOR HIGH RISK PATIENTS

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High risk lung cancer patients represent a challenge in thoracic oncology, they are often related to heavy smoke habit with increased cardiovascular or respiratory diseases that prevents for getting optimal results in their lung cancer treatment. In the other hand it is widely accepted that lobectomy and lymphadenectomy is the standard treatment for younger patients with adequate cardiopulmonary function, specially in solid lung cancer patients (1). High risk patients with early stage lung cancer, often undergo sublobar resections, regardless of histology or tumor size, which increases the risk of local recurrence and may decrease long-term survival. However, a significant group of these patients have a good prognosis, either because their histology or tumor size are favorable, they present slow growing tumors or because they can undergo anatomical sublobar resections and a lymphadenectomy that provides an adequate disease control. In patients without respiratory or cardiovascular impairement it is accepted that sublobar resections have the same possibility of controlling the disease than lobectomy for ground glass opacity lesions, partially solid lesions (<50%) or with invasion area less than 5mm (2,3,4). The biggest problem appears in high-risk patients with solid lesions, in whom sublobar resections have not demonstrated the same oncological performance compared to lobectomy. This group will face the dilemma of decreasing operative morbimortality and the risk of postoperative respiratory disability versus decreased global and disease-free survival (5). Reports and our own expeience with the treatment of T1 and T2 patients with segmentectomies and wedge resections suggests that it is appropriate to try these patients with economical resections to improve the quality of life and survival in a group of patients whose survival curve does not depend only on cancer, but it is also important the competitive causes of mortality (ex. cardiovascular disease, pulmonary fibrosis, emphysema) (5). In our group, we evaluate cardiovascular risk with echocardiography and provocative test for myocardial ischemia, preferably exercise stress test. Respiratory risk is evaluated with spirometry, DLCO and cardiopulmonary exercise testing (peak VO2 and ventilatory equivalent VE/VCO2) (6,7). If ppoFEV1 <60%, ppoDLCO <60%, VO2 <10-15ml/kg/min and/or CO2 equivalent >35, values that show that the patient is high-risk or inoperable, we incorporate the patient to an exercise training program. Our protocol considers 1-1.5 hours/day of training, with progressive load to improve muscular strength, cardiovascular and respiratory capacity, associated with full medical treatment (LABA/LAMA inhalers plus inhaled and eventually systemic corticosteroids). After completing the training period, the patient is reevaluated and the treatment plan is defined: 1.- If he leaves the high-risk group (VO2 >15ml/kg/min with VE/VCO2 <35), he will receive standard oncological surgery, according to tumor size and radiological/histological findings (TNM, GGO vs solid component, invasion). 2.- If the surgical contraindication persists (VO2 <10ml/kg/min with VE/VCO2 >35), we prefer non-surgical treatments (like SBRT). In our institution, less than 5% of patients that enter the training program remain inoperable. 3.- If the patient persists in the high or moderate-risk group (VO2 10-15ml/kg/min with VE/VCO2 <35), we prefer sublobar resections. In patients where the tumor is pure GGO or predominantly GGO (<50% solid) and measure less than 2 cms, we perform a VATS wide wedge resection plus hilar and mediastinal sampling. Frozen section must confirm that less than 50% is invasive or invasion area is smaller than 5mm. Margins should be larger than 1cm to persevere with wedge resection. If these requirements are not met: solid tumors larger than 10mm or mostly solid/GGO tumors, or GGO tumors greater than 2 cm with >25% solid, or has an invasive component larger than 5mm, we perform an anatomic segmental resection, by VATS or thoracotomy, associated with hilar and mediastinal lymphadenectomy (2,8,9,10). 4.- Even in larger tumors, we will attempt segmental resection in high-risk patients. We consider that although the risk of local recurrence is high, the lower morbidity and mortality rate of sublobar resections justifies this approach in high-risk patients. We believe that a sublobar resection with margins larger than 1 cm, grant better quality of life than a patient who becomes oxygen dependent, dies in the postoperative period or has not been resected due to the impossibility of lobectomy. In our institution, we have a prospective registry of morbidity that allows us to evaluate M&M rate and the relation with VO2 in patients with lobar and sublobar resections (5,9).(Fig1) Finally, in those patients with solid tumors and lymphovascular invasion, that are staged as clinically an pathological N0, the problem is that the intralobar lymph nodes are not completely accessible or evaluable. This implies that actually the N1 barrier is not adequately studied with sublobar resections, especially in those patients undergoing a training program and become candidates to wedge or even anatomical segmental resections as a treatment choise. This lack of information may be acceptable in AIS or MIA tumors, but constitute a greater risk in patients with solid or partially solid tumors, and even greater risk in those with lymphovascular invasion in the paraffin section. Should we consider these patients as potential N1 and add treatment to avoid the risk of relapse? There is no evidence to support this approach yet, but we feel it should be considered. References 1.- De Zoysa MK et al. Is limited pulmonary resection equivalent to lobectomy for surgical management of stage I non-small-cell lung cancer? Interactive CardioVascular and Thoracic Surgery 14(2012) 816-20 2.-Asamura H et al. Radiographically determined noninvasive adenocarcinoma of the lung: Survival outcomes of Japan Clinical Oncology Group 0201. J Thorac Cardiovasc Surg 2013;146:24-30 3.- Sakurai H, Asamura H. Sublobar resection for early stage lung cancer. Transl Lung Cancer Res 2014;3(3):164-172 4.- Suzuki K, Asamura H et al. 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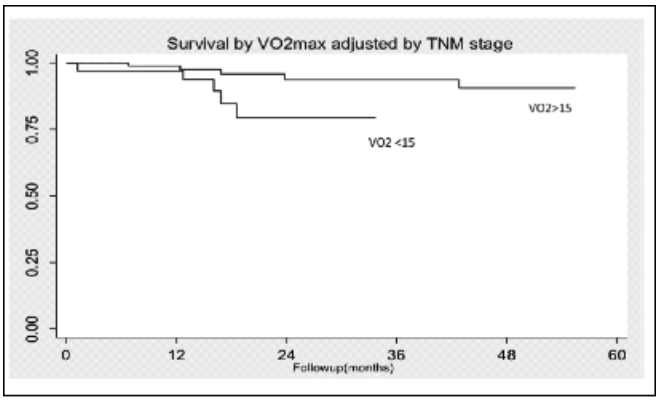

Fig 1: Survival in Resected NSCLC Lung Cancer by peak VO2, adjusted by TNM Patients with peak VO2 less than 15 ml/kg/min present a worse survival. Data obtained in a serie of 55 patients in the last preoperative evaluation, after training. Clinica Santa María, Santiago, Chile

Keywords: High risk patients, lung cancer

ES 05 SURGICAL SKILLS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 05.06 SALVAGE SURGERY

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Salvage thoracic surgery has become an increasingly common indication in patients with lung cancer (1). In principle, three different indicative fields of salvage surgery in patients with lung cancer can be distinguished: a) the surgical resection of a

persistent or recurring primary lung tumor after stereotactic radiotherapy, b) salvage lung resection after definitive chemoradiation therapy for Stage III non-small-cell lung cancer, or c) palliative surgery in cases with e. g. massive haemoptyses or bronchial obstruction with treatment-resistant retention pneumonia. Common to all indications is that they are always individual case decisions. The published series are all retrospective, comprise only a small number of patients and refer to a long period at a single institution. All studies show that these operations are often surgically challenging and demanding and require careful consideration of individual patient related factors. The presentation will provide an overview of the current literature, and will discuss own clinical experiences from selected cases. SBRT is an increasingly used modality in patients with stage I lung cancer. Whereas in the past SBRT was typically considered an alternative to surgery for patients unfit or at high risk for surgery, the modality is now being used more often also for healthier, potentially operable patients. In a recent study from MD Anderson Cancer Center, Antonoff and colleagues presented a retrospective analysis of the largest series of pulmonary resections after local SBRT failure reported to date, along with a cumulative review that incorporates all patients who have been previously reported. (2) They demonstrated that resection after local failure of SBRT in highly select individuals is feasible and safe, and has an overall acceptable morbidity and mortality, albeit higher than what is typically observed in nonirradiated patients. It is of note that in their series the majority (73%) of patients underwent lobectomy, and only 24% of patients underwent sublobar resections. In considering salvage resection, the authors recommend careful consideration of the patient's performance status and the likely extent of required resection, to be discussed thoughtfully both with the patient and in a multidisciplinary tumor board setting. Local recurrence is observed in 20% - 35% of patients after definitive chemoradiation therapy for Stage III non-small-cell lung cancer. In selected cases salvage surgery may be considered. A recent study from Italy identified 35 cases that underwent salvage surgery after definitive chemoradiation therapy for locally advanced non–small cell lung cancer over a period of 10 years, representing 1.2% of all lung resections for lung cancer performed at their institution. (3) The authors showed acceptable postoperative survival (2- and 3-year OS was 39% and 33%, respectively) and complication rates (25.7% of both minor and major complications). Another recent study from the Netherlands reported on 15 patients that underwent salvage surgery for locoregional recurrence or persistent tumor after high dose chemoradiation therapy for locally advanced non-small cell lung cancer. The authors concluded that selected patients with locoregional recurrence or persistent tumor after high dose chemoradiation therapy, can undergo salvage surgery with acceptable morbidity and mortality, even when a pneumonectomy is required (4). Factors that might have contributed to their favourable results included adequate pre-operative staging, ability to obtain an R0 resection and a good performance status. Based on the favourable results, the authors emphasised that medically operable patients presenting with locoregional recurrence or persistent tumor after definitive chemoradiation therapy for NSCLC, should have all treatment options reviewed in an experienced multidisciplinary tumor board. In conclusion, salvage surgery after stereotactic radiotherapy or after definitive chemoradiation therapy for Stage III non-small-cell lung cancer has become a new challenge for thoracic surgeons. References: 1. Van Schil PE. Salvage surgery after stereotactic radiotherapy: a new challenge for thoracic surgeons. J Thorac Oncol; 2010. p. 1881-2. 2. Antonoff MB, Correa AM, Sepesi B, Nguyen QN, Walsh GL, Swisher SG, Vaporciyan AA, Mehran RJ, Hofstetter WL, and Rice DC. Salvage pulmonary resection after stereotactic body radiotherapy: A feasible and safe option for local failure in selected patients. J Thorac Cardiovasc Surg; 2017;154(2):689-699. 3. Casiraghi M, Maisonneuve P, Piperno G, Bellini R, Brambilla D, Petrella F, Marinis FD, and Spaggiari L. Salvage Surgery After Definitive Chemoradiotherapy for Non–small Cell Lung Cancer. Seminars in Thoracic and Cardiovascular Surgery. Elsevier BV; 2017;. 4. Dickhoff C, Dahele M, Paul MA, van de Ven PM, de Langen AJ, Senan S, Smit EF, and Hartemink KJ. Salvage surgery for locoregional recurrence or persistent tumor after high dose chemoradiotherapy for locally advanced non-small cell lung cancer. Lung Cancer; 2016;94:108-13.

Keywords: lung cancer, salvage surgery, recurrence

ES 06 COMMUNICATION SKILLS IN THE END OF LIFE/ SYMPTOM MANAGEMENT IN LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 06.01 ADVANCED DIRECTIVES - ARE THEY USEFUL?

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It is required to improve patient-physician communication and that patients be offered participation in informed decisions regarding their care ethically in the context of serious and life-limiting illnesses, citing effects of good communication on quality of care and life. Many patients with advanced cancer and caregivers seek empathetic communication from physicians. Inadequate communication about prognosis and treatment choices is common and is associated with unrealistic patient expectations regarding curability, provision of aggressive treatment that is not concordant with patients' wishes and enrollment in hospice too late to deliver discernable benefit. Conversations related advance directive and advance care planning typically do not happen, or happen in hospital shortly before a patient's death. In order to complete advance directives and prepare an appropriate advance planning, it is necessary to promote physicians' empathic communication. Therefore, we developed the 2-day communication skills training (CST) for physicians based on patient preferences and confirmed the effectiveness for both patients' psychological distress and physicians' empathetic communication behaviors through a randomized controlled trial. After confirming the effectiveness at RCT, CST was conducted for doctors nationwide as a clinical implementation as a consignment project by the Ministry of Health, Labor and Welfare. Meanwhile, we developed question asking prompt list (QPL) for patients who were newly advanced lung and gastrointestinal cancer use in consultations and confirmed the usefulness through a randomized controlled trial. However, the QPL did not affect the number of actual question from the patient to the physician. It was needed to develop apamphletn intervention with QPL. Furthermore, the evaluation of caregivers is also needed. This presentation aims to determine the effectiveness of an integrated communication support program for promoting empathetic communication between rapidly progressive cancer patients, families and doctors, and to estimate the intervention effects on distress and QOL of patients and caregivers, faith in their physicians. These evidence of an effective intervention to promote communication and decision-making process based patients' values and preferences between patients, caregivers and physicians with reducing physicians' burden will be created. Based on the results, we will reflect clinical guideline regarding communication between patients and physicians in cancer care and develop a train-the-trainer workshop program with related academic society. It is also expected that providing supportive therapy at cancer hospitals will be standardized and subsequently the quality of life of cancer patients will be improved.

Keywords: patient-physician relationship, Communication, QOL

ES 06 COMMUNICATION SKILLS IN THE END OF LIFE/ SYMPTOM MANAGEMENT IN LUNG CANCER
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ES 06.03 PALLIATIVE MANAGEMENT OF DYSPNEA

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[Introduction] Dyspnea is one of the most frequent, refractory and distressing symptoms in lung cancer patients. It is reported that dyspnea interferes will to live in terminally ill cancer patients. Palliation of respiratory symptoms is important to improve quality of life (QOL) of cancer patients and their families. [Definition of dyspnea] 'Dyspnea' is defined as 'a subjective experience of breathing discomfort', while 'respiratory failure' is defined objectively as 'pulmonary dysfunction with hypoxia and/or hypercapnia'. Dyspnea and respiratory failure are different entities, and it is shown that the severity of those do not always correlate with each other. [Impact of dyspnea] Dyspnea experience is derived from interactions among physiological, psychological, social, and environmental factors, and may include secondary physiological and behavioral responses. Dyspnea often triggers panic, fear, anxiety, depression, hopelessness, sense of loss of control to patients. Dyspnea is closely associated with fatigue, pain, and depression, and interfering with general activities, mood and enjoyment of life. Dyspnea at rest is also known to correlate with survival, identified as a predictor of poor prognosis in cancer patients. [Clinical Assessment of Dyspnea] As for the assessment of dyspnea, multi-disciplinary team approach and paying attention to patients' own words are important. The assessment should focused on the following three dimensions; 1) quantities (intensity), 2) qualities, 3) symptom impact or burden. Several appropriate scales in each dimensions will be shown in this session. [Management of Dyspnea] Objectives of dyspnea management are to reduce its frequency and severity, minimize its physical, psychological and spiritual distress, and maximize patients' function and QOL. To achieve these goals, the first step is to identify all the underlying causes, and when they are reversible and modifiable, to treat them with specific modalities accordingly. It is, therefore, important for oncologists to judge treatability, including adverse effects, and to estimate patients' prognosis accurately. This session will provide the outline of palliative management of dyspnea with focus on pharmacological and non-pharmacological means. [Pharmacological interventions] The Japanese Society for Palliative Medicine (JSPM) published 'Clinical guidelines for respiratory symptoms in cancer patients' in 2016. These guidelines are unique because they are more directly focused on 'dyspnea' management specifically, based on the formal development process for clinical guidelines. Some of the important recommendations will be introduced in this session. *Note: Strength of recommendation: 1 (strong) = recommended, 2 (weak) = suggested. Level of evidence: A (High), B (Moderate), C (Low), D (Very low) 1) Opioids Systemic morphine is recommended to be used (1B). Systemic oxycodone is suggested to be used, as alternative to morphine (2C), while systemic fentanyl is suggested not to be used (2C). Systemic codeine/dihydrocodeine is suggested to be used (2C). 2) Benzodiazepine anti-anxiety Benzodiazepine is suggested to be used in combination with opioid (2C), while it is suggested not to be used alone (2C). 3) Corticosteroid Systemic corticosteroid is suggested to be used in patients with lymphangitis carcinomatosa, superior vena cava syndrome and major airway obstruction (2D). It is, however, suggested not to be used routinely without consideration of dyspnea etiology (2D). [Non-Pharmacological interventions] The effectiveness of non-pharmacological interventions for dyspnea in advanced cancer and non-cancer (mostly chronic obstructive pulmonary disease) has been reported in Cochrane reviews. Interventions supported by good evidence include breathing training, walking aids, and exercise. Those with some evidence include handheld fan, follow-up programs by nurses and acupuncture/ acupressure. [Conclusion] It is difficult to conduct high-quality clinical research on symptom control in advanced cancer patients because of patients' vulnerability as well as the ethical conflict. More clinical researches of good designs need to be conducted in this field, so that standard palliative care may be delivered to all the cancer patients anytime and anywhere, helping them live their own lives with dignity. [References] 1) Chan K, Tse DMW and Sham MMK. Dyspnoea and other respiratory symptoms in palliative care. In: Cherny NI, Fallon MT, Kaasa S, Portenoy RK, Currow DC. Oxford Textbook of Palliative Medicine (5th ed). Oxford University Press, 421-434, 2015 2) Yamaguchi T, Goya S,

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Keywords: respiratory failure, dyspnea, palliation

ES 06 COMMUNICATION SKILLS IN THE END OF LIFE/ SYMPTOM MANAGEMENT IN LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

ES 06.04 THE LUNG CANCER PATIENT, THE NURSE AND THE REHABILITATION OPPORTUNITIES IN DENMARK

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Lung cancer is the most deadly cancer disease in Denmark, one out of four cancer deaths, is due to lung cancer. 4656 Danes are living with a lung cancer diagnosis in late 2015. There are 4700 new cases each year. This means that lung cancer is responsible for 7,8 % of all deaths in Denmark and 24 % of all cancer deaths.[1]Getting lung cancer has major personal consequences - and major consequences for society. There are rehabilitation services for Danish lung cancer patients, and it has a great potential for improvement. The purpose of lung cancer rehabilitation is to support and assist lung cancer sufferers and their relatives, dealing with the changes in everyday life – including at work – that the disease causes. A lung cancer patient in Denmark meets a nurse in many contexts. Nurses are a necessity for the lung cancer patient and rehabilitation in Denmark. I will present a small sample of the rehabilitation possibilities a lung cancer patient meets in Denmark. My focus is, nurse involvement and whether they have sufficient education for the task. Copenhagen Centre for Cancer and Health provides rehabilitation programs including physical activities, education, and discussion groups or sessions. The rehabilitation programs are for cancer patients living in the City of Copenhagen. A referral from the patient´s GP or hospital department is required in order to participate. There are similar centers in many other cities in Denmark. These centers provide good opportunities for lung cancer patients and rehabilitation. At the Health Care Centre, the lung cancer patient meets nurses.[2] *"Well, you know – you have symptoms of something and you come here and tell the others about it and they say "I know just what you are talking about, that is how I´m feeling" – it´s a nice experience and makes me feel that I am all right"*

- Statement from a man with lung cancer, Copenhagen Centre for Cancer and Health The Danish Cancer Society is the largest disease-fighting organization in Denmark. The organization has more than 430,000 members. They have 3 main work areas in the fight against cancer: #prevention of cancer #giving advice to and supporting cancer patient and their relatives #cancer research. Via this organization, the lung cancer patient can talk to nurses and gets the opportunity to receive information, counseling, social networking and you can be anonymous – if you want to.[3] A Danish lung cancer patient can become a member of the Patient Association for Lung Cancer. It is a nationwide independent association for people with lung cancer and mesothelioma, and their families. You can stay up-to-date on lung cancer treatment, health policy, networking and you can also be a part of a community. You can also help put lung cancer on the agenda. There are 500 members in Denmark.[4] In order for the lung cancer patient›s possibilities / conditions to improve, there are many projects in Denmark. **The Vision Project** - a multidisciplinary working group with professionals across the country and dealing with all aspects of the disease, from surgery to palliative care. Action areas are formulated and concrete initiatives made. In this context, there will be a particular focus on rehabilitation that can improve the life quality of lung cancer patients during and after treatment.[5] **Social inequality in cancer rehabilitation** - The University Hospital in Copenhagen and the Health Care Center in Copenhagen are developing a concept for motivational conversations offered to vulnerable patients. The hospital assesses the need for cancer rehabilitation to those expected to be at risk of saying no to a rehabilitations process. It is a nurse who coordinates the project.[6] **Proluca** (**the value of Postoperative Rehabilitation of Operation for cancer**) is a research project in which the effect of early training after surgery for lung cancer is evaluated. The project aims to investigate whether training shortly after surgery for lung cancer can lead to an improved performance in the post-operation phase. It is as a nurse who coordinates the project in the health care center in Copenhagen.[7] Good lung cancer care is related to nurse education. In Denmark the Bachelore's degree programme in Nursing has a duration of 3 and a half years; you can also get an Advanced Cancer Nurse Education – this requires 1 and a half year of training.[8] Taking care of a lung cancer patient can often be complicated and requires nursing care at a high level. On a global scale, Denmark has a lot to offer lung cancer patients, but there is obviously still room for improvement, since this group of patients faces so many different challenges in their everyday life. And it takes well-educated nurses to meet the complex demands of lung cancer patients. [1] www.lungecancer.dk/ [2] www.kraeftcenter-kbh.dk/ [3] www.cancer.dk/international/ [4] www.lungekraeft.com/ [5] lungecancer.dk/documents/F1BFDA1D-EBFD-409A-A26A-15FF5385F00A.pdf [6] www.kraeftcenter-kbh.dk/projekter/social-ulighed [7] www.kraeftcenter-kbh.dk/projekter/proluca [8] www.dsr.dk/

Keywords: Rehabilitation, nursing, Denmark

ES 06 COMMUNICATION SKILLS IN THE END OF LIFE/ SYMPTOM MANAGEMENT IN LUNG CANCER
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ES 06.05 APPROACH TO MALIGNANT PLEURAL EFFUSIONS

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The onset of an MPE usually indicates a significant reduction in prognosis, with a median life expectancy of 3 to 12 months from onset. MPE associated with breast cancer is usually associated with a better than average prognosis whilst lung cancer has the worst prognosis. Confirmation of malignancy and determination of the cell type may be established by increasingly invasive techniques; pleural aspiration cytology, facilitated by ultrasound guidance if the effusion is small or loculated, pleural biopsy, blind or image guided, thoracoscopy (usually now video-assisted) under local or general anaesthesia. Whilst it is reasonable to start with the least invasive procedure suitable in the circumstances, in patients who are reasonably fit it is important to avoid an escalating cascade of failed procedures, each with the risk of causing pleural adhesions and clot formation, making effective palliation more difficult. There is much to commend early acceptance of an approach which combines the best chance of a tissue diagnosis with the best chance of effective palliation. This decision will be influenced by an assessment of prognosis. Prognosis once an MPE has been confirmed is dependent upon the extent of metastatic disease and associated co-morbidity. In a surgically palliated population in-hospital and 30-day mortality was statistically related to blood albumen levels, being 0% and 0.98% in those with normal albumen levels and 6.8% and 19% in those with hypoalbumenaemia (p=0.001) (1). In a series of 278 patients referred to the Department of Thoracic Surgery at the Royal Brompton Hospital over a 72 month period 195 underwent thoracoscopic talc pleurodesis, 39 had a pleuro-peritoneal shunt inserted, 38 had pleurodesis through an intercostal drain, 29 had pleural biopsy alone and 9 were treated with long-term pleural drainage, a total of 310 surgical procedures. Overall median survival was 211 days post operatively. Survival was not significantly different for tumour type or method of palliation but was related to leucocytosis (p<0.0001), hypoxaemia (p=0.014) and hypoalbumenaemia (p<0.0001) (2). The summative effect of these factors is shown in the table below. Table 1

No of factors	n	Median survival (days)	95% CI	p
None	39	702	473-931	<0.00001
One or two	74	200	111-289	
Three	23	42	23-61	

How might this information be used to personalise treatment options in patients for whom effective systemic therapy does not exist. Those whose prognosis is judged to be less than 2 months (having all 3 adverse prognostic factors) palliation may be achieved by repeated pleural aspiration. If prognosis is judged to be greater than 2 months, and especially if the patient is in a poor general condition, adequate palliation could be achieved by the insertion of an indwelling pleural catheter under local anaesthesia. In fitter patients with an estimated survival greater than 6 months VATS insufflation of talc or the insertion of a pleuro-peritoneal shunt should be considered. The choice of talc or shunt will be dictated by the adequacy of lung expansion during positive pressure ventilation. In many respects these 2 techniques are complementary but having both of these techniques available at thoracoscopy allows affective long-term palliation to be achieved in 95% of patients (3). However pleuro-peritoneal shunts can be complicated by occlusion within 4 months in 15% of cases but spontaneous pleurodesis has usually been achieved by this time (4). Pleurectomy is rarely indicated in the palliation of MPE. Reference List (1) Pilling JE, Dusmet M, Ladas G, Goldstraw P. Predictors of early mortality and morbidity follwoing surgical palliation of malignant pleural effusion. Journal of Thoracic Oncology 2[8], s430. 2007.

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Keywords: Malignant effusions, palliation, pleural malignancy

ES 06 COMMUNICATION SKILLS IN THE END OF LIFE/ SYMPTOM MANAGEMENT IN LUNG CANCER
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ES 06.06 DIGNITY CONSERVING THERAPY

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Dignity has been defined as the "quality or state of being worthy, honored or esteemed"[1]. While dignity-conserving therapy is popularly defined as assisted suicide in the setting of terminal illness, it may also be considered as a larger goal of palliation and achieving a "good death". Chochinov has defined 8 subthemes in the conservation of dignity at the end of life, including continuity of self, role preservation, maintenance of pride, hopefulness, autonomy/control, generativity/legacy, acceptance and resilience or fighting spirit [1]. Based on how patients and their caregivers define dignity, different interventions may be used to target or support physical and/or psychological distress, a patient's level of independence, patient perspectives and interactions with others. Dignity Therapy as developed by Chochinov involves a brief therapy session, which may be delivered at the bedside, transcribed and shared with friends and/or family, to support the patient in his or her desire to live in the moment, maintain normalcy as best as possible and to seek spiritual comfort. More commonly, however, dignity conserving therapy refers to physician-assisted death. This has been legalized in at least 8 countries, including the Netherlands, Belgium, Switzerland, Germany, Luxembourg, Columbia, Canada and 6 states in the USA [2]. In Canada, recent legislation decriminalized medically assisted death. Li et al have reported the University Health Network (UHN, Toronto, Canada) experience of establishing a hospital-based physician-assisted program of medical assistance in dying (MAiD) [2]. Three teams were developed including a clinical team, an assessment team and an intervention team. The clinical team is involved in the usual care of the patient, including nurses, allied health professionals, consulting physicians and the physician most responsible for the patient's care. Upon patient request, the most responsible physician refers the patient to the hospital MAiD program. At this point, full palliative consultation and support is offered if not already in place. An assessment team of two physicians, with expertise in the assessment of prognosis, patient suffering and capacity or ability to provide informed consent, evaluate the patient (MAiD medical specialist, palliative care physician, psychiatrist). To be eligible for MAiD through the UHN program, a person is required to have health care services covered through the Canadian public healthcare system, to be at least 18 years old and capable of making his or her own health care decisions, and to have a grievous and irremediable medical condition. This includes a serious and incurable illness, disease or disability, to be in an advanced state of irreversible decline in capability, such that the illness or state of decline causes enduring physical or psychological suffering that is intolerable to the person and cannot be relieved by means that the person considers acceptable. Natural death must be reasonably foreseeable based on medical circumstances, the request for medical assistance in dying must be voluntary and the person is required to voluntarily provide informed consent after being informed of alternative means to relieve suffering including palliative care. Disagreements between assessors are resolved through discussion involving leaders of the MAiD program. Once deemed eligible for MAiD, the patient completes a request form for the procedures, followed by a mandatory reflection period of at least 10 days unless death or loss of capacity is imminent. The intervention team, comprised of physicians and/or a nurse practitioner, conducts a final evaluation of the person and ensures they retain capacity before obtaining final informed consent and providing the intervention. Psychosocial professionals are available to provide support to family as needed and to conduct debriefing sessions for staff before and after the intervention. A multidisciplinary quality committee provides oversite and reports to the hospital Medical Advisory Committee. Since the program's inception in March 2016, 111 inquiries have been received, 39% information-seeking only [Dr. Madeline Li, personal communication]. Of these, 71% have a cancer diagnosis, commonly lung cancer. Other diagnoses include neurologic disorders such as ALS (14%), cardio-respiratory chronic disease including CHF, COPD, and interstitial lung disease (9%). Assessments have been conducted for 41 individuals, 7 were found ineligible, 35 have been approved and 24 have completed interventions. Many of these were already receiving specialty palliative care services. The most common reason for not proceeding with the intervention was clinical decline or loss of capacity. Those that received MAiD cited loss of autonomy as the main reason behind their request [2]. Preserving dignity in the face of incurable lung cancer remains a challenge for patients, families and their health care providers. An individualized approach and involving a multidisciplinary support team including palliative care remains key. References: 1. Chochinov HM. Dignity-conserving care – a new model for palliative care. JAMA 2002;282:2253-60. / 2. Li M, Watt S, Escaf M, Garedam M, Heesters A, O'Leary G, Rodin G. Medical assistance in dying – implementing a hospital-based program in Canada. New Engl J Med 2017;376:2082-8.

ES 07 RECENT ADVANCES IN DIAGNOSTICS AND INTERVENTIONAL BRONCHOSCOPY
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

ES 07.01 ENDOSCOPIC STAGING OF LUNG CANCER

K. Yasufuku

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Endoscopic Staging of Lung Cancer Kazuhiro Yasufuku During the management of patients with lung cancer, accurate lymph node staging is important not only to determine the prognosis but also to decide the most suitable treatment plan. Non-invasive staging such as computed tomography (CT) and positron emission tomography (PET) indicate size and metabolic activity, respectively. However imaging alone is inaccurate and therefore tissue sampling is the preferred and most reliable. Surgical staging by mediastinoscopy has been the gold standard for mediastinal lymph node staging but requires general anesthesia and complications cannot be ignored. Endoscopic ultrasound techniques provide a minimally invasive alternative for surgical staging and have become available for oncologists around the world. The current available endoscopic ultrasound techniques for mediastinal staging include transesophageal endoscopic ultrasound guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA). Both procedures are performed in an outpatient setting under local anesthesia. EUS-FNA is a sensitive and safe method of evaluating the inferior mediastinal nodes (stations 7, 8, and 9) and some parts of the anterior mediastinal nodes if the lymph nodes are accessible from the esophagus. However, in spite of the strength of EUS-FNA for evaluating the inferior mediastinal nodes, its ability to evaluate lesions anterior to the trachea is limited. On the other hand, EBUS-TBNA has reach to the paratracheal and subcarinal (stations 2R, 2L, 4R, 4L, 7), as well as the N1 lymph nodes (stations 10, 11, 12). In experienced hands, EBUS can be used through the esophagus for a EUS-like approach to sample inferior mediastinal lymph nodes. With the transvascular approach, AP window lymph nodes (station 5) can be sampled by EUS-FNA and/or EBUS-TBNA. Specialized centers have reported the sampling of station 6 via EUS-FNA. Thus, EUS-FNA and EBUS-TBNA are complementary methods for lymph node staging in lung cancer and most of the mediastinum and the hilum can be evaluated with these endoscopic procedures beyond the reach of mediastinoscopy. Based on the current evidence, EBUS-TBNA and EUS-FNA presents a minimally invasive endoscopic procedure of choice for mediastinal staging of NSCLC with discrete N2 or N3 lymph node enlargement, provided negative results are confirmed by surgical staging. When combined the techniques offer safe and accurate assessment of mediastinum, with accuracy surpassing that of the pervious gold standard – cervical mediastinoscopy. EBUS-TBNA and/or EUS-FNA can also be repeated with ease and have been used for mediastinal restaging in patients who underwent neoadjuvant therapy in preparation for definitive surgical intervention. New size needles are now available for sampling of the lymph nodes during EBUS-TBNA including 25-gauge and 19-gauge needles. Smaller needles may provide greater reach with good quality samples, whereas larger 19-gauge needle may provide bigger tissue for histological evaluation of the lymph nodes samples. There are limitations of using cytological samples obtained during EBUS-TBNA or EUS-FNA for PD-L1 expression. The use of the 19-gauge needle may solve this problem.

Keywords: EBUS, EUS, Invasive mediastinal staging

ES 07 RECENT ADVANCES IN DIAGNOSTICS AND INTERVENTIONAL BRONCHOSCOPY
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ES 07.02 GUIDED BRONCHOSCOPY FOR PERIPHERAL LUNG NODULES

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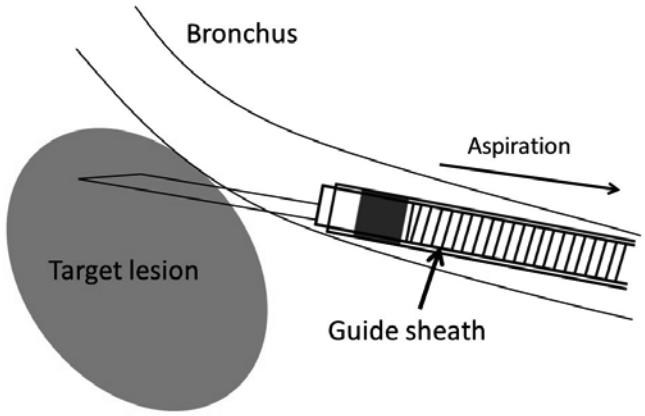
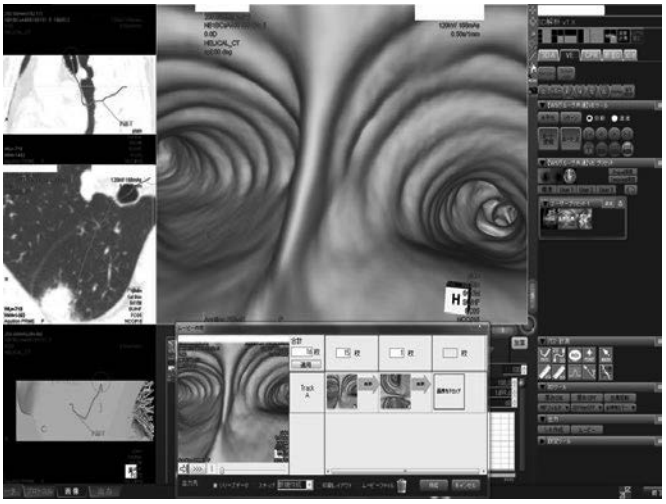
In the past several years, X-ray fluoroscopy had been commonly employed to determine the lung field during transbronchial biopsy (TBB); however, precise localization of a PPL has not always been possible leading to low diagnostic yield. For ground glass opacities (GGOs), the value of X-ray fluoroscopy even becomes less. The value of virtual X-ray fluoroscopy and CT fluoroscopy has potential but remains to be known. The advent of endobronchial ultrasound (EBUS) has dramatically increased precise bronchoscopic confirmation of the location of a PPL before sampling. In particular, the radial probe EBUS is used to indicate that a lesion has been reached. For solid peripheral pulmonary lesions (PPLs), Kurimoto et al have described three major types of echogenicities that might differentiate between benignity and malignancy. For GGOs, we have observed constant radial-EBUS patterns that we called blizzard and mixed blizzard signs. Currently, several acquired resistance mechanisms and rare driver oncogenes are identified in non-small cell lung cancer (NSCLC) relapses. Re-biopsy increases valuable information to guide treatment strategies, but the utility and feasibility of bronchoscopic re-biopsy especially endobronchial ultrasound (EBUS) guided re-biopsy has not been investigated. We recently reported the utility of bronchoscopic (EBUS-guided) re-biopsy for detecting the mutation in NSCLC. Re-biopsy by both EBUS-TBNA and EBUS-GS were useful and safe sampling procedures for mutation analysis of EGFR-TKI resistant NSCLC. Another alternative approach, specifically liquid biopsy, now present as a crucial point in the field. Liquid biopsy has grown in importance because the genetic profile of tumors can affect how well they respond to a certain treatment. A recent paper showed that the concordance between re-biopsy and liquid biopsy, including plasma DNA and circulating tumor cell, was 57–60%. The usefulness of monitoring T790M status in liquid biopsy was already reported. Although liquid biopsy has the potential to detect new mutations after chemotherapy, several reports have demonstrated some difficulties in detecting tumor-derived mutations in plasma. Therefore, liquid biopsy and re-biopsy may be considered to be complementary methods of mutation analysis. I would like to share our data and actual cases in this talk.





Keywords: re-biopsy, transbronchial needle aspiration through a guide sheath (GS-TBNA), virtual bronchoscopic navigation (VBN)

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ES 07.03 BRONCHOSCOPIC MANAGEMENT OF CENTRAL AIRWAY OBSTRUCTION

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Introduction: Malignant airway obstruction can result from primary airway tumors, extension of adjacent primary tumors, or metastatic tumors. Partial or complete airway obstruction can deteriorate functional status of patients and result in impending respiratory failure. Malignant airway obstruction is considered to be one of the most distressing causes of morbidity and mortality in lung cancer patients. Bronchoscopic intervention can provide immediate relief from suffocation, improve general condition, and provide a bridge, allowing time for additional treatment such as surgery, radiation, or chemotherapy in patients suffering from malignant airway obstruction. **Indication:** Any patients who suffer from respiratory distress due to central airway obstruction are indicated for bronchoscopic intervention. However, patients should tolerate the morbidity of intervention, the length of the airway obstruction less than 4cm, and the duration of obstruction less than 2 month due to the technical limitation. **Method:** Due to it is safe from massive hemoptysis and respiratory failure, most experienced bronchoscopists prefer rigid bronchoscopy under general anesthesia, using intravenous propofol injection. After the induction of anesthesia, the patients are intubated with a rigid bronchoscope tube and a flexible bronchoscope is introduced through the rigid bronchoscope tube, and the narrowed central airway was evaluated. In every case, the obstructed airway is dilated gently using an 10 mm rigid bronchoscope tube initially and then progressively larger bronchoscope tubes until an adequate airway caliber was established. When indicated, a controlled radial expansion balloon is used to enlarge the airway sufficiently to allow bronchoscopic dilatation. Any intraluminal mass is removed mechanically using rigid bronchoscopic forceps or a snare. Frequently, a neodymium-yttrium aluminum garnet (Nd-YAG) or diode laser is used to ablate the residual endobronchial tumor or to cauterize the tumor bed after most of the tumor had been excised. After mechanical dilatation, the airway is maintained by inserting a silicone stent (Dumon-style stent) in patients whose airway is not maintained due to extrinsic compression or malacia. The silicone stents are inserted through the rigid bronchoscope using a standard Dumon technique. **Outcome:** In experienced center, the overall success rate is more than 90% after the emergency bronchoscopic intervention. A successful outcome is accompanied by subjective improvement in the symptoms and radiographic findings. After stabilizing the airway with the bronchoscopic treatment, favorable outcome is expected if additional definitive therapy can be applied, such as surgery, radiation, or chemotherapy. Nowadays, bronchoscopic intervention can achieve prolonged survival with sustained significant improvement of quality of life. **Complications:** Tracheal perforation, massive bleeding, respiratory failure and cardiac arrhythmia can develop after bronchoscopic intervention. However, the overall complication rate is not over 5% in experienced center. **Conclusion:** Bronchoscopic intervention in patients with malignant airway obstruction is helpful for the palliation the airway, allowing the multimodality therapeutic approach and prolonging the life of the patients. **References** 1. Jeon K, Kim H, Yu CM, et al. Rigid bronchoscopic intervention in patients with respiratory failure caused by malignant central airway obstruction. *J Thorac Oncol* 2006;1:319-323. 2. Cavaliere S, Venuta F, Foccoli P, et al. Endoscopic treatment of malignant airway obstructions in 2,008 patients. *Chest* 1996;110:1536-1542. 3. Han CC, Prasetyo D, Wright GM. Endobronchial palliation using Nd:YAG laser is associated with improved survival when combined with multimodal adjuvant treatments. *J Thorac Oncol* 2007;2:59-64. 4. Chhajed PN, Eberhardt R, Dienemann H, et al. Therapeutic bronchoscopy interventions before surgical resection of lung cancer. *Ann Thorac Surg* 2006;81:1839-1843. 5. Stratakos G, Gerovasili V, Dimitropoulos C, et al. *J Cancer.* 2016;25: 794-802.

Keywords: stent, laser, Intervention

ES 07 RECENT ADVANCES IN DIAGNOSTICS AND INTERVENTIONAL BRONCHOSCOPY
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

ES 07.04 ENDOSCOPIC OPTIONS FOR SOLITARY PULMONARY NODULES

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World-wide, aside from men in France, Spain and the Netherlands, peripherally located adenocarcinomas have now overtaken squamous cell carcinoma as the predominant lung cancer cell type. With the implementation of lung cancer screening programs using low dose CT and increasing use of CT imaging for clinical investigations, a large number of people are found to have lung nodules. In contrast to symptomatic lung cancer, the size of screening CT detected or incidental lung nodules suspicious of malignancy is much smaller. Over 75% of screening CT detected lung cancers are ≤20 mm with 20% to 47% of the lung cancers found in the first screening CT and 33% to 62% of lung cancers found in annual repeat screening CT are ≤10 mm.[1-4] Because of the small size of these lesions, currently only 20% to 34% of screening CT detected lung cancers are diagnosed by endoscopy. The diagnostic yield of bronchoscopic biopsies is modest.[1,2] In the real world setting, even with advanced bronchoscopic methods such as navigation bronchoscopy and radial ultrasound, the diagnostic yield of peripheral lung lesions is less than 60%.[5,6] Several factors account for the suboptimal diagnostic yield. The diameter of the airways leading to the lesion may be smaller than the 1.4 mm diameter radial EBUS probe. The lesion may be eccentric rather than perpendicular to the biopsy forceps. Removable of the imaging probe from a guide sheath and re-insertion of biopsy forceps or needle may cause displacement or migration of the guide sheath to a different airway. To improve the diagnostic accuracy, other methods are being developed for endoscopic detection and biopsy of peripheral lung lesions ≤20 mm. Bronchoscopic transparenchymal approach to access peripheral lung nodules from more central airways and real time flouroscopic transbronchial guidance systems are under evaluation.[7,8] Flexible 21G peripheral needles are becoming commercially available for transbronchial aspiration or core biopsy. Small optical imaging probes < 0.5 mm that can be inserted within a 21G needle to confirm abnormal pathology in real time using optical frequency domain imaging[9,10] or diffuse reflectance spectroscopy before taking a biopsy. These newer endoscopic approaches hold promise to improve diagnostic accuracy while maintaining the advantage of lower complication rates such as pneumothorax and bleeding compares to CT guided transthoracic lung biopsy. **References**

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Keywords: Endoscopic biopsy

ES 08 MOLECULAR DIAGNOSTICS AND TARGETED THERAPY
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

ES 08.01 OVERVIEW OF DIAGNOSTICS AND PATHOLOGY

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Recent advances in molecular biology have revealed that lung cancer is not a single disease and that there are subsets of non-small cell lung cancer (NSCLC) with specific genetic alterations that are critical to the growth and survival of cancer cells. Alterations of the EGFR, ALK and ROS1 gene, which are present in a mutually exclusionary fashion, are representative driver oncogene mutations. Targeted drugs against each driver oncogene usually result in dramatic tumor shrinkage and prolongation of progression free survival (PFS) compared with conventional platinum doublet chemotherapy. However, there is only a weak association between WHO pathologic classification 2015 and type of driver oncogenes. Therefore, it is of utmost importance to identify who are likely to benefit from targeted drugs by performing molecular tests for each lung cancer patient who is a candidate for drug therapy. A list of driver oncogenes is further expanding; BRAF, RET, MET, HER2, NTRK1 are being recognized as new drivers that can be exploited in the clinic. It is getting more practical to screen these molecular alterations by use of next generation sequencing technology, rather than to detect each gene alterations one by one using different platforms. We have also known that not all the tumors with mutations of the same gene behave similarly. For example, while deletional mutation in exon 19 and L858R in exon 21 are two representative mutations that sensitize cancer cells to EGFR-tyrosine kinase inhibitors (TKI), G719X in exon 18 has an intermediate sensitivity and insertional mutation in exon 20 or de novo T790M are known to be resistant. It has been shown that there is a heterogeneity in efficacy of EGF-TKIs depending on the class of mutation. For example, afatinib is active among other EGFR-TKIs for exon 18 mutations. Furthermore, a certain molecular context is known to be associated with primary resistance even within lung cancers with the same EGFR mutations. For example, it is reported that mutations in the PI3K/AKT/mTOR pathway (AKT1, PIK3CA, STK11, PTEN) or TP53 mutations are more frequent in non-responders and are associated with shorter PFS. This context dependence may present in other driver oncogenes, too. Acquired resistance is almost inevitable in the treatment of lung cancer with targeted drug. Mechanisms of this resistance has been extensively studied and now we know there are at least 3 types of mechanisms; i.e., 1) target modification by the secondary mutation that alters the affinity between the drug and the target relative to the affinity between ATP and the target (e.g., T790M in EGFR, L1196M in ALK), 2) accessory pathway activation that bypass the inhibitory effect of the drug(e.g., Met amplification in EGFR), and histologic transformation, such as small cell lung cancer transformation and epithelial-mesenchymal transition. We are now able to use the newer generation of TKIs to treat some of the resistance due to the secondary mutation of the target gene. Osimertinib has recently been shown to prolong PFS of patients who acquired resistance to EGFR-TKI through T790M mutation compared with platinum-pemetrexed in the AURA 3 trial. Therefore, detection of this mutation which accounts for about 50~60 % of the acquired resistance against EGFR-TKI is important. However, re-biopsy is sometimes more challenging compared with that in the first-line setting, and therefore detection of T790M in cell-free DNA in plasma has been rapidly developed and is now approved in regulatory authorities in several countries. There is another issue which should be taken into consideration when treating patients with acquired resistance. When there are multiple metastatic lesions, resistance mechanisms may vary from one tumor to another. Hence, it can happen that while one tumor shrinks but others increase in size. It may be reasonable and thus beneficial for patients when treatment is planned according to most prevalent mechanism of resistance in the plasma as a sum of total resistant mechanism. In this talk, I would like to overview recent advances of molecular diagnosis in targeted therapy of lung cancer and also like to discuss future perspectives in this field.

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ES 08.03 UPDATE OF THE MANAGEMENT OF ALK-POSITIVE NSCLC

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ALK positive NSCLC represents 2-7% of advanced NSCLC. Three ALK TKIs have shown positive first line trials against either platinum-doublet chemotherapy (ceritinib and crizotinib) or against crizotinib (alectinib). At least three other first line trials against crizotinib are ongoing (brigatinib, ensartinib and lorlatinib). Activity of different ALK TKIs post crizotinib are characterized by comparable response rates but differing toxicity profiles, durations of benefit and extent of CNS activity. With changes in the first line standard, data post non-crizotinib ALK TKIs continues to emerge with attendant caution re the applicability of both biological and clinical data currently available for clinical decision making. Advances in our understanding of CNS trial endpoints has also helped facilitate cross trial comparisons of CNS activity of these different agents. Chemotherapeutic, radiotherapeutic and immunotherapeutic options other than ALK TKIs have all generated different clinical datasets - defining both some reasonable clinical options and some clearly in need of additional research.

ES 08 MOLECULAR DIAGNOSTICS AND TARGETED THERAPY
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ES 08.04 EMERGING TARGET THERAPY IN NSCLC

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As a result of recent advances, systematic genomic testing for patients with non-small cell lung cancer (NSCLC) is the new standard of care in clinical decision-making, due to the identification of driver molecular alterations that have triggered the development of new molecules targeting these specific alterations in cancer cells. Several studies have enabled to conclude that both EGFR-mutant and ALK-positive NSCLC constitute two defined subgroups of oncogene-driven tumors with potentially effective targeted therapy. Furthermore, approximately 15-20% of NSCLC diagnosed in Europe and North America bear EGFR mutations or ALK rearrangements, enhancing the significance of the development of drugs capable of interfering with their intracellular effects. Based on these results, the identification of other activating mutations has been pursued in hopes of improving survival in NSCLC by specifically treating these genomic alterations. These potential therapeutic targets include ROS1, BRAF, RET, HER2, MET exon 14 skipping mutations and NTRK, among others. Here, we seek to review the characteristics of emerging targets that enable interaction with molecules that specifically target these receptors in lung adenocarcinomas, as well as the results of preliminary studies that assess the efficacy of these new strategies applied to NSCLC. **ROS1** *ROS1* rearrangement characterizes a small subset (1%–2%) of NSCLC and is associated with slight/never smoking patients and adenocarcinoma histology. Crizotinib was shown to harbor relevant activity in *ROS1*-rearranged NSCLC. A number of agents including ceritinib, lorlatinib and entrectinib are now been developed in order to overcome the resistance to crizotinib. At present, *ROS1*-rearranged patients represents a clearly defined NSCLC molecular subgroup with highly active therapeutic options. **BRAF** *BRAF* mutations occur in 2%–4% of patients with NSCLC, with the most common resulting in a glutamate substitution for valine at codon 600 (V600E). Non V600E *BRAF* mutations make up the remaining *BRAF* mutations and may be either activating (i.e., G469A/V, K601E, L597R) or inactivating (i.e., D594G, G466V). Efforts targeting *BRAF* mutant NSCLC to date have almost exclusively focused on patients with V600E mutant disease. Direct inhibition of mutant BRAF and/or the downstream mitogen-activated protein kinase kinase has led to good outcomes survival in patients with *BRAF*-mutant metastatic NSCLC. Dabrafenib plus trametinib achieved 63·2% response rate (RR) in BRAF(V600E)-mutant NSCLC. **RET** RET fusions are detected in 1-2% of lung adenocarcinomas and a number of genes, such as KIF5B, CCDC6, NCO4 and TRIMM33, can act as fusion partners. In a global registry of RET positive NSCLC patients, 41 received a RET inhibitor achieving a median progression-free survival of 2.9 months and a median overall survival of 6.8 months. Response rate was 34% for those patients receiving cabozantinib and 27% for those receiving vandetanib. Overall RET inhibitors strategies seem active in a subgroup of patients with RET-rearranged NSCLC. However, RR is lower to that observed in EGFR-mutated/ALK-positive patients. **HER2** *HER2* mutations are identified in about 2-4% of NSCLC and are critical for lung carcinogenesis. A number of series shows the chemosensitivity of HER2-driven NSCLC, and the potential interest of HER2-targeted agents. In a recent study, NSCLC patients with *HER2* mutations were treated with T-DM1 and achieved a 44% RR. **MET** Approximately 2-3% of NSCLCs harbor activating mutations of the *MET* proto-oncogene that cause exon 14 skipping (*METex14*) and accumulation of c-Met lacking a juxtamembrane domain. Recently, the clinical activity of anti-Met-targeted therapy was demonstrated in patients harboring *MET* exon 14 skipping lung cancer. MET seems a relevant target in NSCLC and a number of clinical trials with MET inhibitors in this population are now ongoing. **NTRK** TRK rearrangements represent the molecular driver of a subset of solid tumors, including 1-2% of NSCLCs. Preliminary data indicate that molecularly selected NSCLC patients harboring NTRK fusions derive an unprecedented clinical benefit from Trk-directed targeted therapies. There are two different targeted agents, entrectinib and larotrectinib, that are in phase II testing for any patients who have solid tumors with NTRK rearrangement, including NSCLC patients. Both drugs have achieved dramatic responses, regardless of histology in earlier phase I studies. In a study presented at ASCO 2017, larotrectinib has demonstrated consistent and durable antitumor activity in TRK fusion cancers, across a wide range of ages and tumor types.

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Keywords: Targeted therapies, NSCLC

ES 09 RECENT PROGRESS IN THE MANAGEMENT OF SMALL CELL LUNG CANCER
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

ES 09.02 CYTOTOXIC CHEMOTHERAPY

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Untreated small-cell lung cancer (SCLC) is highly sensitive to both chemotherapy and radiotherapy, although its growth is very rapid. Clinically, SCLC is classified into limited-diseases (LD) and extensive-disease (ED). Although there is no distinct criteria, LD is generally accepted to be a disease which is confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes without malignant effusion, i.e., a disease that curative radiotherapy is applicable. Nearly 30% of SCLC is LD at initial diagnosis. LD-SCLC is potentially curable disease, and standard treatment is chemo-radiotherapy, especially concurrent use of chemotherapy and radiotherapy is chosen if performance status of patient is 2 or less and organ function is good. Cisplatin plus etoposide is usually administered together with radiotherapy, since the combination chemotherapy is one of the most effective regimens and also risk of radiation pneumonia is low when the combination is chosen. Median survival time of LD-SCLC is 16 to 24 months and 5-year survival is nearly 15%. On the other hand, median survival time of ED-SCLC is 6-12 months, and long-term disease-free survival is rare. Chemotherapy alone is chosen to ED-SCLC. Globally, combination of cisplatin/carboplatin plus etoposide is recognized as a standard chemotherapy. In Japanese guideline, a combination with cisplatin plus irinotecan is the first choice if tolerable. One of the reasons why standard therapy is different between western and eastern countries is based on distribution of uridine diphosphate glucuronosyltransferase (UGT) 1A1 gene polymorphisms. Although drug therapy with cytotoxic agents to SCLC used be the only successful treatment modality for metastatic lung cancer in the past century, its development now appears to slow down. To maximize the effect of cytotoxic agents, combination with immune checkpoint inhibitors or novel targeted drugs would be critical.

Keywords: cytotoxic drug, chemoradiotherapy, UGT 1A1

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WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

ES 09.03 IMMUNOTHERAPY

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Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor which accounts for 10-15% of all lung cancers[1]. It is extremely lethal with rapid recurrence and dismal prognosis. Although it is sensitive to chemotherapy with 50%-80% overall response rate (ORR), it inevitably recurs within 6 months, especially those in extensive-stage (ES) SCLC[2, 3]. However, treatment options are limited for those who relapse after first-line chemotherapy and standard options have few improvements in SCLC for several decades. How to tackle the chemo-resistant SCLC patients with rapid recurrence after first-line chemotherapy? How to prolong the effective duration of standard chemotherapy? How to improve the prognosis after the second line treatment? These tough concerns need to be addressed. Immunotherapy, especially the inhibitors targeting immune checkpoints such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed death-1(PD-1) and programmed death ligand-1(PD-L1), achieved great success and durable anti-tumor response across multiple tumor types[4, 5]. In terms of SCLC, the high frequency of somatic mutations[6], along with the approximately 10% incidence rate of para-neoplastic and neoplastic triggered autoimmune disease, for instance, Lambert-Eaton myasthenia[7], prompts that the SCLC is a immunogenic type of cancer and possibly, responds to immunotherapy. Therefore, several clinical trials come up then. At present, in the context of high ORR of the first-line chemotherapy treatment, the purpose of the clinical studies based on the immune checkpoint inhibitors (ICI) in the treatment of SCLC can be divided into two categories: 1) integrating ICI into standard chemotherapy as first-line regimen or maintenance therapy 2) single ICI (nivolumab/ipilimumab/atezolizumab)/ combined with chemotherapy/combined with multiple immune checkpoint inhibitors as compelling options as second or subsequent line regmen. In summary, these regimens could be subdivided into: 1) Ipilimumab plus chemotherapy 2) PD-1/PD-L1 inhibitors alone or together with chemotherapy 3) combination of CTLA-4 blockade and PD-1/PD-L1 inhibitors with or without chemotherapy. Since the outcome from a phase III trial regarding ipilimumab plus chemotherapy was dismal[8], the paradigm has been shifted from single CTLA-4 blockade plus chemotherapy to PD-1 inhibitor, and indeed, PD-1 inhibitor alone or combined with CTLA-4 blockade seem more promising in the treatment of SCLC. In 2017 ASCO, a phase II study evaluating the role of maintenance pembrolizumab in newly diagnosed SCLC patients demonstrated that this regimen didn't improve the PFS (median PFS: 1.4 months). However, an exploratory analysis from this study suggested that patients with expression of PD-L1 in tumor stromal interface had better outcome(longer PFS: 5.5 months VS 1.3 months and OS: 10.1 VS 7.2 months)[9]. Multiple trials are ongoing to define the roles of this drug in SCLC patients, for instance, pembrolizumab plus chemotherapy in first-line settings (Keynote011), in second or subsequent settings. Additionally, a phase III study is ongoing to determine the effectiveness of nivolumab monotherapy compared to chemotherapy in relapsed SCLC (Checkmate 331). As for atezolizumab, a phase I/III study is underway to evaluate the efficacy of combination of atezolizumab and carboplatin/etoposide as first-line treatment of ES-SCLC (IMPOWER 133). In terms of combination of PD-1 inhibitors and CTLA-4 blockade, Checkmate 032, the first trial evaluating the combination of nivolumab and ipilimumab in the treatment of patients with SCLC who had progressed after one or more treatment regimens was reported in ASCO recently. Both nivolumab monotherapy and nivolumab plus ipilimumab showed promising anti-tumor activity with durable responses and manageable safety profiles[10]. These data prompted nivolumab alone or nivolumab-ipilimumab combination regimen to be incorporated into NCCN guidelines for SCLC as second line treatment recommendation. Moreover, in 2017 ASCO, the updated data from Checkmate032 was reported. With longer follow up in non-randomized cohort, the response remains encouraging. 2-year OS could be achieved 14% and 26%, respectively in monotherapy and combination therapy[11]. In this setting, a phase III trial, termed Checkmate451 assessing the role of nivolumab monotherapy, nivolumab-ipilimumab combination and placebo as maintenance therapy in ES-SCLC and a phase II trial, STIMULI, in LS-SCLC were initiated. Plus, a phase II trial regarding the tremelimumab and durvalumab with or without radiation in relapsed SCLC patients is ongoing and more data are warranted . However, many questions remain. The immune microenvironment in SCLC is distinct from other tumor types for SCLC cells express low levels PD-L1, though with high mutation burdens. In Checkmate032, there is no observation on clear association between tumor PD-L1 expression and clinical benefit. However, as mentioned above, patients with positive PD-L1 expression in the stromal interface had better PFS and OS observed in a phase II trial[9]. The prediction value of PD-L1 expression is supposed to be shifted from tumor cells to surrounding immune cells in SCLC. Thus, it is important to define a specific biomarker to predict the response to immunotherapy and explore the distinct tumor microenvironment in SCLC. Moreover, potential toxicity is not supposed to be underestimated, especially the immune-related adverse effects. Immune related side effects will happen in the course of the treatment. Close monitoring is essential and oncologists are suggested to balance the risks and benefits of immunotherapy in the clinical practice. **References 1.** Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med.* 2008;359:1367-1380. **2.** Rossi A, Di Maio M, Chiodini P, et al. 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Keywords: small cell lung cancer, Immunotherapy, Immune checkpoint inhibitors

ES 09 RECENT PROGRESS IN THE MANAGEMENT OF SMALL CELL LUNG CANCER
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ES 09.05 MANAGEMENT OF PARANEOPLASTIC SYNDROMES IN SCLC

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Small cell lung cancer (S.C.L.C.) represents approximately 15% of lung cancers and offers a unique profile of clinical and biological features) S.C.C.L. is a fast growing tumor with are estimated doubling time of 10 days, high propensity to metastatic diffusion since the early beginning of the disease, high sensitivity to chemoradiotherapy but early and common development of pleiotropic drug resistance. Unfortunately in the past 30 years very few advances have been realized in the treatment of S.C.L.C. which in most of the patients is a fatal disease with a median survival of 16-18 months in limited thoracic and 11 months in extensive

disease. S.C.L.C. is the most common cancer associated with paraneoplastic syndromes because of it's propensity to release endocrine peptides, ectopic hormones and neoantigens that can develop the para neoplastic syndromes. Paraneoplastic syndromes constitutes different and heterogeneous clinical conditions associated with cancer development, affecting various tissues at remote locations from theprimary tumour , with an unpredictable clinical behavior. In SCLC, a large number of paraneoplastic syndromes have been reported, involving different organ functions and complicating the clinical course of the disease, including endocrine, neurological and miscellaneous less frequent manifestations. The most common paraneoplastic syndromes in SCLC, can be divided in ectopic hormone-associated syndromes, and immunomediated neurologic syndromes. According to the S.C.L.C. produced hormones we can recognized among the ectopic hormone-associated syndromes, the Hyponatremia (10%) of S.C.L.C., the ectropic Cushing syndrome (5%) Hypertension reninrelated (1%), galactorrhea (1%) and hyperamylasemia (1%). S.C.L.C. has the unique feature to be often heralded or accompanied by a number of immune-mediated neurologic syndromes, the Lambert-Eaton myastemic syndrome 1%, the limbic encephalopaty and the encephalomyelitis, the sensory polyneuropathy, the cerebellar degeneration the opsoclonus myoclonus, all accounting for less than 1%. In most of the cases the neurological symptoms develop before the onset of clinical overt S.C.L.C manifestation and the stage seems not to be related to the presence of paraneoplastic neurological syndrome, whose evolution usually mirrors the behavior and the clinical manifestation. In most of the cases the starting of systemic chemoterapy can induce a dramatic improvement of neurological symptoms in advance to clinical response, and viceversa the worsening of the neurological condition can indicate progressive disease and resistance to the treatment.The study and the improved understanding of pathophisiolgy mechanisms of paraneoplasic syndromes in SCLC can contribute to elucidate the natural history of a fascinating and still largely unknown disease which was erroneously predicted to be a potential curable disease in the eighty years. From that time the treatment strategies and the therapeutic results have been only marginally improved and the undersanding and resolution of paraneoplastic syndromes can contribute substantially to the cure improvement of SCLC.

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ES 09.06 NCI'S SMALL CELL LUNG CANCER CONSORTIUM: NEW ANSWERS TO OLD QUESTIONS

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The worldwide toll in mortality due to small cell lung cancer (SCLC) is still unacceptable. Based on an analysis conducted by the National Cancer Institute US (NCI) in 2014, there are five priorities in SCLC that need to be addressed by scientists and clinicians: 1. Development of better research tools for the study of SCLC; 2. Conduct of comprehensive genomic profiling of SCLC; 3. Creation of new diagnostic and prevention approaches for SCLC; 4. Therapeutic development efforts; and 5. Study of mechanisms underlying both high rate of initial response and rapid emergence of drug and radiation resistance. These priorities are being currently addressed by the newly established NCIs SCLC Consortium, an effort to coordinate and network investigators focusing on pre-clinical studies of the disease. The SCLC Consortium currently includes a coordinating resource center, members with their individual projects, and associate members funded through other grant mechanisms. The Principal Investigator of the Coordinating Center is Dr. Charles Rudin from the Sloan Kettering Institute for Cancer Research in New York, NY and he is joined by Drs. John Minna (University of Texas South Western), Tyler Jacks (Broad Institute), You Shyr (Vanderbilt University), and Afshin Dowlati (Case Western Reserve University). The Coordinating Center provides administrative, meeting, and communication support, a bioinformatics database, centralized tissue banking and virtual biospecimen database, centralized biostatistics, cell line and animal model repository. The four Research Projects in the Consortium were selected by a standard peer review process and they focus on: 1) the use of extracellular vesicles for early detection of SCLC; 2) preclinical development of a DLL3-targeted theranostic for SCLC; 3) targeting the transcriptional and epigenetic landscape in chemo-refractory SCLC; and 4) novel therapeutic approaches for enhancing anti-tumor immunity in SCLC. The first project, led by Drs. Serge Nana-Sinkam from Virginia Commonwealth University and James Lee from Ohio State University attempts to carry out an analysis of nucleic acids found in exosomes using molecular beacons contained on biochips to detect specific mRNA and miRNA sequences. The hypothesis is that unique nucleic acid differences in exosomes exist that can differentiate among normal smokers and SCLC patients. The goal is to obtain a biochip that can be used as a biomarker for early stage SCLC that can be applied broadly to blood samples. The second project is conducted by Dr. John Thomas Poirer (Sloan Kettering Institute for Cancer Research) and it builds on the earlier clinical success of the antibody-drug conjugate against a ligand of the Notch pathway, DLL3, selectively expressed on the surface of SCLC cells. The new project will develop a radioimmunotherapy reagent targeted against DLL3, expressed in 70-80% of SCLC. If even moderately successful, this work may provide therapeutic options to some patients who currently have none. The third project designed by Drs. Kwok Kin Wong from New York University and Nathanael Schiander Gray from Dana-Farber Harvard Cancer Institute aims to define transcriptional and epigenetic factors that contribute to chemotherapy-resistance in both tumor cells and the surrounding microenvironment and assess the efficacy of transcriptional CDK inhibitors alone or in combination with novel investigational therapies, utilizing in vivo SCLC models. This is a compelling, well-rationalized, project that pursues an important new direction for both understanding the fundamental biology of SCLC tumor cells and exploiting that information for therapeutic development. The latest addition to the Consortium is project 4 by John Heymach, Lauren Byers (both from the University of Texas MD Anderson Cancer Center), and Julien Sage from Stanford University. The investigators seek to identify improved treatment strategies in SCLC using immunotherapeutic agents targeting the PD1 pathway. The overarching goals of this project are to exploit the intersection of DNA damage repair and immunotherapy in SCLC for new targets and therapies, and to enhance the benefit of existing therapeutic options or ongoing clinical studies. Besides the main Research Projects, the Consortium serves as a hub for Associate Members with additional SCLC projects funded through NCI grants. The topics of these projects include new determinants of acquired resistance, Notch signaling in SCLC, molecular and cellular mechanisms of metastasis, therapeutic strategies for targeting PARP1, kinase dependent chemotherapy resistance mechanisms, and investigating CREBBP as a tumor suppressor. The NCI accepts applications for membership in the SCLC Consortium through two program announcements PAR-16-049 and PAR-16-051. International teams are encouraged to apply.

Keywords: small cell lung cancer, Early Detection, Therapy

ES 10 RADIATION TREATMENT UPDATE
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

ES 10.04 CARBON-ION THERAPY

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Introduction Approximately 68 particle therapy facilities are in operation worldwide. Among them, only 11 offer carbon-ion treatment (5 in Japan, 2 in Germany, 2 in China, 1 in Italy, and 1 in Austria; 6 also offer proton), and the remainder offer proton treatment. More than 150,000 patients have been treated with particle therapy worldwide from 1954 to 2015, 87% of which were treated with protons and 13% with carbon-ions or other particles. (from the website of the Particle Therapy Co-Operative Group: http://www.ptcog.ch/). The National Institute of Radiological Sciences (NIRS) in Chiba, Japan, has been treating cancer with high-energy carbon-ions since 1994. The majority of patients curatively treated with carbon-ions worldwide were treated at NIRS (1). Through the data they have generated, carbon-ion radiotherapy (CIRT) for non-small cell lung cancer (NSCLC) has been suggested as safe and efficacious. Here, I review those results and discuss this modern technology. Characteristics of CIRT In comparison with photon radiotherapy, CIRT has better dose distribution to tumors while simultaneously minimizing dose to surrounding normal tissues. Moreover, CIRT offers potential advantages over protons, which have similar dose distribution benefits. Carbon-ions provide a better physical dose distribution, because lateral scattering is lessened, and offer a higher relative biological effectiveness with a lower oxygen enhancement ratio; desirable features for eradication of radioresistant, hypoxic tumors. This difference between densely ionizing nuclei and sparsely ionizing x-rays/protons further offers potential radiobiological advantages, such as reduced repair capacity in irradiated tumors, decreased cell-cycle dependence, and possibly stronger immunological responses. CIRT of early NSCLC Surgical resection with lobectomy has been the standard treatment of choice for early-stage NSCLC. From a Japanese lung cancer registry study of 11,663 surgical cases in 2004, overall survival (OS) rates at 5 years for stages IA and IB disease were 82.0% and 66.8%, respectively (2). Radiotherapy is an option for patients who are not suitable for surgery or refuse it. Recently, hypofractionated radiotherapy is regarded as an alternative for surgery in cases of localized NSCLC, employing x-ray stereotactic body radiotherapy, protons, or CIRT. Regarding CIRT, for peripheral stage I NSCLC, the number of fractions delivered per treatment at NIRS has been reduced through consecutive trials from 18 to 9, then 4, and finally to a single fraction (3-7). This latest result , conducted via dose escalation study, was recently reported by NIRS, demonstrating results comparable to those with previous fractionated regimens (8). The Japan Carbon-ion Radiation Oncology Study Group (J-CROS) has further reported that the results of a multi-institutional retrospective study of CIRT for stage I NSCLC were similar with the results of previous single institutional reports (9). The results of CIRT in stage IA NSCLC are similar to the best stereotactic body radiotherapy results reported worldwide. For stage IB disease, CIRT results appear tentatively superior to those reported for photon stereotactic body radiotherapy in terms of local control and lung toxicity, but will require randomized controlled trials to verify. Despite this high local control, however, disease-specific survival is much lower in stage IB than in stage IA, due to distant metastatic recurrence. A combination of CIRT with systemic therapy is therefore essential to improve survival. CIRT demonstrates a better dose distribution than both SBRT and proton therapy in most cases of early-stage lung cancer. Therefore, CIRT may be safer for treating patients with adverse conditions such as large tumors, central tumors, and poor pulmonary function. CIRT of locally advanced NSCLC There has only been one report regarding CIRT for locally advanced NSCLC. A prospective nonrandomized phase I/II study of carbon-ion therapy in a favorable subset of locally advanced NSCLC was reported from NIRS (10). They showed that short-course carbon-ion monotherapy (72GyE/16Fr) was associated with manageable toxicity and encouraging local control rates. Among them, cT3-4N0M0 patients were particularly favorable candidates for CIRT. However, there is a relative dearth of evidence for CIRT in the setting of locally advanced NSCLC, and more trials, including those combined with systemic immunological or chemotherapy agents, are required. Future directions We have organized a multi-institutional study group of carbon-ion radiation oncology in Japan (J-CROS) and have been conducting a number of trials involving a multitude of tumor sites. A number are emerging as particularly attractive for CIRT with possibility of new levels of achievable disease control, including in NSCLC, head and neck cancer, locally advanced unresectable pancreatic cancer, hepatocellular carcinoma, locally recurrent rectal cancer, as well as others. The outcomes of CIRT

for stage I NSCLC in Japanese multi-institutional datasets were retrospectively analyzed. As a result, CIRT is considered a low-risk and effective treatment option for patients with stage I NSCLC. Confirmative multi-institutional prospective studies via J-CROS began last year, so as to validate these results. References: 1. Kamada T, Tsujii H, Blakely EA, et al. Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. Lancet Oncol 2015; 16: e93-100. 2. Sawabata N, Miyaoka E, Asamura H, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol 2011; 6: 1229-35. 3. Miyamoto T, Yamamoto N, Nishimura H, et al. Carbon ionradiotherapy for stage I non-small cell lung cancer. Radiother Oncol 2003; 66: 127-140. 4. Miyamoto T, Baba M, Yamamoto N, et al. Curative treatment of Stage I non-small-cell lung cancer with carbon ion beams using a hypofractionated regimen. Int J Radiation Oncol Biol Phys 2007; 67: 750-758. 5. Miyamoto T, Baba M, Sugane T, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer using a regimen of four fractions during 1 week. J Thorac Oncol 2007; 10: 916-926. 6. Sugane T, Baba M, Imai R, et al. Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer. Lung Cancer 2009; 64: 45-50. 7. Karube M, Yamamoto N, Nakajima M, et al. Single-fraction carbon-ion radiation therapy for patients 80 years of age and older with stage I non-small cell lung cancer. Int J Radiation Oncol Biol Phys 2016; 95: 542-548. 8. Yamamoto N, Miyamoto T, Nakajima M, et al. A dose escalation clinical trial of single-fraction carbon ion radiotherapy for peripheral stage I non–small cell lung cancer. J Thorac Oncol 2016; 12: 673-680. 9. Shioyama Y, Yamamoto N, Saito J-i, et al. Multi-institutional retrospective study of carbon ion radiation therapy for stage I non-small cell lung cancer: Japan Carbon Ion Radiation Oncology Study Group. Int J Radiation Oncol Biol Phys 2016; 96: S10. 10. Takahashi W, Nakajima M, Yamamoto N, et al. A prospective nonrandomized phase I/II study of carbon ion radiotherapy in a favorable subset of locally advanced non-small cell lung cancer (NSCLC). Cancer 2015; 121: 1321-7.

Keywords: carbon-ion therapy, non-small cell lung cancer

MEET THE EXPERT SESSIONS

MTE 01 MANAGEMENT OF SMALL NODULES DETECTED BY CT SCREENING (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 01.01 MANAGEMENT OF SMALL NODULES DETECTED BY CT SCREENING; A SURGEON'S PERSPECTIVE

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Along with the prevalence of screening with computed tomography (CT), small pulmonary ground-glass density nodules (GGN) have been detected more frequently. A GGN is a round area of increased pulmonary opacity with intact bronchial and vascular structures. GGNs showing no or slow growth during follow-up period are most likely to be "early" adenocarcinomas showing lepidic pattern pathologically. There are three problems in diagnostics and therapeutics of GGNs. First, should they be treated or not? They might not change for years. We might take a risk of postoperative comorbidity for a harmless disease. Some large prospective observational studies on these pulmonary small GGNs have been performed: From clinical practice performed in these clinical trials, We found that 5-30% of GGN were resected during the observation period, because of the increased size or appearance of solid part in the GGN. Almost all of the pathologies of the resected GGN were adenocarcinomas. Part-solid GGNs were more likely to be diagnosed as invasive adenocarcinomas than pure GGNs. That is, we can correctly diagnose small pulmonary GGNs as adenocarcinomas when their CT images are changed. However, it is still unclear whether surgical intervention will contribute to increased survival from lung cancer. Second, how to detect pulmonary GGOs at surgery, if they are located deep in lung parenchyma? GGNs are difficult to identify even by bimanual palpation through open thoracotomy, because they are as soft as lung parenchyma if they show pure GGN appearance. Preoperative marking of these GGN is mandatory to ensure a definite resection. Many methods for detecting small pulmonary nodules have been developed: Preoperative hookwire placement under CT observation has been most widely performed. The punctured hook wire with thread can easily be identified that excisional biopsy may be done through thoracoscopy. However, arterial air embolism is reported to be occasionally associated with the placement of hookwire which can cause lethal results. Instead, dye marking, or fiducial placement through bronchoscopy has been revived to replace the hookwire method. We have recently developed Virtual-assisted lung mapping (VAL-MAP), a relatively brand-new lung marking technique using dye multiple dye markings through bronchoscope. Before bronchoscopy, we create a virtual 3-D bronchoscope map with CT and plan where to mark. Multiple dye markings enable us to determine the extent of resection with safe margin from the tumor. Actually safer margin from the tumor was shown to be secured by this method. Third, how to determine the extent of pulmonary resection for these small GGNs? Still there is no evidence other than lobectomy and lymph node dissection for early non-small cell lung cancer (NSCLC), clinical trials have been performed to prove feasibility and no-inferiority of sublobar resections (wedge resection and segmentectomy) for small NSCLC, especially those ≤2cm in diameter. In Japan and USA, prospective randomized studies are on the way to obtain more reliable evidence. In conclusion, management of small pulmonary nodules suspected of an early carcinoma includes the determination of operative indication, detection technique of the tumor, aiming to safer and effective treatment of these tumors.

Keywords: ground glass density nodules, surgical indication, tumor detection

MTE 02 APPROPRIATE AND OPTIMIZED HANDLING OF SPECIMENS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 02.01 APPROPRIATE AND OPTIMIZED HANDLING OF SURGICALLY RESECTED SPECIMENS

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Guidelines for gross handling are to our knowledge not formulated in the literature. However, the College of American Physicians (CAP) formulates "required elements" for synoptic reporting regarding gross handling of pulmonary resection specimen, mainly focusing at pathology staging, but does not include grossing requirements[1]. The current practice of handling resection specimen in Amsterdam involves interaction with surgeons for submission of specimen. This includes i) Information about pretreatment, type of surgery (including pneumonectomy, (sleeve) lobectomy, segmentectomy, and wedge resection), site of specimen, number of tumors; ii) eventual frozen section for diagnosis and/or resection margin; iii) eventual additional information of specimen e.g. adhesion from parietal pleura, additional wedge from adjacent lobe adhesion; iv) agreement on marking the 'cold' side from bronchial resection slice [see note A]; For the pathologist, the order of handling the fresh specimen is i) to maintain the 3 dimensional orientation of the resection specimen along the axial, coronal and sagital planes; ii) to describe outer surface of specimen; iii) to photograph overview from medial and lateral side; iv) to cut slice of bronchial resection margin; v) to cut tumor, preferably in axial plane for sampling of normal lung tissue and tumor for research (culture, freezing) [see notes B and C]; vi) to perform perfusion fixation of peripheral lung; vii) and to immerse whole specimen in large volume neutral buffered formalin. After 24 hours, fixation the specimen is handled in the following way: i) Intrapulmonary lymph nodes are separately embedded ii) the specimen is further cut in slices along the same plane as done for the fresh specimen; iii) the slices are positioned in order of cutting, numbered and photographs taken; iv) description of specimen with tumor characteristics: focality (size; vital, necrosis, fibrosis), distance from tumor to margins recorded (to bronchial resection, pleura). If tumor is present in sequential slices, cumulative tumor thickness is measured; v) other characteristics are described (mucus in dilated bronchi; post-obstruction pneumonia; emphysema etc.) vi) sample representative blocks from tumor, normal tissue, resection margin arteria pulmonalis, and nearest point(s) to pleura for embedding in paraffin; vii) annotate the location of sampled blocks on a copy of the gross slices. After a few days during first microscopy, the 3 dimensional orientation can be reconstructed and the pTNM parameters extracted from the gross and microscopic information. If needed, additional samples can be taken [see note C]. Classification is performed for most parts according to the WHO[2], except for not reproducible categories and immature concepts. Pathology reporting contains pTNMR [see note D]. The pathology report is usually made within 9 working days, except if bony structures are included, then the process will contain an additional week. If postoperative radiotherapy is indicated, the 3 dimensional approach also supports determination of the position(s) for radiation, especially if clips were not placed during surgery. Note A As for frozen section, the cold side of the bronchial resection margin [i.e. the side distant from the patient] is placed downwards on the frozen template, the first cut frozen section sections [representing the nearest to the patient tissue margins (warm side)] are sequentially placed on the microscope slide. In case of uneven surface maximally 6 sections, until complete circumference is achieved, are placed on two microscopic slides, and stained for H&E The bronchial resection margin is considered tumour-free, if the complete circumferential margin does not contain tumor. If needed, in this judgement sequential complementarity of the 6 sections may be taken into account. The sleeve lobectomy has two resection margins: one on the cold side and the other on the warm side (larger bronchial diameter). These are separately examined. If only tumor cells are found in lymph vessels (but no direct tumor spread), this will be reported, but not considered necessary for indication of additional bronchial margin, as lymphangitic distribution is associated with N2 disease[3,4]. Note B As it has been proven that loose tissue fragments are caused by gross cutting[5,6], the knife is rinsed and quickly wiped after each slice that happens to contain tumor. STAS is considered to be an artifact and in contrast to CAP and WHO classification, is not considered as part of the tumor. Note C In Pancoast tumor, the 'en-bloc resection' incorporates extrapulmonary structures directly invaded by tumor, usually ribs. During the fresh handling, the thoracic wall is cut from the lung. Subsequently, both cut surfaces are coloured to denote the artifical edges. Bone requires after fixation extra time for decalcification, extending reporting with one week. Note D The R = defined as follows: R0 = free resection margins; R1 = microscopic margins not free; R2 = margins not free during gross examination/surgery;. Peripheral wedge resections contain a parenchymal margin, which is represented by the tissue at the staple line(s). The staples are cut from the specimen, but not further examined. Adjacent tissue is sampled for microscopic examination. If this section does not contain tumor, the margin is free (R0). However, if this contains tumor, an educated guess is reasonable, encompassing the amount of tumor compared to the other sections, and the estimation of the staple thickness (±2mm). 1. College of American Pathologists. Cancer Protocol Templates. Lung cancer vs4. http://www.cap.org/web/oracle/webcenter/portalapp/pagehierarchy/Cancer_protocol_templates.jspx?_afrLoop=445529225217710#!%40%40%3F_afrLoop%3D445529225217710%26_adf.ctrl-state%3Dxmm1doio_4. 2. 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Ex Vivo Artifacts and Histopathologic Pitfalls in the Lung. *Arch Pathol Lab Med*. 2016;140(3):212-220. doi:10.5858/arpa.2015-0292-OA.

MTE 02 APPROPRIATE AND OPTIMIZED HANDLING OF SPECIMENS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 02.02 APPROPRIATE AND OPTIMIZED HANDLING OF BIOPSY OR CYTOLOGY SPECIMENS

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The recent advance in personalized medicine along with minimally invasive endoscopic techniques in the field of lung cancer has brought significant complexities to handling of tissue samples. Due to the histology-directed therapy, additional stains are frequently required to achieve accurate histologic subtyping on small biopsy and cytology samples. It is recommended that epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS1 testing be performed for patients with advanced non-squamous small cell lung cancer (NSCLC) in a reflex manner. In addition, multiplex assays, including next generation sequencing (NGS), are increasingly being used for detection of the molecular targets. Furthermore, immunohistochemistry (IHC) for programmed death ligand-1 (PD-L1) is now routinely performed in NSCLCs with wild type *EGFR* and *ALK* to determine eligibility for PD-1/PD-L1 blockade.(1) In most advanced NSCLC patients, a small biopsy or cytology specimen is often the only sample available for the diagnosis and biomarker analyses.

Thus, appropriate tissue acquisition, processing and management for multiple tests are crucial and are best achieved by the interaction of all physicians involved in the patient care.(2, 3) Tissue acquisition All the necessary work-up is usually performed on a small biopsy or cytology specimen taken from a patient with advanced disease, tissue sampling should be aimed at obtaining the largest yield of tumor in the safest and least invasive manner.(4) Tissue processing Appropriate pre-analytic tissue handling is one of the keys to successful implementation of IHC-based and molecular assays in general.(3, 5) An ischemia time from tissue procurement to the initiation of fixation should be short (as short as possible), and biopsies should immediately be immersed in fixative for 6-48 hours. Of note, multiple tissue fragments in a biopsy sample (obtained from one lesion) may be submitted in a few tissue cassettes to avoid tissue exhaustion that is not infrequently seen when the single available tissue block is cut and used for multiple purposes. Neutral buffered formalin is historically the preferred and most common fixative used in the practice of histopathology. (6) Consequently, the majority of pathology laboratories typically perform the initial validation of IHC and molecular protocols on FFPE tissue. Decalcifying solutions used for bony specimens vary in their effects on retention and integrity of nucleic acids and proteins. Thus, results of IHC on decalcified specimens are unpredictable because of wide variations in specimen types and sizes, fixation time, and the particular solution(s) used.(7) Similarly, alcohol fixation used for cytology specimens, including alcohol-fixed cell blocks, decreases IHC accuracy by causing loss or decrease of immunogenicity when IHC protocols optimized with FFPE tissue samples are used.(8) For molecular assays, samples fixed with acidic solutions (including decalcifying salutations) and heavy metal fixatives are not recommended due to further degradation of nuclear acid and heavy metals hampering PCR reaction, respectively.(9) Thus, tissue sampling of a bone metastasis for this purpose should be avoided, if possible. In case the bone metastasis is the only accessible lesion for sampling, the pathologist may try to separate a soft tissue component submitted in the formalin. Up to 40% of advanced NSCLC patients are diagnosed by cytology alone. Cytology smears, cytospins and liquid-based cytology (LBC), processed from fine needle aspiration (FNA) or other modalities, are typically treated with alcohol-based solution or sprays devoid of exposure to formalin that leads to fragmentation of nuclear acids, thus often contain tumor cells with intact nucleic acid ideal for molecular testing. However, formalin-fixed paraffin-embedded (FFPE) cell blocks processed from the residual material from FNA or LBC or body fluid are the preferred samples for ancillary testing in many laboratories, since they can be handled in the same way as biopsy/resection specimens.(2) Tissue management To maximize small samples, the number of times when the tissue block needs to be cut for diagnosis, IHC and molecular testing should be minimized. It is because a decent amount of tissue is cut and wasted for trimming of the block at each round of sectioning. Thus, extra sections may be cut up front at the first cutting for diagnostic histology sections. Many pathology laboratories already have protocols in place per local requirements under close supervision by pathologists. It is also important that the pathologist is in close communication with oncologists and proceduralists to ensure that relevant clinical information is provided before sectioning is done. Diagnostic work-up between the lesion with high probability of a lung primary and a possible metastasis, and that between primary diagnosis and progression/recurrence after targeted therapy are often different, thus lack of the critical information may lead to unnecessary IHC. Last, but not least, the pathologist needs to evaluate tissue adequacy (tumor cellularity, the presence or absence of necrosis and tissue quality, etc.) before submitting samples for molecular testing. **References**: 1. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 8.2017 – July 14, 2017. 2. Bubendorf L, Lantuejoul S, de Langen AJ, et al. 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Keywords: tissue handling, biopsy, cytology

MTE 03 SURGERY FOR T4 LUNG CANCER (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 03.01 DO EXTENDED RESECTIONS IMPROVE T4 LUNG CANCER OUTCOMES?

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T4 lung cancers invading neighboring structures comprise a heterogenous group of locally invasive tumors. In a small subset of these localized tumors whose extrapulmonary invasion preceded any lymphatic extension, an adequate excisional procedure can achieve surprising long term survivals. The indications for such procedures and the anticipated outcomes should be weighed on a case by case basis, in terms of potential perioperative complications and expertise of the surgical team. Advanced surgical techniques are now being applied for T4 lesions due to improvements in surgery and anesthesiology and progress in combined treatment modalities. In the present staging, T4 tumors without mediastinal nodal metastasis are now considered to be potentially curable if complete resection is possible.

A summary of the literature, under the light of personal experience allows a critical point of view, knowing that a surgical procedure which would not be reproducible in other centers would never be recognized as an option for practice. Therefore among the published series it is important to distinguish the real progress given by innovative techniques or procedures that could be applied throughout the world, even only in selected centers, from the simple reports of individual performances or exploits. Proximal tumors from the lower lobe may involve the atrial wall of the heart. In some cases a left atrial resection can be performed, followed by direct closure, or replacement of the atrial wall. Fukuse reported a series of 42 patients, from which left atrium was resected in 14 patients, Mortality rate was low (2.4%), regarding complexity of the procedures. Low stages in nodal status were associated with increased survival (p = 0.0013). More recently was reported a series of 19 patients who underwent extended lung resection involving the left atrium without cardiopulmonary bypass [2]. An interatrial septum dissection is performed, thus increasing the length of the atrial cuff. R0 resections were observed in 89% of the patients. Ninety-day mortality rate was 16%. Five-year survival rate is 44%, and 3 patients (16%) are alive more than 6 years after surgery. Other reports advocate the use of cardiopulmonary bypass in these occasional situations [3-5]. Invasion of the superior vena cava (SVC) by a T4 non small cell lung c ancer (NSCLC) led surgical teams to attempt lobectomies or pneumonectomies extended to the vena cava [6]. Actually direct extension to the vessel by the tumor mass itself is a rare situation. SVC involvement generally results from a bulky disease, in which the nodal disease is the greatest component. The rationale of resecting SVC in N2 disease remains questionable, in view of the high potential of metastatic spread and the poor prognosis. Nevertheless, different techniques were proposed, including lateral clamping of SVC, partial, or total reconstruction. These procedures are associated with high morbidity rates. A multicentric international review of prosthetic replacement after SVC resection for nsclc in 28 patients (N2 involvement in 50%) showed morbidity and mortality rates of 39% and 14%, respectively. Overall 5-year survival rate was 15% [7]. Despite some reports who claim better survival rates, close to 50% at five years, the latter seems more realistic, and this warrants a thorough evaluation with the aim to preclude these patients from surgery in case of N2 involvement. A bronchial carcinoma extended to the tracheal bifurcation can be resected in selected patients [8]. A high rate of post-operative morbidity (10 to 30%), including bronchial dehiscences, jeopardizes the outcome, but long-term survivals have been observed in 15 to 23% of the cases. A meticulous mediastinal assessment is mandatory to eliminate invasion of the airway by a bulky disease. Only patients with T-invasion will be offered surgical resection. NNSCLC invading the thoracic inlet can easily penetrate spinal structures because of their particular anatomic situation. The best local control for resectable tumors is achieved by surgical operation, provided the resection is complete and respecting oncologic principles. Direct invasion of the vertebral body became an option following the first report in 1996 of a successful en bloc total vertebrectomy for lung cancer invading the spine [9]. Reported experiences from Europe, North-America and Asia demonstrate feasability and encouraging results of these challenging procedures, . Recently a comprehensive literature search, on a total of 1,001 abstracts and 93 articles found overall 5-year survival rates ranging from 37% to 59% and the mortality rate ranged from 0% to 6.9% [10]. Undoubtly enbloc resection for lung cancer invading the spine is reaching the stage of current practice in expert centers. This is probably due to a particular biology of these tumors which are peripheral and whose noisy symptoms lead to a relatively early diagnosis, thus permitting a high rate of complete resections. Evidence suggests that triple modality therapy with complete resection of locally advanced Pancoast tumors with involvement of the spine offers an advantage over other therapeutic modalities. Despite the absence of such an evidence in other T4 lung cancers, recent advances in patient's care and surgical techniques allowed surgeons to become more aggressive, and to propose occasionally extended resections with encouraging long-term survival rates to patients suffering from tumors invading the tracheal bifurcation, the left atrium, or the great vessels. The 8th edition of TNM classifies,T4N0-1 tumors in a «surgical» category, stage IIIA. 1. Fukuse T, et al. Extended operation for nsclc invading great vessels and left atrium. Eur J Cardiothorac Surg 1997;11:664–9 2. Galvaing G, et al. Left atrial resection for T4 lung cancer without cardiopulmonary bypass: technical aspects and outcomes.Ann Thorac Surg 2014;97:1708-13 3. Klepetko W, et al. T4 lung tumors with infiltration of the thoracic aorta: is an operation reasonable? Ann Thorac Surg 1999;67:340–4 4. De Perrot M, et al. Resection of locally advanced (T4) nsclc with cardiopulmonary bypass. 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Keywords: T4 NSCLC surgery

MTE 04 RADIOTHERAPY FOR SCLC (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 04.01 ROLE OF RADIOTHERAPY IN MULTIMODALITY TREATMENT FOR SCLC

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Major advances in SCLC include improvements in RT techniques, the use of prophylactic cranial irradiation (PCI) for all stages of SCLC and the improved combination of chemotherapy and RT (Califano). The role of thoracic radiotherapy is well established in the management of stage I-III SCLC (Pignon). There is increasing evidence in the literature in favour of early concurrent chemo-radiotherapy, and a standard of care for patients with a good performance status is twice-daily thoracic radiotherapy (45 Gy in 3 weeks) with concurrent cisplatin and etoposide (Turrisi). Although current clinical trials are exploring the efficacy of new chemotherapeutic strategies, essential questions related to the optimisation of thoracic radiotherapy and the benefit of chemo-radiotherapy in sub-groups of patients remain unanswered, e.g. the elderly (Blackhall). The CONVERT trial (twice-daily (BD) versus once daily (OD) radiotherapy given concurrently with chemotherapy in stage I-III SCLC) was reported at ASCO 2016 (Faivre-Finn). OD RT did not result in a superior survival or worse toxicity than BD RT (two-year survival was 56% (95% CI 50-61) vs 51% (95% CI 45-57), p= 0.14). The survival for both regimens was higher than previously reported and using modern RT techniques radiation toxicities were lower than expected. In the stage IV setting the CREST trial as shown that the addition on thoracic RT to chemotherapy and PCI leads to a significant reduction in intrathoracic recurrence and, despite the lack of a significant benefit in overall survival at 1 year, there were significant improvements in overall survival at 2 years (Slotman). It is crucial that patients with SCLC are given the opportunity to participate in clinical research in order to continue to improve the survival of this disease. Molecular studies are ongoing aiming to gain improved insight into the molecular biology of SCLC, discover and/or validate candidate biomarkers for response, resistance to or toxicity of systemic treatment and radiation. It is expected that this understanding will lead to the development of targeted therapies that will not only prove efficacious but also less toxic than more conventional chemotherapy treatments. In combination with advanced RT techniques and better imaging, it is hoped that the rates of long term survivors will increase significantly in the future. We will address the following controversial questions • Should BDRT be considered standard of care in stage I-III SCLC? • Role of CTRT in stage I-II SCLC • Role of CTRT in elderly patients with LS-SCLC • Should thoracic RT be given to all patients with stage IV SCLC? **References** Califano R, et al. Management of small cell lung cancer: recent developments for optimal care. Drugs. 2012 5;72(4):471-90 Pignon JP, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327:1618-1622. Turrisi AT, et al. Twice daily compared to once-daily thoracic radiotherapy in limited-stage small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999; 340: 265-271. Auperin A, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341(7):476-84. Blanchard P, et al. Prophylactic cranial irradiation in lung cancer. Curr Opin Oncol. 2010; 22(2):94-101 Blackhall F et al. Treatment of limited small cell lung cancer: an old or new challenge? Curr Opin Oncol. 2011; 23(2):158-62 Faivre-Finn C, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18(8):1116-1125 Slotman BJ, et al.Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015 3;385(9962):36-42 Slotman BJ, et al. Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: A secondary analysis of the Phase III CREST trial. Lung Cancer. 2017; 108:150-153

Keywords: small-cell, radiotherapy, thoracic

MTE 04 RADIOTHERAPY FOR SCLC (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 04.02 GENERAL PRINCIPLES OF PCI IN THE TREATMENT OF SCLC

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The brain is a well recognized sanctuary site for micrometastases in patients with small cell lung cancer (SCLC) treated with chemotherapy. The administration of prophylactic cranial irradiation (PCI) in patients responding to chemotherapy reduces the incidence of clinically detectable brain metastases in patients with both limited [1] and extensive disease [2, 3]. In patients with limited disease, this translated into a survival benefit in a meta-analysis of 987 complete responders, but in patients with extensive disease, one trial of 286 responders to chemotherapy showed a survival benefit [2], whilst in another of224 patients it did not [3]. The design of this latter trial suggested that regular surveillance with MRI and treatment at the time of metastasis detection might be an equally effective strategy. This could reduce the incidence of the most serious toxicity of PCI which is delayed neurotoxicity. Limiting the total dose is another possible means of reducing neurotoxicity. A randomized trial of three dose prescriptions restricted to patients with limited disease showed no difference in rate of brain metastases between 25 Gy in 10 fractions versus two higher dose schedules, but there was a higher mortality associated with the higher doses, due to an unexplained increase in disease progression [4]. In spite of this high level evidence there are still numerous uncertainties facing the clinician when deciding whether to recommend PCI. 1. Is the classification limited versus extensive disease still appropriate when selecting patients? 2. Are there subgroups of patients with metastatic disease more likely to benefit from PCI than others because their overall prognosis is better? [5] 3. Should there be an upper age limit? 4. Are pre-existing neurologic conditions or paraneoplastic syndromes contraindications? 5. In patients with extensive disease, is pretreatment MRI required? 6. Is MRI surveillance cost effective? 7. Is there a role for hippocampal sparing techniques or neuroprotective agents? 8. Is there a place for lower dose/shorter fractionation schedules? 9. In patients with extensive disease having consolidative chest irradiation, is there any difference between giving PCI simultaneously versus sequentially? 10. What will be the role of PCI in the era of immunotherapy? Question 7 is currently the subject of an actively recruiting randomized trial (NRG-CC003), but for the other questions, physician and patient discretion will be required for the forseeable future. References 1. Auperin, A., et al., *Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group.* N Engl J Med, 1999. **341**: 476-84. 2. Slotman, B., et al., *Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer* N Engl J Med, 2007. **357**: 664-672. 3. 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, 2017. **18**: 663-671. 4. Le Pechoux, C., et al., *Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial.* Lancet Oncol, 2009. **10**:467-74. 5. Eberhardt, W.E., et al., *The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer.* J Thorac Oncol, 2015. **10**:1515-22.

Keywords: small cell lung cancer, prophylactic cranial irradiation

MTE 05 NEUROENDOCRINE TUMORS: PATHOLOGY AND GENETIC UPDATE (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 05.01 NEUROENDOCRINE TUMORS: PATHOLOGY AND GENETIC UPDATE

E. Brambilla

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Pathology In the current WHO 2015 classification[1] neuroendocrine lung tumors are listed in the order of their frequency with SCLC first as it is the most common (15% of lung cancer). Despite the grouping of these tumors together, it is clear that the carcinoids have major clinical, epidemiologic, histologic and genetic differences compared to the high grade SCLC and LCNEC. SCLC and LCNEC have much higher mitotic rates (more than 11 per 2mm2), more necrosis than carcinoids and can show combinations with other lung cancer types including adenocarcinoma or squamous cell carcinoma, which testify of a common progenitor cell derivation, not shared by carcinoid which is never mixed with a non-neuroendocrine (NE) tumor type Immunohistochemistry (IH) / neuroendocrine markers can be very helpful in diagnosing pulmonary NE tumors especially in small biopsies with crushed artefact. Endocrine morphology and neuroendocrine IH markers are both required for the diagnosis of LCNEC. The cases with one missing (Endocrine morphology or NE markers) are considered as large cell carcinoma in the absence of other differentiation marker on resection specimens, and as non- small cell lung carcinoma on small samples. **Genomic update Small cell lung carcinoma** [2-3]The universal biallelic alteration of both *TP53* and *RB1* gene was remarkable (100% for *P53* and 93% for *RB1)* by different alterations of each of the 4 alleles. Other significantly mutated genes are *KIAA1211* and *COL22A1* with unclear functions, as well as *RGS7* and *FPR1* involved in G-protein-coupled receptor signalling. Locally clustered mutations occurred on *CREBBP* (15%) and *EP300* (13%) genes, inactivating their histone acetylase functions. *Notch* family genes were recurrently mutated (25%) whereas RNA transcriptome analysis revealed a rate of *Notch* inactivation of 77% associated with up regulation of neuroendocrine (NE) lineage genes *(DLK1 a Notch* inhibitor, *CHGA (*chromogranin A*), ASCL1* a master regulator of NE lineage, and *GRP* (gastrin releasing protein)). Another Notch inhibitor DLL3 was reported to be upregulated in 65% of SCLC[3]. DLL3 is considered as a therapeutic target tested in several clinical trials[4]. The mouse model validated *NOTCH* as a tumor suppressor and master regulator of NE malignant differentiation in SCLC[3]. *TP73* gene breaks inducing intragenic fusions and rearrangements, creates the N-terminally truncated transcripts variants lacking a fully competent transactivation domain and exerting dominant negative functions on both wild type p73 and p53. With additional mutations in *TP73*, 13% SCLC showed alteration in *TP73* gene. Somatic copy number alterations (CNA) include focal events on 3p14.3-3p14.2 (*FHIT* gene) and 3p12.3-3p12.2 *(ROBO1)* with reduced expression of theses 2 genes. Homozygous deletion of the *CDKN2A* locus (chromosome 9p) and amplification of the *MYC* family genes (*MYCL1, MYCN, MYC)* as well as of *FGFR1* (6%) and *IRS2* (2%) were recurrent events. The remarkable largely mutually exclusive mutations in the five key genes: *CREBBP, EP300, TP73, RBL1, RBL2* (equivalents of *RB1* in the mouse model) and Notch suggest they may exert similar pro-tumorigenic functions in the development of SCLC and are candidate drivers[3]. **Large cell neuroendocrine carcinoma (LCNEC)** *TP53* was the most frequently inactivated gene (92%) followed by *RB1* (42%) Biallelic inactivation of both *TP53* and *RB1* (the hallmark of SCLC) was seen in 40%.Mutations in *STK11/ LKB1 (30%,* characteristic of ADC) and *KEAP1* (22%, detected in both ADC and SCC but not in SCLC). The mutations were deleterious (nonsense, splice and frameshift mutations) or missense affecting

important protein domain mutations in *RB1* and *STK11/KEAP1* which occurred in a mutually exclusive fashion (p<0.0001). Damaging mutations also occur in chromatin-remodelling genes *ARID1A* and *MEN1/PSP1* in 10% and 7% of LCNEC respectively; Ras family alterations were found in 10% of cases. Overall RAS family, BRAF and NKX2-1 alterations were mutually exclusive with RB1 (P=0.0049) suggesting again distinct genomic patterns in LCNEC. Analyses of CNA on 60 LCNEC reveals similarities to SCLC[3]. As mutations, the pattern of copy number alterations of LCNEC share characteristics with SCLC, ADC, or SCC. Overall from genomic profiles, while certain alterations (*RB1 MYCL1)* resemble thoses found in SCLC, others are typical of adenocarcinoma (*STK11, NKX2-1, RAS, BRAF*) or of squamous cell carcinoma *(KEAP1, NFE2L2*), showing the heterogeneity of LCNEC which can be divided into molecular subsets by similarities with other major lung cancers. At transcriptional level[5] an unsupervised consensus clustering showed a common cluster including both SCLC and LCNEC characterized by high expression of neuroendocrine lineage transcription factors, as well as high levels of cell cycle regulation and DNA damage response genes, and centrosomal functions. Although LCNEC shared characteristics with ADC and SCC, theses were dissimilar and strongest correlation was being found with SCLC. The transcriptional relationship of LCNEC and SCLC revealed 4 consensus clusters I-IV. Tumors in cluster I exclusively contained LCNECs with STK11 or KEAP1 alterations (type1-LCNEC) characterized by a high level-expression of chromogranin A and synaptophysin. The majority of LCNECS in cluster 2 enriched in cases with RB1 alterations exhibited reduced levels of NE markers and elevated Notch signalling, low expression of ASCL1 and DLL3 an inhibitor of NOTCH signalling pathway (type 2 LCNEC). Whereas type1-LCNECs harbor STK11 or KEAP1 alterations but share NE expression profiles with SCLC, type2- LCNEC (40% of LCNEC) bear genetic resemblance with SCLC with RB1 alterations ,but profound transcriptional differences with SCLC. **Carcinoid Tumors** Molecular alterations underlying pathogenesis of this tumor were enlighted only recently[6] Genome/exome sequencing data from 44 tumor/normal pairs, allowed identification of *MEN1, ARID1A*, and *EIF1AX* as significantly mutated genes. *MEN1, PSIP1(13%)* and IRID1A play important roles in chromatin remodelling process showed mutually exclusive frameshifts and truncating mutations. Mutations in histone methyltransferases (*SETD1B, SETDB1, NSD1*) and demethylases *(KDM4, PHF8*) as well as members of the polycomb complex 1 and 2 (*CBX6* and *EZH1*) mutations were accompanied with LOH. In total 40% of carcinoids carried mutually exclusive mutations in genes involved in covalent histone modification. Truncating and frameshift mutations occur in ARID1A (6,7%), and other mutations in this SWI/SNF chromatin remodelling complex in 22%. With sister chromatid cohesion affected by reccurrent mutations (*COHESIN, STAG1, NIPBL*, the microRNA processor *DICER* and ERCC6L), 51% of carcinoid carried mutations in chromatin remodelling genes. There was no genetic segregation between typical and atypical carcinoid, neither between the expression clusters generated from both subtypes. **References** Travis WD, Brambilla E, Burke A, Marx A, Nicholson A. *WHO Classification of the Tumours of the Lung, Pleura, Thymus and Heart*. 4th Edition. Lyon: IARC Press; 2015. Peifer M, Fernandez-Cuesta L, Sos ML, et al. Nat Genet 2012;44:1104-10. George J, Lim JS, Jang SJ, et al. Nature 2015;524:47-53. C.Rudin, M.C. Pietenza, M. Todd et al. *Lancet Oncol* 2017; 18: 42–51. Georges et al. Nature communication. In press 2017 Fernandez-Cuesta L, Peifer M, Lu X, et al. Nature communications 2014;5:3518.

Keywords: neuro-endocrine lung tumors, pathology, genetics

MTE 06 LUNG CANCER PATHOLOGY UPDATE (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 06.01 LUNG CANCER PATHOLOGY UPDATE

A. Moreira[1], P. Russell[2]

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This session will focus on some new definitions and concepts in the recently published 2015 WHO classification of lung tumors (1), some of which were showcased in the 2011 IASLC/ATS/ERS lung adenocarcinoma classification (2), while others are introduced for the first time. We will focus on resected lung adenocarcinoma as well resected squamous cell carcinoma, large cell carcinoma and the neuroendocrine tumor spectrum. Adenocarcinoma: In the 2015 WHO classification, the definition of adenocarcinoma has been expanded from a malignant epithelial tumor with glandular differentiation or mucin production to include tumors that also express pneumocyte immunomarkers (e.g. TTF1, Napsin A). This means that undifferentiated carcinomas formerly classified as large cell carcinoma that express pneumocyte immunomarkers, like undifferentiated carcinomas that show mucin expression, are now included in the solid adenocarcinoma category. Invasive adenocarcinomas account for >70% of all surgically resected cases and consist of a complex admixture of histologic subtypes. In an effort to represent this morphologic complexity, comprehensive histologic subtyping was introduced in the 2011 IASLC/ATS/ERS classification. A number of recent studies have demonstrated the utility of comprehensive histologic subtyping in identifying prognostically significant groups of tumors . Studies published both before and after the 2011 IASLC/ATS/ERS classification have highlighted the importance of the secondary patterns in addition to the predominant pattern in resected lung adenocarcinoma. Comprehensive histologic subtyping, its pitfalls and the emerging significance of secondary patterns in tumour recurrence and prognosis will be discussed further in this session. Grading: There is no well-established, internationally accepted grading system in resected lung adenocarcinoma. A simple grading system based on predominant histologic subtype has been proposed due to the prognostic significance of predominant histologic subtype. Other suggested grading schemes include different combinations of mitotic count, second predominant pattern and nuclear features with predominant histologic subtype. The emerging concept of an objective grading system for pulmonary adenocarcinomas will be briefly explored in this session. Another newly introduced concept in the 2015 WHO classification is that of tumour spread through alveolar spaces (STAS) which may occur with micropapillary clusters, solid nests or single cells. STAS was found to be associated with an increased recurrence rate in patients with stage I adenocarcinomas <2cm who underwent sublobar resections (3). Tumour size and staging: A recent study confirmed that in resected non-mucinous adenocarcinoma, the size of the invasive component, excluding the lepidic (equated with in situ) component of the tumor, correlates better with patient outcome than total tumour size (4). This finding has been supported by other studies and is expected to be included in the upcoming 8th edition TNM staging system for the T descriptor for pathologic staging in resected non-mucinous adenocarcinoma (5). Squamous cell carcinoma (SQCC) is the second most prevalent Non-small cell lung cancer (NSCLC), behind adenocarcinoma. Contrary to the latter where most changes in nomenclature, diagnosis and molecular pathology have occurred, SQCC has a strong association to smoking and remains a challenge for oncologists with few therapeutic advances. To reduce the risk of over diagnosing SQCC, the definition of SQCC became stricter in the 2015 WHO classification. For the diagnosis of this entity it is necessary to have evidence of keratinization and intercellular bridges. For non-keratinizing SQCC it is necessary to demonstrate evidence of squamous differentiation by immunohistochemical (IHC) stain (diffuse positivity for p40 or p63 and absence of adenocarcinoma markers such as TTF-1 and napsin-A). Non-keratinizing SQCC shares a solid pattern of growth with adenocarcinoma; in addition, solid type adenocarcinomas can have squamoid features such as glassy and abundant cytoplasm that can mimic SQCC (6), therefore it is recommended the use of IHC for any NSCLC with solid pattern of growth. Presence or absence of mucin is not a criterion for diagnosis of SQCC. Similar to adenocarcinoma, there is no grading system for SQCC. There is evidence that tumour budding is associated with worse prognosis (7). Basaloid carcinoma is now classified in the same group of SQCC and no longer part of large cell carcinoma. In contrast, Lymphoepithelioma-like carcinoma of the lung that share IHC profile with squamous cell carcinoma is grouped in the category of other undifferentiated tumours that also include NUT carcinoma. Large cell carcinoma: remains a separate category; however, the diagnosis of this entity is greatly reduced. Large cell carcinoma is an undifferentiated carcinoma (positive for cytokeratin markers), which lacks evidence of differentiation by morphology and lineage specific immunohistochemical profile (TTF-1/Napsin-A and p40 negative). This classification is supported by molecular profile (8). High Grade Neuroendocrine Carcinomas. This tumour category remains largely the same from previous classification with the exception that Large Cell Neuroendocrine Carcinoma (LCNC) is now grouped with neuroendocrine tumours. It is no longer part of a Large Cell Carcinoma category. Recent studies have suggested that LCNEC is a heterogeneous group ranging in the spectrum from NSCLC-like to small cell carcinoma-like tumours (9). LCNEC that resemble NSCLC have higher incidence of KRAS mutations, whereas those morphologically closer to small cell carcinoma have higher incidence of RB mutation. The significance of these findings for tumour classification and especially for therapeutic options are still unknown as more studies need to be done. There have been several studies on the genetic and epigenetic profile of small cell carcinoma that could lead to new therapeutic options (10). However, the diagnosis and classification of this tumour remains the same. Carcinoid Tumours: Typical and atypical carcinoid tumours maintained the same morphological criteria for diagnosis and classification. Recent molecular studies have showed however that these tumours have distinct molecular profiles from the high grade relatives (LCNC and small cell carcinoma) (10). 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Keywords: carcinoma, Pathology, classification

MTE 07 MOLECULAR BIOLOGY: MINIMUM REQUIREMENT FOR CLINICIANS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 07.01 MOLECULAR BIOLOGY THAT CLINICIANS SHOULD KNOW: FROM A CLINICAL VIEWPOINT

P. Adusumilli

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This presentation will summarize the basics of cancer molecular biology and its application in lung cancer. The optimal treatment for patients with EGFR mutations in 2017, the need for tissue rebiopsy and plasma detection, and semiquantification methods will be discussed. The role of next-generation tyrosine kinase inhibitors that are approved in different countries will be summarized. The evolution of new targeted therapies and their current status of investigation will be presented. Additionally, the current status of combination targeted therapies with immunotherapy will be reviewed. The role of quantitative proteomics, plasma circulating tumor DNA, and high-throughput sequencing in current clinical practice will be summarized. By the end of the session, the audience will be familiar with the current status of driver genes, approved targeted therapies, and emerging concepts of combination therapies.

Keywords: Molecular biology, mutations, targeted therapy, non small cell lung cancer

MTE 08 TECHNICAL DETAILS OF EBUS AND EUS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 08.01 TECHNICAL ASPECTS OF EBUS-TBNA FOR CLINICIANS

T. Nakajima

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Since the clinical introduction of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in 2004, EBUS-TBNA has become accepted worldwide due to its minimal invasiveness but high diagnostic ability. EBUS-TBNA is an image-guided procedure, and the instruments and devices used for endobronchial ultrasonography as well as transbronchial needle aspiration have continuously evolved. Furthermore, such device improvements have been accompanied by improvements in the techniques of ultrasound visualization, sampling with a dedicated needle, and specimen handling. Initially, the only indication of EBUS-TBNA was nodal staging of lung cancer; however, now its indications have expanded to not only malignant diseases but also benign diseases, such as sarcoidosis or tuberculosis. EBUS-TBNA has also recently been used for the important tasks of "core sampling" and "rebiopsy". The advent of immune checkpoint inhibitors and novel tyrosine kinase inhibitors has resulted in additional applications of EBUS-TBNA in the era of precision medicine. In 2016, the American College of Chest Physicians published a guideline focusing on the technical aspects of EBUS-TBNA. This guideline described several techniques of EBUS-TBNA for which the evidence level had been thought too difficult to grade. The ungraded consensus-based statement managed this limitation well and thus became a useful technical guide for clinicians. The guideline also described sedation to be used when performing EBUS-TBNA. Since many patients who underwent EBUS-TBNA suffered from severe coughing during the procedure, the guideline recommended performing moderate or deep sedation in the first paragraph. In addition, performing the procedure in a more comfortable condition for clinicians was required, which would help them perform the procedure repeatedly following the necessary treatment course as mentioned above. The first report of an EBUS image analysis was the classification of B-mode features of benign and malignant lymph nodes by the first generation EBUS ultrasound processor with 7.5MHz radiofrequency. Owing to improvements in ultrasound processors and increased radiofrequency to 10MHz, EBUS image analyses are now being increasingly performed, including the use of various new Doppler features and image analysis technologies, such as gray scale texture analyses and fractal dimension analyses. The latest ultrasound processor equipped with elastography is capable of depicting the relative stiffness of the targeted tissue within the region of interest. However, whether or not a spectrum analysis of EBUS radiofrequency can provide precise information of the target histology is still being investigated. After all, EBUS-TBNA is a sampling modality, so "tissue is the issue" remains the point of focus. However, we often encounter cases with multiple nodes within the same nodal station. In addition, some metastatic lymph nodes are unable to be diagnosed due to the limited metastatic area within the lymph node (micrometastasis). Advances in EBUS image analyses may help reduce examination time and medical resource usage as well as allow for more precise TBNA needle control. The dedicated TBNA needle was originally developed from the needle used for endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). The handle of the needle was designed to be manipulated by the operator alone. The initial size of the needle was 21 and 22 gauge. Now, however, several types of dedicated needles are commercially available from different manufacturers; currently available needle sizes are 19, 21, 22, and 25 gauge, and each tip is designed for a specific purpose. The size (amount) of the biopsied material, the degree of blood contamination, and the quality of the histological structure (degree of tissue crushing) can all be affected by needle selection. Although the optimum needle type is still unclear, clinicians may need to select a needle depending on the character of the targeted lesion and the purpose of the biopsy. Specimen handling is another important issue. EBUS-TBNA is basically a needle biopsy procedure; therefore, the obtainable material is fundamentally cytological material. We can often obtain "core" specimens, even when using TBNA which is a cytological sampling procedure. We first introduced the "tissue coagulation clot" method for the EBUS-TBNA "core" specimen. The "core" usually consists of tumor tissue fragments floating in coagulation tissue. By modifying the specimen-processing protocol, a good quality cell block can be made and used for pathological evaluations, including immunohistochemistry and ancillary testing, such as fluorescence *in situ* hybridization. We now need to determine any genetic alterations in lung cancer prior to starting treatment. The rapid on-site evaluation of the obtained material during the procedure may play a crucial role in sample processing, despite the lack of any clear evidence that this improves the diagnosis rate so far. We still need to develop the optimum specimen handling protocol in order to maximize the utility of microsamples obtained by EBUS-TBNA. Finally, training for EBUS-TBNA is still important for both mentors and mentees. We recently described the utility of a biosimulator for advanced EBUS-TBNA training to encourage efficient sampling. Many training models, including low- and high-fidelity models, and courses were developed, and the trainees were evaluated by dedicated evaluators. Performing high-quality training is crucial to ensuring a safe procedure as well as a high diagnostic yield. EBUS-TBNA is a still-evolving technology, and we clinicians need to continue brushing up our skills and seeking better ways to examine and treat patients. More clinical studies are needed to address the issues still unresolved by the current technical guideline.

Keywords: transbronchial needle biopsy techniques, specimen handling, endobronchial ultrasound-guided transbronchial needle aspiration

MTE 08 TECHNICAL DETAILS OF EBUS AND EUS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 08.02 CLINICAL ASPECTS OF EUS(B)-FNA

B. Hwangbo

National Cancer Center, Goyang/KR

Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) has been used for lung cancer staging and diagnosis since '90s. However, the usefulness of EUS-FNA has not been addressed in the lung cancer field due to the limited accessibility to mediastinal lymph nodes and the low availability of the technique by thoracic physicians. The development of endobronchial ultrasound guided-transbronchial needle aspiration (EBUS-TBNA) changed the staging process of lung cancer markedly. EBUS-TBNA, which can target mediastinal nodal stations accessible by cervical mediastinoscopy, has replaced standard cervical mediastinoscopy. In the era of EBUS-TBNA, the role of EUS-FNA in lung cancer staging is being re-estimated. Moreover, endoscopic ultrasound with bronchoscope guided fine needle aspiration (EUS-B-FNA) which uses an ultrasound bronchoscope for transesophageal sampling has increased the use of EUS procedure by bronchoscopists. EBUS-TBNA and EUS-(B)-FNA have different accessibility to the mediastinum, therefore the two approaches are considered to be complementary in lung cancer staging. Among mediastinal nodal stations, EBUS-TBNA can access stations 2R, 2L, 3P, 4R, 4L and 7. Some lymph nodes at station 1 and station 8 can be targeted by EBUS-TBNA. EUS-(B)-FNA has limited ability to target pre-tracheal lesions that are easily accessed by EBUS-TBNA. EBUS-TBNA has a higher accessibility to mediastinal nodal stations than EUS-(B)-FNA in the mediastinal staging of potentially operable lung cancer. However, EUS-(B)-FNA can access the inferior mediastinum (stations 8 & 9) and some areas of the aorto-pulmonary window (station 5). The additional benefit of combined EBUS/EUS staging over EBUS-TBNA has been studied. According to a recent meta-analysis by Korevaar et al that evaluated 10 studies that looked at the additional benefit of the combined approach, the pooled sensitivity improvement by adding EUS-(B)-FNA to EBUS-TBNA was 12% in mediastinal staging of lung cancer. It is clear that adding EUS-(B)-FNA following EBUS-TBNA is beneficial for lung cancer staging in some patients. More studies are needed to find indications for adding EUS-(B)-FNA to EBUS-TBNA. As well as for mediastinal staging, EUS-(B)-FNA is useful for lung cancer diagnosis and tissue acquisition when the target is accessible by EUS-(B). In general, EUS-(B) is a better tolerated procedure than EBUS-TBNA. EUS-B-FNA can be performed following bronchoscopic procedures in the same session when bronchoscopy is difficult due to dyspnea, cough, etc. EUS-FNA and EUS-B-FNA are safe procedures with low complication rates. There are still issues regarding adequate training and cost in applying EUS for lung cancer staging. More efforts are necessary to increase the availability of EUS-(B)-FNA in the staging and diagnosis of lung cancer.

Keywords: EBUS-TBNA, lung cancer, EUS-FNA

MTE 09 MANAGEMENT OF DIFFICULT SYMPTOMS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 09.01 MANAGEMENT OF DIFFICULT SYMPTOMS

R. Gralla

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Studies conducted over many years have documented the highly symptomatic nature of lung cancer. Presenting symptoms are largely due to the cancer; however, the common co-morbidities frequently seen in patients with lung cancer, complicate diagnosis, treatment, and all areas of care. Even in early stage disease, high rates of COPD and cardiovascular disease influence treatment. In advanced disease at presentation, typically over 90% of patients will have at least two major symptoms and 80% will report three or more. In addition to symptoms, side effects of treatment must be considered. Further affecting care is the fact common patient issues can be both symptoms of the lung cancer and side effects of treatment. This includes anorexia and fatigue which are reported by the majority of patients prior to treatment and are complications of radiation therapy and chemotherapy. In a recent trial, these

two symptoms were more predictive of survival than respiratory symptoms or pain. New therapeutic modalities, such as checkpoint inhibitors and TKIs have offered new opportunities and challenges. When effective, both of these modalities can positively influence patient reported outcomes (PROs) fairly rapidly and make management of symptoms easier for patients. On the other hand, they can be associated with complications that previously were uncommon such as cutaneous toxicities, diarrhea, and endocrine abnormalities. While pulmonary toxicities have long been an occasional problem with radiotherapy and some chemotherapeutic agents, this complication can be especially severe with the newer modalities. Many recent trials in advanced lung cancer have focused on combinations of systemic therapy. This includes combinations of immuno-oncology agents, or combinations of immune-oncology agents with chemotherapy. Not surprisingly, these approaches are associated with increased side effects. Careful analysis will be required to examine the true survival and quality of life benefits of such combinations when the agents are given together or sequentially. Patient reported outcomes have many roles. Following patients for benefit in quality of life and symptom control is of great value. These aspects are crucial in new agent evaluation as well, and need to be better performed in future studies. There are, however, additional roles for PROs. Several new studies indicate that aspects of PROs provide a better assessment of a patient's 'tumor burden' that is only partially estimated by performance status. Newer, simple PRO tumor burden assessments at baseline are highly predictive of survival (more so than performance status), and can indicate risk groups of patients likely to require hospitalization. Use of these PRO tumor burden assessments may allow better identification for additional health care resources for patients with the greatest needs, may guide better stratification for clinical trials, and may identify futility in treatment at an earlier point than imaging and standard assessments. Enhanced evaluation of patients' symptoms and risks, may guide in appropriate treatment selection. In turn this may allow prevention of side effects with better individualized treatment choices. Precision medicine is meant to go beyond molecular assessment or the results of laboratory analysis. Challenges include identifying tumor burden assessments that are practical for clinical use and incorporating these approaches in daily care.

Keywords: Symtoms, side effects, PROs

MTE 09 MANAGEMENT OF DIFFICULT SYMPTOMS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 09.02 SYMPTOM EXPERIENCES AND SYMPTOM CLUSTERS IN ADVANCED LUNG CANCER

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Advanced lung cancer is characterized by a number of debilitating symptoms from the disease itself and also potentially its treatment. Toxicities from systemic therapies undoubtedly contribute significantly to patient experiences. For patients with oncogene-addicted lung cancer, long-term treatment is now considered routine given the excellent outcomes with EGFR, ALK, and ROS1-directed therapies. Nevertheless, toxicities from therapies can be debilitating often requiring dose reduction. Whilst toxicities for EGFR-directed therapy are common, variation between agents used contributes to differences in tolerability and rates of grade 3-4 adverse events, ranging from 29-42%. Moreover, whilst variation in rates of serious class-specific adverse events eg diarrhoea are again observed, most data is limited to patients suitable for randomization against chemotherapy and performance status (PS) 0/1, whilst the majority of patients with lung cancer have comorbidities and poorer PS. Thus, the TIMELY trial of afatinib in EGFR mutant non-small cell lung cancer (NSCLC) patients with comorbidities that precluded use of chemotherapy identified a grade 3 or more toxicity rate of 59%, considerably more frequent than in other studies of afatinib. Moreover, the management of tyrosine kinase inhibitor (TKI)-associated toxicities has been poorly investigated with limited data suggesting that prophylaxis improves cutaneous toxicities, and that further investigating additional causes of diarrhea can be beneficial. The implementation of immune-checkpoint inhibitors into routine clinical practice has markedly changed survival for those that respond. Nevertheless, such therapies can be associated with marked toxicities, with grade 3-5 toxicities seen in around 20% of patients, and immune-related toxicities seen in 11-16%, from pooled data, with a slight excess in pneumonitic events with PD1 inhibitors. These drugs result in a different spectrum of patient symptoms reported principally from immune-related adverse events (irAEs). Nevertheless, the reporting of irAEs in the literature is generally suboptimal for onset, management, and reversibility. The recognition of irAEs is key to optimal management and maintaining quality of life, with consensus around management of irAEs with international guidelines. Such symptom experiences and their temporal change can be measured through use of health-related quality of life measures or patient-reported outcome measures (PROMs). These include the EORTC-QLQ-C30 questionnaire, dividing symptoms into 4 domains, and is supplemented by the lung cancer-specific module QLQ-LC13 evaluating 133 items. These two latter instruments are the commonest used in lung cancer populations. The FACT-L questionnaire is another popular module, specific to lung cancer by modifying the original FACT-G module. Finally, the Lung Cancer Symptom Scale (LCCS) is a highly popular brief inventory analyzing the functional and physical aspects of lung cancer symptoms on routine quality of life. The implementation of PROMs into routine clinical care has been shown to impact on improving communication, patient satisfaction, and potentially outcome. Whilst tools for evaluating PROMS are previously validated, no tool has yet been prospectively validated for immune-checkpoint inhibitor therapy, with efforts currently ongoing. Nevertheless, current trial data using established PROMs measures suggests improvements in many quality of life domains for patients receiving immune-checkpoint inhibitor therapy compared to chemotherapy.

Keywords: adverse events, quality of life

MTE 10 BRIDGING THE GAP BETWEEN GENOMICS AND CLINICS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 10.01 BRIDGING THE GAP BETWEEN GENOMICS AND CLINICS

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Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide. For many years, NSCLC has been considered an easy to treat disease, with few chemotherapeutic agents producing a limited survival improvement in unselected patients. In the last decade, identification of key genetic events driving tumor growth and metastatic spread led to postulate the concept of oncogene-addiction. According to this model, the inhibition of certain molecular drivers by targeted agents could be effective in reducing tumor burden and improving patient outcome. This is the case of Epidermal Growth Factor Receptor (*EGFR*) and its activating mutations. Strategies against *EGFR* mutant ($EGFR^{mut}$) NSCLC represent a relevant example on how genomic discoveries dramatically changed clinical practice. The most common – also named classic - *EGFR* mutations are inframe deletions in exon 19 or the Leu858Arg (L858R) point mutation in exon 21. Nine large randomized trials conducted in more than 1900 patients harboring classical *EGFR* mutations clearly demonstrated the superiority of EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib or afatinib, when compared to conventional platinum-based chemotherapy. Additional rare *EGFR* mutations, such as point mutations in exon 18, have been associated with some sensitivity to first and second generation EGFR TKIs, although their ability to predict radiological and clinical response to such drugs is less striking than that of classic *EGFR* mutations. However, despite an initial dramatic response, virtually all $EGFR^{mut+}$ NSCLC progress due to the occurrence of acquired resistance. So far, several mechanisms underlying acquired resistance to EGFR-TKIs have been elucidated and they conventionally belong to two categories. The first group of mechanisms is considered as target-dependent, because they preserve the dominance of EGFR signaling and occur preferentially through secondary mutations in the kinase domain of the receptor. The first and most well characterized is the *T790M* mutation, also called 'gatekeeper' mutation for its ability to interfere with the ligand site of EGFR TKIs. The second group includes non-target dependent mechanisms, as they determine i) activation of other oncogenes, such as *BRAF* and *PIK3CA*, ii) up-regulation of other signaling pathways, such as MET, HER2, fibroblast growth factor receptor (FGFR), and AXL and iii) histologic transformation, mainly represented by small cell transformation or epithelial to mesenchymal transition. Identification of the molecular mechanisms responsible for resistance to EGFR-TKIs is of crucial relevance in clinical practice so that new effective therapeutic strategies may be developed for our patients. As the *T790M* accounts for approximately 60% of the EGFR TKIs failures, investigations have focused on the potential efficacy of a new class of drugs that irreversibly inhibit mutant *EGFR*, in particular *T790M*, with minimal or no activity against wild-type EGFR. This new class of agents includes several new drugs, with osimertinib (Tagrisso, AZD9291) as the most promising. Osimertinib is a mutant-specific EGFR-TKI currently approved for the treatment of pretreated $EGFR^{T790M+}$ patients. In the AURA 3 trial, 419 $EGFR^{T790M+}$ patients who had disease progression after first-line EGFR-TKI therapy, were randomized to receive either osimertinib or chemotherapy. The study demonstrated that osimertinib was superior to standard chemotherapy in terms of response rate (RR, 71% versus 31%, $p<0.001$) and progression-free survival (PFS, 10.1 versus 4.4 months, $p<0.001$). Among 144 patients with metastases to the central nervous system, the median duration of progression-free survival was longer among patients receiving osimertinib than among those receiving platinum therapy plus pemetrexed (8.5 months vs. 4.2 months). The proportion of patients with adverse events of grade 3 or higher was lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%). An ongoing study evaluating osimertinib versus first-generation TKIs as first-line treatment for patients with EGFR mutation-positive NSCLC may help to define the role of the drug as front-line therapy (FLAURA trial). Unfortunately, acquired resistance to osimertinib therapy also occurs and identification of mechanisms responsible for drug failure is of clinical relevance. A report first describing the development of a resistance mutation, *C797S*, in a patient enrolled in the AURA phase I trial was submitted for publication 10 months prior to the FDA approval of osimertinib. Interestingly, preclinical models harboring an *EGFR* activating mutation alone (*exon 19* deletions or *L858R* point mutations) that develop resistance through *C797S* are still sensitive to gefitinib or afatinib. The immediate clinical consequence is that the latter EGFR-TKIs could be offered to patients developing resistance after initial therapy with osimertinib. By contrast, models harboring three *EGFR* mutations (*Del 19* or *L858R* plus *T790M* plus *C797S*) were resistant to all currently available EGFR-TKIs, with cetuximab still retaining some activity. Similarly to first or second-generation EGFR-TKIs, additional mechanisms of resistance have been described, including small-cell lung cancer transformation, activation of the *NRAS* pathway, *MET* amplification or *FGFR3* mutation. Therefore, identification of mechanisms of resistance to EGFR-TKIs is of crucial relevance for defining which agent should be used first and the best sequencing of treatment. In conclusion, discovery of *EGFR* mutations led to a dramatic change in approaching NSCLC therapy. Several additional molecular events have been more recently identified, including *ALK* or *ROS1* rearrangements, providing evidence that investigations at the genomic level are crucial in defining new and more effective strategies against cancer.

Keywords: EGFR, Osimertinib, NSCLC

MTE 10 BRIDGING THE GAP BETWEEN GENOMICS AND CLINICS (SIGN UP REQUIRED)
MONDAY, OCTOBER 16, 2017 - 07:00-08:00

MTE 10.02 BRIDGING THE GAP BETWEEN GENOMICS AND CLINICS

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Small cell lung cancer (SCLC) is a neuroendocrine subtype of lung cancer characterized by a fast growth rate, extensive dissemination, and rapid resistance to chemotherapy. Survival rates are dismal and have not significantly improved in the past few decades. Sequencing the genomes of over 100 human SCLC demonstrates universal inactivation of p53 and RB and identified inactivating recurrent mutations in NOTCH family genes (1). Accordingly, we found that activation of Notch signaling in a pre-clinical SCLC mouse model dramatically reduces the number of tumors and extends the survival of the mutant mice (1). Thus, Notch plays a key tumor suppressive role in SCLC and strategies to re-activate Notch in SCLC tumors may be beneficial to patients. We will present recent work focusing on the possible role of Notch-negative and Notch-positive cells in SCLC tumors during cancer progression and in response to chemotherapy (2). We will discuss how these results may be translatable to the clinic. At the histological level, SCLC tumor cells are often viewed as homogeneous. Our new studies and previous studies (3) identify several levels of intra-tumor heterogeneity in SCLC, which may contribute significantly to SCLC aggressive nature and resistance to therapy. 1. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature* 2015;524:47-53. 2. Lim JS, Ibaseta A, Fischer MM, et al. Intratumoural heterogeneity generated by Notch signalling promotes small-cell lung cancer. *Nature* 2017;545:360-364. 3. Calbo J, van Montfort E, Proost N, et al. A functional role for tumor cell heterogeneity in a mouse model of small cell lung cancer. *Cancer Cell* 2011;19:244-256.

Keywords: Genomics, NOTCH, SCLC

MTE 12 ONCOLOGY NURSING (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 12.01 PERIPHERAL NEUROPATHY IN LUNG CANCER PATIENTS

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Introduction Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity. Its prevalence and impact on quality-of-life (QOL) has variable documentation in the literature, due to differing assessment modalities utilized. Objectives To discuss the natural history and characteristics of chemotherapy-induced peripheral neuropathy (CIPN) in patients receiving taxane- and platinum-based chemotherapy. Methods for the study Prospective longitudinal study including patients commencing on taxane or platinum-based therapy, with assessment time-points at baseline, end of each chemotherapy cycle, and 6, 9 and 12-months. Assessments of neuropathy included: sensory assessment using 10gr monofilament and cotton wool, clinician neuropathy grading systems: WHO scale(1-item) and NCI-CTCAE(2-items), and FACT&GOG-Ntx scale. Results In total, 348 patients were recruited to undergo up to 10 assessments over 12 months from three centres in Hong Kong (n=215), Singapore (n=95) and UK (n=38). Participants received taxanes (n=157,46%), platinum (n=111,32%) or a combination of both (n=78,22%). CIPN demonstrated cumulative increase through the chemotherapy cycles and reached a peak at 6 months. Each assessment method showed different CIPN incidence The sample included 343 patients providing 2,399 observations. There was wide variation in CIPN prevalence rates (14.2-53.4%) using different assessments. Patient self-reported scales tended to double or triple the CIPN estimates compared to clinician-based or objective measures. Peak prevalence was around cycle six and the 6-month assessment (Figure 1). Prevalence was highest in taxane-based chemotherapy, followed by taxane-platinum combination. Platinum-based chemotherapy showed the lowest CIPN rate. Motor symptoms were more predominant than sensory ones. Time since chemotherapy was the only predictive factor of CIPN (ORs=9.6-66 depending on the scale used). Cumulative dose had no impact in the development of CIPN. There were relatively moderately to low correlations between the scales, suggesting validity issues. Quality of Life was significantly affected (p=0.48 to <0.001 for different domains at 6-months, 9-months,12-months assessment). Conclusions CIPN is common with taxane/platinum chemotherapy although less prevalent in this largely Asian population compared to past studies involving predominantly Caucasians. Current assessment methods are suboptimal and often limited only to sensory problems, while motor disturbances receive less attention. The variability in CIPN prevalence seen in past work may be the result of the type of assessment used. CIPN prevalence may be lower than that reported in the literature. It seems that from the moment CIPN appears it will run its course over time, irrespective of the chemotherapy cumulative dose, raising issues around the current practice of dose reduction/discontinuation. Assessment in practice needs to also consider motor neuropathic problems. Current scales may not be all appropriate to measure CIPN in a valid way, and a combination of scales is needed in practice. **Key References:** Cavaletti G., Frigeni B., Lanzani F., Mattavelli L., Susani E., Alberti P., CortinovisD., Bidoli P. (2010). Chemotherapy-Induced Peripheral Neurotoxicity assessment: A critical revision of the currently available tools. European Journal of Cancer, 46(3):479-494. Haryani H, Fetzer SJ, Wu CL, Hsu YY. Chemotherapy-Induced Peripheral Neuropathy Assessment Tools: A Systematic Review. Oncol Nurs Forum. 2017; 44(3):E111-E123. 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Keywords: assessment, peripheral neuropathy, Cancer

MTE 12 ONCOLOGY NURSING (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 12.02 ADVANCE CARE PLANNING: THE PROS AND CONS

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Patients and their family and friends consistently report that communication with health care providers has a major impact on their experience of lung cancer. In particular, being informed of treatment choices and being involved in care decisions are highly valued elements of health care by patients. Effective communication has become an increasingly important element of person centred care as treatment advances mean that patients with lung cancer are faced with more complex decisions and treatment choices. In this context, the process of advance care planning has grown in popularity as an important strategy to achieve optimal end of life care. Advance care planning is a process where a person discusses their values and healthcare preferences with their family, friends and healthcare team.[1]Advance care planning is a process that can be undertaken at any time and documented to inform health care decisions if the person can no longer communicate them. Various approaches to advance care planning have been described and a range of health care professionals can be involved in the process. Key elements of advance care planning include discussions of personal values and preferences for healthcare at end of life, establishing clear recommendation regarding future treatment, including discussions about palliative care, documenting patient values and preferences in an accessible site in the medical record, and encouraging the patient to discuss wishes with family/proxy.[2] The process also involves discussions about substitute decision makers who will act on the person's behalf should the patient not be able to do so.[1] Studies report advance care planning improves ongoing and end-of-life care and personal and family satisfaction, and that families of people who have an advance care plan have less anxiety, depression, and stress.[3] However, studies across a number of countries suggest limited uptake by community members and by health care professionals, as well as poor knowledge and skills of health team members in advance care planning.[4] This is due to a range of factors, including health care professionals' lack of confidence and skills in conducting sensitive and challenging conversations about end of life issues. Health care professionals are encouraged to have advance care planning conversations early, however there is no clear consensus about what early means in this context and how readiness for such conversations is interpreted from patient to patient. Advance care planning can also oversimplify the decision making process, as such decisions are inherently personal, will change of time, and are influenced by a range of sociocultural and health literacy factors. Negotiating the different perspectives of health professionals, family members, and patients is also very complex. In addition, legal issues give rise to confusion about the process in practice and current pressures to contain costs in health care means that some patients could feel pressured to make choices that do not reflect their true preferences. To address these concerns, advance care planning documentation is often extremely complex, creating even more barriers to the process. A further critical limitation of advance care plans is that even when they are documented, they are not accessible in practice, and where they are available, health care professionals and family members do not always follow the documented preferences. Significant advances are being made across many countries to address the limitations of advance care planning and optimise its use in practice. These advances are in areas including health care professional education and skills building, development of tools to guide practice, greater clarity about the inclusion of advance care planning in care pathways, and leveraging off developments in electronic medical records. Important work in terms of community awareness and understanding of advance care planning

is also underway. References 1. What is advance care planning? Available at www.advancecareplanning.org.au, accessed 5th July 2017 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care V.1.2016. © 2016 National Comprehensive Cancer Network, Inc. 3. Detering, KM, Hancock, AD, Reade, MC, Silvester, W, 2010, 'The impact of advance care planning on end of life care in elderly patients: randomised controlled trial', British Medical Journal, 340: c1345. doi:10.1136 4. Lovell, A, Yates, P. 2014, Advance care planning in palliative care: A systematic literature review of the contextual factors influencing its uptake 2008-2012. 28(8), 1026-35.

Keywords: advance care planning; palliative care

MTE 13 MALIGNANT PLEURAL MESOTHELIOMA: STATE OF THE ART (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 13.01 SURGERY FOR MALIGNANT PLEURAL MESOTHELIOMA

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Surgery for malignant pleural mesothelioma Surgical treatment for malignant pleural mesothelioma (MPM) has an interesting history and currently remains the foundation of the best treatment for select cases of MPM. At its outset a radical pleural pneumonectomy was fraught with very high surgical mortality which overshadowed any possible benefit. As surgical technique, anesthesia and post-operative care improved the mortality plummeted to low single digits thus allowing the benefit of surgery to emerge. Currently the median survival for patients with MPM is 21, 19, 14 and 10 months for stage I, II, III and IV disease per IASLC data (1) Certain well selected subgroups of patients treated surgically in a multimodal fashion have a median survival up to 4 years or more (2). The optimal surgical procedure and multimodal protocol is currently in flux but the principles that are important include a complete macroscopic resection either by extended pleurectomy and decortication that generally includes resection of the diaphragm and pericardium or by an extrapleural pneumonectomy that includes the entire pleural envelope, lung and en-bloc pericardium and diaphragm. A complete node dissection is vital as nodal involvement is a negative prognostic factor in most series. Reconstruction of the diaphragm and pericardium is an important feature of the operation and when done well will limit the post-operative morbidity significantly. Intra-operative adjuncts such as photodynamic therapy, heated intrapleural chemotherapy or heated povodone-iodine have been shown in select series to likely improve local control and perhaps survival. Systemic chemotherapy and radiation therapy also are important to the outcome but the exact type and sequence is controversial. (3-5). The correct surgical technique and sequence is critical to a good outcome. Similarly, choosing the best patient for surgery is complex and of vital importance. Generally patients should have reasonable cardiopulmonary reserve and limited co-morbidities. Age is not a sole determinant and probably less important than the functional status of the patient but patients over age 80 should be approached with caution. An extensive cardiopulmonary workup and staging evaluation is mandatory. Assessment of pulmonary function including split function with a quantitative ventilation and perfusion scan, cardiac reserve with an echocardiogram (look at pulmonary artery pressures) and stress test and general assessment of functional status are basic points of information that are needed to move forward with surgery. Evaluation of tumor burden with a magnetic resonance chest scan, PET scan and mediastinal node evaluation with either endobronchial ultrasound or cervical mediastinoscopy are important to avoid operating on patients with disease outside the chest or disease involving N2 nodes. Induction therapy on a protocol is reasonable particularly if patients have mediastinal nodal disease or non-epithelial histology. Also assessment of either tumor thickness or tumor volume helps prognosticate and determine likelihood of nodal involvement. Other factors such as severe pain or a high platelet count portend a poor outcome. Right sided resections particularly pneumonectomy have a higher risk and if at all possible a pleurectomy/decortication procedure is preferred . However if the lung is contracted or so involved by tumor that the only way for complete resection is to remove the lung then it should be done particularly if the functional contribution is 20% or less. A generous posterolateral thoracotomy through the bed of the resected 6th rib is carried out. The extrapleural plane is entered and fully mobilized so that it is clear the tumor is resectable. Posteriorly, the aorta and esophagus must be free, apically the tumor should come off the subclavian artery, anteriorly the tumor should be able to be freed from the pericardium. The pericardium is often resected en-bloc with the tumor. It should be opened early to be sure there is no invasion of the heart. Inferiorly the diaphragm is resected bluntly at its origin from the chest wall and care is taken to be sure the pleural recesses are respected such that all of the pleura is taken with the specimen. The peritoneum is left intact from the overlying diaphragm. Care is taken to avoid injury to the inferior vena cava near its entrance into the right atrium. At this point the pleural envelope should be opened and the lung assessed. If the tumor can be completely resected by taking the visceral pleura then this is preferred and the lung is spared. If the lung is so involved that gross tumor will be left behind if significant lung is not removed then a pneumonectomy is carried out. A full mediastinal node dissection is performed and hemostasis is obtained. If an intra-operative adjunct is to be used it is given at this point. Following that, the stump is covered with local tissue, likely a strip of pericardium and in some cases omentum. The pericardium and diaphragm are reconstructed, each with a goretex patch, which has been described in referenced publications. For the left side the operation is very similar other than the inferior vena cava is not an issue and if a pneumonectomy is required is generally well tolerated (6). Newer molecular techniques are proving very useful in aiding the surgeon in making decisions about how aggressive a strategy to use (7). References 1. Rusch VW, Chansky K, Kindler HL et al. 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Keywords: Surgery, Mesothelioma

MTE 14 IMAGING OF LUNG CANCER (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 14.01 COMPUTED TOMOGRAPHIC FEATURES OF SMALL PULMONARY NODULES: A FOLLOW-UP STUDY

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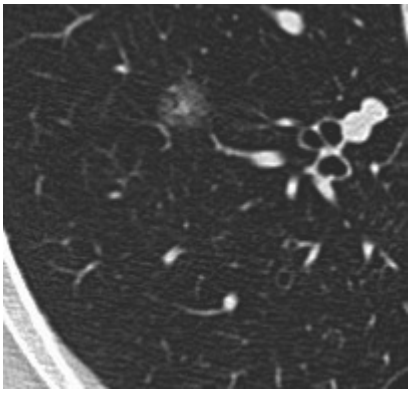
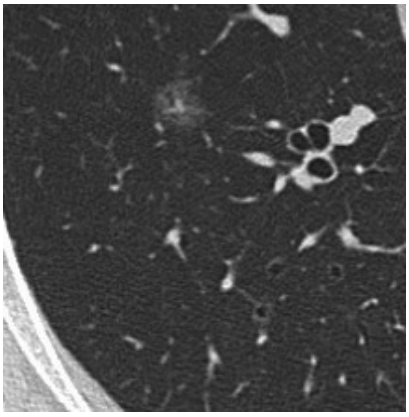
A ground-glass nodule (GGN) is a morphologic description of pulmonary nodule category on thin-section chest computed tomography (CT). Pure GGNs are defined as focal nodular areas of increased pulmonary attenuation through which pulmonary parenchymal structures, such as pulmonary vessels or bronchial structures, can be observed. Part solid nodules present with ground-glass and solid components, in which the underlying pulmonary architecture cannot be visualized, whereas solid nodules are without ground-glass components. These nodules differ in pathological condition and natural history by type, and management corresponding to these differences is required. Transient GGNs, which disappear after 3 months in repeated CT, are likely due to inflammation or infection. If many small GGNs are present, these are more likely to represent atypical adenomatous hyperplasia (AAH), and follow-up with annual CT scans is advised. The majority of persistent solitary pure GGNs are pathologically atypical adenomatous hyperplasia, adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA); these nodules do not grow, or progress very slowly. Pure GGNs less than 15 mm in diameter are followed up after 3 months, 1 year, and 2 years with CT. In the meantime, when the GGN increases in size, or if solid components appear in the nodule, a definite diagnosis is made, although such cases are extremely rare. Even when a solid component appears inside the GGN, there are options for further follow-up as long as the diameter of the solid component remains less than 5 mm. A solitary pure GGN that is unchanged for 5 years could remain unchanged even after 10 years. Of solitary pure GGNs 5 mm or less in diameter, approximately 10% will grow, with 1% developing into invasive adenocarcinomas or MIAs. Therefore, it is recommended that solitary pure GGNs smaller than 5 mm be rescanned after 3 to 5 years, in order to look for development of a solid component. In cases of part solid nodules, which present with both ground-glass and solid components, the underlying pulmonary structures cannot be observed. These nodules are more suspicious than pure ground-glass nodules and thus require more aggressive management if they persist. Persistent part solid nodules usually represent lepidic predominant adenocarcinomas or MIAs. In particular, if the margin of a part solid nodule is well-defined on thin-section CT, it is often dianogsed as lepidic predominant adenocarcinoma or MIA. Some inflammatory lesions show part solid nodules on CT; if the nodules do not disappear or decrease in size on CT after 3 months, they are highly likely to be adenocarcinomas. Usually, a lung adenocarcinoma showing part solid nodules on CT does not grow rapidly in 3 months. Therefore, a 3-month CT follow-up is effective for diagnosing a partly solid nodule (which is difficult to diagnose). Small solid nodules are most commonly observed, although few are malignant. These nodules are easily detected on CT, but it is difficult to diagnose their malignancy. Nodules over 10 mm in diameter are suspicious for malignancy, and an attempt should be made to obtain a definitive diagnosis. Solid nodules with a maximum diameter of 5 to 10 mm in smokers should be followed up until after 3 months, 6 months, 1 year, and 2 years on CT. In non-smokers, however, intervals of follow-up could be longer. Solitary nodules less than 5 mm in diameter are very rarely malignant and only require annual follow-up if patients have risk factors such as smoking. The reasons why intervals of follow-up differ between smokers and non-smokers are because smokers have a higher risk of lung cancer, and the tumor doubling time is shorter in the case of lung cancer in smokers. If the size of a nodule increases during follow-up, a definitive diagnosis is needed. If the size of a solid nodule is unchanged for 2 years, the possibility of lung cancer is extremely low, and follow-up observation may be completed; however, in smokers, emphysema is often complicated, and the diagnosis is more difficult as the shape and margin of the nodule also vary. In the case of small cell carcinoma, hilar and mediastinal lymph node metastasis may occur 3 months after nodule detection, and the early diagnosis of small cell lung cancer is extremely difficult. In the present lecture, the outcomes of follow-up of these various small pulmonary nodules will be illustrated.



CT image at detection



10 years later

Keywords: computed tomography, lung nodule, lung cancer

MTE 14 IMAGING OF LUNG CANCER (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 14.02 DIAGNOSTIC INTERVENTION FOR LUNG CANCER

D. Yankelevitz

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Diagnostic procedures for lung cancer can broadly be defined as those that lead to the initial diagnosis, evaluation of extent of disease, and obtaining tissue for further characterization of molecular and genetic properties of the cancer. In each of these areas there have been tremendous technologic advances which ultimately lead to added complexity in terms of best utilization of tissue. Tissue can be obtained by the radiologist through either the use of fine needles (either single-needle or co-axial) or through the use of cutting needles which obtain cores of tissues) and through a variety of guidance techniques including fluoroscopy, CT guidance (including CT fluoroscopy), sonography, and MR. Most commonly, now for lung procedures is CT guidance. With the increasing use of CT imaging lung nodules are detected at smaller and smaller sizes and the diagnostic approach becomes increasingly challenging. In addition, since there is better chance for cure when treatment is performed earlier the desire to obtain early diagnosis is strong. The question that arises primarily relates to what level of confidence is needed before a definitive surgical procedure is performed. Factors to be balanced are the diagnostic accuracy of competing non-invasive tests such as growth analysis or PET-CT, compared to needle biopsy. All this must also be balanced with the type of surgical procedure that is being considered and the tremendous improvements that often allow patients to be discharged within 1-2 days post surgery. Evaluating extent of disease includes biopsy of either lymph nodes or other structures such as ribs, adrenal glands, liver etc. Within the chest, evaluation of lymph nodes pre-operatively has been greatly enhanced through the use of bronchoscopy with ultrasound. However, there are many nodal stations that remain difficult to reach using this approach that can be reached with CT guided needle biopsy, including all compartments of the mediastinum and hilum. Lesions outside the lung can also be evaluated including the soft tissues and the ribs. These lesions are often detected on PET-CT and are amenable to needle biopsy. Most rib lesions can easily be accessed with simple aspiration type needles. The need for further characterization of cancers through molecular or genetic testing is rapidly gaining in importance. As new therapeutic techniques become available the need for more complete characterization of tumors becomes increasingly important. Here the question relates to how much tissue is needed to perform the desired test. This is a continuously evolving area and depends on which particular tests are being requested, availability of the institution to perform the particular test, and the potential to obtain the appropriate amount of material given the particular characteristics of the lesion. Critical to these considerations is developing a close working relationship with the pathology department so as to make sure all of these considerations are taken into account prior to performing a procedure. Collaboration with the pathology department is critical on many levels and may need to vary depending on available resources. Best would be having rapid on-site evaluation (ROSE), although this is not always possible. For each situation, a plan as to how to best maximize yield needs to be developed. In this talk, I will outline the many considerations for how best to optimize the diagnostic yield of material obtained by interventional radiologist depending on the characteristics of the lesion and present various strategies to integrate these approaches into various scenarios where tissue is required.

MTE 16 TECHNICAL ISSUES AFTER NEOADJUVANT CHEMORADIATION - SURGEON'S PERSPECTIVE (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 16.01 DIFFICULTIES OF SURGERY AFTER INDUCTION OF CHEMORADIOTHERAPY

E. Vallieres

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Difficulties of surgery after induction chemoradiotherapy (CRT) Surgery after induction therapy can 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 CRT or even induction C alone) where fibrosis of the responding lymph nodes may make the hilar vascular mobilization more difficult. 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. 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 for 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 even 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 "routine" 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 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. In a R pneumonectomy, when we have stapled the bronchial stump, 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 with the IC muscle flap. POSTOP Remember to keep the patient dry. We give amidorone prophylaxis for 72 hours after pneumonectomies' or other patients considered at elevated risk of going into atrial fibrillation post op. Beware of possible left vocal cord palsy after L pneumonectomy and 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 medialization (not negotiable)

Keywords: surgery after induction therapy

MTE 16 TECHNICAL ISSUES AFTER NEOADJUVANT CHEMORADIATION - SURGEON'S PERSPECTIVE (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 16.02 SURGERY FOR STAGE IIIA NSCLC - SURGEON'S PERSPECTIVE

G. Darling

Surgery, University of Toronto, Toronto/CA

Surgery for Stage IIIA NSCLC - Surgeon's Perspective Gail E Darling MD FRCSC, University Health Network, University of Toronto, Toronto Canada Outline Indications for operating on IIIA Choice of Induction regimen: chemotherapy vs chemoradiation Restaging the mediastinum: why or why not? how (EBUS vs med, redo med?) ,

Factors in decision making whether or not to proceed with surgery after induction Salvage resection after definitive chemoradiation Indications for Surgery for Stage IIIA NSCLC 1.T3N1M0, T4N0M0, T4N1M0: if primary is resectable with R0 resection 2.T1-3N2M0: single station microscopic N2, resectable with R0 resection, selected multistation N2 if microscopic N2 and nodal disease is resectable with R0 3.Patient is fit for planned resection Contraindications to surgery for Stage IIIA NSCLC 1. Extracapsular N2 2. Fixed bulky nodes 3. Inability to achieve an R0 resection 4. T4N2 5. Patient not fit for planned resection (right pneumonectomy required?) Choice of Induction: Chemotherapy alone vs Chemoradiation 1. Intergroup 0139 trial: concurrent cisplatin + etoposide + 45 Gy improved disease free survival over surgery alone 2. SAKK trial: RCT Chemo vs chemoRT (sequential) No difference in survival 3. Concurrent chemoRT higher rates of mediastinal downstaging compared to chemotherapy alone 4. Radiation may be undesirable if sleeve resection of bronchus or artery is planned Restaging after Induction therapy 1. CT scan: to assess response but primarily to confirm resectability and exclude progression 2. PET: to rule out progression; assess response to determine if surgery is required? 3. Mediastinum: a) restage only if surgeon will not operative if persistent N2. Intergoup 0139 trial reported best survival if mediastinum was sterilized by induction but even if persistent disease survival was better with surgery than chemoRT alone. B) Restaging: if first mediastinal staging was performed by mediastinoscopy PET is most accurate; EBUS/EUS not reliable (sampling error); redo mediastinoscopy difficult, not reliable. If first staging was performed by EBUS/EUS then mediastinoscopy is appropriate and reliable for restaging. Factors in Decision Making to Proceed with Surgery after Induction 1. Patient is fit (recovered fully from induction, good performance status) 2. Cancer has not progressed 3. Lack of radiographic response is not a contraindication to resection 4. R0 resection is possible Salvage Surgery after Definitive Chemoradiation 1. Patient is fit with good performance status 2. Primary site is only site of disease

Keywords: nonsmall lung cancer, surgery, neoadjuvant therapy

MTE 17 NEUROENDOCRINE TUMOR (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 17.01 PATHOLOGICAL FEATURES OF NEUROENDOCRINE TUMORS

Y. Ishikawa

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In the WHO 2015 classification, neuroendocrine tumors (NETs) have become one of the 4 major histological types of lung cancer. NET includes typical carcinoid (TC), atypical carcinoid (AC), small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC). In this presentation, I'll talk about problems of diagnosis of SCLC, and challenge "common knowledges" of NETs as follows: 1. SCLC is highly malignant and only very rarely the patients survive after 5 years. What are pathological characteristics of tumors with longer survival? 2. There are no subtypes of SCLC, only combined SCLC is described in the WHO 2015. Isn't subtyping of pure SCLC needed? Also, is SCLC a hilar-type cancer? 3. Diagnosis of SCLC doesn't require immunohistochemistry (IHC) although IHC is used to diagnose even adenocarcinoma and squamous cell carcinoma. Isnt' IHC useful for SCLC? 4. NET includes TC, AC, SCLC and LCNEC. Is this a spectrum of NET, showing progression of NET? In other words, does AC progress to LCNEC? 5. For adenocarcinoma diagnosis, transcription factor TTF-1 is useful even when the tumor doesn't express glandular phenotypes such as mucin and CEA. In case of NET, we usually pay attention to NE phenotypes such as synaptophysin and NCAM, not to transcription factors. Aren't transcription factors such as ASCL1 and INSM 1 useful for SCLC diagnosis? 6. Is the Kulchitsky an origin of SCLC? I'd like to answer these questions, mainly based on our own experiences.

Keywords: Pathology, subtyping, SCLC

MTE 17 NEUROENDOCRINE TUMOR (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 17.02 SURGICAL STRATEGY FOR THE TREATMENT OF NEUROENDOCRINE TUMORS

E. Ruffini[1], P.L. Filosso[2], P. Lyberis[2], A. Oliaro[2]

[1]Thoracic Surgery, University of Torino, Torino/IT, [2]Department of Thoracic Surgery, University of Torino, Torino/IT

Neuroendocrine tumors (NETs) are a distinct subgroup of neoplasms arising from the neuroendocrine cells. Due to the peculiar morphological, immunohistochemical and molecular characteristics, NETs are usually classified as a separate group of tumors among solid malignancies. Thoracic NETs include the pulmonary and the thymic NET. Pulmonary NETs (PNETs) comprise well-differentiated neuroendocrine tumors (typical carcinoid), moderately-differentiated neuroendocrine tumors (atypical carcinoid), the latter two grouped as Bronchial Carcinoids (BCs); large cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). There are also two preneoplastic conditions, the Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) and the tumorlets whose role in the neuroendocrine carcinogenesis are yet to be fully clarified. PNETs represent about 25% of all lung cancers, most of them represented by SCLC. Thymic NETs (NeuroEndocrine Thymic Tumors, NETT) are considered as a subgroup of thymic carcinoma, although in most series they are classified separately, and are further classified as well-differentiated NETT (typical carcinoid), moderately-differentiated NETT (atypical carcinoid) and poorly-differentiated NETT (Large cell and small cell neuroendocrine carcinoma). NETTs are exceedingly rare and represent about 5% of all thymic tumors. The present lecture will focus on PNETs and NETTs, with a particular insight in the surgical management of these tumors. **1, Pulmonary NETs.** The most recent TNM staging classifications of lung cancer (7th and 8th edition) suggest that PNETs should be staged similarly to Non-Small Cell Lung Cancer (NSCLC). Surgical indications largely depend on histology and stage. Bronchial carcinoids (BCs) represent about 10% of PNETs. The vast majority are typical carcinoids (TC, well-differentiated neuroendocrine tumors); they are usually located centrally in the lung parenchyma/airways (70%), and they are frequently confined to the lung without evidence of loco-regional or distant spread, which occur in about 5-10% of the cases. Atypical carcinoids (AT) share most of the characteristics of typical carcinoids, although they present a higher rate of mytoses and necrosis. They are more aggressive than TCs and they present with lymphnodal metastatic involvement in 30%-50% of the cases. LCNEC are usually diagnosed after resection, since a preoperative characterization on small biopsies is challenging. They are aggressive tumors, and more than 50% of the patients present with an advanced disease at diagnosis, for whom surgery is not indicated. As for SCLC, the vast majority of the patients present at an advanced stage, with hematogenous spread. The role of surgery in the treatment of PNETs is similar to what is currently employed for NSCLC. BCs are often amenable to surgery, due to the early stage at presentation. Anatomical resections (segmentectomy, lobectomy or more extended resections) offer the best outcome, while sublobar wedge resection should be avoided in fit patients, and should be reserved only for patients not amenable to anatomical resections. Parenchymal-sparing techniques (bronchial/vascular sleeve resection) should be employed whenever possible to avoid pneumonectomy in centrally-located tumors. Lymphadenectomy should be carried out according to the current guidelines (IASLC/ESTS), including a minimum of 6 nodes/stations of which 3 mediastinal including the subcarinal one. Endoscopic resection may have a role only in case of lobar/lung atelectasis to restore the bronchial patency before definite surgical resection Endobronchial resection is also employed with palliative intent in unresectable disease. Survival after resection of BCs is excellent, with more than 90% of the patients with typical carcinoids alive at 10 years, and 70% and 50% with atypical carcinoids alive at 5 and 10 years. The role of adjuvant therapy after complete resection of BCs is not fully determined and it is often discussed on an individual basis in a multidisciplinary tumour board setting. LCNEC are poor candidates for surgery, because of the loco-regional and distant spread at presentation. Anatomical resections, including extended resection to neighboring organs are needed in order to achieve a complete resection. Despite this, local recurrence and distant metastases are frequent after surgery. Adjuvant therapy (chemotherapy or chemoradiotherapy) is almost always needed after surgery for the disease control. SCLC has customarily been considered nonsurgical because of the high aggressiveness and the chemosensitivity of this neoplasm. However, in carefully selected patients with limited disease (T1-T2N0) surgery as part of a multidisciplinary protocol (chemoradiotherapy) may be proposed after a careful assessment of loco-regional (including mediastinal) and distant spread. **2, Thymic NETs.** Thymic NETs (NETTs) are usually aggressive thymic tumors, very often presenting atypical features (atypical carcinoid). They express somatostatin receptors which may justify the use of Octreotide scintigraphy for the diagnosis and follow-up. About 30-40% have metastases at presentation and in some cases they are associated with endocrinopaties (Cushing syndrome, MEN-1 syndrome, etc). The staging system for NETTs has traditionally been the Masaoka system. The 7th edition of the TNM of thymic tumors included also the NETTs. As for other thymic malignancies, surgery is the treatment of choice for local and loco-regional disease (Stage I/II and selected Stage III). The resectability rate for NETTs is far lower than that of thymoma, ranging between 30% and 100% in most series. Complete (R0) resection is the most important prognostic factor. Median sternotomy and open surgical approaches are the optimal accesses for NETTs. The role of minimally-invasive techniques (MIT) in the treatment of NETT is extremely limited, due to the aggressive nature of the tumor. The role of induction and adjuvant treatments (radiotherapy or chemotherapy) has not been established yet, due to the rarity of the condition. **3, The collaborative effort.** As for many rare diseases, also for NETs a collaborative, multi-Institutional, society-based effort is the single most important factor that can provide a real advancement in the research and management of this condition. The European Society of Thoracic Surgeons (ESTS) launched in 2012 a Neuroendocrine Tumors Working Group with the aim of collecting data from interested Institutions across the world. An amazing database collating more than 2100 patients has been designed which represents a tremendous opportunity for the study of these rare conditions. A number of studies have been published so far which constitute a solid backbone for the management of NETs.

Keywords: Surgery, lung, Neuroendocrine tumors

MTE 18 TREATMENT FOR SQUAMOUS CELL CARCINOMA (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 18.01 TREATMENT FOR SQUAMOUS CELL CARCINOMA

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Squamous cell lung cancers (SQCLC) account for between 15-25% of non-small cell lung cancer (NSCLC) cases. They are, biologically, quite distinct from lung adenocarcinomas, though this remains a fact that has had little positive effect to date in the management of this disease. Indeed, despite the FDA approval of a handful of new drugs for patients with SQCLCs since 2014, progress has been, for most, limited, reflecting the modest gains in survival achieved by these new agents. Navigating the

treatment landscape has been, by turns, straight-forward and frustrating. This is most evident in the first-line setting where, apart from patients whose tumors exhibit high expression of PD-L1, a variety of platinum-based chemotherapy options are available, all with more or less equivalent efficacy as shown in Table 1:

	cisplatin + gemcitabine + necitumumab(1)	cisplatin + gemcitabine(1)	carboplatin + nab-paclitaxel(2)	carboplatin + paclitaxel(2)	cisplatin + docetaxel(3)
ORR (%)	31	29	41	24	37
Median PFS (mo)	5.7	5.5	5.6	5.7	-
Median OS (mo)	11.5	9.9	10.7	9.5	11.3

Second-line therapy is dictated then largely through exclusion. Patients who received pembrolizumab as first-line treatment will cycle through platinum-based chemotherapy. Patients who received platinum-based chemotherapy will, by and large, cycle through any one of a number of FDA-approved PD-1/PD-L1 antibody therapies, all with equivalent efficacy (pembrolizumab, nivolumab, atezolizumab). Docetaxel +/- ramucirumab is thus relegated to the de facto third-line option. There are, arguably, few clinically meaningful therapeutic options beyond this; the data behind these options will be discussed in further detail. Most recently, attempts have been made to target putative oncogenic drivers in this disease, based on larger scale genomic analyses and pre-clinical experiments generated TCGA and others.(4-6) Three relatively large-frequency signaling pathways and targets have been tested in early phase trials, including *FGFR1* amplification, PI3K pathway alterations, and G1/S checkpoint aberrations both by individual groups and SWOG (LUNG-MAP, S1400). In short, there has been modest to no efficacy in targeted therapy trials to date. These studies are summarized in Table 2:

Target	Frequency	Drug	ORR
FGFR1 amplification	Up to 20%	AZD4547(7)	8%
		BGJ-398(8)	15%
		Dovitinib(9)	11.5%
PI3K pathway	Up to 50%	BKM120(10)	0%
		GDC-0032(ASCO 2017)	5%
G1/S checkpoint	Up to 50%	Abemaciclib(11)	17%

Most of these studies have lacked detailed molecular analyses of patient tumor samples, hampering our ability to determine why these targeted efforts have largely failed. One exception is the study of AZD4547 in *FGFR1* amplified SQCLCs, where correlative tests demonstrated that focal amplification of *FGFR1* in the 8p11 amplicon does not occur in the majority of cases, commensurate with relatively low mRNA and protein expression of the gene.(7) Overall, heterogeneity with regard to aberrations in overlapping signaling pathways and clonal diversity remains a concern. The rationale for and data from other studies will also be discussed, including early data from combination chemotherapy plus PD-1/L1 inhibition trials as well as potential future directions for research. References 1. Thatcher N, Hirsch F, Luft A, Szczesna A, Ciuleanu T, Szafranski W, et al. A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC). J Clin Oncol. 2014:abstr 8008. 2. Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, et al. Weekly nab-Paclitaxel in Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Final Results of a Phase III Trial. Journal of Clinical Oncology. 2012;30:2055-62. 3. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, et al. Phase III Randomized Trial of Docetaxel Plus Cisplatin Versus Vindesine Plus Cisplatin in Patients With Stage IV Non-Small-Cell Lung Cancer: The Japanese Taxotere Lung Cancer Study Group. Journal of Clinical Oncology. 2004;22:254-61. 4. TCGA Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012;489(7417):519-25. 5. Paik PK, Shen R, Won H, Rekhtman N, Wang L, Sima CS, et al. Next-Generation Sequencing of Stage IV Squamous Cell Lung Cancers Reveals an Association of PI3K Aberrations and Evidence of Clonal Heterogeneity in Patients with Brain Metastases. Cancer Discovery. 2015;5:610-21. 6. Kim Y, Hammerman PS, Kim J, Yoon J-a, Lee Y, Sun J-M, et al. Integrative and Comparative Genomic Analysis of Lung Squamous Cell Carcinomas in East Asian Patients. Journal of Clinical Oncology. 2014;32:121-8. 7. Paik PK, Shen R, Berger MF, Ferry D, Soria J-C, Mathewson A, et al. A Phase 1b Open Label Multicentre Study of AZD4547 in Patients with Advanced Squamous Cell Lung Cancers. Clinical Cancer Research. 2017. 8. Nogova L, Sequist LV, Garcia JMP, Andre F, Delord J-P, Hidalgo M, et al. Evaluation of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Kinase Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in Fibroblast Growth Factor Receptors: Results of a Global Phase I, Dose-Escalation and Dose-Expansion Study. Journal of Clinical Oncology. 2017;35:157-65. 9. Lim SH, Sun J-M, Choi Y-L, Kim HR, Ahn S-M, Lee JY, et al. Efficacy and Safety of Dovitinib in Pretreated Advanced Squamous Non-small Cell Lung Cancer with FGFR1 Amplification: A Single-arm, Phase II Study. Cancer. 2016. 10. Vansteenkiste JF, Canon J-L, De Braud F, Grossi F, De Pas T, Gray JE, et al. Safety and Efficacy of Buparlisib (BKM120) in Patients With PI3K Pathway-Activated Non-Small Cell Lung Cancer (NSCLC): Results From the Phase II BASALT-1 Study. Journal of Thoracic Oncology. 2015;Publish Ahead of Print. 11. Patnaik A, Rosen LS, Tolaney SM, Tolcher AW, Goldman JW, Gandhi L, et al. Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non–Small Cell Lung Cancer, and Other Solid Tumors. Cancer Discovery. 2016.

Keywords: squamous, FGFR1, PI3K

MTE 19 LASER THERAPY FOR EARLY STAGE AND AIRWAY OBSTRUCTION (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 19.01 LASER THERAPY FOR AIRWAY OBSTRUCTION

K. Sakata
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Malignant central airway obstruction (mCAO) occurs in patients with lung cancer and in patients with pulmonary metastases from other malignancies, including thyroid, breast, renal cell, and colon(1). It is loosely defined as obstruction of >50% of the central airways(2). Malignant CAO results in dramatic alterations to quality of life (QOL), decreased functional status, bleeding, post-obstructive pneumonia, and a poor prognosis(3, 4). The principle goal in the management of mCAO is to restore airway patency, palliate, improve QOL and symptoms, spirometric values, and survival(1, 5-7). There are 3 classifications of mCAO: endobronchial, extrinsic, or mixed. Multiple ablative bronchoscopic tools are available to relieve endobronchial or mixed obstructions(8). Ablative techniques include lasers, electrocautery, argon plasma coagulation, photodynamic therapy, microdebriders, and cryotherapy(1). Stents are primarily used to treat patients with mixed and extrinsic airway obstruction(1). Lasers have no role in the management of extrinsic airway obstruction(9). Ost and colleagues(1) showed that among 26 physicians from 15 centers, performing over 1,100 procedures, there was significant practice pattern variability. They also report that there was no single best ablative technique with regard the primary goal of improvements in dyspnea or QOL. There are no large clinical trials comparing various ablative modalities head-to-head and thus, superiority of one technique over another remains undefined(3). However, all ablative techniques can be used alone or in combination(8). In order to obtain optimal treatment outcomes, physicians should be competent and versatile in the use of multiple complementary modalities. Herein, we provide a clinical review of lasers, a technique that delivers a non-contact heat energy by light via catheter(9, 10), in the management of mCAO. The effectiveness of lasers in achieving relief of obstruction and symptomatic improvement from mCAO in very large series established credibility of this modality(11). Although outcome data is limited, laser therapy appears to be effective in providing rapid relief of endobronchial obstruction with symptomatic improvement in 70-80%(9, 12-15). One-year survival following treatment was around 30%(9). Local disease recurrence with mCAO is typical unless tumor debulking is followed by adjunctive therapies(16). Several types of lasers exist and each use different media to generate light(10). The details and specific role of each laser is beyond the scope of this discussion. Special focus has been placed on the Neodymium:Yttrium Aluminum Garnet (Nd:YAG) laser because it has become the most frequently used nonsurgical technique in the management of malignant and benign endobronchial disorders(12, 13, 17-19). One significant advantage of the Nd:YAG laser is its balanced properties in its ability to photocoagulate or vaporize tumor and cut stenotic lesions. Its ability to photocoagulate and vaporize before mechanical debulking allows for improved control of hemorrhage in the airway during bronchoscopy(9, 10). Dumon et al. and Cavaliere et al were among the first to report their experience of the Nd:YAG laser in benign and mCAO(12, 13). Cavaliere and colleagues showed an improvement in airway lumen in 92% of patients with mCAO(12). In a follow up article, the largest series to date, radiographic improvement was noted in 93% of patients with bronchogenic carcinoma, and their overall complication rate was 2.3%(20). A disadvantage of the Nd:YAG laser is the associated considerable set-up, maintenance costs, and its bulky size. The power and distance of the fiber from the lesions as well as the ration of absorption and scattering coefficients of laser determine the tissue effect(10). Lower power or the farther the distance between the laser fiber and the lesion lead to a shallow effect and cause superficial tissue coagulation. Conversely, higher power settings or a shorter distance between the laser and lesion result in deeper penetration causing tissue carbonization and vaporization(10). Safety of Nd:YAG laser in airway procedures has been well established and with appropriate precautions, the safety record of laser therapy is excellent. Protective eyewear is mandatory when the laser beam is activated(17). A "timeout" should be performed to confirm that the fraction of inspired oxygen setting is <40%, which reduces the risk of airway fire. Literature suggests that complications can be minimized if particular attention is paid to keeping the power settings to less than 40W, pulse duration of 0.5-1 second, and always having the laser beam aimed parallel to the airway(9). Complete or nearly complete mCAO without adequate visualization of distal lumen is a relative contraindication due to a possible risk of perforation(4). Significant complications develop in fewer than 5% of cases. One study showed that in 7,000 laser treatments, the reported overall complication rate was 0.99%(16). Reported complications include marked fluctuations in oxygen saturations and end-tidal CO2, massive hemorrhage, airway perforation, pneumothorax, pneumomediastinum, airway fire, gas embolism, myocardial infarction, cardiac arrest, and death. Air embolism is a result of high flow of air coolant and contact probes. It is recommended that a non-contact mode be used while keeping the coaxial coolant air flow at a minimum level(21). Continuous suction is used during the procedure to remove smoke. Continuous inspection of the airways is performed to remove any debris and to optimize ventilation. Both rigid and flexible bronchoscopes are used successfully. With flexible bronchoscope, the lesion is either photocoagulated or carbonized prior to removal, or the whole lesion is vaporized(17). Flexible bronchoscope allows easier access to areas that

may require acute angulation. Rigid bronchoscopy provides a wide operating channel allowing simultaneous use of multiple tools. Specifically, the patient can be ventilated, blood and secretions aspirated, and laser coagulation utilized. The aim is to devascularize the tumor and subsequently core out the tumor with the tip of the rigid bronchoscope(17). Additionally, mechanical sequential rigid bronchoscopic dilations can also be performed. When skilled in both techniques, the rigid technique is generally favored by many due to its multiple stated advantages(11, 13, 17, 22). However, in the absence of randomized controlled trials, expert opinion continues to guide therapeutic approaches. Most patients are managed in a multimodality fashion for the optimal outcome. Selection of a specific modality remains operator and institution specific. Irrespective of the type of ablative technique or choice of laser, the goal of treating mCAO remains the same, relieve the obstruction.

Keywords: Malignant central airway obstruction, Interventional Pulmonology, laser

MTE 19 LASER THERAPY FOR EARLY STAGE AND AIRWAY OBSTRUCTION (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 19.02 ABLATIVE THERAPY FOR EARLY STAGE LUNG CANCER

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The fact that an early cancer is early in its nature implies that a curative therapy should be offered. However, radical treatments such as surgery and radiotherapy might not be the best options for various reasons. Firstly, the amount of normal tissue that has to be removed or denaturalized can contraindicate the treatment, secondly the unresectabilitiy for some central tumors, and finally the concern that metachronous lesions can occur and might need further intervention. Thus, the use of bronchoscopic therapies in the management of lung cancer limited to the airways has brought light to the management of early lung cancer. Several techniques are available to treat endoluminal superficial lesions, including laser, electrocautery, argon-plasma coagulation, photodynamic therapy, cryotherapy and brachytherapy. The curative potential of all these therapies has been demonstrated, as all of them are able to effectively destroy the depth of an early lung central cancer, which counts no more than 5 mm of malignant tissue. The definition of early lung cancer used in the studies of bronchoscopic therapies does not exactly correspond with the actual definitions of the TNM classification and differs among authors. Nagamoto et al. observed that squamous cell carcinoma (SCC) ≤ 3 mm thick and with longitudinal extension < 20 mm was associated with no nodal involvement (1). Konaka et al. suggested that hypertrophic lesions of < 1 cm are either carcinoma in-situ (CIS) or micro-invasive tumor within the muscle layer, while nodular and polypoid lesions ≥ 1 cm are more likely invasive beyond the cartilaginous layer (2). According to these, Mathur et al. defined early stage cancer as radiographically occult SCC that is endoscopically superficial, < 2 cm in surface area with clearly visible margins and not invading beyond the bronchial cartilage (3). Later, the Japan Lung Cancer Society defined the bronchoscopic criteria of central type early stage lung cancer as that located subsegmental or more proximal, < 2 cm with bronchoscopically recognizable margin and proven SCC (4). The new 8th edition of the TNM classification incorporates new definitions in the early stages including some special situations. Superficial spreading tumors in the central airways are those confined to the tracheal or bronchial wall regardless of size and location, and are labeled T1a*ss*. Carcinoma in situ (classified as Tis) now includes both squamous cell carcinoma in situ (SCIS, or squamous dysplasia) and adenocarcinoma in situ (AIS, which is localized, ≤ 3 cm and shows pure lepidic growth, lacking stromal, vascular, alveolar space or pleural invasion). Minimally invasive adenocarcinoma is classified as T1a(mi) and corresponds to solitary adenocarcinoma ≤ 3 cm with a predominantly lepidic pattern and ≤ 0.5 cm invasion. The invasive component is defined as histologic type other than lepidic or tumor cells infiltrating myofibroblastic stroma. In our setting, it is important to remark that examination of small biopsy specimens cannot exclude or quantify invasive components for AIS and T1a(mi) respectively. Although AIS can be highly suspected from biopsies with pure lepidic pattern together with a CT correlation of the ground glass component, AIS and T1a(mi) require examination of the entire resection specimen. The accuracy of the diagnostic techniques for early lung cancer represents the first step for defining the lesions suitable for endobronchial therapy. High definition bronchoscopy, autofluorescence bronchoscopy (AFB) and narrow band imaging (NBI) have been used for defining the margins of the lesion, the latter having a higher specificity. To evaluate the shallowness of the tumor, radial endobronchial ultrasound (rEBUS) and optical coherence tomography (OCT) have been used (6). Also, the combination of AFB and OCT have shown good results for both detection and characterization of premalignant lesions of the centrals airways (7). Thin-section CT (≤ 1 mm) and PET-CT might also be useful in the evaluation of premalignant lesions (8,9). Treatment success is directly dependent on lesion accessibility and the capability to correctly delineate the margins and shallowness of the lesions (10). Once the boundaries of the lesion are defined, choosing a technique over another depends mainly on the expertise of the bronchoscopist and availability of the therapy. Bibliography: 1. Nagamoto N, Saito Y, Ohta S, et al. Relationship of lymph node metastasis to primary tumor size and microscopic appearance of roentgenographically occult lung cancer. Am J Surg Pathol. 1989;13(12):1009-13. 2. Konaka C, Hirano T, Kato H, et al. Comparison of endoscopic features of early-stage squamous cell lung cancer and histological findings. Br J Cancer. 1999;80(9):1435-9. 3. Mathur PN, Edell E, Sutedja T, et al. Treatment of early stage non-small cell lung cancer. Chest. 2003;123(1 Suppl):176S-80S. 4. The Japan Lung Cancer Society Classification of Lung Cancer Kanehara. Tokyo. 2010. 5. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors. J Thorac Oncol. 2015;10:1243-60. 6. Kurimoto N, Murayama M, Yoshioka S, et al. 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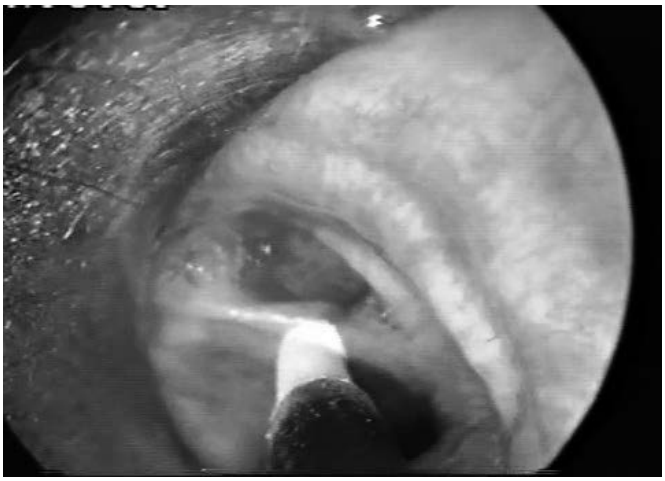

Endobronchial therapies for early lung cancer

Therapy	Principle	Depth	Main Risks	Considerations
LASER	Thermal ablation with laser light	+++ (but variable)	Airway perforation, hemorrhage, airway fire, respiratory failure.	Those of thermal therapies*
Electrocautery	Thermal ablation through electric flow current	+++ (but variable)	Airway perforation, hemorrhage, airway fire, respiratory failure.	Those of thermal therapies*. Caution with pacemakers. Cheaper than laser.
Argon Plasma Coagulation (APC)	Thermal ablation with electric current through argon gas	2-3 mm	Airway fire, respiratory failure.	Those of thermal therapies*. Caution with pacemakers.
PDT	Non-thermal ablation with light in previously photosensitized tissues	3 mm	Respiratory failure. Skin sun burn.	Produces intense photosensitivity. Delayed results and need for repeat bronchoscopy.
Cryotherapy	Thermal cellular damage though freezing and tawing	3 mm	Respiratory failure. Superficial bleeding	Delayed results.
Brachytherapy	Radiation therapy applied directly to tumor through endobronchial catheter	Variable	Ulcera, fibrosis, stenosis, haemoptysis	Accumulative radiation dose. High-complexity and need for multidisciplinary team.

Keywords: bronchoscopy, laser, early

MTE 20 LIQUID BIOPSY (SIGN UP REQUIRED)
TUESDAY, OCTOBER 17, 2017 - 07:00-08:00

MTE 20.02 RECENT ADVANCES IN LIQUID BIOPSY

G. Oxnard

Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston/MA/US

Genotyping of plasma cell-free DNA (cfDNA) is rapidly changing our management approach for genotype-defined lung cancers. Widely available assays now have the ability to noninvasively identify driver mutations in cfDNA, monitor response to therapy, and characterize emerging resistance. However, such liquid biopsies also have clear limitations – existing assays are unlikely to replace tumor biopsies completely. This presentation will discuss an optimal approach for integrating liquid biopsies into lung cancer care, while also envisioning how liquid biopsies may become a routine part of lung cancer treatment in the years ahead.

Keywords: liquid biopsy

MANAGEMENT OF ELDERLY PATIENTS WITH LUNG CANCER (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 22.01 ANY DIFFERENCES IN THE MANAGEMENT OF ELDERLY PATIENTS WITH LUNG CANCER BETWEEN EAST AND WEST?

K. Fong

Thoracic Medicine, The Prince Charles Hospital Uq Thoracic Res Centre, Brisbane/AU

Lung cancer is one of the commoner cancers in the world, accounting for 1.6 million cases annually. In many western countries, lung cancer rates have declined in contrast to the predicted increase in the incidence of lung cancer in Asia, especially among males. Many patients with lung cancer are older and this applies to all parts of the world. There are relatively few data for the older age group, since many studies have an age restriction, such that there can be uncertainty in the extrapolation of trial findings to the average older person. On the other hand it is clear that there are differences in lung cancer in the East and the West including genetic and biological differences such as smoking habits between genders, genetic aberrations such as the frequency of EGFR gene mutations, in addition to cultural and local preferences. Moreover clinical trials are often performed either in the East or the West, as are studies of lung cancer in the older population, such that extrapolation may be needed. In the work up of suspected lung cancer, the older patient may be less tolerant of diagnostic tests given the ageing process and potential concurrent co-morbid disease, especially smoking related diseases which can differ between East and West. In addition in terms of treatment apart from well-known somatic mutation differences, ethnic differences in efficacy and toxicity from therapies may differ, in addition to non-patient factors such as affordability, cultural sensitivities and preferences. Thus the challenge in interpreting and applying research and clinical trials data is includes the relative paucity of data on the older population as well as uncertainty whether the data that is available on the older population applies equally to those in the East and the West, even allowing for known biological differences. This presentation will examine knowledge gaps and differences that should be considered for the management of the older person with the lung cancer from the East and West, in the setting of cultural and genetic uniqueness.

MTE 22 MANAGEMENT OF ELDERLY PATIENTS WITH LUNG CANCER (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 22.02 TREATMENT OPTIONS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) IN THE ELDERLY: AN EVOLVING LANDSCAPE

C. Langer

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Chemotherapy Treating the elderly with advanced NSCLC remains a major challenge. ELVIS (Elderly Lung Cancer Vinorelbine Italian Study) was the first elderly-specific phase III randomized trial to be conducted in advanced NSCLC; this study demonstrated improved survival and quality of life in patients 70 years of age and older, receiving weekly vinorelbine compared to best supportive care. The most studied non platinum-based regimen has been the combination of gemcitabine plus vinorelbine, which proved active and well tolerated in several phase II trials. However, in a large phase III randomized Multicenter Italian Lung cancer in the Elderly Study (MILES), which enrolled about 700 patients, combination chemotherapy with gemcitabine and vinorelbine failed to improve outcomes (response rate, time to progression, survival or quality of life) compared to single agent chemotherapy with either vinorelbine or gemcitabine. Based on these trials, single agent chemotherapy, until relatively recently, was considered the standard of care in PS 0-2 elderly advanced NSCLC patients. However, over the past two decades, retrospective analyses of randomized phase III trials and multiple phase II studies have confirmed the activity and tolerability of cisplatin-based and carboplatin-based chemotherapy in fit elderly patients. In aggregate, these trials suggested that the elderly fared as well or nearly as well as their younger counterparts with respect to response rate and survival, albeit with more toxicity. A randomized phase III trial led by Quoix et al in advanced NSCLC patients between the ages of 70 and 90 with PS 0-2 showed superiority in all outcome parameters for carboplatin and weekly paclitaxel versus either single agent gemcitabine or vinorelbine. Response rate was nearly triple at 29% vs 11% ($p < 0.0001$) with progression-free survival of 6.1 mos vs 3.0 mos ($p < 0.0001$), median survival of 10.3 mos vs 6.2 mos ($p=0.00004$), and 1-year overall survival rate of 45% vs 26% ($p < 0.001$). Quality of life was preserved or improved with the combination regimen. Survival benefit was seen in those 80 years of age and older (n = 114; HR 0.56 [95% CI: 0.37 -0.85], $p = 0.0067$), and in individuals with PS 2 (n = 122; HR 0.65 [95% CI: 0.44 – 0.95] $p = 0.027$). More recently, in a retrospective subset analysis of elderly individuals enrolled on a phase III study of carboplatin plus either conventional solvent based (sb) paclitaxel administered every three weeks or nanoparticle, albumin-bound (nab) paclitaxel given weekly, the latter regimen resulted in a significant improvement in overall survival at 19.9 mos vs 10.4 mos ($p = 0.009$). To date, there has been no formal, prospective, phase III comparison of weekly sb- vs weekly nab- paclitaxel in combination with carboplatin in advanced NSCLC in the elderly or any other population. At ASCO 2017, ABOUND 70+ showed that therapy with carboplatin and weekly nab-paclitaxel x 3, followed by a one week break (Arm B) was well tolerated with no dilution in efficacy compared to the "uninterrupted" weekly nab-pacliaxel regimen (Arm A) used in the phase III trial: median PFS (Arms A and B) 3.9 vs 7.0 mo (HR 0.49; 95% CI, 0.30 - 0.79; $P = 0.003$), confirmed ORR 23.9% vs 40.3% ($P = 0.037$), and median OS 15.2 vs 16.2 mo (HR 0.76; 95% CI, 0.46 - 1.26; $P = 0.292$). In addition, the feasibility of cisplatin-based chemotherapy was also reported during ASCO 2017. The results from two separate phase III randomized trials (MILES 3 and 4) led by Gridelli et al comparing single agent gemcitabine to cisplatin+gemcitabine in squamous cell histology or single agent pemetrexed to cisplatin+pemetrexed in non-squamous cell NSCLC, showed a significant improvement in ORR (15.5% vs 8.5%, $p=0.02$) and PFS (4.6 mos vs 3.0 mos, $p=0.005$, HR 0.76) and suggested a non-significant trend toward improved median OS (9.6 vs 7.5 mos, $p= 0.136$, HR: 0.86) in patients receiving the platinum-based combinations. In clinical practice, non-platinum monotherapy remains the standard treatment for unfit elderly patients with advanced NSCLC, but a carboplatin-based combination is a reasonable option for those who are fit enough. Bevacizumab and targeted therapies**:** E4599 showed a survival advantage for combination bevacizumab and paclitaxel/carboplatin (PCB) vs chemotherapy alone, though a subsequent analysis of those over 70 years of age suggested that this benefit was diluted in older patients. More nuanced analyses by Wakelee and Ramalingam suggested that males of any age sustained a survival benefit, while women up to the age of 60 also realized an OS advantage. It was only in women $\geq$60 years of age where this benefit seemed to be lost, in part because the control arm performed better in this group. A more recent joint analysis pooling the data from the experimental arm of E4599 and the "control" arm of POINT BREAK, both featuring combination PCB, and comparing these data to PC alone (E4599), showed that a survival benefit was sustained up to age 75 with median survival (MS) of 13.4 vs 10.2 mos (HR, 0.78; 95% CI, 0.68–0.89). However, above the age of 75 in a limited cohort (n=157), combination PCB offered no advantage: MS of 9.6 mos vs 13.0 mos for those < 75 yo (HR, 1.05; 95% CI, 0.70–1.57). As for tyrosine kinase inhibitors (TKIs), a retrospective analysis of the elderly enrolled on BR 21, which compared erlotinib to placebo in the 2nd and 3rd line setting in

advanced NSCLC showed a consistent response (OR%), progression-free survival (PFS) and OS benefit, albeit a bit more toxicity in older subjects. More recently, in patients with actionable mutations or translocations, phase III trials have demonstrated a consistent OR% and PFS advantage for erlotinib, afatinib, and crizotinib compared to standard front-line or second line chemotherapy regardless of age. Sub-analyses using 65 to 75 as cut points consistently show similar benefits, although the individual comparisons for the elderly have been frequently underpowered to demonstrate statistical significance. In the EURTAC trial comparing erlotinib to platinum-based chemotherapy in patients with exon 19 or 21 mutations, the magnitude of PFS benefit for the TKI was very similar in those above and below 65 years of age: amongst 88 individuals > 65, the HR was 0.26 (95% CI: 0.16 – 0.51), while it was 0.49 for 85 subjects < 65 years of age (95% CI: 0.25- 0.75). In Lux Lung 3, which compared afatinib to cisplatin/pemetrexed in advanced, treatment-naïve patients with EGFR mutations, PFS favored afatinib over chemotherapy in 135 patients 65 years of age and older (HR 0.64, 95% CI: 0.39 – 1.03), not too different from the benefit seen in 211 patients under the age of 65 (HR 0.53, 95% CI 0.36- 0.79). More recently, the J-ALEX trial demonstrated a statistically significant and clinically meaningful PFS advantage for alectinib vs standard crizotinib in TKI-naïve ALK (+) NSCLC. Amongst 207 enrollees, 22 subjects were 75 years of age and older; the hazard ratio for alectinib's PFS benefit in this very small population was impressive at 0.28, but because of small numbers and an under-powered comparison, the 95% confidence intervals overlapped unity (0.06 – 1.19), and so the putative difference was not statistically significant. Immunotherapy Novel immunotherapy with check-point inhibitors nivolumab, pembrolizumab and atezolizumab have yielded an overall survival benefit compared to standard docetaxel in second-line setting of advanced NSCLC with less toxicity. As of 2017, PD1/PDL1 inhibitors have effectively replaced chemotherapy in the second line setting independent of histology. In these trials, the benefits have been confirmed consistently in subgroup analysis of the elderly, particularly in those between 65 and 75 years of age. Representation of those above 75 years of age in these studies, unfortunately, has been relatively sparse. In some series, there is no indication of increased toxicity of nivolumab in older patients. To date, there are no ongoing elderly-specific trials evaluating immunotherapy in advanced NSCLC. Summary: Elderly NSCLC patients who are fit for clinical trials do reasonably well in comparison to their younger counterparts. However, extrapolating clinical trial data to the general population, is problematic. Clearly, more evidence is required, particularly among octogenarians and patients with multiple chronic conditions. Older patients are at risk for tolerating chemotherapy poorly because of comorbidity and organ dysfunction; in this regard, modified comprehensive geriatric assessments may help facilitate appropriate treatment selection.

MTE 23 MEDIASTINAL TUMORS INCLUDING THYMIC TUMORS, LYMPHOMA, GERM CELL TUMORS: BIOPSY, DIAGNOSIS AND TREATMENT (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 23.01 THYMIC NEOPLASMS

F. Detterbeck

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Thymic malignacies are distintive by being relatively rare and by their generally more indolent behavior; nevertheless all thymomas are malignant tumors. Progress in the understanding of these tumors has been limited until recently. The advent of several regional and international collaborative groups (e.g. the Japanese Association for Research on the Thymus [JART] and the International Thymic Malignancy Interest Group [ITMIG] has provided an infrastructure to facilitate progress, and the field has advanced significantly. The level of understanding available now makes the previously common approach of empiric management of thymic malignancies inappropriate. Three major categories of thymic malnignancies with different biologic behavior are distinguished: thymoma, thymic carcinoma (TC) and Neuroendocrine tumors of the thymus (NETT, also known as thymic carcinoid). Thymomas are subdivided into 5 histotypes with slightly different clinical features, but these clinical differences are small and mixed histotypes are frequent. Through international collaboration, the first fromal stage classification system has been developed. Many patients with thymic malignancies have associated autoimmune conditions, most prominently myathenia gravis. Chest CT with intravenous contrast is the primary imaging modality for patient evaluation. A combination of patient demographics, clinical and imaging features allows a reliable clinical diagnosis of a thymic malignancy to be made in most patients; this can be supplemented with a needle biopsy if needed. However, the ability of imaging to accurately define the degree of local invasion or pleural dissemination is limited. In general, surgical exploration is warranted (in a facility prepared to handle resection of all possibly involved structures) unless imaging clearly demonstrates unresectable invasion. A complete resection of all involved structures is the cornerstone of treatment. The role of adjuvant radiotherapy after an R0 resection remains unclear, especially after resection of more invasive tumors or int he case of TC/NETT. It is easier to argue for adjuvant RT after an R1 resection or an R0 resection with close margins. Surgeons should be prepared to resect involved structures; a planned subtotal (debulking) resection is not recommended. When more invasive thymic tumors raise questions about the ability to achieve an R0 resection, preoperative chemo- or chemoradiotherapy is typically given. Recurrences are relatively low after complete resection. Longer-term (5- and 10-year) survival rates with aggressive multimodality treatment are fairly good, evin in tumors that invade major mediastinal structures or demonstrate pleural dissemination. When resection is not possible, management with palliative chemotherapy (± RT) can be useful. Several regimens have been shown to be active, and an optimal chemotherapy regimen has not been identified.

Keywords: thymic, Thymic malignancies, thymic carcinoid

MTE 23 MEDIASTINAL TUMORS INCLUDING THYMIC TUMORS, LYMPHOMA, GERM CELL TUMORS: BIOPSY, DIAGNOSIS AND TREATMENT (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 23.02 MEDIASTINAL GERM CELL TUMOR

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Extragonadal germ cell tumors (EGCTs) are among the most perplexing and embryologically intriguing entities in clinical oncology. They represent only 2-5% of adult germ cell malignancies. Their histology is identical to germ cell tumors (GCTs) derived from primary gonadal sites. However, their biology, especially primary mediastinal non-seminomatous GCT (PMNSGCT), is substantially different. PMNSGCT represents a clinically and biologically distinct subset of EGCT. It carries a poor prognosis with 40-50% overall survival after platinum-based chemotherapy and surgery (1-3). The cure rate is even worse if there is metastatic disease of the lung, liver, or supraclavicular lymph nodes with only 25% overall survival. In contrast, mediastinal seminomas have a good prognosis with 88-90% overall survival (4,5). Survival outcome for PMNSGCT is dependent on successful chemotherapy and expert thoracic surgery to remove residual disease when feasible. Patients presenting with anterior mediastinal tumor do not have a testis primary and there is no need to evaluate with testis ultrasound. The significant elevation in tumor markers including human chorionic gonadotrophin (hCG) > 1,000 U/1 and/or any elevation in alphafetoprotein (AFP) confirms the diagnosis of NSGCT and no biopsy is needed. The patient should be treated with 4 courses of platinum-based triple chemotherapy. We recommend using etoposide (VP-16), ifosfamide and cisplatin (VIP x 4) as the standard chemotherapy for PMNSGCT followed by surgical resection (2). Patients with normal tumor markers or mild elevation in hCG require a biopsy to establish the diagnosis of pure seminoma vs. NSGCT vs. other etiology such as thymic malignancy or lymphoma. Between 1980 and 2013, 221 patients with PMNSGCT who underwent postchemotherapy surgery at Indiana University were retrospectively reviewed. Our initial experience was entirely with BEP x 4. Because of our clinical observation of unacceptable pulmonary toxicity, we subsequently substituted ifosfamide for bleomycin. One hundred sixty-six patients received BEP and 55 received VIP. There were 11perioperative deaths when bleomycin was part of the preoperative chemotherapy (6.6%). By contrast, we saw no perioperative deaths on the VIP arm. Furthermore, 30 patients (18.1%) had prolonged ventilator use for greater than 48 hours. Only 2 patients (3.6%) had this complication on the VIP arm (6). A phase III intergroup study of 181 patients with poor-risk germ cell tumors, including patients with PMNSGCT, demonstrated equivalent survival in patients with VIP compared to BEP. Given the high rate of postoperative pulmonary failure and mortality after BEP, we feel these results strongly support our present policy of preferring to use VIP chemotherapy in patients with PMNSGCT before major thoracic surgical procedure. Surgical resection of residual disease after chemotherapy is an integral part of the management of patients with PMNSGCT. Surgical resection after chemotherapy serves to assess response, remove chemotherapy-resistant disease and direct additional chemotherapy. Viable teratoma or germ cell cancer is present in 30-47% of patients who undergo resection post-chemotherapy (7,8). Chest CT scan every 4 months for 2 years, then every 6 months for years 3-5 is recommended if teratoma or malignant transformation of teratoma is present in the surgical specimen. However, if there is persistent germ cell cancer in the surgical specimen, then patients should receive 2 post-operative courses of etoposide and cisplatin (EP). Surgical treatment for relapsed PMNSGCT in the presence of rising tumor markers after chemotherapy is controversial. Our preferred treatment option is surgery, if feasible, especially if carried out by experienced thoracic surgical oncologists. We recently reported our results with surgery alone in 35 patients with relapsed PMNSGCTs with rising serum AFP (32 patients) or hCG (3 patients). Seven (20%) of 35 patients remained continuously disease-free, with median followup of 64 months (range, 25-220 months) (10). If surgery is not feasible, then high dose chemotherapy in an experienced center is a reasonable approach. Mature teratoma is the most common GCT in the mediastinum. Patients present with large circumscribed anterior mediastinal mass with normal serum hCG and AFP. The treatment of mature teratoma is surgical resection and there is no role for chemotherapy unless elevated tumor markers are present. Mediastinal pure seminomas comprise 30-40% of malignant mediastinal GCT. Mediastinal seminoma carries an excellent prognosis and should be treated with good-risk chemotherapy regimen (3 cycles of bleomycin, etoposide, and platinum or 4 cycles of EP) with no surgical resection needed. 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Keywords: Mediastinal Tumor, germ cell tumor, chemotherapy

MTE 25 TOBACCO CONTROL - PRACTICAL ISSUES (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 25.01 SMOKING AFTER DIAGNOSIS OF CANCER

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Around one-third of all malignancies are attributable to tobacco smoking. Diagnosis of cancer is a turning point in life and an alarming signal, motivating for smoking cessation. This is particularly true for patients with tobacco-related malignancies, such as cancers of the lung, head and neck, esophagus, pancreas, uterine cervix, kidney, bladder or stomach. Indeed, the quit and quit attempts rates shortly after cancer diagnosis are relatively high, nevertheless a significant proportion of patients continue to smoke or relapse after initial quit attempts. In consequence up to one-third to one-half of cancer patients or cancer survivors continue to smoke, and the smoking rates in cancer survival do not significantly differ from those in the general population[1,2]. Most smoking cessation efforts have been aimed at primary prevention, whereas the importance of stopping smoking in people diagnosed with cancer have been given less attention. In consequence, the provision of tobacco cessation treatment for cancer tobacco users is still not widely available. Patients with tobacco-related cancers feel more guilt and shame resulting from previous smoking, and tend to underreport their current tobacco dependence[3-5]. Many believe that there is no point to stop smoking once being diagnosed with cancer. Additionally, some health care professionals, in fear of increasing patients' guilt and stress, do not encourage them to stop smoking. Patients who continue smoking experience several adverse effects. Apart from disease site and stage, abstinence from smoking is the strongest and independent predictor of survival in cancer patients who have ever smoked. Several studies have consistently shown that continued tobacco use compromises the effectiveness and increases the complication rates of three main cancer treatments: surgery, chemotherapy and radiotherapy[6]. In patients managed with surgery, continued cigarette smoking is associated with increasing risk of necrosis, slower wound healing, higher surgical site infection rates and prolonged hospitalization[7]. Components of tobacco smoke significantly impact clearance and delivery of many cytotoxic agents, resulting in their decreased efficacy and higher toxicity[8]. Current, compared to former smokers and patients who stopped smoking before starting treatment, have lower response rates to radiation therapy and acerbated radiation side effects, such as oral mucositis, xerostomia, weight loss and fatigue[9,10]. Smoking after a cancer diagnosis results in higher risk of developing secondary cancers, poorer general health and increased all cause mortality[11,12]. In consequence, patients who continue to smoke after cancer diagnosis almost double their risk of dying, compared to those who quit. A deleterious impact of continued smoking on survivorship is particularly high for tobacco-related cancers. Cancer survivors who continue to smoke have also poorer emotional and social functioning, vitality and quality of life[13-15]. In conclusion, quitting smoking and prevention of smoking relapse represent an important opportunity to mitigate cancer treatment complications and to improve survival, general health and quality of life. It also allows avoiding much of the excess risk of secondary cancers and other tobacco-related diseases. Enhanced focus on smoking cessation and its active promotion among cancer patients may increase their motivation to quit. All cancer patients, irrespective of treatment setting, should be screened for tobacco use and advised on benefits of tobacco cessation. Patients who continue to smoke should be offered individualized pharmacologic and behavioral therapy to assist in the quitting process. References Bellizzi KM, et al. 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Keywords: smoking cessation, cancer patients, cancer survivors

MTE 27 CT SCREENING FOR LUNG CANCER (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 27.01 WHO SHOULD BE SCREENED FOR LUNG CANCER?

J. Jett

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The National Lung Screening Trial (NLST) demonstrated that screening for lung cancer could reduce lung cancer (LC) mortality by 20%[1]. Screening with low-dose CT (LDCT) resulted in more early stage lung cancers and fewer late-stage cancers as compared to chest X-ray screening. It has been estimated that 12,000 lung cancer deaths could be averted each year if all eligible Americans were to undergo LDCT screening[2]. An Italian screening study with LDCT reported that stopping smoking reduces overall mortality by 39% compared with current smokers[3]. Tanner and associates also reported a 20% LC mortality reduction in the NLST in the chest X-ray arm (control arm) in the absence of smoking for 7 years[4]. The maximum mortality benefit was seen in the absence of smoking in combination with LDCT that resulted in a LC mortality reduction of 38% (HR=0.62). Accordingly, current-screening programs must include tobacco cessation counseling and treatment to current smokers[5].
The US Preventive Services Task Force has approved LDCT screening in high-risk individuals (asymptomatic persons aged 55 to 80 years who have a 30-pack-year or more smoking history and have quit within the past 15 years)[6]. However, from 2010-2015 less than 5% per year of those eligible are currently undergoing LDCT screening. Of the 6.8 million smokers eligible for LDCT screening, only 262,700 received it[7]. In the last two years a large number of centers have ramped up their screening programs in the US. Another issue is that of all lung cancers patients in the United States only 30-40% of these individuals were actually eligible for LDCT screening based on the NLST criteria for screening[8]. Tammemagi et al developed an LC-risk-prediction model based on the PLCO (Prostate, Lung, Colon, Ovarian) screening trial[9]. At a six-year LC risk of ≥1.5%, this risk prediction model detected 12% more LC and screened 8.8% fewer individuals than those using the NSLC screening criteria[10]. The number needed to screen to detect one LC was 255 with this model as compared with 320 in the NLST. None of the never-smokers in the PLCO trial had a risk of >1.5%. **Do not screen never-smokers!** In an effort to detect more lung cancers at an earlier stage, additional risk factors need to be included in screening programs and evaluated for their efficacy. Young and colleagues evaluated a subset of the NLST participants who had pulmonary function testing (PFT) and observed a two-fold increase in lung cancer incidence with COPD[11]. There was a linear relationship between increasing severity of airflow limitation and risk of lung cancer[12]. The heritability of lung cancer is not well explained. The OncoArray Consortium has identified 18 genetic susceptibility loci for LC across histological types[13]. Dr. Stephen Lam in Vancouver, BC is testing this 18-gene array as a risk factor in an international screening trial. The European Study of Cohorts of Air Pollution Effects (ESCAPE) identified particle matter (PM 10 and PM 2.5) as having significant association with LC risk (HR 1.22 and 1.18 respectively)[14]. The hazard ratios (HR) associated with adenocarcinoma was 1.51 and 1.55 respectively. Satellites are able to measure air pollution and have good correlation with simultaneous ground measurements (accessed 8/4/2017). There is extensive research into biomarkers for risk of lung cancer that might be of use in screening for LC or in identifying risk of malignancy in indeterminate pulmonary nodules. Sources of biomarkers to date have included breath, sputum, urine and blood. Categories of blood biomarkers have included micro-RNA, proteins, circulating tumor DNA and autoantibodies. A randomized prospective trial (RCT) in Scotland is evaluating an autoantibody panel against tumor antigens for early detection of LC[15]. The trial randomized 12,000 high-risk participants to the blood test alone or routine care (no screening). Those with a positive blood test undergo a CT chest scan. Results of this RTC should be available in late 2018. If we (IASLC) are going to decrease the mortality of lung cancer then we must promote tobacco use intervention and implement LC screening so that more LCs are detected in an early and more curable stage. The optimal paradigm for screening has yet to be developed and is likely to vary in different countries. The NLST was a starting point and reveals that is can be accomplished. Continued innovations and research are required. *References* 1) The National Lung Cancer Screening Trial Research Team. NEJM (2011); 365:395-409 2) Ma et al. Cancer (2013); 119:1381-5 3) Pastorino et al. J Thorac Oncol (2016); 11:693-699 4) Tanner et al. Amer J Resp Crit Care Med (2016); 193:534-541 5) Tammemagi et al. JNCI (2014); 106:doi.1043/jnci/dju168 6) Moyer et al. Ann Int Med (2014); 160:330-338 7) Jemal and Fedewa. JAMA Oncol, published online February 2, 2017 8) Wang et al. JAMA (2015); 313:853-855 9) Tammemagi et al. NEJM (2013); 368:728-736 10) Tammemagi et al. PLOS (2014); 11e 1001764 11) Young et al. Amer J Resp Crit Care Med (2015); 192:1060-1067 12) Hopkins et al. Annals Amer Thorac Society, published online January 11, 2017. 13) McKay et al. Nature Genetics (2017); 49:1126-1132 14) Raaschou-Nielsen et al. Lancet Oncol (2013); 14:813-822 15) Sullivan et al. BMC Cancer (2017); 17:187-196

Keywords: Screening, Risk Assessment,

MTE 27 CT SCREENING FOR LUNG CANCER (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 27.02 PULMONARY NODULE GUIDELINES: HOW DO WE DECIDE BETWEEN THE IELCAP, ACCP, NCCN, FLEISCHNER SOCIETY, BTS, AND LUNG-RADS?

J.M. Goo

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In the era of multidetector CT and lung cancer screening with low-dose CT, there are increasing number of incidentally or screen detected pulmonary nodules. Because a pulmonary nodule is an important finding of lung cancer, how to manage these nodules has become an essential issue in dealing with lung cancer, which explains why many guidelines on this topic are available. In this talk, overview of several well-established guidelines or protocols of International Early Lung Cancer Action Program (IELCAP), the American College of Chest Physicians (ACCP), National Comprehensive Cancer Network (NCCN), Fleischner Society, British Thoracic Society (BTS), and Lung CT screening Reporting and Data System (Lung-RADS) will be introduced. Nodule management protocols are different whether nodules are detected at screening programs or incidentally. Screening programs target high-risk subjects who need consistent monitoring, whereas incidentally detected lung nodules represent a different population that needs a varied clinical management. ACCP, BTS, and Fleischner Society guidelines deal with incidental nodules, while IELCAP and Lung-RADS are protocols for screening programs. NCCN guidelines state both issues with separate algorithms. Most pulmonary nodule guidelines have common components: risk factor assessment, nodule size, and nodule consistency. Baseline and annual repeat protocols are different at screening programs. Risk factors include age, smoking history, family history, previous cancer history, occupation exposure, etc. Nodules smaller than certain thresholds (NCCN, < 4 mm; ACCP and BTS, < 5 mm; Fleischner, IELCAP, and Lung-RADS, < 6 mm) do not require routine follow-up. The management for larger nodules varies with guidelines, but 8 mm and/or 15 mm are frequently recommended thresholds for more workups. Nodules can be classified into solid, part-solid, and pure ground-glass nodule according to their consistency. Because the likelihood of malignancy and growth rates are quite different depending on the nodule consistency, this classification is important in nodule management. Nodule volumetry and risk-prediction models such as the Brock University tool, currently employed in BTS guidelines, may be used more frequently in future guidelines. While the Fleischner Society, IELCAP, and Lung-RADS guidelines are relatively straightforward focused on the initial workup, ACCP, NCCN, and BTS guidelines also deal with the further workup and treatment. Some studies have shown that there is high awareness and adoption of these guidelines, but there are varying degrees of conformance with these recommendations. With the accumulation of large data, these guidelines will be more meticulous and evidence-based. Computerized tools that can assess both clinical and radiologic information will facilitate handling the issue of nodule management. References I-ELCAP protocol documents at http://www.ielcap.org/protocols Gould MK, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e93S-e120S. NCCN guidelines at https://www.nccn.org/professionals/physician_gls/f_guidelines.asp Callister ME, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax. 2015 Aug;70 Suppl 2:ii1-ii54. MacMahon H, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017 Jul;284(1):228-243. Lung-RADS at https://www.acr.org/Quality-Safety/Resources/LungRADS

Keywords: guidelines, lung cancer, lung nodule management

MTE 29 STEREOTACTIC BODY RADIATION THERAPY FOR EARLY STAGE LUNG CANCER (SIGN UP REQUIRED)
WEDNESDAY, OCTOBER 18, 2017 - 07:00-08:00

MTE 29.01 UPDATE AND OVERVIEW OF SBRT FOR EARLY STAGE LUNG CANCER

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Stereotactic body radiotherapy (SBRT) is a technique, introduced in the late 1990s. SBRT is a method of using single 10-20Gy of high dose and hypofractionated radiotherapy. Recently, many papers have been published on its clinical results, especially in early stage lung cancer. In Japan as JCOG 0403 clinical trial, between July 2004 and November 2008, 169 patients from 15 institutions were registered. 100 inoperable and 64 operable in total 164 patients were eligible. Of the inoperable 100 patients, the % 3-year OS was 59•9% (95% CI: 49•6% - 68•8%). Grade 3 and 4 toxicities were observed in 10, and 2, respectively. No grade 5 toxicity was observed. Of the 64 operable patients, the % 3-year OS was 76•5% (95% CI: 64•0% - 85•1%). Grade 3 toxicities were observed in 5. No Grades 4 and 5 toxicities were observed. SBRT for stage I NSCLC is effective with low incidences of severe toxicity. This treatment can be considered a standard treatment for inoperable stage I NSCLC. This treatment is promising as an alternative to surgery for operable stage I NSCLC. The current ongoing protocols for lung cancer as JCOG 1408 comparing two different doses,42Gy in 4 fractions and 55Gy in 4 fractions for T1N0M0 and clinically diagnosed lung cancer will be presented. In the world, RTOG 0618 showed a good result of SBRT in the treatment of patients with operable stage I/II NSCLC. RTOG 0915 showed no difference in survival between 48Gy in 4 fractions and 34Gy in a single fraction. In central hilar lung cancer patients, additional attentions are required to avoid serious complications. RTOG 0813 is a Phase I/II study for finding an optimal dose. 55Gy in 5 fractions are their recommended dose. JROSG 10-1 recommended 60Gy in 8 fractions. Optimal dose and fractions are still unknown for centrally located lung tumor. Most updated status of SBRT will also be reviewed.

Keywords: SBRT, Radiotherapy, early stage lung cancer

GR 01 WHAT TO DO AT THE TIME OF PROGRESSION ON TARGETED THERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

GR 01.03 FIRST-LINE MANAGEMENT OF EGFR MUTANT NSCLC

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Lung cancer is still the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) remains the predominant form of the disease, with majority of patients being diagnosed at advanced stages. The survival benefit offered by chemotherapy regimens has reached a therapeutic plateau. Fortunately, mutation-specific targeted therapies directed against "actionable" genetic alterations have significantly improved the prognosis of advanced NSCLC. Epidermal growth factor receptor (EGFR) mutation is the most common targetable genetic alteration in NSCLC. The prevalence of EGFR mutations range from 10% in Caucasians, to 60% in never-smoking, Asian, adenocarcinoma patients. This presentation will focus on the first-line management of EGFR mutant NSCLC. **Overview of EGFR-TKIs** Nine large randomised controlled studies have established the superiority of EGFR tyrosine kinase inhibitors (EGFR-TKIs) against chemotherapy as first-line treatment in NSCLC harboring EGFR mutations in terms of progression-free survival (PFS), objective response rate (ORR) and quality of life (QoL) (Table 1). Several studies suggest there is no significant difference in efficacy between gefitinib and erlotinib. LUX-lung 7 (afatinib) and ACHER 1050 (dacomitinib) are two randomised head-to head trials comparing second-generation EGFR-TKIs to gefitinib, respectively. Although PFS is significantly improved with second-generation TKIs, the increased rates of grade 3 or higher adverse events such as rash and diarrhea result in more dose modification with second-generation TKIs. FLAURA study, which assesses the efficacy of third-generation EGFR-TKI osimertinib versus first-generation EGFR-TKIs as first-line treatment, has been accomplished recently. This trial may establish the role of osimertinib as first-line treatment for EGFR mutant NSCLC. **Management of uncommon mutations** Exon 19 deletion and L858R mutation account for about 90% of all EGFR mutations. The remaining 10% of EGFR mutations (uncommon mutations) are a heterogeneous group of molecular alterations. Results of retrospective studies and case reports of first-generation EGFR-TKIs show inconsistent responses in this population. According to the post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6, objective responses to afatinib are observed in certain types of uncommon mutations such as G719X (77.8%), L861Q (56.3%), and S768I (100%). However, Patients with de-novo Thr790Met and exon 20 insertion mutations are insensitive to afatinib. Jonathan Riess and colleagues report that osimertinib has *in vivo* activity across multiple exon 20 insertion mutations in preclinical study. Thus osimertinib warrants further study in patients with exon 20 insertion mutations. **Combination treatment strategies** Combinations of EGFR-TKIs with chemotherapy, anti-angiogenetic therapy, and immunotherapy have been explored in clinical trials. JMIT study is a randomized phase II trial comparing addition of pemetrexed to gefitinib with gefitinib alone as first-line therapy in EGFR mutant NSCLC. PFS was significantly longer with pemetrexed+gefitinib than with gefitinib (15.8 months vs 10.9 months; hazard ratio [HR], 0.68; 95% CI, 0.48 to 0.96; P = 0.029). According to JO25567 study, combination of erlotinib with bevacizumab also significantly prolongs PFS than erlotinib. Several phase III trials evaluating combination of EGFR-TKIs with anti-angiogenetic therapy are ongoing. Attention should be paid to adverse events such as interstitial lung disease when EGFR-TKIs are used with immunotherapy. **Management of brain metastases** Brain metastases is a major challenge when managing EGFR mutant NSCLC as up to 40% of patients would develop central nervous system (CNS) metastases during the course of their disease. Novel EGFR-TKIs provide new strategies for brain metastases treatment. AZD3759 is a CNS penetrable and reversible EGFR-TKI. The phase I study (BLOOM) of AZD3759 in TKI naïve EGFR mutant NSCLC with CNS metastases is reported in 2017 ASCO annual meeting. Intracranial response is observed in 83% of patients with measurable brain metastases lesions at baseline. The extracranial anti-tumor efficacy of AZD3759 is also promising. 13 out of 18 patients with extracranial lesions have confirmed objective response. CNS response to osimertinib in patients with T790M-positive advanced NSCLC from AURA3 study is also presented in 2017 ASCO annual meeting. In 30 patients with more than one measurable CNS metastases, the intracranial response is 70%. The median CNS PFS with osimertinib is 11.7 months. Furthermore, osimertinib shows encouraging activity in patients with leptomeningeal metastases.
Table 1. First-line treatment of EGFR mutant NSCLC: EGFR-TKIs *vs.* Chemotherapy

Trial	TKI	PFS (month)			OS
		TKI	Chemo	HR (95%CI)	HR (95%CI)
IPASS	Gefitinib	9.5	6.3	0.48 (0.36-0.64)	0.78 (0.50-1.20)
First Signal	Gefitinib	8.4	6.7	0.61 (0.31-1.22)	0.82 (0.352-1.922)
NEJ002	Gefitinib	10.8	5.4	0.322 (0.236-0.438)	0.88 (0.634-1.241)
WJTOG3405	Gefitinib	9.6	6.6	0.52 (0.378-0.715)	1.185 (0.767-1.829)
OPTIMAL	Erlotinib	13.1	4.6	0.16 (0.10-0.26)	1.19 (0.83-1.71)
ENSURE	Erlotinib	11.0	5.5	0.34 (0.22-0.51)	0.91 (0.63-1.31)
EURTAC	Erlotinib	9.7	5.2	0.37 (0.25-0.54)	0.80 (0.47-1.37)
Lux-lung 3	Afatinib	11.1	6.9	0.58 (0.43-0.78)	0.88 (0.66-1.17)
Lux-lung 6	Afatinib	11.0	5.6	0.29 (0.20-0.33)	0.93 (0.72-1.22)

Keywords: uncommon EGFR mutations, first-line treatment of EGFR mutant NSCLC, combination treatment strategies of EGFR mutant NSCLC

GR 01 WHAT TO DO AT THE TIME OF PROGRESSION ON TARGETED THERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

GR 01.05 FIRST-LINE MANAGEMENT OF ALK MUTANT NSCLC

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The identification of anaplastic lymphoma kinase (ALK) gene rearrangements as an oncogenic driver in NSCLC has radically changed the treatment of a subset of patients harboring this molecular alteration. [1] ALK mutations occur in 3-7% of NSCLCs and are more frequently associated with never/light smoker, younger age and adenocarcinoma histology. Crizotinib, an oral small-molecule multitargeted ALK/c-MET /ROS1 tyrosine kinase inhibitors, was the first-in-class agent approved from FDA for advanced, ALK-rearranged NSCLC. The accelerated approval in 2011 was granted on the basis of pronounced activity observed in early phase I and II clinical studies, coupled with a favorable toxicity-profile and concurrent development of a diagnostic test for ALK rearrangement. [2] More recently, the results from a front-line phase III trial in ALK-positive NSCLC, PROFILE 1014, revealed the superiority, in terms of progression free survival (PFS) and overall response rate (ORR), of crizotinib versus standard pemetrexed-platinum chemotherapy.[3] Based on these data, crizotinib represents standard fist- line therapy in patients with advanced ALK mutant NSCLC. [4] Despite marked and durable initial responses to crizotinib, most patients develop progressive disease after a median of 11 months, with the brain as a common site of relapse. This can be explained by pharmacokinetic limitations rather than a biologic resistance. Several acquired resistance mechanisms have been characterized, including secondary mutations in the ALK kinase domain and/or ALK copy number alterations. ALK-independent resistance mechanisms can also occur through activation of alternative bypass signaling pathways, such as EGFR activation, KIT amplification, KRAS mutation and IGF-R1 activation.[5] This evidence has prompted the development of increasingly potent, selective and brain-penetrant ALK inhibitors, with differential spectrum of activity against the most common resistance mutations. [6] Several next-generation ALK inhibitors, such as ceritinib, alectinib, brigatinib have demonstrated clinical benefit in patients with crizotinib-refractory NSCLC patients also at the central nervous system (CNS) level. This observation has supported the assessment of these drugs as frontline therapy in patients crizotinb-naïve with advanced ALK+ NSCLC.[7] Soria and colleagues have published the results of the ASCEND-4 trial, randomizing ALK+ treatment naïve patients to ceritinib or chemotherapy. Ceritinib treatment significantly has improved median PFS compared to chemotherapy (16.6 vs 8.1 months; hazard ratio [HR] 0.55,P<0.00001). This molecule was also associated with a better control of the disease in the brain (PFS 10.7 vs 6.7 months, HR 0.70, 95% CI: 0.44–1.12). Dose-limiting gastrointestinal adverse events were common with ceritinib at the starting dose of 750 mg daily and 80% of cases required dose reduction or interruption. Although ceritinib has not been compared head-to-head with crizotinib, data confirm ALK inhibitor superior efficacy compared to standard chemotherapy in the ALK-rearranged NSCLC and suggest ceritinib as another option for the front line management. [8] First Line Head to Head trials are ongoing or recently completed. Findings from J-ALEX trial, involving untreated Japanese patients with ALK-rearranged advanced NSCLC, have shown that alectinib induces longer durations of response compared to crizotinib. Median PFS exceeded 2 years in the alectinib group, compared with just over 10 months in the crizotinib group. [9] Recently, Peters et al. have presented the results of global ALEX study. Data are consistent with previous Japanese analysis: PFS was significantly improved with alectinib as compared to crizotinib (25,7 5% vs 10,4%, HR 0.5, p<0.0001). In addition, 12% of patients in alectinib arm vs 45% in crizotinib

arm has experienced brain progression (cause specific HR 0.16; 95% CI, 0.10 to 0.28; P<0.001). Alectinib appeared to be better tolerated than crizotinib with grade 3 to 5 adverse events occurring in 41% vs 50% of patients, respectively.[10] Other studies with next-generation ALK inhibitors versus crizotinib—such as lorlatinib, brigatinib, are ongoing and they will help define optimal sequencing therapy for patients with ALK-rearranged NSCLC. To improve outcomes in this patient population, some studies are also currently investigating several combination strategies, including immunotherapy, anti-angiogenetic agents or radiotherapy approach in association with ALK inhibitors as shown in Table 1. Table 1

DRUGS (dose)	Clinical trial (phase)	Patient Number	Comparator	ORR (%)	PFS (mo)
Crizotinib (250 mg twice/day)	PROFILE 1014 (III)	343	Pemetrexed +platinum	74 vs 45	10.9 vs 7.0
Ceritinib (750 mg/ die)	ASCEND 4 (III)	376	Pemetrexed +platinum pemetrexed ±maintenance	72.7 vs 27.3	16.6 vs 8.1*
Alectinib (300 mg twice/day)	J-ALEX (III)	207	crizotinib (250 mg twice/day)	85 vs 70	NE vs 10.2
Alectinib (600 mg twice/day)	ALEX (III)	303	crizotinib (250 mg twice/day)	82.9 vs 75.5	25.7 vs 10.4*
Brigatinib (90 mg/ die for 7 days, 180 mg/die)	ALTA 1L (III)	ongoing	Crizotinib (250 mg twice/day)	-	
Lorlatinib (150 mg/ die)	NCT03052608 (III)	ongoing	Crizotinib (250 mg twice/day)	-	
Crizotinib +Bevacizumab (250 mg twice/day; 7.5 mg/kg every 3 wks)	CAMAR01 (II)	ongoing	_	_	_
Crizotinib +Pembrolizumab	NCT02511184 (I)	ongoing	_	_	_
ORR: overall response Rate, PFS Progression free survival, NE not evaluable, *independent review committee					

Treatment paradigms continue to evolve for patients with advanced ALK-positive NSCLC subsequently to rapid development of ALK inhibitors history. It is expected that one of the next generation of ALK inhibitors will be used as first-line. In this landscape it is necessary to define the impact of first-line choice on patterns of progression and mechanisms of resistance. [11] It is uncertain if a specific sequence of therapeutic agents influences the biology of the cancer and therefore the clinical course of the patient. The spectrum of ALK resistance mutations varies according to ALK inhibitor and it is unclear if the mechanisms of resistance to these agents as the first ALK inhibitor will be similar to the mechanisms of resistance identified when they are used after crizotinib. Future efforts should be focused on determining the best treatment sequence to maximize clinical outcomes. Key factors to guide the selection of therapies could be include: molecular characteristics of the patient's tumor, different toxicity profile of different ALK inhibitors, availability of combinations/ multimodal therapy. **References** 1. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Soda M et al. Nature 2007; 448:561–567 2. The continuum of care for ALK-positive NSCLC: from diagnosis to new treatment options-an overview Solomon & Soria, Ann Oncol Vol 27 Supp 3 2016 3. First-line crizotinib versus chemotherapy in ALK-positive lung cancer Solomon et al N Engl J Med 2014 Dec 4;371(23):2167-77 4. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Novello S et al. Annals of Oncology 27 (Supplement 5): v1–v27, 2016 5. Crizotinib resistance: implications for therapeutic strategies. Dagogo-Jack & Shaw Ann Oncol Supp 3 2016 6. Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged LungCancer. Gainor et al Cancer Discov2016Oct;6(10): 1118-1133. 7. Ascending role of next-generation ALK inhibitors. Costa. Lancet Oncol.2017 Jul; 18(7):837-839. 8. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomized, open-label, phase 3 study. Soria et al Lancet 2017; 389: 917–29 9. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomized phase 3 trial Hida et al. Lancet 2017; 390: 29–39 10. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer Peters et al for for the ALEX Trial Investigators NEJM N Engl J Med. 2017 Jun 6. 11. First-line treatment options for ALK-rearranged lung cancer. Solomon. Lancet Oncology 2017 Mar 4; 389(10072): 884-886

Keywords: NSCLC, Alk, First line

GR 02 MANAGEMENT OF IMMUNOTHERAPY-RELATED ADVERSE EVENTS
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

GR 02.03 PATHOPHYSIOLOGY OF IMMUNOTHERAPY-RELATED TOXICITY

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Clinical development and approval of immune-checkpoint inhibitors have transformed the treatment of many types of tumors. In recent years, three anti-PD-1 or –PD-L1 antibodies have been approved for advanced NSCLC, including nivolumab, pembrolizumab, and atezolizumab. These antibodies have entered into the routine practice of treatment for patients with advanced NSCLC. In addition, all clinical trials, which compared the efficacy of anti-PD-1 or PD-L1 antibodies with chemotherapy, demonstrated that these antibodies are less toxic than chemotherapy (1-4). However, these immunomodulatory antibodies have led to the emergence of unusual autoimmune toxicities, also called immune-related adverse events (IrAEs). IrAEs management is challenging because they may concern many organ systems, including the skin, hepatic, gastrointestinal, endocrine, and pulmonary systems. Furthermore, given the recent success of immunotherapy, the incidence of immunotoxicity will likely continue to rise as these therapies become more widely used not only in advanced diseases but also in early stage diseases (5). Treatment-related toxicities have correlated with better response in some cases, and it is probable that serious adverse events from immune-mediated reaction will increase as immunotherapeutic approaches become more effective (6). Adding more complexity, the natural history of certain irAEs is unpredictable. The onset of clinical disease manifestation can vary from weeks to decades after the appearance of autoantibodies (7). Thus understanding irAEs is critical for early detection and appropriate management of patients. We will discuss the mechanisms that might be related with the induction of anutoimmunity from immunotherapy. References: Lancet. 2016; 387(10027):1540-50. N Engl J Med. 2015;373(2):123-35. N Engl J Med. 2015; 373(17):1627-39. Lancet. 2016;387(10030):1837-46. Eur J Cancer. 2016 ;54:139-48. Blood. 2011;118(3):499-509. Nat Med. 2017 ;23(5):540-547.

Keywords: immunotherapy, autoimmunity, lung cancer

GR 02 MANAGEMENT OF IMMUNOTHERAPY-RELATED ADVERSE EVENTS
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

GR 02.04 CURRENT STANDARD IN MONITORING OF IMMUNOTHERAPY-RELATED TOXICITY

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Checkpoint protein inhibition is associated with on- and off-target, cell and metabolic toxic effects that need to be carefully monitored and managed during and after treatment[1]. Despite important clinical benefits, immunotherapy is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. IrAEs include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events. Most irAEs remain mild in intensity but approximately 10% of patients treated with immune checkpoint blockade agents will develop severe, sometimes life-threatening, grade 3–4 dysimmune toxicities. Before prescribing immune checkpoint blockade agents to patients, oncologists need to be aware of the toxicity spectrum and must identify potential risk factors that could favor the emergence of irAEs[2]. Patients should be informed that most of these irAEs are mild and reversible if detected early and specifically addressed. Therefore, patients should be educated about signs of organ inflammation that would require prompt referral such as diarrhea, blood or mucus in the stool, severe abdominal pain, fatigue, weight loss, nausea, vomiting, thirst or appetite increase, polyuria, extensive rash, severe pruritus, shortness of breath, coughing, headache, confusion, muscle weakness, numb-ness, arthralgia or swelling joints, myalgia, unexplained fever, hemorrhagic syndrome and severe loss of vision in one or both eyes. Any new symptom or deterioration of pre-existing symptoms must at least be monitored attentively and if necessary be explored to determine its etiology and rule out any dysimmune cause that could be worsened by immunotherapy continuation. Although early recognition and treatment improves symptoms and severity, a broad differential diagnosis should be entertained. It is recommended that all patients receiving these agents routinely have thyroid function studies, complete blood counts, and liver function and metabolic panels at each treatment and at intervals of 6 to 12 weeks for the first 6 months after finishing treatment. Adrenocorticotropic hormone, cortisol, and in men, testosterone should also be checked in patients who develop fatigue and nonspecific symptoms. Follow-up testing may need to increase in frequency based on individual response and adverse events that occur[3]. It is challenging to differentiate between infection, early pulmonary edema, alveolar hemorrhage, immune-mediated pneumonitis, immune-related tumor inflammation, and tumor progression (figure 1). Infections, thromboembolism, congestive heart failure, and COPD are among the many diagnoses to consider before committing patients to a long course of steroid therapy with additional consideration of prophylaxis for opportunistic (i.e., pneumocystis with or without fungal) infections. Pulmonary specialty consultation and consideration of bronchoscopic evaluation with lavage to assess for infections alongside biopsies of lung tissue can help narrow the diagnosis. IrAEs can develop at any time: at the beginning, under treatment and after immunotherapy termination. As shown with nivolumab, the majority of irAEs occur within the first 4 months[4]. On the basis of this median time to onset, irAEs could be classified as early (median time to onset <2 months) and late toxicities (median time

to onset >2 months). Early toxicities include skin (5 weeks), gastrointestinal (7.3 weeks) and hepatic (7.7 weeks), whereas late toxicities include pulmonary (8.9 weeks), endocrine (10.4 weeks) and renal (15.1 weeks). However, clinicians should keep in mind that all toxicities can develop at any time since confidence interval may vary widely among organs: 0.1–57 weeks for skin; 0.1–37.6 weeks for gastrointestinal. Rarely, other irAEs may occur after week 24 with any checkpoint-blocking antibodies. In trials including maintenance ipilimumab, colitis has been seen 47 months from initiation of treatment[5]. Patients with prior autoimmune diseases or a history of viral hepatitis have been excluded from receiving ipilimumab on trials, but recent data suggest that the drug can be given safely to those patients. Nonetheless, extreme caution should be taken in treating patients with recent or ongoing autoimmune conditions, particularly any type of inflammatory bowel disease[6]. Management algorithms have been established for patients treated with immunotherapy, which may be useful in helping to manage irAEs but they are based upon clinical experience, since no prospective trials have been conducted to guide the treatment of irAEs. Resolution of irAEs usually follows a temporal pattern: 2 weeks for gastrointestinal, 4 weeks for hepatic, 6 weeks for skin, and 20 weeks for endocrine irAEs[7]. The key to successful management of checkpoint protein antibody toxicities is early diagnosis, high suspicion, excellent patient-provider communication, and rapid and aggressive use of corticosteroids and other immune suppressants for irAEs. Effective biomarkers to predict toxicity could be valuable in the development of these agents.

FIGURE 1: CT scan of a patient with non-small cell lung cancer presenting with cough, dyspnea, and hypoxia on an immunotherapy drug. References: Fecher LA, et al: Ipilimumab and its toxicities: A multidisciplinary approach. Oncologist 18:733-743, 2013 Champiat S. et al., Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper Annals of Oncology Volume 27, No. 4, 559-74, 2016 Weber JS et. al. Toxicities of Immunotherapy for the Practitioner, J of Clin Oncol., volume 33, No 18, 2092-2099, 2015 Weber JS et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): a pooled analysis. J Clin Oncol 2015; 33 (suppl): abstr 9018 Sarnaik AA et al: Extended dose ipilimumab with a peptide vaccine: Immune corre- lates associated with clinical benefit in patients with resected high-risk stage IIIc/IV melanoma. Clin Cancer Res 17:896-906, 2011 Hodi FS, et al: Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: A randomized clinical trial. JAMA 312:1744-1753, 2014 Weber JS, et al. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30:2691-2697

GR 02 MANAGEMENT OF IMMUNOTHERAPY-RELATED ADVERSE EVENTS
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

GR 02.07 TOXICITY OF INDUCTION IMMUNOTHERAPY FOLLOWED BY RADIOTHERAPY: HOW TO MINIMIZE IT?

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Checkpoint inhibitors have changed the outcome of patients with metastatic non-small cell lung cancer (NSCLC). 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. At the time of writing, the most compelling data in human studies come from Shaverdian et al. (Lancet Oncol 2017). In 97 patients with advanced NSCLC treated on the phase 1 KEYNOTE-001 trial it was shown that patients having received prior radiotherapy, the six-month PFS rate was 54.3% vs. 21.4% among never irradiated patients. The median OS was 11.6 months and the six-month OS estimate was 75.3% among patients who previously received extra-cranial radiation therapy vs. a median OS of 5.3 months and a six-month OS estimate of 45.3% among patients who did not receive extra-cranial radiation therapy. Patients with prior thoracic radiotherapy had more overall pulmonary toxicity compared to never irradiated patients: 12.5% vs. 1.4%. Unfortunately, no dose-volume parameters such as the mean lung dose are available of these patients. The biggest concern of combining radiotherapy and immune treatment is indeed a higher incidence of pneumonitis. Many studies are investigating the combination of radiotherapy, chemotherapy and immune therapy in lung cancer, including the PACIFIC, the STIMULI and the NICOLAS studies. The results of these studies have not been reported at the time of writing, but none of the trials have been closed prematurely. Moreover, as radiotherapy is used to stimulate the immune system, classical concept in dose and volume will have to be investigated again. Less dose in a few fractions may suffice, and margins may be reduced, which in turn will lead to less side effects. When studied meticulously, radiotherapy and immune therapy may well turn out to be efficacious and with few side effects and additional costs.

Keywords: Immune therapy, Radiotherapy, side effects

GR 03 TREATMENT OPTIONS FOR EARLY STAGE LUNG CANCER PATIENTS WITH LIMITED PULMONARY RESERVE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

GR 03.03 THORACOSCOPIC SEGMENTECTOMY FOR EARLY-STAGE LUNG CANCER

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Lobectomy with mediastinal lymph node dissection has been established as the most effective therapy for patients with resectable non-small cell lung cancer (NSCLC). Over the past 20 years, it has also been demonstrated that thoracoscopic (VATS) approaches are associated with better outcomes than open approaches. With the adoption of lung cancer screening protocols, more patients with early stage lung cancers (<2 cm) are going to be candidates for surgical resection, and some of these patients may benefit from anatomic sublobar resection (segmentectomy). The VATS approach to segmentectomy for stage I NSCLC has been shown to be feasible and safe and has found to be associated with decreased perioperative mortality and equivalent or improved overall survival when compared to segmentectomy via thoracotomy [1]. In addition, thoracoscopic segmentectomy may be particularly advantageous in patients with poor pulmonary function, with advantages in overall complication rates and other outcomes compared to open approaches. [2-6] Sublobar resection, as opposed to lobectomy, is appropriate for some patients with lung cancer: patients with ground glass opacities which are found to be adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA). In addition, sublobar resection is considered an acceptable compromise procedure for patient with tumors less than 2 cm in diameter and co-morbidities that preclude lobectomy, although lobectomy is associated with superior outcomes in most patients [7-8]. Specific indications to consider anatomic sublobar resection in patients with tumors <2cm include: age >80, compromised pulmonary function (FEV1 or DLCO <30% predicted), and favorable tumor location. [1, 2, 5, 7, 8] While it is feasible to achieve sublobar resection of any of the 10 segments, some of the segments are more technically challenging to remove. The typical (commonly performed) sublobar resections include superior segmentectomy (S6), lingulectomy (L S4+5), lingula-sparing left upper trisegmentectomy (L S1-3), posterior segmentectomy of the right upper lobe (R S2), and basilar segmentectomy (S 7-10). [9]. **Outcomes** Much of the data comparing outcomes of segmentectomy to lobectomy has come from patients with GGOs. When comparing patients with solid nodules <2cm, lobectomy is associated with better outcomes in several studies. In one study of 39,403 patients from the National Cancer Database (NCDB), 29,736 (74%) underwent lobectomy. [7] Of the 26% sublobar resections, 85% were wedge resections. In addition, lymph node evaluation not performed in 29%. Sublobar resection associated with smaller T and low-volume institutions. 5-year survival for lobectomy was superior to sublobar resection: 66% vs. 51% (P < 0.001). Another study analyzed the outcomes of patients with stage I lung cancer over 80 years of age, also from the NCDB. [8] In this study, sublobar resection was associated with significant reductions in survival, even among patients with T1a tumors and patients >85 years. Sublobar resection was inferior in all patients except those >85 years of age and Charlson/Deyo comorbidity index >2. It has been demonstrated that superior oncologic outcomes are associated with lobectomy; however, anatomic sublobar resection or non-anatomic (wedge) resection may be appropriate in selected patients. One study of the Society of Thoracic Surgeons database compared the morbidity and mortality of wedge resections (n=3733) with that of anatomic lung resections (lobectomy and segmentectomy) (n=3733) for stage I and stage II NSCLC using propensity-matched analysis. [10] The operative mortality rate was 1.2% for wedge resections versus 1.9% for anatomic resection (p=0.01) while major morbidity occurred in 4.5% for wedge resections and 9.0% for anatomic resection (p<0.01). The authors noted the mortality bene t was most apparent in patients with FEV1 less than 80% predicted although the morbidity benefit was observed regardless of age, lung function or type of incision. [10] Another study from the NCDB reported by Rosen and colleagues found a higher perioperative mortality rate of 4.2% for wedge resections for NSCLC. [11] In comparison, the segmentectomy and lobectomy groups had a perioperative mortality rate of 3.6% and 2.6%, respectively. The difference in perioperative rates may be explained by a difference in baseline comorbidities between the groups; the wedge resection group

was sicker than the other two groups. **Summary** Thoracoscopic segmentectomy is a sound option for lung-sparing, anatomic pulmonary resection in selected patients for experienced thoracoscopic surgeons and can be safely applied to the treatment of a variety of pulmonary disorders, including small primary lung cancers, metastatic pulmonary disease, and benign disorders. The minimally invasive approach appears to have distinct advantages compared with thoracotomy, including reduced hospital length of stay, less postoperative pain, and fewer overall complications. The decision to perform sublobar anatomic resection for NSCLC may be complex, and the best candidates appear to be those with clinical stage I disease and tumors <2cm in diameter and other significant co-morbidities precluding lobectomy, or in patients with AAH, AIS, or MIA. **References**

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GR 03 TREATMENT OPTIONS FOR EARLY STAGE LUNG CANCER PATIENTS WITH LIMITED PULMONARY RESERVE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

GR 03.05 ANY ROLES OF SYSTEMIC THERAPY (CHEMOTHERAPY, TARGETED THERAPY, IMMUNOTHERAPY) FOR EARLY STAGE NSCLC WITH LIMITED PULMONARY RESERVE?

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The standard treatment of early stage non-small cell lung cancer (NSCLC) is lobectomy with systematic mediastinal lymph node evaluation. Unfortunately, up to 25% of patients with stage I NSCLC are not lobectomy candidates because of severe medical comorbidity including limited pulmonary reserve. During the past decade, stereotactic ablative radiotherapy (SABR) has resulted in local control in excess of 90% of tumours with medically inoperable and operable clinical stage I NSCLC. The local treatment including surgery and SABR is the stand of care for these patients . No definite evidence-based medicine data about the systemic therapy had been reported in this subgroup patients. A systemic therapy approach to the treatment of patients with medically inoperable, early stage NSCLC is not warranted. The management suggestions were unanimously agreed upon based on available literature. Systemic Therapy combined with local treatment could be a good option for these patients. 1. Chemotherapy+ local treatment: It seems that it is not recommended to add chemotherapy to local treatment for those medically inoperable, early stage NSCLC. It is reported that no evidence of an improvement in event-free survival was seen with the addition of weekly gemcitabine at this dose for patients with early stage NSCLC unfit for surgery, although the power of the study was low. 2. Targeted Therapy+ local treatment: No clear data about the targeted therapy for those medically inoperable, early stage NSCLC patients. For those driven gene positive patients, targeted therapy combined with local treatment seems to be a good choice. Some people worried about the combined therapy may increase the potential for pulmonary toxicity in patients with baseline pulmonary dysfunction, however, there is no cases of interstitial lung disease in early stage NSCLC as adjuvant therapy in 2017 ASCO (CTONG 1104). Further studies should be developed for these patients. 3. Immunotherapy + local treatment: The integration of radiation with immunotherapy is a conceptually promising strategy, as radiation has potent immune-modulatory effects and may contribute not only to local control but also augment systemic antitumor immune response. The advent of novel immunotherapy agents affords patients and clinicians therapeutic modalities to improve patient longevity and avenues to study innovative combinations of therapies. Preclinical data and case reports suggest the potential for robust clinical responses in metastatic NSCLC patients using this strategy, but prospective clinical trials evaluating the integration of radiation and immunotherapy are limited. The use of immunotherapy in non-metastatic settings is also intriguing but understudied. Summary: The assessment of treatment options for limited pulmonary reserve patients that requires uniform reporting of comorbidities and outcomes in clinical studies, which often is lacking. Systemic Therapy combined with local treatment could be a good option for these patients. Trials involving systemic therapy for patients with medically inoperable NSCLC should be developed.

PC 01 1-1. SURGERY VS NON-SURGICAL LOCAL TREATMENT FOR SMALL-SIZED NSCLC
MONDAY, OCTOBER 16, 2017 - 15:45-16:40

PC 01.01 SABR AS FIRST LINE TREATMENT OPTION

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SBRT for small-sized non-small cell lung cancer: Surgery has historically been the primary treatment option for patients with Stage I non–small-cell lung cancer (NSCLC). Although Stage I NSCLC is technically curable, the presence of significant co morbidity increases the risk of postoperative complications and reduces the potential role of surgery even early stage NSCLC. Because nonsurgical treatment options such as conventional radiotherapy have historically achieved suboptimal outcomes, some have argued that the risks associated with surgery in patients with severe COPD were justified. The reason for poor tumor control with conventional radiation therapy has been shown to be due to insufficient total radiation doses which is usually 60 Gy or lower. Dose escalation with CRT have shown that a total dose of just above 80 Gy seems to be tolerable while doses exceeding 90 Gy, necessary for optimal tumor control, were associated with high risk of unacceptable lung toxicity. Since the 2000s, stereotactic body radiation therapy has rapidly spread as medical physics improved. Stereotactic body radiation therapy has been revealed to be equivalent to surgery in tumor ablation. With stereotactic body radiotherapy (SBRT) the radiation dose to normal tissue is minimized and the dose per fraction can be increased resulting in biologic doses up to twice as high as in CRT. This has resulted in improvement of local tumor control rates up to 88% to 100%, comparable to the rates after surgery. SBRT is a safe and effective treatment option for these patients, with outcomes that do not appear to be inferior to surgery. SBRT is not associated with the considerable initial risks of operative mortality and prolonged hospitalization. Patients who do undergo surgery may benefit from avoiding open lobectomy, instead using less invasive approaches such as video-assisted thoracoscopic surgery or open segmentectomy. All patients with Stage I NSCLC and severe COPD should be evaluated in a multidisciplinary setting and afforded an informed decision of the risks and benefits of both surgery and SBRT. In role of SBRT can also be extended even in patients with oligometastases and oligo-recurrence, the oligometastases and oligo-recurrence who sometimes cured with only local therapy. Radiotherapy (RT) can cause immunogenic tumor cell death resulting in cross-priming of tumor-specific T-cells, acting as an in situ tumor vaccine; however, SBRT alone has limit in inducing effective anti-tumor immunity resulting in systemic tumor rejection. Immunotherapy can complement SBRT to help overcome tumor-induced immune suppression, as demonstrated in many pre-clinical tumor models. There are many trials underway for combinations of different immunotherapies and SBRT.

Keywords: SBRT. early stage NSCLC, inoperable

PC 01 1-1. SURGERY VS NON-SURGICAL LOCAL TREATMENT FOR SMALL-SIZED NSCLC
MONDAY, OCTOBER 16, 2017 - 15:45-16:40

PC 01.02 SURGERY AS FIRST LINE TREATMENT OPTION

R. Downey
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Surgery as First Line Treatment Option for Small-Sized NSCLC Surgical resection has been the preferred standard of care for patients with well established expectations for survival after resection. A standard of care for patients who are deemed medically inoperable is definitive radiation therapy. Because of the proven effectiveness of radiation therapy in treating the medically inoperable patient with lung cancer, consideration is being given to treating medically operable lung cancer patients with definitive radiation therapy instead of surgery. However, recent clinical guidelines issued by ASTRO (Videtic et al) based on a review of the published data include among other recommendations, that 'For stage I NSCLC patients with anticipated risk of operative mortality of <1.5%, SBRT is not recommended as an alternative to surgery outside of clinical trial settings. The recommended treatment for these patients remains lobectomy with systematic mediastinal lymph node evaluation'. The problem with such recommendations is as follows. The operative morbidity and mortality following pulmonary resection for the overall population of patients undergoing surgery have also been established. The morbidity and mortality in the overall population of patients following definitive radiation therapy is also well documented. What is not available is reliable data on the treatment-related risks faced by subgroups of patients treated with surgery or with definitive chemotherapy who differ in terms of competing risk factor for death, including age (Eguchi et al.) or their overall functional status ((or what is becoming known as the 'fitness' or conversely, the 'frailty' of a patient) Korc et al)). Emerging data shows that the frailty of a patient affects the likelihood of survival after surgery of diverse types and for diverse diseases. We have found that frail patients undergoing diverse surgeries for diverse malignancies require ICU admission after a given grade of complication at rates far above those required for fit patients (after Grade I complication 0% vs 20%, after Grade 2 complication 6% vs. 17%, and after Grade 3 complication 5% vs. 35% for fit vs. frail respectively) After ICU admission, frail patients remain at a persistent increased risk of death lasting at least to 600 days when compared to fit patients (50% survival vs. 90% survival for frail patients vs. fit patients after ICU care at 600 days) (unpublished data courtesy of Armin Sharokhni, MD). Similar data is not available for patients with NSCLC treated with definitive radiation therapy. Because of this lack of information, objective comparisons of the feasibility and effectiveness of surgical resection with definitive radiation therapy are likely prone to error due to selection biases.A plausible hypothesis is that the population of patients referred for definitive radiation therapy for NSCLC are frailer, and the decreased long-term survival after radiation therapy is due to frailty rather than cancer-related. In this talk, we will review the data available on: 1. Current perioperative morbidity and mortality following lung resections including MIS and sub-lobar procedures 2. Current likelihood of long-term survival following curative lung cancer surgery 3. The competing risks for short- and long-term survival after surgery including age and frailty 4. The methods of risk stratification, including frailty, for a patient being considered for lung cancer surgery 5. The methods of risk stratification that have been used in retrospective and prospective comparisons of surgery and definitive radiation therapy Based on this review, proposals for prospective trials comparing SBRT and surgery for objectively defined medically operable early stage NSCLC will be made. References: Eguchi et al. Impact of Increasing Age on Cause-Specific Mortality and Morbidity in Patients With Stage I Non-Small-Cell Lung Cancer: A Competing Risks Analysis. J Clin Oncol. 2017;35:281-290 Korc-Grodzicki et al. Surgical considerations in older adults with cancer. J Clin Oncol 2014;32:2647-53. Videtic et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Practical Radiation Oncology (in press)

Keywords: lung resection, radiation, frailty

PC 01 1-1. SURGERY VS NON-SURGICAL LOCAL TREATMENT FOR SMALL-SIZED NSCLC
MONDAY, OCTOBER 16, 2017 - 15:45-16:40

PC 01.03 OTHER FIRST LINE TREATMENT OPTIONS

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The approach that has most commonly been reported as an alternative to surgery or SBRT for non-small lung cancer (NSCLC) is thermal ablation. There are also different ablative modalities, of which radiofrequency ablation (RFA) has been the most widely reported. RFA was reported for human lung tumors in 2000[1]. RFA has been shown to be feasible and safe in several studies[2,3]. However, many studies have involved heterogeneous patient populations that included patients with metastatic tumors and NSCLC. Additionally, in those series focusing on NSCLC, patients with different stages. Have been included. Another consideration is that in several centers, these procedures have been performed by interventional radiologists, who are not traditionally part of the multidisciplinary oncology team, and rarely have follow-up clinics, so accurate reporting of recurrence and survival rates has not been optimal. Lastly, other modalities such as microwave or cryoablation, are gaining in popularity[4,5] Despite some perceived improvements in technology, there is no clinical data that supports one ablative modality over another with respect to cancer outcomes[6]. Currently thermal ablation is reserved for medically inoperable patients with NSCLC. In those series that have reported outcomes specifically for stage I NSCLC outcomes have been good, and comparable with studies of SBRT, when looking at survival rates. One study included 56 patients with stage I NSCLC[7]. Median survival was 29 months. A prospective multi-center phase II trial involving 54 patients was recently reported[8]. Overall survival was 87.3% at 1-year, and 69.8% at two-years. Two-year survival was superior in patients with tumors <2cm (83%). There were only two grade 4, and one grade 5 event within 90 days (not attributable to the RFA). Our group has also treated 21 patients with stage Ia NSCLC (submitted for publication). Three-year survival in our series was 52%. One issue when comparing results of trials using different modalities is how comparable are patient groups. The medically inoperable group in this prospective phase II trial were compared to a medically group in an RTOG phase II trial of SBRT[9]. Although both groups were labelled medically inoperable, lung function was significantly better in patients treated with SBRT. This argues for the need for prospective studies comparing these modalities for medically inoperable patients. The main issue with thermal ablation has been higher rates of local recurrence in most studies. Tumor size is important, and results are better for tumors <2cm[7,8]. This certainly would be an argument for SBRT over RFA. However how recurrence is measured and defined may impact on reporting of local control, and there are differences in how these have been identified in different studies. In the absence of a prospective trial using similar end-point recording, overall survival is the cleanest endpoint with which to make comparisons. In summary, thermal ablation remains a viable option for small stage I NSCLC patients who are deemed medically inoperable. Future innovations include developments in energy source and, also in bronchoscopic delivery to peripheral tumors[10]. References 1. Dupuy DE, Zagoria RJ, Akerley W, et al: Percutaneous radiofrequency ablation of malignancies in the lung. AJR Am J Roentgenol 174:57-9, 2000 2. Ambrogi MC, Fanucchi O, Cioni R, et al: Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. J Thorac Oncol 6:2044-51, 2011 3. Lencioni R, Crocetti L, Cioni R, et al: Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol 9:621-8, 2008 4. Zhong L, Sun S, Shi J, et al: Clinical analysis on 113 patients with lung cancer treated by percutaneous CT-guided microwave ablation. J Thorac Dis 9:590-597, 2017 5. Ahrar K, Littrup PJ: Is cryotherapy the optimal technology for ablation of lung tumors? J Vasc Interv Radiol 23:303-5, 2012 6. Vogl TJ, Nour-Eldin NA, Albrecht M, et al: Thermal Ablation of Lung Tumors: Focus on Microwave Ablation. Rofo, 2017 7. Simon CJ, Dupuy DE, DiPetrillo TA, et al: Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. Radiology 243:268-75, 2007 8. Dupuy DE, Fernando HC, Hillman S, et al: Radiofrequency ablation of stage IA non-small cell lung cancer in medically inoperable patients: Results from the American College of Surgeons Oncology Group Z4033

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Keywords: Stage 1, thermal ablation, medically inoperable

PC 01 1-2. WHAT IS THE ROLE OF LOCAL THERAPY IN NON-CNS OLIGOMETASTATIC NSCLC?
MONDAY, OCTOBER 16, 2017 - 16:45-17:30

PC 01.04 THERE IS A ROLE OF SURGERY IN NON-CNS OLIGOMETASTATIC DISEASE

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For certain extra-pulmonary malignancies, such as colorectal cancer or sarcomas, the existence of curable oligometastatic disease state has been well established. Oligometastasis is a state of stage IV disease associated with limited spread of disease at the time of diagnosis. This condition may reflect a more indolent phenotype than that associated with more widespread disease at presentation. Recently, it becomes more clear that the patients with Stage IV NSCLC are heterogenous and hence, some patients have high disease burden whereas others have isolated metastatic lesions. In the 8th TNM staging system, M-stage was reclassified into M1a, M1b, M1c, and the patients with M1b may represents the oligometastatic status of NSCLC. It has been demonstrated that the predominant pattern of failure in patients with oligometastasis treated with the first-line systemic chemotherapy was mainly a local failure, the fact which leads an idea that the local treatment may improve cure rates in such patients.

The incidence of oligometastasis in NSCLC has been reported 7-26% of NSCLC [1, 2], with the major sites of metastases being bone, brain, adrenal glands and liver. In general, the successful treatment of patients with oligometastasis requires the ability to eradicate the primary site, the ability to image all sites of metastatic disease, the ability to ablate all metastatic sites, and having effective systemic therapy to eradicate undetected micrometastatic disease. Recently, routine use of improved diagnostic imaging tools such as PET-CT or Brain MRI, can better detect latent metastases in patients who would otherwise have been thought to have a localized disease, and hence, the diagnosis of "true" oligometastatic disease may be increasing [3]. Development of local treatment modalities such as minimally invasive surgery (MIS) or stereotactic radiotherapy (SABR) enabled effective local abrasion of the metastatic sites without major morbidities. Above all, rapid development of effective molecular target agents and immune check point agents in the treatment of NSCLC are encouraging to reconsider surgery for the treatment of oligometastatic NSCLC patients. Most evidence of treatment effect of local treatment for oligometastasis derives from the survival data from retrospective patients groups. For brain metastases, 5-year survival rates have been reported 6.6-35% and adrenal gland metastases showed similar results (5-year survival rates 12-40%). In a well-designed propensity score matching study suggested an improvement in survival favoring local abrasive therapy, but definite conclusions on the efficacy of local therapy for the treatment of extra-cranial oligometastatic NSCLC could not be reached [4]. A meta-analysis which included 49 studies, suggested overall median overall survival of 19 months after local ablative treatment (5.9-52 months)[5]. Most recent study by Gomez and colleagues demonstrated a progression free survival benefit favoring local consolidative therapy [6]. Hopefully, ongoing prospective trials may provide more strong evidence of the effect of local ablative therapy for oligometastasis in near future. Despite many reports that support local treatment for oligometastasis, the lack of control data in almost all reports is a problematic issue. Since local treatment for the oligometastasis is only performed in selected patients with relatively indolent disease, there is often no actual denominator for the entire group of patients who developed metastasis [7]. Thus, determining the survival advantage of ablative local treatment of oligometastasis compared to palliative systemic therapy is difficult because the majority of existing data are with a substantial degree of selection bias. In the other aspect, however, we have learned that the patient selection is critical for the application of local treatment on the oligometastasis. In general, local treatment is indicated in metastatic NSCLC patients with favorable prognostic factors including absence of mediastinal lymph node metastasis, small number of metastases, complete control of primary lesion, meta-chronous metastasis, and good performance status of the patients. Although there are relatively large numbers of papers on the brain or adrenal metastases, the reports of extra-cranial or extra-adrenal metastases are rare. In a meta-analysis, the 5 year overall survival rates of extra-cranial / extra-adrenal metastasis was 50% and the prognosis was mainly influenced by lymph node metastasis status [8]. First used in the literature in 2012 [9], the concept of oligoprogressive disease has been rapidly adopted. It can be best described in patients with tumors harboring actionable mutations who are treated with molecular targeted therapies. Initially, the response rate is great but the duration of response is relatively short, with resistance to therapy generally emerging within a year of start of treatment as a result of various genetic mechanisms. Not uncommonly, disease progression during molecular targeted therapy occurs at a limited number of anatomic sites. Recently, several studies reported improved progression free survival and overall survival in either intra-cranial or extra-cranial oligopregressive diseases by applying local abrasive therapy on those acquired resistant oligoprogressive diseases and by resuming target agents [10]. Furthermore, the combination of immune check point agents and SABR on primary tumor and/or metastatic sites may be promising for treating oligometastatic NSCLC, due to a possible abscopal effect. In conclusion, although current evidence of local treatment of oligometastases is limited in NSCLC, with aid of recent diagnostic tools by which more stringent patient selection is possible, local ablative treatment of metastatic lesions can lead improved survival of patients with oligometastasis in conjunction with molecular target agents or immune check point agents.

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Keywords: Oligometastasis, local therapy, Oligopregression

PC 02 IS RADIOTHERAPY NECESSARY FOR EXTENSIVE SCLC? (THORACIC RADIATION/PCI)
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

PC 02.01 THORACIC RADIATION - YES

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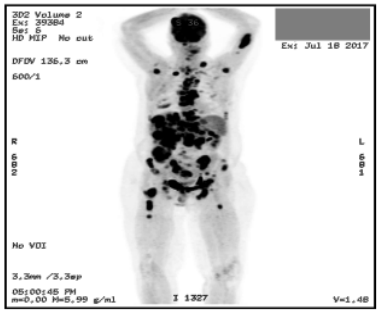
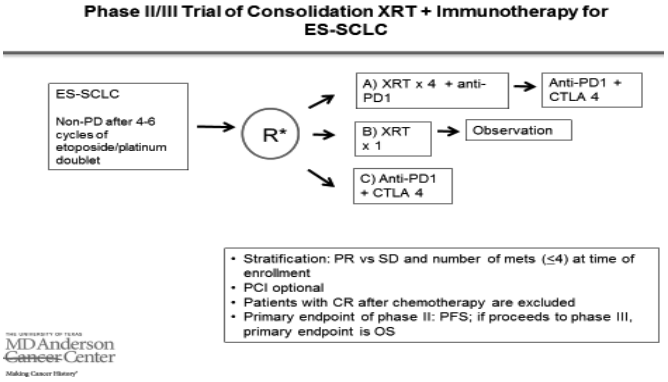
Small cell lung cancer (SCLC) accounts for 15%–20% of all lung cancers, and the overwhelming majority (>95%) are associated with tobacco exposure. The incidence of all types of lung cancer, including SCLC, has been declining in the United States with the onset of tobacco smoking cessation programs, although this trend took nearly 20 years to become evident among men. Overall survival (OS) rates for patients with lung cancer have also increased by about 5% since the advent of low-dose spiral computed tomography (CT) scanning to detect early lung cancer. The prognosis for patients with SCLC continues to be poor but has improved with the advent of smoking cessation campaigns, more effective chemotherapy agents and radiation planning and delivery techniques, and the use of prophylactic cranial irradiation (PCI) for those who experience a complete response to therapy. Consolidation with chest radiotherapy has improved OS among patients with extensive-stage SCLC who achieved a complete response to chemotherapy. SCLC often presents as bulky symptomatic masses, and mediastinal involvement is common with or without pleural effusion and extrathoracic disease. Extrathoracic spread (i.e., extensive-stage disease) is also quite common, being present in 80%-85% of cases at diagnosis. Brain metastases are present in approximately 20% of patients at diagnosis; roughly half of these metastases are symptomatic and the other half are detected by imaging. Predictors of poor prognosis include poor performance status, older age, and being male. The pathologic subtypes of the disease (small cell carcinoma and combined small cell carcinoma) all carry a similarly poor prognosis. Current guidelines of the U.S. National Comprehensive Cancer Network recommend the use of positron emission tomography (PET), CT scanning, or fused PET/CT scanning of the chest, liver, adrenals, bone, and other areas of concern in the diagnosis and staging of SCLC (NCCN guideline-SCLC 2017) . Thoracic radiotherapy has also become important for improving OS among patients with SCLC who achieved a complete response to chemotherapy. In one prospectively randomized study of 498 patients with extensive-stage SCLC (WHO performance

status score 0-2) who achieved complete response to chemotherapy, patients who received consolidation thoracic radiotherapy (30 Gy in 10 fractions) had significantly better 2-year OS rates than did those who did not receive thoracic radiotherapy (13% vs. 3%, *P*=0.004). Thoracic radiotherapy further improved thoracic-only failure rates (19.8% vs. 46% without, *P*=0.001) (Slotman B et al, Lancet Oncol 2015;385:36-42). However, many patients with extensive-stage SCLC do not respond to the standard etoposide/cisplatin chemotherapy (Figure 1). Those patients may need to receive molecular-targeted therapies or immunotherapy with the consolidating thoracic radiotherapy. Several histologic and immunohistochemical markers have been evaluated for diagnosing or monitoring treatment response in SCLC, including transcription thyroid factor-1 (positive in >85% of SCLC cases); cytokeratin 7; deletions in chromosome 3; Leu-7; chromogranin A; synaptophysin; *myc* amplification; and *p53* mutations (present in ~75% of cases). Deletions in tumor-suppressor genes are also relatively common and include fragile histidine triad (*FHIT*) (80%); RAS effector homologue (*RASSF1*) (>90%); *TP53* (>75%); retinoblastoma-1 (*RB1*) (>90%); and retinoic acid receptor-beta (72%). However, to date no biomarkers have been validated for use in diagnosing SCLC. Moreover, mutations that are often present in non-small cell lung cancer (such as epidermal growth factor receptor [EGFR] mutations and anaplastic lymphoma kinase [ALK]) are rare in SCLC. Several clinicopathologic features have been linked with worse prognosis, including poor performance status, significant weight loss, high lactate dehydrogenase levels, large numbers of metastatic sites, and the presence of paraneoplastic syndromes. Because SCLC has the among the highest rates of somatic driver mutations, and because more than 95% of patients with SCLC are former or current smokers, immunotherapy seems a reasonable approach, as high mutation burdens correlate with good response to chemoradiotherapy and sensitivity to immunomodulators (Peifer M et al., Nat Genet 2012;44(10):1104-10). At MD Anderson Cancer Center, an ongoing phase I/II study of patients with extensive-stage SCLC has been proposed to the NRG as a prospective randomized study (PI J Welsh) (Figure 2). Use of thoracic radiotherapy to consolidate a site at which SCLC is quite likely to recur is reasonable, given that recurrence considerably reduces quality of their life as well as OS. In summary, in most cases SCLC presents as extensive-stage disease, for which outcomes are very poor. Consolidation with thoracic radiotherapy for patients who achieve a complete response to chemotherapy can improve 2-year OS rates. However, less toxic and more effective systemic treatment is also required to derive the greatest benefit from consolidation thoracic radiotherapy.

Keywords: thoracic radiotherapy extensive small-cell lung cancer, immunotherapy



(Figure1)



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PC 02 IS RADIOTHERAPY NECESSARY FOR EXTENSIVE SCLC? (THORACIC RADIATION/PCI)
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PC 02.03 PCI---YES

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Radiation therapy (RT) has an important role in both limited stage and extensive stage (M1) small cell lung cancer (SCLC), although more recent randomized trial results have led to increasing discussion and opposing views regarding the indications and type and degree of benefit conferred. This is one such debate, in which I am arguing in favour of recommending Prophylactic Cranial Irradiation (PCI) in extensive stage (ES) SCLC. There is no disagreement about the prevalence of brain metastases (BM) in SCLC. There is strong randomized trial evidence that delivery of modest doses of RT, such as 25 Gy in 10 fractions (fr) over 2 weeks, can reduce the incidence of BM. The simplistic explanation is that RT reduces the tumor cell burden and affects the ability of cancer cells to multiply, thus delaying or preventing the progression of microscopic intracranial metastases, and reducing the likelihood, that patient will develop symptomatic metastases – thus the term "prophylactic" brain RT. A meta-analysis[1] of previously conducted randomized clinical trials (RCTs) in patients with limited stage (LS) or ES SCLC with response to chemotherapy demonstrated not only a reduction in symptomatic BM (from 58% to 33% at 3 yrs) but also a survival benefit (15.3% to 20.7%). A large RCT[2] in LS SCLC confirmed that 25Gy/10 fr is the optimal dose fractionation, and described the potential negative neurocognitive and quality of life (QOL) impact of PCI[3]. Other studies[4] provided further data to inform patients regarding the potential risks and benefits of PCI. The EORTC group conducted a RCT in ES SCLC[5], randomizing 286 patients who had a response to 4-6 cycles of chemotherapy and had no clinical evidence of BM (but who did not have brain imaging to confirm absence of radiological metastases) to PCI vs observation. Their primary endpoint was time to symptomatic BM. A range of fractionation schedules was allowed; 62% of pts were treated with 20 Gy/5fr, 22% with 30 Gy/10-12 fr and only 4% with 25Gy/10 fr. There was a large reduction in symptomatic BM, 16.8% in the PCI group vs 41.3% in the control group (p < 0.001, hazard ratio (HR) 0.27 (95% confidence intervals (CI) 0.16-0.44). Disease-free survival (DFS) was significantly longer in the PCI group (median 14.7 weeks, vs 12 weeks, p = 0.02, HR 0.76 (95% CI 0.59-0.96), as was the overall survival (OS) (median 6.7 mo vs 5.4 mo, p = 0.003). This study let to the more widespread recommendation of PCI to patients with ES SCLC who have responded to chemotherapy. Practice guidelines on management of ES SCLC include PCI in their recommendations. A more recent Japanese RCT[6] randomized patients with ES SCLC who had a response to chemotherapy and no BM on MRI, to PCI (25 Gy/10 fr) vs observation. Follow up MRIs were mandated every 3 mo initially, then q6 mo. If patients were discovered to have radiological brain progression, whole brain RT was utilized regardless of whether they were symptomatic or not. Primary endpoint was OS. The study was closed after interim analysis, as the PCI group was not going to have a superior OS; 224 patients were enrolled in all. There was a reduction in BM in the PCI group, with the cumulative incidence at 6 mo15% vs 46% in the observation arm; at 12 months there was also a difference (33% and 59% respectively). PFS was identical, and there was no significant difference in OS (11.5 mo median OS in the PCI group vs 13.7, p = 0.094, HR 1.27 (95% CI 0.96-1.68)). The study concluded that PCI doesn't result in longer OS and is thus "not essential for patients with ES SCLC (.) and a confirmed absence of BM, if patients will be followed by periodic MRIs". Those are indeed very fair conclusions of their data, although it is interesting that some, perhaps many, especially in the medical oncology community, after hearing the presentation at ASCO 2015, seem to have concluded that PCI may be detrimental to survival (given the small and statistically non-significantly longer survival in the observation group). Comments have been made that in the era of staging/ restaging MRIs, there may be no benefit to PCI in ES SCLC, and that perhaps the EORTC study showed improved survival because patients may have had clinically undetected gross metastatic disease (ie not just microscopic disease). That is clearly an incorrect interpretation of the Japanese data, and an assumption that has no proof in terms of the EORTC study. Every study that looked at local control ie ability of PCI to eradicate metastatic disease showed a benefit to RT, whether assessed radiologically or clinically. The incidence of BM in the control arms of the EORTC and Japanese trials was similar, suggesting that patients staged with MRIs did not have a different risk of brain disease than patients staged clinically. Even if restaging MRIs are routinely available in many parts of the world, close surveillance with regular MRIs is not routinely done for ES SCLC; it should be noted that Japan has the highest ratio of MRI to population. A very large proportion of patients in the observation arm of the Japanese study (83%) had whole brain RT for BM – no wonder there was no survival difference as it was really a comparison of early vs late RT. Finally, the risk of systemic disease in ES SCLC is high, so that a treatment that clearly has an impact in reducing brain relapse would be expected to have a relatively small OS benefit. Thus, Japanese study provides valuable data that continue to support the role of PCI in ES SCLC, and emphasize the need for a more realistic and holistic view of the expected role and benefit of RT – ie reducing BM, prolonging survival in some, and aiming to provide good neurological functioning and QOL. Rather than trying to argue against PCI as a strategy, we should continue with attempts to reduce its toxicity, such as through hippocampal sparing techniques[7] and to identify groups of patients who are more or less likely to benefit in terms of survival[8, 9]. **References:** Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med. 341(7):476-84, 1999. Le Péchoux C, Dunant A, Senan S, et al. 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Keywords: small cell lung cancer, radiation therapy

PC 02 IS RADIOTHERAPY NECESSARY FOR EXTENSIVE SCLC? (THORACIC RADIATION/PCI)
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PC 02.04 PCI---NO

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What does prophylactic cranial irradiation (PCI) prevent in ED-SCLC? - Why isn't the presence of brain metastasis evaluated before performing PCI? **Background:** In a European trial, prophylactic cranial irradiation (PCI) was performed on patients with extensive-disease small cell lung cancer (ED- SCLC). As a result, PCI was reported to reduce the incidence of symptomatic brain metastasis and to prolong patient survival. However, their treatments were completely different from our routine medical care. For example, they did not perform tests to examine whether there was a metastatic brain tumor before assignment to the PCI group or observation group and, after assignment, symptoms alone were observed and no imaging test was performed. For this reason, in Japan, we corrected this inconsistency of protocol and repeated the trial to determine whether PCI contributes to prolonged survival. **Participants and method:** Included in the current trial were patients who underwent two or more cycles of platinum-based combination chemotherapy, had achieved at least stable disease (SD), and had no metastatic brain tumor on their MRI. They were randomly assigned to either the PCI group or observation group. Follow-up with brain, chest and abdominal diagnostic imaging tests was performed every three months in both groups. **Results:** In the first pre-specified interim analysis, it was found that there was no possibility of improving patient prognosis using PCI even if the trial were continued. An independent data monitoring committee therefore terminated the trial. At that time, 224 cases had already been enrolled, with 113 cases assigned to the PCI group and 111 cases to the observation group. Median survival period in the final analysis was 11.6 months for the PCI group and 13.7 months for the observation group (hazard ratio, 1.27; 95% CI, 0.96 to 1.68). There was no statistically significant difference between the groups, but PCI actually tended to make the prognosis somewhat worse or, at least, did not improve prognosis in patients with ED-SCLC. **Discussion:** The biggest difference between the two trials was whether follow-up assessments were conducted using symptoms or brain MRI. In the current trial, it is impossible to estimate the proportion of asymptomatic brain metastasis cases; however, in the European trial, asymptomatic brain metastasis cases were also included, which means that there were in fact two different subgroups in the PCI group: a subgroup of patients with asymptomatic brain metastasis undergoing therapeutic cranial irradiation and a subgroup of patients without brain metastasis undergoing true PCI. It seems that the survival difference between patients with asymptomatic brain metastasis in the PCI group and in the observation group caused the apparent improvement of survival period. On the other hand, it is conjectured that PCI generated a lot of toxic effects in the patients without brain metastasis and that their survival curve tended to be inferior. PCI is a treatment to prevent new brain metastasis. One year of PCI reduces the incidence of new brain metastasis in no more than 30% of cases. For patients with MRI showing no metastatic brain tumor, needless PCI can be avoided by performing regular brain imaging tests, without impairing survival.

Keywords: ED-SCLC PCI OS

PC 03 3-1 WHAT IS THE OPTIMAL SEQUENCE OF ALK-TKI FOR ALK-POSITIVE LUNG CANCER? (ALECTINIB FIRST OR CRIZOTINIB FIRST)
WEDNESDAY, OCTOBER 18, 2017 - 11:00-11:40

PC 03.01 CRIZOTINIB FIRST

S. Ou

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Crizotinib is the first ALK TKI that has demonstrated statistically superior progression-free survival over standard of platinum-based chemotherapy in treatment-naïve ALK+ NSCLC patients (PROFILE1014, PROFILE 1029). Since then next generation ALK TKI such as ceritinib (ASCEND-4) has also demonstrated statistically improved PFS over platinum-base chemotherapy (ASCEND-4) and alectinib has demonstrated statistically improved PFS over crizotinib (J-ALEX, ALEX). In ALEX, a global randomized phase 3 study comparing alectinib to crizotnib demonstrated that alectinib achieved an median PFS of 25.7 months compared to median PFS of 10.4 months for crizotinib. Additionally, the cumulative incidence of CNS metastasis was significantly lower over for patients treated with alectinib than patients treated with crizotinib the duration of study period. Crizotinib did achieve higher than expected confirmed overall response rate in patients with CNS metastasis in the ALEX trial than has previously published. In fact the median PFS achieved by patients without CNS metastasis at study enrollment and treated by crizotinib was 14.8 months. There is a retrospective study that demonstrated two-third of the patients treated with crizotinib would continue to benefit from continuation of crizotinib beyond disease progression with local ablative therapy with a median overall survival of additional 16 months from the time of disease progression. Next generation ALK inhibitor such as brigatinib has achieved a median PFS of > 15 months in patients who are crizotinib-refractory or intolerant. Furthermore, "third-generation" ALK inhibitor, lorlatinib, achieved clinically meaningful overall response rate presented at this conference. Thus sequencing crizotinib to brigatinib could potentially achieve the additional 15.3 months of additional PFS achieved by using alectinib first. Finally, one of the major resistance mechanism of alectinib is the generation of ALK G1202R solvent front mutation while the incidence of ALK G1202R resistance mutation in crizotinib-refractory cases are much lower. Currently only lorlatinib and TPX-0005 (next generation ALK inhibitors presented at this WCLC) have shown reliably in vitro inhibitory against solvent front mutation. Thus the up-front use of alectinib could potential generate resistance mechanisms that allow limited further treatment options.

Keywords: lorlatinib, crizotinib, Alectinib

PC 03 3-2 WHICH DO YOU PREFER: LIQUID BIOPSY OR TISSUES BIOPSY FOR MOLECULAR DIAGNOSIS?
WEDNESDAY, OCTOBER 18, 2017 - 11:40-12:30

PC 03.03 LIQUID BIOPSY

H. Wakelee

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Tissue biopsy has been the gold standard in cancer diagnosis and molecular diagnosis of NSCLC for years. However, "liquid biopsy" is gaining in popularity as the sensitivity and availability of the assays increase. Plasma testing is now a standard approach for EGFR mutation testing with US FDA approved tests (Cobas), and much broader applications are available. Liquid biopsies are preferred, especially from the patient perspective. Would you prefer a simple blood draw or an invasive biopsy with high complication risk? The answer is obvious. As tumor cells die they shed DNA into peripheral blood. This circulating tumor DNA (ctDNA) is transient in nature, but can be detected in the plasma samples of patients. Plasma assays require simple phlebotomy compared to the risks of tissue biopsy. This technology can be applied to many malignancies, but is of particular interest in NSCLC given the number of known actionable driver mutations. Rapid detection of these mutations, and monitoring for development of resistance is already part of standard practice. Tissue biopsy strategies are significantly hampered by difficult to access tumors such as those in the brain or bone, and risks such as hemorrhage or pneumothorax. The issue of tumor heterogeneity is also of significance, as a biopsy in one lesion may not reflect the resistance biology of another location.[1] The application of ctDNA is best illustrated in the setting of EGFRmutant (EGFRmut) NSCLC. Though most patients have an EGFR activating mutation identified in the initial tumor biopsy, on June 1, 2016 the US FDA approved the cobas Mutation Test v2, a real-time PCR based assay for EGFR mutations, for use with plasma for detection of EGFR exon19del and L858R (and others in exons 18-21). ctDNA testing for the T790M EGFR resistance mutation is of greater practical utility as biopsy can be avoided in this setting with a positive liquid biopsy. AURA3 established the third generation EGFR TKI osimertinib as superior to chemotherapy for patients with T790M mutations, making T790M testing of high clinical significance.[2] In addition to tissue testing AURA3 was designed with an imbedded plasma assay. Based on the trial results the cobas EGFR Mutation Test v2 approval was expanded to include detection of T790M mutation in plasma samples. The Cobas assay established liquid biopsies as a standard approach for EGFRmut NSCLC, but has limited sensitivity and more sensitive liquid biopsy approaches exist including droplet digital PCR (ddPCR) and BEAMing (beads, emulsion, amplification, and magnetics), in addition to broader next generation sequencing (NGS) assays. Osimertinib activity has been demonstrated in T790M+ NSCLC patients regardless of how T790M is detected.[3] In a large analysis of hundreds of matched tissue, plasma and urine samples from EGFRmut NSCLC patients, both plasma and urine T790M detection sensitivity were 81% versus tissue testing. In the 181 patients with matched tissue, plasma and urine specimens there were 23 patients with T790M detected in plasma but not tissue, and 24 patients with T790M found in tissue but not plasma. The study utilized BEAMing technology, and a sensitive urine assay with quantitative NGS focused on EGFRdel 19, L585R and T790M.[4] One challenge for liquid biopsy is in the setting where there is limited ctDNA shedding, such as in lung only disease (M1a) in which case EGFRmut detection rates can be <50%,[5] but increasingly sensitive assays will ameliorate this issue. In a comparison across various platforms of Cobas (non-digital PCR), ARMS (therascreen EGFR amplification refractory mutation system (ARMS), digital detection droplet PCR (ddPCR) and BEAMing dPCR, the sensitivity ranged from 78-100% for the sensitizing mutations and 29-81% for T790M with specificity of 93-100% for the activating mutation and 58-100% for the T790M assays.[6] As outlined above, there is variability in the assays available for plasma analyses, however these assays correlate well with the tissue testing. In a meta-analysis of 26 studies comparing EGFR mutation detection in plasma versus tissue the specificity was 0.97 (95% CI 0.93-0.99) and sensitivity was 0.65 (95% CI 0.54-0.74).[7] Sensitivity is increased with more modern techniques such as BEAMing and droplet digital PCR. As this and other comparisons highlight, specificity is exceedingly high in all available assays, but sensitivity varies amongst the tests and thus a positive ctDNA test should be believed and can spare the patient a biopsy, but a negative test should be followed by further evaluation, bearing in mind that tissue

testing can also result in false negatives. Another advantage of "liquid biopsy" is the speed of obtaining results. In a comparison of plasma ddPCR versus biopsy the median turnaround time was significantly faster for the plasma testing (3 days versus 12 days, not including time to arrange the biopsy).[8] Thus, for EGFRmut NSCLC it is clear that compared to tissue biopsy, liquid biopsy is highly sensitive and specific, faster, and much more convenient and safe for patients. There should be no debate on the utility of liquid biopsy at initial diagnosis and around development of resistance to 1st/2nd generation EGFR TKIs. We already have an FDA approved assay in these settings with many improved technologies available as well. EGFR testing lays the foundation for ctDNA testing in NSCLC, but the utility of ctDNA has already expanded to testing for *BRAF* and other actionable mutations, and tumor rearrangements such as *ALK*. As an example, a commercially available ctDNA NGS assay performed on 362 NSCLC patients with paired tissue samples identified 51 additional actionable driver mutations via ctDNA analysis compared to the tissue assay, demonstrating real world practicality of this approach and theoretically improved patient outcomes.[9] Other highly sensitive NSCLC platforms looking at panels of dozens to hundreds of genes are available and rapidly changing our ability to detect mutations in larger groups of actionable mutations.[10] Utilization of these technologies at the time of diagnosis and for identification of resistance mechanisms is no longer theoretical but practical. Use of these technologies to monitor treatment response may one day replace or at least supplement imaging, and of particular utility, ctDNA analysis is already showing promise as a measure of minimal residual disease after curative therapy in early stage disease and will likely help guide us in decisions regarding adjuvant therapy in the near future. Liquid biopsy is an established, approved standard for EGFR testing, widely available and practical for tumor genotyping for other actionable mutations, and poised to radically change our surveillance strategies and our management of earlier stages of disease and likely even screening, which is far beyond the scope of what can be done with tissue. The preference for liquid biopsy over tissue biopsy should be clear. REFERENCES: 1) Hata A, Katakami N, Yoshioka H, et al. Spatiotemporal T790M Heterogeneity in Individual Patients with EGFR-Mutant Non-Small-Cell Lung Cancer after Acquired Resistance to EGFR-TKI. *J Thorac Oncol* 10 (2015) 2) Mok TS, Wu YL, Ahn MJ, et al. AURA3 Investigators, Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med* (2016) 3) Oxnard GR, Thress KS, Alden RS, et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 34 (2016) 4) Wakelee HA, Gadgeel SM, Goldman JW, et al. Epidermal growth factor receptor (EGFR) genotyping of matched urine, plasma and tumor tissue from non-small cell lung cancer (NSCLC) patients (pts) treated with rociletinib. *J Clin Oncol* 34, (abstr 9001) (2016) 5) Karlovich C, Goldman JW, Sun JM, et al. Assessment of EGFR mutation status in matched plasma and tumor tissue of NSCLC patients from a phase I study of rociletinib (CO-1686). *Clin Cancer Res* 22(10) (2016) 6) Thress KC, Brant R, Carr TH, et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291. *Lung Cancer* (2015). 7) Wu Y, Liu H, Shi X, Song Y. Can EGFR mutations in plasma or serum be predictive markers of non-small-cell lung cancer? A meta-analysis, *Lung Cancer Amst. Neth.* 88 (2015) 8) Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective validation of rapid plasma genotyping for detection of EGFR and KRAS mutations in advanced NSCLC. *Jama Oncology* (2016) 9) Zill O, Banks K, Mortimer S, et al. Somatic genomic landscape of over 15,000 advanced stage cancer patients from clinical NGS analysis of ctDNA. *J Clin Oncol* 34, (LBA11501) (2016) 10) Newman AM, Lovejoy AF, Klass DM, et al. Integrated digital error suppression for improved detection of circulating tumor DNA. *Nat Biotechnol* 34(5) (2016)

Keywords: liquid biopsy, circulating tumor DNA (ctDNA)

MINI SYMPOSIA

MS 01 CLINICAL DEVELOPMENT OF NOVEL AGENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 01.04 IS "BIG DATA" THE SOLUTION TO THE COMPLEX THERAPEUTIC LANDSCAPE?

Y. Shyr

Center for Quantitative Sciences, Vanderbilt University Medical Center, Nashville/TN/US

The Holy Grail of precision medicine is the comprehensive integration of patient genotypic with phenotypic data to develop personalized disease prevention and treatment strategies. Single cell sequencing, single cell mass cytometry (CyTOF), microbiome, and other types of high-throughput assays have exploded in popularity in recent years. The ability to generate big data brings us one step closer to the realization of precision medicine; nevertheless, across the life cycle of such data, from experimental design to data capture, management, analysis, and utilization, many challenges remain. In this session, I will discuss the artificial intelligence in cancer research, common statistical and bioinformatic mistakes for designing, analyzing, and interpreting the Omics based biomarker research. I will also discuss potential pathways for the seamless integration of cellular and molecular data with clinical, behavioral, and environmental parameters – a critical next step in advancing the goals of precision medicine.

MS 02 ETHNIC DIFFERENCES: BIOLOGY OR MYTH
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 02.01 LUNG CANCER GENOMICS

R. Govindan

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By sequencing lung cancers via an unbiased approach, The Cancer Genomic Atlas (TCGA) and similar analyses have elucidated commonly altered pathways and the molecular heterogeneity that underlies this disease. Data from these studies have shown that mutations in TP53, RB1, and MYC family amplifications are frequently associated with small cell lung cancer, while alterations in RTK/RAS/RAF pathway genes such as *KRAS*, *EGFR*, *ALK*, BRAF, and *ROS1*, and alterations in genes regulating squamous differentiation are frequently found in adenocarcinomas (LUAD) and squamous cell lung cancers (LUSC) respectively [1-8]. Sequencing rare histologies of lung cancer have also provided some insights into the alterations that underlie these diseases. For example, a recent analysis showed that it is possible to segregate large-cell neuroendocrine carcinoma (LCNEC) tumors into SCLC-like or NSCLC-like based on genomic profiling. This study showed that SCLC-like LCNEC tumors were characterized by co-alteration of *TP53* and *RB1* and/or *MYCL* amplification, while NSCLC-like LCNEC tumors were characterized by a lack of *TP53* and *RB1* co-alteration and presence of *STK11, KRAS*, and *KEAP1* alterations [9]. Results such as these emphasize the need for additional efforts to comprehensively study the genetic landscape of rare histologic subtypes of lung cancer to advance our understanding of these subtypes and facilitate the development of novel therapeutic approaches. This is particularly important considering that outcomes with conventional chemotherapeutics remain dismal in patients with these cancers. For many years, events leading to development of cancers such as colon adenocarcinoma have been well catalogued [reviewed in 10], while a thorough understanding of the events leading to the development and progression of lung cancer remains unclear. Defining these events may lead to the development of novel screening and prevention strategies. Recent efforts utilizing next-generation sequencing (NGS) technologies and circulating tumor DNA (ctDNA) assays have facilitated a study of pre-invasive lesions in lung cancer. Apart from cataloguing genomic alterations in pre-invasive lesions, NGS studies have also facilitated the study of the heterogeneity within these lesions. Evaluating this heterogeneity has the potential to reveal the temporal events leading to lung cancer initiation and progression. In one such analysis of precursor lesions in LUAD, sequencing of atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA) lesions demonstrated frequent mutations in DNA repair genes, with increasing rates of mutations in *EGFR* and *TP53* along the AAH-MIA spectrum, suggesting that serial acquisition of mutations in established driver genes and ongoing genomic instability play an potentially important role in LUAD development. However, in this small study, a single dominant pathway underlying progression from AAH to LUAD was not identifiable [11]. To this end, this study noted significant heterogeneity in mutations depending on the location of sampling suggesting intratumoral heterogeneity even at early developmental stages of LUAD. Using ctDNA, this group could detect mutations that were identified within different regions of the precursor lesions, suggesting that ctDNA may provide an effective method in determining and monitoring molecular heterogeneity in lung cancer development [11]. The Tracking Non-Small Cell Lung Cancer Evolution through Therapy (TRACERx) study was recently conceived to better understand the development and progression of NSCLC. Preliminary results from this multi-center, prospective study, which is still currently accruing patients, revealed that mutations in disease-specific drivers such as *KRAS, EGFR, BRAF*, and *MET*, and *TP53* were predominantly clonal in both LUAD and LUSC tumors [12]. The study also showed that alterations affecting chromatin remodeling, histone methylation, DNA damage response or repair were subclonal or late alterations in both LUAD and LUSC. While only a preliminary analysis of a much larger planned cohort, results from TRACERx also suggested a positive correlation between increased subclonal copy-number burden and risk of recurrence or death [12]. This correlation was independent of smoking history, histologic subtype, tumor stage, or adjuvant therapy. Taken together with observations in other cancers, these results suggest a role for genomic instability as a prognostic biomarker in lung cancer [13]. Analysis of ctDNA from the same 100 patients enrolled to TRACERx, demonstrated that nearly half (48%) of early-stage NSCLC patients had two detectable SNVs prior to surgical resection. Histologic subtype appeared to be an important factor in ctDNA detection, as ctDNA positivity was seen in only 19% (11/58) of LUAD patients compared with 97% (30/31) in LUSC patients. Clonal SNVs were identified in all ctDNA-positive patients in the study; whereas, only 27/46 (68%) of these patients demonstrated identifiable subclonal SNVs, suggesting that ctDNA analyses may have a higher sensitivity in detecting clonal than subclonal SNVs [14]. In this analysis, reliable detection of ctDNA required an estimated tumor volume of approximately 10 cm^3, which is considerably larger than the 4mm required for detection by low-dose CT [15], leaving the utility of ctDNA monitoring as a screening tool for lung cancer unclear. Longitudinal monitoring of ctDNA using patient-specific ctDNA assay panels, however, could identify patients who eventually relapsed after surgery. This analysis demonstrated subclonal SNVs at a similar allelic frequency to that of clonal SNVs, suggesting that the relapse process in these patients was likely driven by subclones [14]. With the advent of newer sequencing technologies and less invasive methods such as ctDNA monitoring, it is likely that molecular characterization rather than the histopathologic classification of lung cancer alone, will play an increasingly essential role in guiding screening and management strategies. **References** 1. Network CGAR. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543-50. 2. Network CGAR. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519-25. 3. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-34. 4. Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 2012;150:1107-20. 5. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53. 6. Rudin CM, Durinck S, Stawiski EW, et al. 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Keywords: lung cancer, Genomics, Targeted Therapies

MS 02 ETHNIC DIFFERENCES: BIOLOGY OR MYTH
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 02.02 MOLECULAR EPIDEMIOLOGY

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It has been recognized that ethnic differences contribute to disparities in carcinogenesis and treatment outcomes in lung cancer. The disparities can be due to the variety of mutations which are developed and triggered by the evolutionary forces over time and across populations. Although several single nucleotide polymorphisms as genome-wide significant signals can be associated with the mutations, environmental factors including smoking, dust exposures, obesity and potential viral infections (human papilloma virus) are also essential to the genomic diversity. Frequent occurrence of EGFR mutations is likely to be a feature of lung adenocarcinoma in Asian female never smokers including Japanese, while KRAS mutations are more common in Caucasian smokers. Because Japanese women are likely to have more environmental tobacco smoke (ETS) exposure, we conducted a single-center prospective study to examine an association between ETS and EGFR mutations in never smokers with non-small cell lung cancer (NSCLC) and clarify the reason for the unique background. We showed the development of EGFR mutations was inversely proportional to the dose of ETS exposure in never-smokers.[1] However, there are conflicting data published regarding the relationship, and mystery of the mutation still deepens. Based on recent developments in next-generation sequencing techniques detecting many genetic alterations, the Japan Molecular Epidemiology for lung cancer (JME) study has been designed and conducted beyond the scope of EGFR and KRAS mutations.[2] The aim of this prospective, multicenter, molecular epidemiology study is to elucidate the relationship between tumor developmental biology and exposure to environmental factors. A total of 876 surgical samples from 441 ever- and 435 never-smokers with early stage NSCLC underwent molecular

analyses. In smokers, the most frequent mutations were TP53 (38%), EGFR (20%), KRAS (13%), NFE2L2 (6%) and PIK3CA (4%), whereas in never-smokers, EGFR (61%), TP53 (15%), KRAS (4%) and PIK3CA (2%) were the most frequent. Dominant base substitutions were C>A transversion and C>T transition in TP53, C>A transversion in KRAS, C>G transversion in NFE2L2 and C>T transition in PIK3CA. Mutations in P53 and KRAS increased proportionally with smoking status, while EGFR mutations decreased. KRAS mutations in smokers were more frequently observed in proportion to body mass index. As for the ethnic difference on these mutations, our data can be compared with another integrative genomic analysis from The Cancer Genome Atlas (TCGA).[3,4] The study population in the TCGA was mostly Caucasian smokers with mixed smoking dose in early stage NSCLC, while the JME study was exclusively in Japanese patients, half of which were smokers and the other half never-smokers in the similar stage. In adenocarcinoma, the frequency of EGFR mutations was inversely proportional to the degree of smoking exposure both in the US and Japan. The mutation rates were always higher in Japan than in the US in each smoking status. While in KRAS and TP53 mutations, the frequencies increased proportionally as smoking; however, the mutation rates were always higher in the US than in Japan. The mutation rates of KEAP1, NF1 and STK11 seemed to be higher in the US than in Japan, regardless of smoking status (Table). In squamous cell carcinoma, KEAP1 and NF1 were also lower in Japan as well as TP53. The difference in ethnicity and potentially unveiled environmental factors can explain differences in the mutations prevalence.

Comparison of somatic mutations according to smoking status between TCGA and JME in early stage lung adenocarcinoma

	Never smokers		Current reformed smoker for > 15 years		Current reformed smoker for < or = 15 years		current smokers	
	TCGA N=32 frequency (%)	JME N=417 frequency (%)	TCGA N=69 frequency (%)	JME N=68 frequency (%)	TCGA N=73 frequency (%)	JME N=92 frequency (%)	TCGA N=45 frequency (%)	JME N=74 frequency (%)
EGFR	31.3	61.6	20.3	44.1	8.2	29.3	4.4	25.7
KRAS	15.6	4.3	33.3	13.2	37.0	21.7	37.8	18.9
BRAF	0.0	1.0	13.0	1.5	8.2	1.1	13.3	2.7
PIK3CA	3.1	2.4	5.8	4.4	5.5	3.3	8.9	1.4
HER2	9.4	0.2	1.4	0.0	2.7	0.0	0.0	0.0
TP53	25.0	14.1	42.0	23.5	45.2	35.9	64.4	36.5
KEAP1	6.3	0.0	20.3	2.9	20.5	1.1	17.8	0.0
NF1	0.0	0.5	7.2	0.0	17.8	0.0	13.3	1.4
STK11	6.3	0.2	14.5	0.0	27.4	1.1	15.6	4.1
RBM10	6.3	0.2	7.2	0.0	6.8	0.0	15.6	0.0
SMARCA4	0.0	0.2	4.3	0.0	6.8	0.0	8.9	0.0
ARID1A	6.3	0.0	11.6	0.0	4.1	0.0	6.7	0.0
U2AF1	0.0	0.0	2.9	0.0	4.1	1.1	6.7	1.4
RB1	6.3	0.2	5.8	0.0	4.1	0.0	2.2	1.4
MET	15.6	0.2	5.8	0.0	9.6	0.0	2.2	0.0
HRAS	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0
NRAS	0.0	0.2	0.0	0.0	1.4	1.1	0.0	0.0
AKT1	0.0	0.0	1.4	0.0	0.0	0.0	0.0	1.4

TCGA; The Cancer Genome Atlas, JME; Japan Molecular Epidemiology

From the beginning, the JME study has been designed to investigate the relationship between ethnicity and NSCLC carcinogenesis. Our potential counterpart study is S0424 which is a molecular epidemiological study in the US by using a detailed questionnaire and NSCLC tissue specimens from smoker and never-smoker men and women with early stage NSCLC. The JME study follows and extends the concept of S0424 by using a similar questionnaire that will allow us for direct comparison of data. We believe that the real value of genomic data will be realized only when they are linked to high-quality and solid clinical information, allowing us to identify precise genotype–phenotype associations. In conclusion, ethnicity is an important and complex characteristic that needs to be recognized and considered even in the era of precision medicine. We should collaborate to share the data from different ethnicity and translate them into the clinical practice and the design of a global clinical study. Carefully designed molecular epidemiological studies focused on ethnic differences are warranted. Reference 1. Kawaguchi T, Ando M, Kubo A, et al. Long exposure of environmental tobacco smoke associated with activating EGFR mutations in never-smokers with non-small cell lung cancer. Clinical cancer research 2011;17:39-45. 2. Kawaguchi T, Koh Y, Ando M, et al. Prospective Analysis of Oncogenic Driver Mutations and Environmental Factors: Japan Molecular Epidemiology for Lung Cancer Study. Journal of clinical oncology 2016;34:2247-57. 3. Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543-50. 4. Cancer Genome Atlas Research N. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519-25.

Keywords: oncogenic mutations, smoking, molecular epidemiology

MS 02 ETHNIC DIFFERENCES: BIOLOGY OR MYTH
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 02.03 CHEMOTHERAPY: EFFICACY AND TOXICITY DIFFERENCE ACCORDING TO ETHNICITY

M. Edelman

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Despite advances in immunotherapy and targeted therapies for lung cancer, cytotoxic chemotherapeutic agents remain the backbone of therapy for most patients. There has long been evidence that different populations demonstrate differential sensitivity and toxicity to chemotherapy agents. With the increasing globalization of trials, understanding and adjusting for these differences will be of increasing importance for the development of new agents as well as the safe and effective use of existing drugs. **Mechanisms of differential toxicity/efficacy** Different populations may experience altered safety profiles. Differential toxicity is not surprising as different populations demonstrate variability in detoxifying liver enzymes (e.g.cytochrome P450). Depending upon the drug, this could alter metabolism to an active agent or to an inactive compound. Metabolism can also affect aspects of drug clearance. Differential efficacy could be the result of several factors. Altered metabolism or clearance (as discussed above) may result in greater exposure of the tumor to active agent. Alternatively, accelerated metabolism/clearance could result in less exposure and potentially less activity. Another, less well appreciated aspect, is the different incidence of activating mutations in the populations, such as EGFR or ALK. Dietary differences may also alter metabolism and activity. Some of this is due to regulatory requirements. For example, the United States requires folate supplementation of bread and many other products to prevent congenital neural tube defects. This is not required in the European Union. Pemetrexed toxicity is significantly impacted by folate repletion and as early development in the EU demonstrated that additional folate obviated rash and led to the requirement for folate supplementation. It is

possible that this has resulted in over supplementation in the US. Conversely, capecitabine becomes more toxic (and possibly more effective) in folate replete patients. **Trial evidence for differential toxicity/efficacy** Observed differences in efficacy could potentially be due to differences in entry criteria, study execution etc. Investigators in the United States (Southwest Oncology Group, SWOG) and Japan addressed these issues through a series of "common arm" trials in small cell (SCLC) and non-small cell lung cancer (NSCLC). Trials comparing cisplatin/etoposide with cisplatin/irinotecan were conducted in Japan (J9511) and the United States (S0124). A retrospective analysis of patient level data was undertaken. Drug doses, eligibility criteria, assessments and analysis were similar between the two studies. There were significant differences in toxicity and efficacy. Both cisplatin/etoposide and cisplatin/irinotecan demonstrated greater hematologic toxicity in the Japanese. In terms of efficacy, cisplatin/etoposide demonstrated higher response rate, but similar survival endpoints. In contrast, cisplatin/irinotecan demonstrated a higher response rate, progression free and overall survival in the Japanese vs. US population. An analysis of the US trial demonstrated significant associations of GI and hematologic toxicity with ABCB1 (Odds Ratio, OR: 3.9) and UGT1A1 (OR: 24) polymorphisms, respectively. A prospective "common arm" study was undertaken in the NSCLC setting by the same groups. In this case, the common arm was carboplatin/paclitaxel. Once again there were significant differences in terms of both toxicity and activity. In this prospective study, the investigators obtained information regarding germline CYP and DNA repair enzymes. There were significant differences between patients from Japan and the USA in genotype distribution for CYP3A4*1B ($p = 0.01$), CYP3A5*3C ($p = 0.03$), ERCC1 118 ($p < 0.0001$), ERCC2 K751Q ($p < 0.001$) and CYPC28*3 ($p = 0.01$). Mutational status may influence response to chemotherapy and there are clear geographic variations for some driver mutations. The incidence of activating mutations of EGFR is approximately 10% in Western countries but >25% in many Asian countries. In addition to predicting outcome for EGFR tyrosine kinase inhibitors (TKIs), EGFR mutations also convey greater sensitivity to cytotoxic chemotherapy. In the IPASS study, the response rate for carboplatin/paclitaxel was 47% vs. 23.5% for mutation positive vs. negative patients. Given the much greater number of patients with EGFR mutation related NSCLC in Asia, this is likely a major source of discrepancy in outcomes. Interestingly, mutational status may also influence the degree of benefit from different chemotherapy agents. In a phase III trial comparing chemotherapy to crizotinib in patients with ALK translocated disease, patients could receive either pemetrexed or docetaxel as their chemotherapy. The HR for crizotinib vs pemetrexed was .59 while it was .30 for patients receiving docetaxel. **Summary** The past 20 years has seen significant progress in our understanding of lung cancer. It is now common to declare that there are many different lung cancers and to focus on susceptibility to targeted or immunotherapy based upon tumor characteristics. It is critical that in this era we not lose sight of the fact that there is still significant potential to improve outcomes with older chemotherapy agents, both in terms of toxicity and efficacy, based upon better understanding and utilization of both germline and tumor characteristics. 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Keywords: ethnic, toxicity, chemotherapy

MS 02 ETHNIC DIFFERENCES: BIOLOGY OR MYTH
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 02.05 IS ETHNICITY A PROGNOSTIC FACTOR IN LUNG CANCER

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Is ethnicity a prognostic factor in lung cancer? If so, it is due to differences in tumor genomic characterization, in response to treatment or some other factors? Do patients with different ethnic backgrounds experience different tolerability to therapy? How about culture factors, life style variants or environmental exposures that may pay a role in outcomes? The results from the Lung Cancer Mutation Consortium did not show significant differences in survival between Whites, African Americans, Asians, and Latinos with adenocarcinomas. However, the number of non-Whites in this study was relatively small. The rate of oncogenic mutations was highest among Asians (81%) followed by Latinos (68%), Whites (61%), and African Americans (53%). It is well documented that the frequency of *EGFR* mutations is higher in Asians (50-60%) than in Whites (10-20%). In fact, based on a case series from a single institution in China, 90% of lung adenocarcinomas from never smokers harbored these oncogenic mutations. Even in Asian current smokers with adenocarcinomas, the frequency of *EGFR* mutations could be as high as 35.3% as compared to 5.8% in White current smokers with the same histology. It remains unclear why Asians harbor such a high rate of *EGFR* mutations. A recent meta-analysis of genome-wide association studies of Asian never-smoking women with lung cancer has identified multiple genetic susceptibility loci, which may serve as a plausible explanation. As patients with oncogenic mutations have significantly better outcomes than those without, ethnicity does carry a prognostic value when it comes to Asians vs Whites. In terms of response to treatment, for patients with *EGFR* mutations, a meta-analysis of 7 randomized trials comparing EGFR tyrosine kinase inhibitors (TKIs) to chemotherapy did not show a clearly better PFS favoring EGFR TKIs for Asians (Hazard ratio [HR]: 0.36, 95% confidence interval [CI]: 0.31-0.42) than for non-Asians (HR: 0.42, 95% CI: 0.31-0.58). For patients with *ALK* rearrangements treated with crizotinib versus chemotherapy in PROFILE 1014, a slightly better PFS favoring crizotinib was seen for Asians (157 patients, HR: 0.44, 95% CI: 0.3-0.65) than for non-Asians (186 patients, HR: 0.53, 95% CI: 0.36-0.76), while the opposite was demonstrated with ceritinib in ASCEND-4 (Asians: 158 patients, HR: 0.66, 95% CI: 0.41-1.06; non-Asians: 202 patients, HR: 0.44, 95% CI: 0.3-0.66). In ALEX study, Asians (138 patients, HR: 0.46, 95% CI: 0.28-0.75) had a similar PFS favoring alectinib over crizotinib as non-Asians (165 patients, HR: 0.49, 95% CI: 0.32-0.75). With regards to immunotherapy, no conclusion can be drawn on outcomes between Asians (40 patients, HR: 0.35, 95% CI: 0.14-0.91) and non-Asians (265 patients, HR: 0.52, 95% CI: 0.38-0.72) in KEYNOTE-024 as the study enrolled significantly fewer Asians accounting for the wide range of confidence interval for PFS favoring pembrolizumab over chemotherapy. The discussion on potential differences between Asians and non-Asians in response to chemotherapy is beyond the scope of this mini-review, but it is unlikely that ethnicity would serve as a surrogate factor for efficacy and even tolerability to predict prognosis. Lastly, according to the American Cancer Society, African Americans continue to have higher death rates from lung cancer than Whites, but the gap has narrowed for men. For *EGFR* mutations, the frequency in African Americans as compared to Whites varied by reports. By using targeted massively parallel sequencing, Araujo *et al.* have suggested that genomic characterization of African Americans with non-small cell lung cancer (NSCLC) may not be significantly different from that of Whites. However, a pooled analysis done by the same group with a larger sample size has shown a different pattern of oncogenic mutations in African Americans than in Whites, although the frequency of *EGFR* or *KRAS* mutations was similar between the two groups. Interestingly, a study utilizing the Veterans Affairs Central Cancer Registry has shown that even though African Americans with NSCLC had worse prognostic factors than Whites, they had a better overall survival. These data suggest that disparity in outcomes between Africans Americans and Whites may be related to barriers to access rather than inherent biology. In summary, ethnicity plays a prognostic role in lung cancer between Asians and non-Asians largely due to the fact that Asians have a higher frequency of oncogenic mutations, which is clearly associated with better outcomes, whereas the disparities between African Americans and Whites are more likely to be driven by healthcare inequality leading to a poorer prognosis among African Americans with lung cancer. Endeavors should be undertaken to provide better access to care for ethnic minorities.

Keywords: Ethnicity, lung cancer, outcomes

MS 03 BEST PRACTICE FOR SMALL-SIZED EARLY STAGE LUNG CANCER: STANDARD SURGERY, LIMITED RESECTION, SBRT
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 03.02 LIMITED VS. STANDARD SURGICAL RESECTION: JAPANESE EXPERIENCE

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The extent of pulmonary resection for peripheral, non-small cell lung cancer (NSCLC) has been defined as "lobe", based on the results of clinical experiences and a randomized trial in 1980's. At present, the possibility of lesser resection such as wedge/segmental resection needs to be evaluated from a updated, scientific viewpoint. For these reasons, JCOG (Japan Clinical Oncology Group) has been prospectively deploying series of clinical trials each for different target lesions to define the proper extent of the parenchymal resection for NSCLC, JCOG 0804, 0802, and 1211. Among these, the most important study is JCOG 0802, in which the non-inferiority of segmentectomy was compared with lobectomy in terms of overall survival for patients with diameter ≤ 2 cm invasive peripheral NSCLC. As a second endpoint, the postoperative pulmonary function was also compared to demonstrate the functional superiority for lesser resection. Between Aug 10, 2009 and Oct 21, 2014, 1,106 patients were enrolled. No mortality was noted. Complications (grade ≥ 2) occurred in 26·2% for lobectomy and 27·4% for segmentectomy. Multivariate analysis indicated a pack-year (PY) smoking >20 (vs. none) as a predictor of postoperative complications (grade ≥ 2), and a complex segmentectomy (vs. lobectomy) and PY > 20 as a predictor of pulmonary complications. The final analyses on the prognostic non-inferiority (primary endpoint) will be available after 2020. Through such series of prospective studies, the proper extent of pulmonary resection for NSCLC is to be defined from prognostic and functional viewpoints. Therefore, especially for JCOG 0802 study, both of two endpoints must meet the hypothetical criteria for lesser resection to be judged as

appropriate. We should realize that a true progress in the surgical oncology might be achieved only by a prospective, collaborative comparison as an applied science.

MS 03 BEST PRACTICE FOR SMALL-SIZED EARLY STAGE LUNG CANCER: STANDARD SURGERY, LIMITED RESECTION, SBRT
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 03.03 LIMITED VS. STANDARD SURGICAL RESECTION: EUROPEAN EXPERIENCE

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Until the beginning of the new century limited resection for pathologically proven, early-stage lung cancer was not frequently applied in Europe. The main reason for this practice were the results of the randomized phase III trial of the Lung Cancer Study Group published in 1995, showing that for peripheral, clinical T1N0 tumors, lobectomy yields better locoregional control with less recurrences compared to sublobar resection (1). This study was very influential in Europe. A majority of thoracic surgeons adopted the principle that lobectomy was the minimally acceptable lung volume to be resected for patients with an early-stage bronchogenic carcinoma and a low cardiopulmonary risk. Limited resection for lung cancer was only considered for elderly persons, patients with severe chronic obstructive pulmonary disease precluding lobectomy, patients with a high comorbidity score and limited life expectancy due to debilitating disease. Quite a substantial variation in practice is observed, not only within countries but also when comparing North America and Europe. In an interesting analysis of the thoracic surgical databases of the Society of Thoracic Surgeons (STS) and European Society of Thoracic Surgeons (ESTS), some important differences were discovered regarding the daily practice of lung resections performed during the period 2010-2013 (2). Patients in the STS database were more frequently operated by video-assisted thoracic surgery (VATS) compared to the ESTS dataset (63% versus 22%), and were more likely to undergo sublobar resection (43% versus 31%). However, most of the sublobar resections were wedge resections. Anatomical segmentectomies were more frequently performed in the ESTS database than in the STS dataset (7.4% versus 3.9%). For the ESTS patients 30-day mortality of wedge resections was lower compared to the STS data (0.1% versus 1.9%); however, mortality for lobectomy was higher (2.6% versus 1.4%) (2). With the start of European screening studies, although not at the scale of the National Lung Screening Trial, a new clinical problem arose for thoracic surgeons, namely how to deal with small pulmonary nodules and how to limit the false-positive rate? Thoracic surgical issues of screening were addressed in a recent paper by a task force of the ESTS (3). Recommendations were made for implementation of CT screening in Europe focussing on the training of thoracic surgeons, their clinical profile and the use of minimally invasive thoracic surgery. In general, it has been clearly demonstrated that the main goal of surgery for an invasive lung cancer is to obtain a complete resection which is a major prognostic factor. This mostly implies a lobectomy for tumors > 2cm, and at least a lobe-specific systematic nodal dissection as defined in 2005 by a working group of the International Association for the Study of Lung Cancer (IASLC) (4). Unfortunately, quite a lot of resections have to be considered uncertain due to the fact that the required number of lymph nodes, especially mediastinal, have not been removed for further pathological analysis (5). The new adenocarcinoma classification published in 2011 by a common task force of the IASLC , American Thoracic Society (ATS) and European Respiratory Society (ERS) and accumulating phase II data mainly coming from Japan, had important surgical implications (6). As new entities, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were introduced and the confusing term bronchioloalveolar cell carcinoma (BAC) is not used anymore. This clearly resulted in a paradigm shift and the concept of sublobar resection was reconsidered for smaller, early-stage lung cancers < 2cm. Anatomical segmentectomy is generally preferred to wide wedge resection because of concerns of local recurrence (7). Regarding the overall oncological results several meta-analyses have been performed. Their results are somewhat conflicting but overall, good long-term results are described for tumors until 2 cm treated by segmentectomy when no lymph node invasion is present. However, for small, early-stage lung cancer no high-level evidence is currently available and the reported evidence should be interpreted with caution. As most studies were not randomized, there was probably a clear selection bias regarding comorbidity, histology and tumor size. Recent guidelines and evidence from a randomized trial indicate that small nodules of ≤10 mm or ≤500 mm^3 that are clearly 100% pure ground-glass opacities (GGO) on chest CT may be considered as AIS or MIA, and hence may be suitable for close follow-up or sublobar resection rather than a formal lobectomy (8). Subcentimeter lung cancers, currently T1a disease, represent a specific subgroup as they comprise the smallest lesions. It should also be emphasized that for subsolid lesions the current tumor size is determined by the solid or invasive part only which represents a major change in the 8th TNM (tumor, node, metastasis) classification (9). For thoracic surgeons another important topic is the accuracy of intraoperative frozen section analysis to determine the intraoperative extent of resection. Recent studies show that a concordance rate of more than 80% can be reached between the frozen section and definitive pathological report (10) . However, AIS and MIA are more difficult to diagnose on frozen section and accuracy becomes less for lesions below 10 mm, which represent the main category to be considered for sublobar resection. This implies that a second intervention to perform a completion lobectomy may be indicated in patients with poor prognostic histological features who initially underwent a limited resection for a presumably low-malignant lesion. In conclusion, sublobar resection is currently more often applied in European countries but more high-level evidence on long-term oncological results is required to refine its indications and make this procedure a generally accepted intervention, not only by thoracic surgeons but also by thoracic oncologists and pulmonary physicians. References 1. 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; 60:615-22; discussion 22-3. 2. 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Keywords: lung cancer; limited resection; sublobar resection

MS 03 BEST PRACTICE FOR SMALL-SIZED EARLY STAGE LUNG CANCER: STANDARD SURGERY, LIMITED RESECTION, SBRT
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 03.04 TECHNICAL ASPECTS OF LIMITED RESECTION

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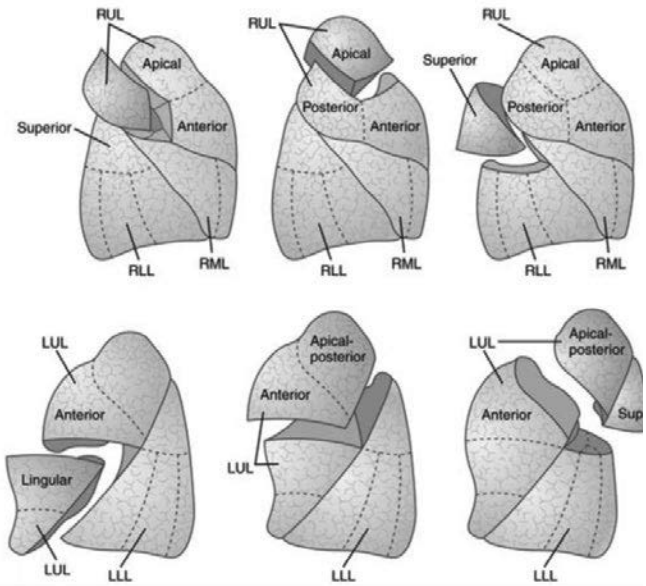
Since its first report by Churchill and Belsey in 1939, and its evolution in lung cancer management described by Jensik in 1973 (Figure), pulmonary segmentectomy use for early lung cancer diagnosis and treatment has remained controversial. Definitive answers must wait regarding the results of the JCOG and Alliance randomized trials before true standards for surgical care for the lung cancer less than 2 cm are determined. Nevertheless, sublobar resections including wedge resection and segmentectomy are being adopted at an increasing rate compared to its use in previously published large databases (SEER, 5%; ACS NSQIP, 4%). Proper preoperative teaching and intraoperative performance of the technical aspects of sublobar resection are now becoming priorities for general thoracic resident and fellow training in an era where minimally invasive techniques are becoming increasingly the standard of care. General thoracic surgeons must have meticulous attention to detail in performing these resections in order to decrease the likelihood of collateral damage to neighboring segments as well as to minimize local recurrence whether there are performing the operation open, hybrid, standard VATS, uniportal VATS, or robotic. The technical aspects of sublobar resection begin before the patient goes to the operating room, and prime objectives in planning these resections include (1) expertise in the segmental anatomy for that particular patient (2) location and size of the nodule with relation to adjoining segmental bronchovascular components (3) careful study and possible supplementation of high resolution computerized tomography with newer 3-D methods to define the spatial relationships of the nodule and segments (4) pre- and intraoperative methods for locating the nodule if there is suspicion that parenchymal palpation will fail (5) whether to perform wedge resection first or proceed directly to anatomic segmentectomy (6) defining and managing the fissure between segments and recognizing when extended segmentectomy is possible or whether to convert to lobectomy and (7) to use other intraoperative strategies to avoid technique related complications. Preoperative planning includes careful examination of the CT scan in the axial, coronal and sagittal plans in order to get a first appreciation of the depth, size, segmental anatomy and relationship of the nodule bronchovascular elements. Three-dimensional reconstruction can be as simple as navigational bronchoscopy planning images, or newer techniques for total 3-D pulmonary reconstruction which are in development (1). When there is a question of whether up front segmentectomy is to be performed and a part solid or non-solid nodule may not be palpable, intraoperative localization techniques such as navigation bronchoscopy(2) or placement of fiducials/microcoils (3) can be very useful. When there is no preoperative histologic diagnosis, whether a wedge or segmentectomy is performed initially will depend on the location and depth of the lesion as well as the fitness of the patient. Segmentectomy for initial diagnosis with intraoperative frozen section of both the primary lesion and suspicious level 13 and 14 stations can be prudent, especially if wedge resection could compromise performing the segmentectomy(4). In order to avoid positive margins, meticulous attention to detail with compulsive dissection and skeletonizing of the bronchovascular elements must be performed. If it is difficult to preserve the margin in a single segment resection, an extended resection of the parenchyma of adjacent segments or bisegmentectomy can be performed(5). There is controversy regarding the chance for loco-regional recurrence for segmentectomy especially in cases of pure solid lesions or segmentectomies which involve portions of the basilar segments or right upper lobe (6-8). Defining the fissure and the method with which it is divided can be one of the

most important yet challenging portions of the operation. A variety of methods to define the fissure have evolved including inflation of the residual lung after segment occlusion, selective inflation of the segment to be removed, or the use of indocyanine green to define the intersegmental vein (4, 5), and the fissure can be divided either with stapling alone or in combination with harmonic scalpel(9). A variety of fibrin sealants are available to decrease postoperative fistulae. With regard to the optimal approach, to date there have been no studies which show any superiority regarding conventional VATs or uniportal VATs for segmental resection, or any difference between the VATs approaches and robotic segmentectomy (10). A recent meta-analysis of over 7438 patients revealed a trend towards increased conversion to open with VATs, while postoperative complications, operation time, length of stay, chest tube duration, and number of lymph nodes were comparable(11).



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Keywords: wedge, segmentectomy, limited resection

MS 03 BEST PRACTICE FOR SMALL-SIZED EARLY STAGE LUNG CANCER: STANDARD SURGERY, LIMITED RESECTION, SBRT
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 03.05 SBRT EXPERIENCE

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In the early 2000s, the revolution in computer-driven radiotherapy technology enabled exquisitely precise direction of radiation beams to specific tumor targets. The advent of 4-dimensional computed tomography (CT), MRI and on-board image-guided intensity-modulated radiotherapy (IMRT), stereotactic ablative radiotherapy (SABR), particle therapy have equipped radiation oncologists with novel tools to tightly conform ablative radiation doses to targets while avoiding inadvertent irradiation of surrounding critical normal structures. SABR, also called stereotactic body radiation therapy (SBRT), as a non-invasive curative therapy, achieves >90% local control, improves survival with minimal toxicity and has become standard therapy in medical inoperable peripheral located stage I NSCLC (1, 2). Particularly for elderly patient, SABR's effectiveness based on lung cancer-specific survival and progression-free survival is the same in the elderly (>75 year old) as it is the average age population (<75 year old). It also poses no increased toxicity. Compared to historical outcomes with surgery in the elderly, SABR outcome is considered comparable for stage I disease but has less morbidity (3). The pattern of failure study showed that the dominant failure of SABR in stage I NSCLC is distant metastasis (10 to 20%), followed by regional lymph node recurrence (10 to 15%) and then local failure (5 to 10%) (4). Up to 1 in 6 patients who received SABR for early-stage NSCLC may develop isolated local-regional recurrence that could be salvaged with definitive treatment. The first long-term results for the largest group of salvaged patients with local-regional recurrence after SABR (n=103) was reported in ASCO 2017 annual meeting (Brooks et al, ASCO 2017 oral presentation in Chicago). 912 patients with clinically early-stage I-II NSCLC from MDACC were treated with SABR with isolated local recurrence (LR, n = 49) or regional recurrence (RR, n = 53). Salvage was performed in 79.6% of LR and 90.6% of RR patients. Median follow-up from time of initial SABR was 57.2 months. 5-year OS was 52% for LR and 27.8% for RR patients. Of LR and RR patients, those receiving salvage had significantly better 5-year OS compared to those not receiving salvage (57.9% LR, 31.1% RR, 0% no salvage; p = 0.006). 5-year OS for LR salvaged patients was not statistically different from patients with NR (53.5% NR, p = 0.92) and 5-year OS for salvaged RR was lower than that of NR (p=0.022). 60% patients never recurred after salvage but subsequent DM occurred in 27.6% of local-regional recurrent patients at a median of 10.5 months. No salvaged patient experienced grade 5 toxicity. There is debate about what is the optimal treatment for operable stage I NSCLC. Majority of the population-based retrospective propensity-matched studies have indicated that SABR has effectiveness comparable to that of surgery for this population, with reported 3-year overall survival rates of 48-91% and local control rates of 85-96% that is significantly better than conventional radiotherapy (5). A pooled analysis of two prospective randomized trials for operable patients showed a better overall survival rate at 3 years for SABR than for surgery (6); however, the efficacy, pattern of failure, and toxicity reported were mostly based upon relatively short follow-up and patient's number is small; therefore, larger studies with longer follow up are needed and are ongoing around the world. Recently, a phase II prospective study investigating SABR for early-stage NSCLC with median follow-up of 7 years demonstrated outstanding OS of 47% with low rates of local (8%), regional (14%) and distant failure (14%) 7 years after SABR, comparable to those of surgery but with lower toxicity (7). Second malignancy remains one of the most common issues with longer follow-up (21%), again consistent with surgical data. There are two major limitations of SABR in treating early stage NSCLC. First, critical nearby normal tissue dose constraints such as esophagus, bronchial tree, brachial plexus, heart, major vessels etc. may limit the ablative dose that could be safely delivered (8); second, the efficacy of SABR is reduced and toxicity is increased with increasing size of the lesion, particularly when the lesion is >5 cm (9). Most of outstanding clinical outcome with SABR reported in the literature are based on lesions less than 5 cm, typically <3 cm, and not close/next to critical normal structures. Finally, we need to keep in mind that cancer is a biological disease, not just a technologic challenge. As our ability to control local tumors improves with the use of new technology, the importance of systemic disease control grows in parallel—after all, in most cases it is metastatic disease that kills the patient. During the past decade, the development of genomic profile–based targeted therapy and immune checkpoint pathway– based immunotherapy has revolutionized the management of stage IV lung cancer. More and more data indicated that cancer cells killed by radiation release tumor-associated antigens and immunoregulatory cytokines, thereby functioning as a kind of cancer-specific vaccine in situ; they further activate tumor-specific systemic immune responses to eradicate tumors even outside the radiation field (the abscopal effect). These effects seem to be more prominent when the radiation used with immunotherapy involves giving high (ablative) doses, a type of therapy for which we coined the term "I-SABR" (immunotherapy and stereotactic ablative radiotherapy, 10). I-SABR protocols are underway for both early-stage disease and advanced cancer. In summary: SABR/SBRT, a novel non-invasive approach with low toxicity, achieves outstanding clinical outcome and is the standard treatment in medical inoperable stage I NSCLC. It remains controversial whether SABR should be used for operable early stage NSCLC and more randomized studies are ongoing. The dominant pattern of failure after SABR is distant metastasis, followed by regional or intra-lobar failure. Patient with isolated local/regional recurrence should be salvaged aggressively and long-term surveillance is crucial to detect early recurrence and the secondary lung cancer. Combined SABR with systemic therapy such as immunotherapy may further improve the efficacy and cure rate. REFERENCES 1. Timmerman R, et al. Jama. 2010;303(11):1070-6. 2. Onishi H, et al. Cancer. 2004;101(7):1623-31. 3. Brooks ED,et al. Int J Radiat Oncol Biol Phys. 2017;98(4):900-907 4. Senthi S, et al. Lancet Oncol. 2012;13(8):802-9. 5. Shirvani SM, et al JAMA Surg. 2014;149(12):1244-53. 6. 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Keywords: SABR/SBRT, lung cancer, early stage

MS 04 JOINT IASLC/GLCC SESSION CURRENT ISSUES IN LUNG CANCER ADVOCACY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 04.01 LUNG CANCER ADVOCACY TOOLS FOR EVERYONE - THE USE OF GLCC DATA

J. Fox

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Background Despite recent advances, lung cancer remains a disease characterised by negativity, late diagnosis and poor outcomes. The need for advocacy in lung cancer is obvious. Recent years have seen an increase in the number of organisations and individuals advocating for improvements in this disease. With limited resources across all advocacy organisations, using external data and tools from other sources is welcome. Such a source is work undertaken by the Global Lung Cancer Coalition. **The Global Lung Cancer Coalition** In 2001, a global search revealed the existence of only nine not-for-profit organisations with an interest in lung cancer advocacy. Of these, only two were lung cancer–specific, the others representing generic cancer or respiratory diseases. In coming together, these organizations established the Global Lung Cancer Coalition (GLCC), an allied group of registered not-for-profit, non-government organizations, dedicated to improving lung cancer outcomes. By 2017, the GLCC has grown to 36 member organisations, from 26 countries and provides a centralised communication and referral network. In recent years, the GLCC has undertaken a number of projects, creating data and tools, for all advocates to use, in their efforts to improve lung cancer outcomes. More information on all of these are available on the GLCC website – **www.lungcancercoalition.org. Key Global Lung Cancer Coalition Projects The Global Lung Cancer e-Atlas** The e-Atlas is available on the GLCC website. It is an easily accessible source of international lung cancer data, including all WHO countries. The purpose was to collate lung cancer data from across the globe and uncover international variations. This includes incidence, mortality and survival data. Also, an indication of whether the country has Cancer Registry, has signed up to the WHO Framework on Tobacco and/or has a National Cancer Plan. The e-atlas brings all of this information together in an easily accessible place. This is a data resource for lung cancer professionals and campaigners. It is easy to compare data across countries and easy to create graphs, for download into powerpoint presentations and reports. This resource has already been used by many advocates, in discussions with politicians and health policy makers, to highlight differences in inter-country survival. The e-atlas will be updated, as international data sets are updated. Where possible, we will also add links to national lung cancer data sources. **International Consumer Polls** GLCC commissioned IPSOS/MORI to undertake two consumer polls in GLCC member countries in 2011 and 2013. These examined issues of stigma and also of general public awareness of lung cancer symptoms. In 2017, these two polls are being repeated by Populus and will be undertaken in 25 countries. This will provide update information in GLCC countries covered by the original polls and new information for newer GLCC member countries. Smoking stigma associated with lung cancer and poor public awareness of signs and symptoms of the disease are of obvious importance. Such polls provide valuable information for advocating and campaigning for improvement and change. **Global Lung Cancer Research data** The GLCC commissioned researchers at King's College in London, to undertake some bibliometric research, to map published lung cancer research, across the globe. This type of research involves the quantitative analysis of publications and research activity, using complex bespoke algorithms This work was published, as an open access article, in June 2016 in the Journal of Thoracic Oncology. (Agarwal A, et al, 'The State of Lung Cancer Research – A Global Analysis)'. Results of this work show the relative lack of lung cancer research globally. Individual Country Toolkits have been created to raise awareness of lung cancer research nationally and advocate for more. GLCC has commissioned further research in this area, investigating how published research is used – for example, does it change practice, how is the research implemented and what research is media reported. **Information on Lung Cancer – Topical Factsheets** GLCC has created factsheets in topical area, available for download from the GLCC website. These include Information on Clinical Trials and the relatively new therapy field of Immunotherapy. The Immunotherapy Factsheet is available in 16 languages. Factsheets are now also available on Lung Cancer Screening and Lung Cancer and Stopping Smoking. These are available for everyone to download and distribute. **Lung Cancer Awareness Information Sheets** The GLCC has created Awareness leaflets. These are designed for the general public, to inform on lung cancer – What to look out for? What to do? Where to go for help and support? The leaflets have been translated into 13 languages and are available for download on the Resource section of the website. In this presentation, all of the above will be expanded on. We invite all who advocate for improvements in lung cancer to use these resources.

Keywords: advocacy, tools

MS 04 JOINT IASLC/GLCC SESSION CURRENT ISSUES IN LUNG CANCER ADVOCACY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 04.02 LUNG CANCER ADVOCATES AND MEASURING VALUE IN HEALTHCARE

C. Aldige

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The United States has no formal system of health technology assessment, compared to, for example, the system in the United Kingdom and many countries worldwide. In the U.S., certain federal agencies review and recommend approval of drugs and devices, while others make determinations regarding reimbursement of costs of treatment and other interventions. With the cost of health care in the U.S. skyrocketing in the absence of cost controls, many organizations, e.g., the American Society of Clinical Oncology, the National Comprehensive Cancer Network, Memorial Sloan Kettering Cancer Center and others, have developed "value frameworks". In virtually all cases, however, the frameworks were developed without input from patients, their caregivers or patient advocates. They were developed from evidence obtained in randomized controlled trials and did not include real-world evidence, such as from observational studies or patient experience reports. Decisions about what patients value were often made by clinicians and economists and not by the patients whose lives would be impacted by the recommendations.The situation becomes even more complex when one considers that all patients do not share the same values with regard to outcomes. While a younger, otherwise healthy patient might accept significant treatment toxicity in order to extend life, an older, less healthy patient might choose treatment that is likely to be less toxic. As treatment costs escalate, financial toxicity is also a consideration and varies among individual patients. A treatment that imposes significantfinancial burden on one individual might not be perceived as overly costly by another.Family/caregiver preference also needs to be taken into consideration, as all demographic groups do not share the same preferences or values. Whereas in some groups, the patient's preference is what counts, in others, family members are much more involved in decision making.In May 2015, researchers from the American Institutes for Research and the Mayo Clinic published a study based on extensive interviews with 721 patients.

Keywords: patient-centric, lung cancer advocacy, value

MS 04 JOINT IASLC/GLCC SESSION CURRENT ISSUES IN LUNG CANCER ADVOCACY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 04.03 ACCESSING NEW LUNG CANCER THERAPIES - CHALLENGES & EXPERIENCE IN LATIN AMERICA

M. Mondragon

Ceo, Respirando Con Valor Ac, Mexico City/MX

Regarding the main disadvantages to access: 1. Where there are structural factors that grant the right and Promote coverage, bureaucratic issues arise that Complicate access. 2. There is in general an underutilization of the available public resource, for lack of information. 3. Many patients who depend on public coverage lack of an education from which they can empower themselves situation. Many times they lack the knowledge and Tools to expand their options. 4. The delay or inefficient response by the public coverage remains, even increases, or extent a claim made by patients and their relatives. 5. Delays both in the delivery of medicines and in obtaining shifts, in order to conduct a study. Problems of transfers, Great distances to treatment centers. Mexico, Brazil, Peru, Argentina and Chile to mention some examples in Latin America we have very fragmented health systems, little or no budget for avant-garde treatments like Immunotherapy or targeted therapies. Lung Cancer patients often do not know their rights, they do not empower themselves and require the inclusion of these therapies. While efforts have been made to tighten anti-smoking laws, there is a long way to go and educate to create awareness.

Keywords: Latinamerica, Access, advocacy

MS 04 JOINT IASLC/GLCC SESSION CURRENT ISSUES IN LUNG CANCER ADVOCACY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 04.04 PATIENT ADVOCACY - MAKING A DIFFERENCE FOR LUNG CANCER PATIENTS IN JAPAN

T. Sawa

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In Asian countries, the concept of cancer advocacy has not been sufficiently recognized. In Japan, there had been few groups of lung cancer patients for a long time, and West Japan Oncology Group (WJOG) has practiced cancer advocacy learned from the USA and Europe as a citizen lecture and a guidebook for patients. We noticed that interactive efforts involving patient groups, companies, academia and governments are necessary rather than providing one way information. In recent years, Lung Cancer Society (JLCS) has led the lung cancer advocacy, and adopted the 2014 Kyoto Declaration, which Representatives of the society, lung cancer patients, citizens, medical personnel, government, companies and research institutes, declared the will to the improvement of lung cancer medical care in cooperation. First, the medical improvement committee against lung cancer was organized to to realize the goal of the Kyoto Declaration, and The committee has carried out the following activities. Initially, the ambassador was commissioned to a lung cancer survivor, a futsal professional athlete and one medical school student of a leader of the idol singer group. In line, we currently commission six medical school students, students of pharmacy, and nursing students. One of our main activities is to provide information on lung cancer medical care using websites and events. In addition to the public lecture, medical workers seminar, the event by the patient association had been supported. These activities are open to the public so that citizens and medical staff can recognize widely in cooperation with medical media. Also, in collaboration with the Lung Cancer Society, we are also requesting early approval of new therapeutic agents. Evaluation of Japan's advocacy To evaluate the awareness and attitude of lung cancer advocacy activity among patients, medical workers, and the general population in Japan, web survey was planned for the perceptions of Kyoto declaration and JLCA (Japanese alliance for lung cancer advocacy) events which were carried

out by JLCS in these 2 years. Furthermore, we tried to reflect the questionnaire result in the subsequent activity plan. An internet survey was conducted which contained 6 closed-ended (selection one or free answers) and open-ended questions, depending on the JLCA network population in June 2016. Results By October 2016, 109 people of responded involving 36% of patients and their family, 25% of MD and medical worker, 19% of pharmaceutical company officials and 16% of news media. Perception of Kyoto declaration was 21% of attendee, 27% of well-known, 13% of partial known and 39% of non-awareness. Also the number of participants to the events of JLCA is, 49% of 0 times, 17% 0f 1-2 times, 24% of 3-4 times and 11% of more than 5 times. The most sympathy events ware voted to 1) lecture by a physician 57%, 2) lecture by survivor and the participants WCLC of cancer patients 46%, 3) information in the facebook and the web site 46% 4) citizen open lecture of lung cancer 39%, 5) Performance by society ambassador 38%, 6) advocacy program in annual meetings 26% and 7) Medical seminars around the country 26%. The proportion of respondents who have a certain reputation in the activities of JLCA was 76%.The requests to JLCA is, 1) is the most participation opportunities for information of new treatment and participation opportunities to clinical trial, followed by 2) wish to participate to all the programs in the Society. Looking for the next difference 1. Activities in the next fiscal year, reflecting the results of the questionnaire, citizen public lectures consisted mainly of lectures by prominent oncologist, announcements of representative survivors, moderators and lectures by public ambassadors. Events were held in major cities and various places across Japan. Also The lung cancer society organizes the patient advocacy program throughout the annual meeting every year. We provide travel grants from 2016 to facilitate patient and family attendance. 2.The committee holds medical seminars in Tokyo four times a year. The theme was the latest current information surrounding lung cancer from time to time, introduction of new treatment and activity of patients group. In addition, journalists, television reporters and medical writers were invited to provide information to the public widely by articles posting. 3. Through the website, we provide topics on diagnosis and treatment for lung cancer using video, activity policy and advocacy activities of the lung cancer society, documentary on participation of the international conference of the patient association. In conclusion, participants from different professions gathered for the purpose of improving lung cancer medical care, shared recognition was born among the participants, and empathy was also obtained with the public relations ambassador. Meanwhile, because of different professions and position, the hope of the content of activities was diverse, and it seems necessary to enhance the priority business that can be shared.

Keywords: Kyoto Declaration 2104, Cancer Advocacy, Internet Survey

MS 04 JOINT IASLC/GLCC SESSION CURRENT ISSUES IN LUNG CANCER ADVOCACY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MS 04.05 LUNG CANCER PATIENTS AND STOPPING SMOKING - WHAT ADVOCATES NEED TO KNOW

A. Mcnamara

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Since the 1950's, smoking has been associated with lung cancer (US National Llibrary of Medicine, 2017). Lung cancer is the most common cancer worldwide and the biggest cancer killer (World Health Organisation, 2017). The majority of lung cancer diagnoses are due to smoking (US National Llibrary of Medicine, 2017), yet these frightening statistics have not deterred people around the globe from smoking. The World Health Organisation estimated that, in 2015, 1.1 billion people smoked tobacco. Within this cohort are lung cancer patients and their families, unable or unaware of why they should quit. This presents a great challenge to patient advocates worldwide. **Awareness** Awareness of the significant health risks associated with smoking vary around the world, so the role of the patient advocate also varies from country to country. In 2013 the Global Lung Cancer Coalition launched a survey, carried out by Ipsos MORI, investigating awareness of the symptoms of lung cancer and smoking prevalence in 21 countries. Researchers found that across all the countries, 22% of people surveyed admitted they could not name any symptoms of the disease. Over 17,000 people were surveyed, among them former smokers were slightly more likely to be aware of symptoms than current smokers or people who have never smoked. Multiple studies have replicated similar differences in awareness of the link between smoking and lung cancer across countries. Research performed by the Irish Cancer Society in 2015 found that; 92 out of 100 smokers know that smoking causes lung cancer. In contrast, the Global Adult Tobacco Survey (2010) found that in China; 23% of adults believe smoking causes stroke, heart attack, and lung cancer. While every country requires a message specific to their population, the common theme is stopping smoking is the most important thing the public can do to reduce their risk of lung cancer and it is never too late to benefit from stopping, even after a diagnosis of a smoking-related disease. **Benefits of quitting** Smoking not only increases your risk of lung cancer, but of multiple cancers, heart disease, stroke, lung disease, and fertility and pregnancy problems (US National Library of Medicine, 2017). Tobacco smoke contains around 7,000 chemicals. Many of these are poisonous and over 60 are known to be cancer causing. For people already diagnosed with lung cancer, smoking cessation can seem pointless but there are clear benefits to stopping smoking including better treatment efficacy, fewer side-effects, less risk of recurrence and less risk of developing other smoking-related health problems (American Society of Clinical Oncology, 2016). There are immediate and long-term health benefits of quitting for all smokers, including those already diagnosed with lung cancer, including (World Health Organisation, 2017): Within 20 minutes, your heart rate and blood pressure drop After 12 hours, the carbon monoxide level in your blood drops to normal Within 2-12 weeks, your circulation improves and your lung function increases At 1-9 months, coughing and shortness of breath decrease By 1 year, your risk of coronary heart disease is about half that of a smoker's Within 5-15years, your stroke risk is reduced to that of a non-smoker By 10 years, your risk of lung cancer falls to about half that of a smoker and your risk of cancer of the mouth, throat, oesophagus, bladder, cervix, and pancreas decreases Within 15 years, the risk of coronary heart disease is that of a non-smoker's. **Role of advocates** Advocates have an opportunity to promote smoking cessation on a National scale as well as at an individual level. This can seem like an overwhelming task in light of the significant health burden smoking presents, however international support is available. In 2005 The World Health Organisation Framework Convention on Tobacco Control (WHO FCTC) was created. This evidence-based treaty reaffirms the right of people to the highest standard of health, provides legal dimensions for international health cooperation and sets high standards for compliance. Each MPOWER measure corresponds to at least 1 provision of the WHO Framework Convention on Tobacco Control. The 6 MPOWER measures are: **M**onitor tobacco use and prevention policies **P**rotect people from tobacco use **O**ffer help to quit tobacco use **W**arn about the dangers of tobacco **E**nforce bans on tobacco advertising, promotion and sponsorship **R**aise taxes on tobacco. At an individual level, advocates can play a vital role in encouraging lung cancer patients and their families to avail of behavioural support and medication to assist their smoking cessation efforts. Lung cancer patients are burdened with elevated levels of distress in comparison to other cancers (Zabora et al., 2001) and research suggests that stigma and the association with tobacco is a very real issue for lung cancer patients (Chapple et al., 2004). This is in addition to being diagnosed with the biggest cancer killer worldwide, a probable late stage diagnosis, poor prognosis and debilitating symptoms. For the lung cancer patient, advocate guidance and support is vital to successfully quit smoking. People diagnosed with cancer often keep quiet about their smoking because (American Society of Clinical Oncology, 2016): they fear judgement or blame from their family or doctor they think they might get less support for their cancer treatment the think it is pointless to stop as they already have cancer they believe smoking helps them cope with stress they have tried to stop before unsuccessfully. The challenge for patient advocates is balancing this support at an individual level with the need to evoke change at a National and International level.

Keywords: smoking, Quitting, advocacy

MS 05 CLINICAL ISSUES OF IMMUNE CHECKPOINT INHIBITORS
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 05.02 FIRST-LINE VERSUS SECOND-LINE ANTI-PD-(L)1 THERAPY FOR PATIENTS WITH POSITIVE PD-L1 EXPRESSION

F. Barlesi

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Lung cancer is the leading cause of cancer-related deaths in other Western countries, with more than 1.8 million new cases and 1.5 million deaths worldwide in 2012 (Globocan, 2012). Recent advances in the management of NSCLC have included use of therapies targeting oncogenes (EGFR, BRAF or HER2 mutations, ALK or ROS1 rearrangements) but molecular alteration is currently detected in only the half of the patients with non-squamous NSCLC (Barlesi et al., 2016). **Immune check point inhibitors** (ICI), the first of which targeted the lymphocyte cell surface inhibitory receptor PD-1 or its ligand PD-L1, have recently become available and have been shown to provide an overall survival advantage over standard second-line chemotherapy (Borghaei et al., 2015; Brahmer et al., 2015; Herbst R et al, Lancet 2016; Rittmeyer et al, 2016), and more recently over first-line standard chemotherapy in monotherapy for a small subgroup driven by PD-L1 expression (Reck et al., 2016) or in combination regardless of PD-L1 expression (Langer et al, Lancet Oncol 2016), for both squamous and non-squamous NSCLC. Unfortunately, the long-term overall survival benefit is driven by only about 20-25% of the patients. **PD-L1 tumor expression** has been proposed to guide the patients' selection but remains controversial (Kerr K, 2016). However, PD-L1 tumor expression of more than 1% and 50% is mandatory for the use of pembrolizumab monotherapy in second and first-line, respectively. Therefore, **how to choose the best way to use ICIs for advanced NSCLC patients?** Many aspects may be considered and will be discussed during the session including the PD-L1 expression and other potential predictive biomarkers (as tumor mutational burden), the current contra-indications to ICIs, the potential suspected factors predicting a higher risk of rapid progression on ICIs, the potential synergy for the concomitant combination of ICIs with chemotherapy or conversely a sequential use, the side effects for monotherapies and combinations, and the recent data on ICIs combinations versus standard chemotherapy. **In summary**, the attendees will have the arguments to globally assess the risk/benefit balance in using ICIs first or at resistance to chemotherapy and discuss the chosen strategies with their patients.

Keywords: Immune Check points inhibitors, First line treatment, Combination immunotherapy and chemotherapy

MS 05 CLINICAL ISSUES OF IMMUNE CHECKPOINT INHIBITORS
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 05.04 PRACTICAL APPROACH TO COMBINATION OF CHEMOTHERAPY WITH IO

Y. Ohe

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Combination of chemotherapy with immune-check point inhibitor is considered to

be one of the most promising strategy to improve efficacy of immune-check point inhibitors. Several clinical trials of chemotherapy with immune-check point inhibitor are conducted and the results have been reported. KEYNOTE-021 cohort G is a randomised, open-label, phase 2 cohort of a multicohort study assessed whether the addition of pembrolizumab to carboplatin and pemetrexed improves efficacy in patients with advanced non-squamous NSCLC. Thirty-three (55%; 95% CI 42–68) of 60 patients in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18 (29%; 18–41) of 63 patients in the chemotherapy alone group (p=0·0016). Progression-free survival (PFS) was significantly longer with pembrolizumab plus chemotherapy compared with chemotherapy alone (HR 0·53 [95% CI 0·31–0·91]; p=0·010). Median PFS was 13·0 months for pembrolizumab plus chemotherapy and 8·9 months for chemotherapy alone. The FDA has granted an accelerated approval to pembrolizumab for use in combination with pemetrexed plus carboplatin as a frontline treatment for patients with metastatic or advanced non-squamous NSCLC, regardless of PD-L1 expression. Antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab that are currently approved for use in the treatment of NSCLC. Bevacizumab, in addition to platinum-based chemotherapy is widely used for the first-line treatment of advanced, metastatic, or recurrent NSCLC, excluding squamous cell carcinoma. VEGF influences lymphocyte trafficking across endothelia to the tumor by inhibiting lymphocyte adhesion and VEGF has a systemic effect on immune-regulatory cell function through multiple mechanisms, such as Tregulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs); suppression of dendritic cell maturation; and inhibition of T-cell development from hematopoietic progenitor cells. Thus, combination of antiangiogenic monoclonal antibody and immune-check point inhibitor is potentially synergistic. National Cancer Center Hospital conducted a single-center phase Ib study investigated the tolerability, safety, and pharmacokinetics of nivolumab combined with standard chemotherapy in patients with advanced NSCLC. In this trial, nivolumab with gemcitabine/cisplatin, pemetrexed/cisplatin, paclitaxel/carboplatin/bevacizumab, or docetaxel were evaluated for six patients each arm. Combination of nivolumab and chemotherapy showed an acceptable toxicity profile and encouraging antitumor activity in patients with advanced NSCLC. Although small number of patients, nivolumab with paclitaxel/carboplatin/bevacizumab seems to be most promising with higher response rate and longer PFS. Based on these data, phase III study of paclitaxel/carboplatin/bevacizumab with/without nivolumab for advanced non-squamous NSCLC is ongoing.

Keywords: antiangiogenic monoclonal antibody, chemotherapy, immune-check point inhibitor

MS 05 CLINICAL ISSUES OF IMMUNE CHECKPOINT INHIBITORS
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 05.06 BRAIN METASTASIS: RATIONALE AND EFFICACY WITH IO

I. Gil-Bazo

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The development of metastases from a primary tumor is the ultimate cause of death in most of patients with cancer. In a non-small cell lung cancer (NSCLC) series of 236 patients with advanced disease, brain metastasis appeared to be the second leading site of metastasis after bone (1). In fact, 31.8% of the patients presented brain metastasis at onset and a total of 42.8% of all patients included developed brain metastasis at any time point (1). Despite recent advances in the treatment of patients with NSCLC, CNS infiltration remains a frequent complication leading to impaired quality of life and shortened survival among NSCLC patients. In the era of personalized medicine for patients harboring oncogenic driver mutations, CNS infiltration has become an especially relevant clinical issue. In fact, an apparent higher incidence of brain metastasis at onset, among patients with molecular alterations, in particular for ALK + tumors has been reported (2). In addition, a higher cumulative incidence of CNS involvement overtime during treatment with targeted agents has been shown and CNS may be the only site of progression to first or second-line tailored therapies. Unfortunately however, most patients with advanced NSCLC present tumors lacking druggable oncogenic driver aberrations. In 2011, the tumors' capacity of avoiding immune destruction was recognized as a new emerging hallmark of cancer. More recently, the constellation of interactions between tumor cells and the immune environment around them has definitely emerged as a potential and valuable source of innumerable novel anti-cancer targets. From the clinical perspective, treatment with immune checkpoint inhibitors targeting programmed-cell death 1 (PD-1) and its ligand (PDL-1) represent the best treatment option for many patients with advanced NSCLC in first-line (3) and most of them in second-line (4-6) due to an improved quality of life and a significant survival benefit. Unfortunately, most phase II randomized/phase III clinical trials assessing the efficacy of monoclonal antibodies against PD-1 (3,4,6) and PDL-1 (5) immune checkpoints in second or first-line settings excluded patients with active or untreated brain metastasis. Additionally, no data on the evolution of previously locally treated CNS lesions during immunotherapy have been provided, nor information revealing the sites of distant progression in patients on the study arm experiencing progression disease to the treatment. The only available results in this regard are reflected in KEYNOTE-024 trial in which the subgroup analysis showed a statistically significant benefit in terms of progression-free survival for patients without baseline brain metastasis on pembrolizumab compared to non-significant differences among patients with brain involvement receiving the PD-1 blocker (3). More interestingly, Goldberg et al. reported the only direct evidence on the potential activity of an immune checkpoint inhibitor against brain metastasis from NSCLC in a non-randomized, open label, phase II clinical trial (7). The study enrolled 36 patients with untreated brain metastases from melanoma (18 patients) or NSCLC (18 patients) receiving pembrolizumab monotherapy. Patients were given 10 mg/kg pembrolizumab every 2 weeks until progression and the primary endpoint was brain metastasis response assessed in all treated patients. In the preliminary results reported, a brain metastasis response was achieved in four (22%; 95% CI 7–48) of 18 patients with melanoma and six (33%; 14–59) of 18 patients with NSCLC. Despite the low number of patients included, this remarkable activity shown by pembrolizumab among brain metastases in patients with NSCLC warrants further investigation in larger series and prompt the analysis of the anatomic, molecular and immune factors involved in those responses. Other studies have focused their attention in the immune microenvironment of the brain in an attempt to unravel the theoretical activity of an immune-directed therapeutic approach. Berghoff at al. investigated tumor-infiltrating lymphocytes (TIL) subsets and their prognostic impact in 116 brain metastases (BM) from different tumor type's specimens using immunohistochemistry for CD3, CD8, CD45RO, FOXP3, PD1 and PD-L1 (8). Interestingly enough, they found TIL infiltration in 115/116 (99.1%) BM specimens. PD-L1 expression was evident in 19/67 (28.4%) BM specimens and showed no correlation with TIL density ($p > 0.05$). High infiltration was most frequently observed for CD3+ TILs (95/116; 81.9%) and least frequently for PD1+ TILs (18/116; 15.5%; $p < 0.001$). Highest TIL density was observed in melanoma, followed by renal cell cancer and lung cancer BM ($p < 0.001$). More importantly, the density of CD3+, CD8+, and CD45RO+ TILs showed a positive and significant correlation with favorable median overall survival (OS) times. The same group has found TIL infiltration and PD-L1 expression as a common feature in Small-cell Lung Cancer (SCLC) BM. In addition, the presence of CD45RO+ memory T-cells and PD-L1+ TILs in SCLC BM seemed to be associated with favorable survival times suggesting an active immune microenvironment in SCLC BM (9). Takamori et al., evaluated the discordance in PD-L1 expression between primary and metastatic lesions and analyzed the association between the discordance and other clinical factors in 21 NSCLC patients (10). Remarkably, among the 16 patients with brain metastases, in three of them there was a good correlation in PDL-1 expression between the primary tumor and the brain metastasis. In other two patients however, positive PDL-1 primary lesions produced PDL-1 brain metastases. Interestingly enough, in two patients with PDL-1 negative NSCLC undergoing radiation therapy for brain metastases followed by surgical resection of BM, irradiated lesions turned to be positive for PDL-1 expression suggesting a potential capacity of radiotherapy to induce PDL-1 expression in BM (10). In fact, these observations along with several preclinical findings have paved the way for the design of clinical trials combining radiation therapy and immune checkpoint inhibitors against brain metastases. In summary, here we present and discuss the most relevant evidences about the particular immune microenvironment of the brain, the clinical activity of immune checkpoint inhibitors against NSCLC brain metastasis as well as their potential combination with local radiation therapy and the hypothetical use of TIL infiltrates and PDL-1 expression as predictive biomarkers for response of brain metastases to immunotherapy. Several clinical cases illustrating these evidences will be also presented and discussed. **References** 1. Castanon E, Rolfo C, Vinal D, Lopez I, Fusco JP, Santisteban M, et al. Impact of epidermal growth factor receptor (EGFR) activating mutations and their targeted treatment in the prognosis of stage IV non-small cell lung cancer (NSCLC) patients harboring liver metastasis. J Transl Med. 2015;13:257. 2. Kang HJ, Lim HJ, Park JS, Cho YJ, Yoon HI, Chung JH, et al. 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Keywords: Brain microenvironment, Immune checkpoint inhibitors, CNS involvement

MS 06 COMBINED MODALITY TREATMENT FOR THYMIC AND PLEURAL MALIGNANCY
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 06.01 PROPOSAL OF CHANGE FOR FUTURE STAGING SYSTEM FOR THYMIC TUMOR

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Although Masaoka clinic-pathological staging system has been accepted as the global standard staging system for thymic epithelial tumors, several problems of this staging system have been pointed out because clinical practices in diagnosis, medical treatment and surgical procedure has enormously advanced during more than 30

years. Furthermore, there has not been a TNM classification system approved by UICC to describe a tumor's clinical status adequately. To overcome these situations, International Thymic Malignancy Interest Group (ITMIG) established global database and proposed a novel staging system based on TNM definition in collaboration with IASLC staging committee in 2016. This is a great progress in clinical medicine in the field of thymic epithelial tumor, but as a matter of fact, stage grouping according to this novel TNM classification is mostly defined by tumor invasion to adjacent organs similarly to Masaoka staging system. Japanese Association for Research of the Thymus (JART) established by Akira Masaoka and colleagues contributed to the ITMIG project of global database, and several studies using JART database were performed and reported from Japanese researchers. Novel findings in the JART database study are reviewed and new insights in further modification in TNM staging system are addressed in the present article. The significance of involved organs as a prognostic factor has been a great interest, because some structures are easily resected while others are difficult to be completely resected. Actually, some previous studies showed prognostic significance of involvement of the great vessels. Based on the ITMIG database, involvement of the pericardium alone is defined as T2 in the UICC TNM classification while involvement of SVC and brachiocephalic vein is defined as T3 and involvement of the aorta, aortic branches and intrapericardial vessels is defined as T4. One of the JART database study focusing on the involved organs in Masaoka stage III tumors showed that invasion to the chest wall is an independent prognostic factor by multivariate analysis while involvement of the great vessels is not. The hazard ratio of involvement of the chest wall is 4.07. Invasion to the chest wall is defined as T3, but when invasion to the sternum is extended, resection of the chest wall including sternum is sometimes a difficult procedure, and complete resection is hard to be achieved. Lymphatic channels are distributed in the chest wall, of which involvement by the tumor can result in nodal metastasis. Thus, invasion to the chest wall might be considered as an important factor to determine the tumor spread, and therefore, as one factor in T definition. Involvement of SVC and brachiocephalic vein is defined as T3, but is heterogenous variable because some tumors invade to the outer surface of the vessel but others enter the lumen of the vessel, which can result in pulmonary metastasis. The extent in involvement of the great vessels could be a significant factor in T definition. Tumor size could reflect the time from initiation of the tumor and the larger tumor is more likely to be in an advanced status. Actually, tumor size is a critical factor in T definition in lung cancers. In thymic epithelial tumors, however, T definition does not reflect the tumor size. Using JART database, oncological significance of the tumor size was examined in thymoma and thymic carcinoma, separately. In thymoma, the rate of R0 resection in the tumors less than 5.0 cm, 5.1 to 10 cm, and more than 10.1 cm was 94.4%, 91.3%, and 84.0%, respectively. Recurrence rate after R0 resection in the tumors less than 5.0 cm, 5.1 to 10 cm, and more than 10.1 cm was 3.0%, 8.9% and 27.2%, respectively. In thymic carcinoma, the rate of R0 resection in the tumors less than 5.0 cm, 5.1 to 10 cm, and more than 10.1 cm was 80.2%, 63.2%, and 62.5%, respectively. Recurrence rate after R0 resection in the tumors less than 5.0 cm, 5.1 to 10 cm, and more than 10.1 cm was 28.2%, 53.7% and 62.5%, respectively. Thus, there was apparent difference in oncological behavior between tumors less than 5.0 cm and those more than 5.1 cm both in thymoma and thymic carcinoma. These observations suggest that tumors size also should be included in T definition in thymic epithelial tumors. Finally, the category of Masaoka stage IVA disease includes pleural dissemination, but the situation of pleural dissemination varies greatly from a single lesion to numerous lesions. Furthermore, some disseminations are resectable while others are not. JART study revealed that the number of disseminated lesions on the pleura In conclusion, T definition remains to be further evaluated in reference to tumor size, chest wall invasion and extent of involvement of the great vessels. M definition also remains to be further discussed in terms of extent of the pleural dissemination.

Keywords: Thymic carcinoma, TNM classification, Thymoma

MS 06 COMBINED MODALITY TREATMENT FOR THYMIC AND PLEURAL MALIGNANCY
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 06.02 IS THERE A ROLE FOR MINIMALLY INVASIVE SURGERY IN LOCALLY ADVANCED THYMIC TUMORS?

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Background: Thymectomy via median sternotomy has been the standard surgical approach for patients with thymic malignancies. However, the last decade has seen an increasing interest in minimally invasive thymectomy for early stage tumors. By avoiding sternal split, video-assisted thoracoscopic surgery (VATS) has been reported to be associated with similar operating time but less blood loss during operation, shorter length of intensive care unit and hospital stays, diminished postoperative pain, and improved postoperative pulmonary function. A recent propensity-score matched study by the Chinese Alliance of Research for Thymomas (ChART) reported 100% complete resection rate in both VATS and open thymectomies for UICC stage I (T1N0M0). Both overall and disease-free survivals, as well as cumulative incidence of recurrence were similar between the matched groups. The role of minimally invasive surgery has thus been well established in early stage thymic tumors. Using the International Thymic Malignancy Interest Group (ITMIG) global database, a recent propensity-score matched study found that complete resection rate was comparable between minimally invasive and open approaches (96% vs. 96%, *P*=0.7), including 33 and 10 patients with Masaoka stage III and IV diseases. And surgical approach was not a predictor of R0 resection in that study. The results suggested that minimally invasive surgery may also have a role in some patients with locally invasive tumors. To prove this, it is necessary to show that VATS is associated with improved peri-operative results, while maintaining similar resection rate and oncologic outcomes as open surgery. We therefore carried out a propensity-score matched study comparing the results of VATS and median sternotmy in UICC T2-3 thymic tumors to see whether minimally invasive surgery might be an acceptable approach. **Patients and Methods:** Surgical patients with UICC stage pT2-3 thymic tumors were retrospectively retrieved from a prospectively maintained database at the Shanghai Chest Hospital. Those who undergone VATS resection were compared with patients receiving median sternotomy (Open). A propensity-score matched study was then carried out to compare resection rate, peri-operative outcomes, and follow-up results between the two matched groups. **Results:** During 2007-2017, 115 patients who undergone surgical resection of thymic malignancies turned out to have UICC pT2-3 tumors upon histological examination. In 29 patients, video-assisted thoracoscopic surgery (VATS) was attempted and completed in 26 cases. In 89 patients (including the 3 conversion cases due to extensive tumor invasion) the lesion was resected via Open median sternotomy. Comparing with the VATS group, the Open group has larger tumor size, higher T stage, and received more induction therapies. A propensity-score match was carried out according to concomitant autoimmune disease, co-morbidity, induction therapy, tumor size, and UICC pTNM stage in 1:2 ratio. This leaves 26 patients in the VATS group and 52 patients in the Open group (Table 1). Induction therapies were given in 7.7% and 9.6% patients in the two groups (p=0.779). The two groups were comparable in patients' age, gender, tumor histology, as well as all the matching factors. Complete resection (R0) rate was comparable (76.9% in both groups), with higher primary tumor resection rate in the VATS group (96.2% vs. 86.7%, p=0.151). Because of local tumor invasion, pericardium, lung (wedge resection), phrenic nerve, and left innominate vein were resected together with the tumor in 21, 17, 3, and 3 patients, respectively. Postoperative morbidity rate was also similar between the two groups (15.4% vs. 17.3%, p=0.830). Comparing to the Open group, VATS patients had less intraopertaive blood loss (127 ml vs. 219 ml, p=0.005), shorter duration of chest drainage (3±1.2 day vs. 5±4.7 day, p=o.oo5) and length of hospital stay (5.9±3.1 vs. 9.6±5.1, p<0.001). During a median follow-up of 35 months, overall survival was 100% in the VATS group and 95.2% in the Open group (Figure 1, p=0.664), and 3-year recurrence rates were 0.052 and 0.167, respectively (Figure 2, p=0.554). **Conclusions:** In addition to UICC stage I thymic malignancy, VATS may also be an acceptable approach for locally advanced thymic tumors. Complete resection rate and follow-up results are comparable to open surgery in well selected cases. And better peri-operative results can be expected via VATS approach as compared to median sternotomy. Based on these results, VATS should be attempted in those patients with potentially resectable thymic tumors. And long-term follow-up is still necessary to confirm its oncological effectiveness. Table 1. Comparison of patient demographics, tumor characteristics, and peri-operative results between the VATS and Open groups.

		VATS N=26	Open N=52	P Value
Gender	male	17 (65.4)	34 (65.4)	1.0
Age	year	58.5±13.0	57.7±10.1	0.781
Autoimmune diseases	yes	5 (19.2)	8 (15.4)	0.667
Co-morbidity	yes	8 (30.8)	14 (26.9)	0.722
Tumor size	cm	5.7±2.0	6.4±1.7	0.161
Histology	Thymoma	15 (57.7)	29 (55.8)	0.889
	Thymic Carcinoma	11 (42.3)	23 (44.2)	
pT	T2	8 (30.8)	14 (26.9)	0.722
	T3	18 (69.2)	38 (73.1)	
pN	N0	25 (96.2)	51 (98.1)	1.0
	N1	1 (3.8)	1 (1.9)	
pM	M0	21 (80.8)	45 (86.5)	0.506
	M1a	5 (19.2)	7 (13.5)	
Operation time	min	136±50	134±47	0.85
Blood lose	ml	127±90	219±150	0.005
Chest tube drainage	day	3±1.2	5±4.7	0.005
Length of hospital stay	day	5.9±3.1	9.6±5.1	0.000
Morbidity	yes	4 (15.4)	9 (17.3)	0.830

Figure 1. Overall survivals between the VATS and the Open groups after propensity-score matching.

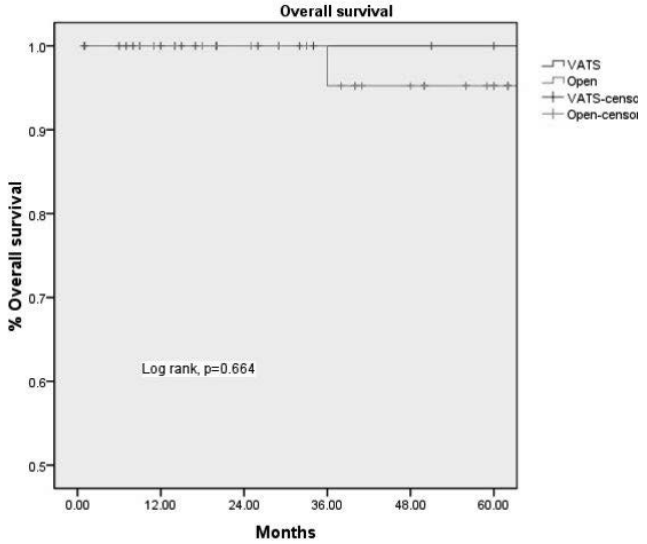
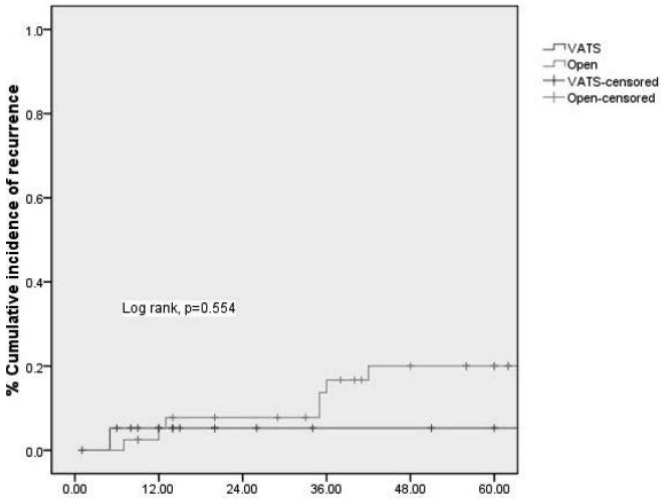


Figure 2. Cumulative incidences of recurrence after propensity-score matching in completely resected patients in the VATS and the Open groups.



Keywords: Minimally Invasive Surgery, Thymic tumors

MS 06 COMBINED MODALITY TREATMENT FOR THYMIC AND PLEURAL MALIGNANCY
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 06.04 THE EFFECT OF THE TIMING OF CHEMOTHERAPY: INDUCTION VS ADJUVANT AFTER PD OR EPP

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Multimodality therapy for malignant pleural mesothelioma (MPM) including radical surgery has been associated with prolonged survival and in selected patients, but the evidence for a long term survival benefit is inconsistent [1,2]. There is little evidence regarding the optimal timing of additional chemotherapy, with some advocating induction treatment or in the immediate post operative setting, and others choosing to delay until progression. We have analysed our experience of the effect of the timing of chemotherapy on the outcome of extrapleural pneumonectomy (EPP) or pleurectomy/ decortication (PD) [3] . Induction chemotherapy The use of a standardized neo-adjuvant chemotherapy regimen has been reported to be feasible in patients treated by EPP and adjuvant hemithoracic radiotherapy [4] . This regime requires high levels of patient fitness and is associated with a median survival of 16.8-25.5 months. However, this decreases dramatically if patients are unable to complete the entire trimodality therapy protocol (9-14 months) [5]. This may select those who will not have a prolonged survival, thus avoiding futile but morbid therapy. There is also the potential for tolerance of an increased number of cycles prior to surgery than in the adjuvant setting. The drawbacks include the risk of progression during chemotherapy, or severe toxicity, leaving the patient unsuitable for radical surgery. It is possible that neoadjuvant chemotherapy may select out chemoresistant cells, and lead to more aggressive disease progression following the inevitable R1 resection. There is currently no evidence to show that there is any long-term benefit to a response to chemotherapy prior to radical surgery. In fact, a true, significant, pathological response to chemotherapy is very rare [5]. Adjuvant chemotherapy The apparent benefit with adjuvant chemotherapy may be due to selection bias; only the fittest can receive the full regime, and will therefore have a survival benefit independent of therapy. Nevertheless, the IASLC staging committee found that the provision of adjuvant therapy was an independent prognostic factor for survival in patients with MPM [6]. Adjuvant chemotherapy may be contraindicated due to low compliance as a consequence of the morbidity of surgery In the case of EPP, many patients are not able to tolerate adjuvant chemotherapy, however in the case of EPD, most patients recover from surgery and are able to commence therapy within 8 weeks [7]. There has been a change in practice over time with regards the number of cycles given in the adjuvant setting, from 4 to 6. Delayed (expectant) chemotherapy Oncologists may wish to reserve an active agent, pemetrexed, until assessable disease or symptom-related progression. It may be beneficial as treatment of low volume residual disease following R1 resection may select out clones with resistance to platinum therapy thus reducing the efficacy at re-challenge during relapse. We found no difference in overall survival when chemotherapy was given in the immediate adjuvant setting or only at progression. However, subgroup analysis revealed that in non-epithelioid MPM delayed therapy was an independent predictive factor for poor survival/progression free survival. This could be explained in part by the continued presence of a subpopulation of aggressive and chemo-resistant stem cells in the sarcomatoid element of biphasic disease following an R1 resection. These more aggressive cells are then able to proliferate, as compared with a more indolent group of stem cells in epithelioid disease, leading to a shorter time to relapse and a more aggressive tumour type if no chemotherapy is given in the adjuvant setting. This is often seen after chemotherapy treatment alone, where these aggressive resistant cells are selected for, giving rise to rapid progression, even after an initial response [8]. Similarly, in those with nodal disease delaying chemotherapy was also found to be detrimental. In these patients tumour cells have already developed the ability to metastasise and it is likely that systemic micrometastases are present following local resection. Intra operative chemotherapy Intraoperative instillation of platinum based chemotherapy into the pleural cavity after resection has been shown to be safe in selected experienced institutions, where favourable median overall and progression free survival outcomes have been reported [9]. We did not include this modality in our protocol but one such study showed an increase in time to progression from 12.8 to 27.1 months, and overall survival from 22.8 to 35.5 months in clinically matched patients [10]. Conclusion Our retrospective study [3] showed no significant overall survival benefit from any particular timing of chemotherapy with either neo-adjuvant, adjuvant, or expectant management. Interestingly, we found no benefit in giving neo-adjuvant chemotherapy, despite the intrinsic bias within this group of patients, as only those who did not progress proceeded to surgery. We suggest that it may be important to tailor chemotherapy in 4 clinical sub-groups. In the poorer prognosis groups, non-epithelioid cell type and/or with pathological lymph node disease, giving chemotherapy in the immediate adjuvant setting (within 3 months of surgery) rather than delaying it until progression gave a survival advantage. Conversely, there was no benefit found in giving therapy in the immediate adjuvant setting in better prognosis patients with epithelioid cell type and with no evidence of lymph node metastases at operation. It may therefore be preferable to reserve first line chemotherapy until there is radiological evidence of disease progression in these patients. Future results from the EORTC NCT02436733 trial : a randomized phase II study of pleurectomy/ decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma [11] will inform this debate. We suggest that the randomization in the trial is stratified in to epithelioid versus non-epithelioid and clinical node positive versus negative. References 1.C. Cao, D. Tian, C. Manganas, P. Matthews, T.D. Yan, Systematic review of trimodality therapy for patients with malignant pleural mesothelioma., Ann Cardiothorac Surg. 2012; 1: 428–37. 2.Nakas A, Waller D. Predictors of long-term survival following radical surgery for malignant pleural mesothelioma .Eur J Cardiothorac Surg. 2014;46:380-5. **3.**Sharkey AJ, O'Byrne KJ, Nakas A, Tenconi S, Fennell DA, Waller DA. 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Thorac.Cardiovasc. Surg. 145 (2013) 955–963. 11. EORTC NCT02436733 trial : a randomized phase II study of pleurectomy/ decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma. https://clinicaltrials.gov/ct/show/NCT02436733

Keywords: Mesothelioma, Surgery, chemotherapy

MS 06.05 THE USE OF ADJUVANT IMRT AFTER PLEURECTOMY/ DECORTICATION

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Intensity-modulated radiation therapy (IMRT) is a highly conformal radiation technique that allows more effective sparing of normal tissues, providing an opportunity for safer, less toxic treatments and increased efficacy by enabling higher radiation doses to the tumor target. It comes with a much higher level of dosimetric control and certainty leading to better target coverage than conventional OR 3D conformal radiation techniques.[1] The higher precision of IMRT delivery when used in the adjuvant setting requires detailed knowledge of the intrathoracic anatomy, incorporation of all diagnostic imaging tools available, incorporation of the pathologic findings at the time of surgery, assessment of the respiratory tumor motion using a 4D scan, and image-guided treatment delivery. IMRT with integration of a boost to areas of gross disease is technically feasible but has not yet been tested in a larger series. The use of 18-fluorodeoxyglucose positron emission tomography (PET) for RT planning purposes may reduce the likelihood of geographic misses and detect radiographically occult lymph node involvement. Small series have suggested that PET may guide the delineation of an integrated boost volume or improve local control.[2] The recent decline in extrapleural pneumonectomies (EPP) in the surgical management of malignant pleural mesothelioma (MPM) due to reports suggesting a lack of survival benefit compared with lung-sparing pleurectomy/decortication (P/D) has posed a particular challenge for adjuvant radiation treatments: how to safely treat the pleural space for microscopic residual disease without exceeding the radiation tolerance of the underlying sensitive normal lung tissue. Older radiation techniques result in unacceptable toxicity and insufficient local control.[3] Thus, an IMRT technique targeting the hemithoracic pleural space including the diaphragm that simultaneously spared the ipsilateral lung, heart, liver, kidneys and abdominal contents was developed (Figure 1).[4] Typically these patients are treated with six to nine coplanar 6 MV beams equispaced over 200-240 degrees around the ipsilateral hemithorax were used. More recently, rotational techniques such as volumetric arc therapy or tomotherapy have been shown to allow for even more effective sparing of organs at risk.[5,6] The first report in 36 MPM patients with 2 intact lungs showed that hemithoracic adjuvant pleural IMRT (50.4 Gy in 28 fractions) could be delivered with a 20% (n=7) ≥ grade 3 pneumonitis risk; 1 patient had grade 5 pneumonitis.[4] The median survival in resectable patients was 26 months. A tomotherapy technique was published with similar toxicity outcomes (20% ≥ grade 2 pneumonitis, one fatal case of pneumonitis).[6] The radiation dose delivered was slightly higher with 50 Gy delivered in 25 fractions including a simultaneous boost to 60 Gy for areas of concern for residual disease based on FDG-PET. A matched analysis of P/D, chemotherapy, and IMRT vs. EPP, chemotherapy and IMRT found favorable median overall (28.4 vs. 14.2 months) and progression-free survival (16.4 vs. 8.2 months) with trimodality therapy involving P/D compared with EPP.[7] Local failure rates vary significantly among studies, ranging from 40 to 68% at 2 years. A systematic review of 67 patients still found a significant risk of local failures in the radiation field, mostly in unresectable patients and sites of gross residual disease, emphasizing the importance of a macroscopic complete resection, need for optimization of radiation targeting and experience with this complex radiation technique.[8] Increasing experience over time led to fewer marginal failures and decreased toxicity, suggesting the improvement in target delineation and RT planning. Most recently an association of radiation dose to the heart and overall survival was reported,[9] similar to observations in locally-advanced non-small cell lung cancer. These encouraging results have led to a 2-institution phase II trial of trimodality therapy using induction chemotherapy with cisplatin and pemetrexed, P/D, and adjuvant hemithoracic intensity-modulated pleural radiation therapy (IMPRINT).[10] Twenty-seven patients were treated and 29.6% developed radiation pneumonitis (6 grade 2; 2 grade 3). Median progression-free and overall survival was 12.4 and 23.7 months, respectively. In resectable MPM patients who received chemotherapy and IMPRINT, 2-year OS was 59%. Based on these findings a multi-institutional phase II study was initiated to demonstrate the safety and exportability of this complex IMPRINT technique in a multicenter setting involving institutions without prior experience of IMPRINT (clinicaltrials.gov: NCT00715611). All patients' treatment contours and plans are centrally reviewed and revised for uniformity. The goal is to accrue 36 patients from 5 institutions. Given the promising outcomes this study may be succeeded by a randomized trial testing the effect of adjuvant IMPRINT vs no additional treatment after lung-sparing P/D and chemotherapy.

Figure 1:

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Keywords: Mesothelioma, IMRT, pleurectomy/decortication

MS 06.06 CHEMOTHERAPY FOR THYMIC AND MESOTHELIAL TUMORS

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Thymic and Mesothelial Tumors are relatively rare. There are few therapies that have been established in prospective studies, so the conditions have poor prognoses. Cisplatin+pemetrexed is the gold standard for unresectable malignant pleural mesothelioma in that it has shown a significantly longer survival than cisplatin in a controlled Phase III clinical study. Moreover, adding on bevacizumab to this combination therapy can extend survival, and these two therapies are recommended as 1L by the NCCN guideline. There have recently been promising results reported with anti-PD-1 antibody and anti-PD-L1 antibody single agent therapies as well as combination therapies with anti-CTLA-4 antibody, and there are many ongoing prospective clinical studies on these now. There are not very many therapies for Thymic malignancies that have already been examined in prospective studies. Carboplatin + paclitaxel, ADOC (cisplatin + doxorubicine + vibncristine + cyclophasphamide) therapy, CAP(Cisplatin + doxorubicine + cyclophosphamide) therapy, and the like are currently used as a result of outcomes in Phase II studies and retrospective studies. Furthermore, there have been reports of responses with molecular targeting therapies such as Sunitinib that target Kit. It has been reported that Thymic tumors express PD-L1, and there are currently several ongoing studies examining the relatively frequency and effect of anti-PD-1 antibody on such. My presentation will provide an overview of the current gold standards, recent clinical study outcomes, and promising pipeline therapies for Thymic and Mesothelial Tumors.

MS 07.01 PATHOLOGY OF NEUROENDOCRINE TUMORS OTHER THAN SCLC

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Neuroendocrine tumors (NET) of the lung comprise approximately 20% of all primary lung carcinomas overall and consist primarily of four malignancies: Typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma(SCLC) using 2015 World Health Organization (WHO) nomenclature. The four tumors have historically been regarded as a spectrum; however, there are significant differences between TC/AC and LCNEC/SCLC on many levels. Additionally, while most TC and AC arise de novo, a small percentage of cases with arise in the setting of diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH), a rare pre-neoplastic condition. DIPNECH has not been associated with the development of LCNEC or SCLC. TC and AC, comprise 1-2% of primary lung cancers with the vast majority being TC. Both TC and AC may occur in either a central or peripheral location, with central tumors resulting in symptoms related to obstruction while peripheral tumors are often asymptomatic and discovered incidentally. TC is considered a "low grade" or "well-differentiated" tumor; however, 5-20% of TC are associated with regional lymph node or distant metastases. AC, considered an "intermediate grade" or "moderately-differentiated" tumor, is associated with metastases in up to 40% of cases. The five and 10 year survival for TC is approximately 90% whereas it drops to 70% and 50% for AC. By current WHO criteria, TC is defined as a neuroendocrine tumor greater than 5mm in size with fewer than 2 mitoses per $2mm^2$ and lacking necrosis, whereas AC is defined as a neuroendocrine tumor with 2-10 mitoses per $2mm^2$ or necrosis. As mitotic activity and necrosis may be focal, the distinction between TC and AC can generally not be made on a small sample. Both tumors classically show an organoid or trabecular pattern of growth and are composed of a relatively uniform population of round to oval cells with granular nuclear chromatin, but may show a wide range of histologic growth patterns, particularly in TC. Given that the main feature distinguishing AC from TC is mitotic activity, one would expect that proliferation markers such as Ki-67 would be of potential value in discriminating these two tumors. Numerous studies have attempted to evaluate this parameter with various cut offs being proposed; however, ultimately there is too much overlap between the Ki-67 scores of TC and AC for it to be reliably useful in discriminating between the two tumors. The Ki-67 score can be useful in separating high-grade from low-grade tumors on small distorted biopsies, and some studies have shown it to have utility as a prognostic marker in TC/AC. As such it may be used to potentially guide treatment and is included as a parameter in the European Neuroendocrine Tumor Society (ENETS) guidelines. Surgery remains the only curative treatment option for TC/AC but there is a lack of consensus in regard to treatment of un-resectable or metastatic disease. Results of the RADIANT-4 trial have led to the approval of everolimus for advanced TC/AC. There is additional evidence that somatostain analogs may be useful in selected patients. Molecular analysis of TC and AC demonstrate distinctly different molecular profiles compared to the high grade NET's, with MEN1 alterations found essentially exclusively in carcinoids whereas alteration of RB1 cell cycle regulation genes and the PI3K/AKT/mTOR pathway were found less frequently in TC/AC and enriched in the higher grade tumors. TC/AC also tend to show frequent mutations of chromatin remodeling genes, as well as mutations of *PSIP1* and *ARID1A*. Actionable mutations such as *EGFR* mutations and *ALK* rearrangements are not found in TC/AC and thus far evaluation of PD-L1 in carcinoids has been negative, suggesting a lack of a role for current targeted therapy or immunotherapeutic agents used in non-small cell lung carcinomas (NSCLC). Several clinical trials are either ongoing or currently recruiting to evaluate the efficacy of several small molecular inhibitors. LCNEC was originally described in 1991 and was initially included as a subtype of large cell carcinoma in subsequent WHO classification, but in the current WHO it is classified as a type of neuroendocrine carcinoma. The tumor is defined as a tumor with neuroendocrine morphology with large cell morphology and greater than 10 mitoses/$2mm^2$, although most cases have substantially higher mitotic rates. By definition, tumors must show evidence of neuroendocrine differentiation, usually identified by immunohistochemical methods. While distinction of LCNEC from SCLC may appear straightforward on the surface, in reality LCNEC can be heterogeneous and the distinction is not always clear cut. Currently, there is no immunostain or other definitive test to discriminate between the two and distinction ultimately rests of subjective evaluation of the tumor morphology. The extreme rarity of this tumor, combined with the tumor heterogeneity and resultant subjectivity inherent in classification has likely contributed to conflicting reports in the literature regarding prognosis, although it is generally agreed that LCNEC is a high-grade tumor with a poor prognosis. Similarly, variable results have been reported in regard to the responsiveness of LCNEC to treatment regimens typically used for SCLC leading to a lack of consensus regarding whether LCNEC should be managed similar to SCLC or similar to other non-small cell carcinomas. Molecular studies have additionally shown variable results. The majority of studies have shown overlapping features with SCLC. Some studies, however, have shown alterations characteristic of other tumor types, most notably occasional *EGFR, ALK* and *KRAS* mutations even in the absence of an overt mixed adenocarcinoma component, which have not been found in SCLC. Interestingly, in 2016, Rekhtman, et al, evaluated 45 LCNEC and pared normal tissue by NGS with 241 cancer gene analysis. This study demonstrated that LCNEC, while having some commonly altered genes, largely fell into two major and one minor subset (SCLC-like, NSCLC-like and a small number of "carcinoid like" tumors). These findings may explain the variability of results in treatment trials and may indicate that more comprehensive analysis of this rare groups of tumors may yield more optimal treatment strategies.

Keywords: carcinoid, neuroendocrine, large cell neuroendocrine carcinoma

MS 07.02 NOVEL CHEMOTHERAPY FOR LCNEC

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Given that large cell neuroendocrine carcinoma (LCNEC) of the lung is rare and histological diagnosis from small samples is difficult, no large-scale clinical trials has yet evaluated the optimal chemotherapy for LCNEC. In a retrospective study of 45 consecutive patients with advanced LCNEC, response rates for small cell lung cancer (SCLC; n=11) and non-small cell lung cancer (NSCLC; n=34) regimen groups receiving first-line chemotherapy were 73% and 50% (P=0.19), median progression-free survival (PFS) was 6.1 and 4.9 months (P=0.41), and median overall survival (OS) was 16.5 and 9.2 months (P=0.19), respectively. SCLC regimens included platinum plus paclitaxel (PTX) and irinotecan plus platinum, while NSCLC regimens included pemetrexed, erlotinib, and gemcitabine[1]. A second retrospective study of the efficacy of first-line chemotherapies in 22 consecutive patients with advanced LCNEC reported an objective response in five of nine patients receiving CDDP+irinotecan (56%) and in three of five receiving carboplatin (CBDCA)+PTX (60%)[2]. Of the two prospective phase II studies of platinum-based chemotherapies for LCNEC (Table), a French study (GFPC 0302) used a chemotherapy regimen comprising CDDP+etoposide (ETP), while a Japanese study used CDDP+irinotecan. Objective response rate (ORR) was about 40% and median PFS was 5 to 6 months in both studies. Central pathological reviews in both studies demonstrated that about a quarter of patients had SCLC or undifferentiated NSCLC[3,4]. Everolimus is an oral mTOR inhibitor that has been approved for the treatment of well-differentiated neuroendocrine tumors of the lung. A recent phase II study of CBDCA+PTX+everolimus as first-line chemotherapy for advanced LCNEC was discontinued prematurely due to low recruitment after enrolling only 49 patients versus a planned sample size of 71. Among them, ORR was 45%, disease control rate was 74%, median PFS was 4.4 months, and median OS was 9.9 months[5]. Ongoing studies include a randomized phase II study comparing CBDCA+ETP and CBDCA+PTX for advanced LCNEC and a randomized phase II/III study of CDDP+ETP with or without veliparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, in patients with extensive stage SCLC or metastatic LCNEC.

Study	GFPC 0302	Japanese study	German study
Regimen	CDDP+ETP	CDDP+Irinotecan	CBDCA+PTX+ Everolimus
N	42	44	49
ORR (%) (95%CI)	38	55 (39-70)	45 (31-60)
Median PFS (months) (95%CI)	5.2 (3.1-6.6)	5.9 (5.5-6.3)	4.4 (3.2-6.0)
Median OS (months) (95%CI)	7.7 (6.0-9.6)	15.1 (11.2-19.0)	9.9 (6.9-11.7)

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Keywords: etoposide, irinotecan, Everolimus

MS 07.03 NOVEL SYSTEMIC THERAPY FOR CARCINOID OF THE LUNG

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Carcinoid tumors of the lung belong to a broad group of neoplasms called neuroendocrine tumors (NETs). These tumors are highly heterogeneous and represent a broad spectrum of phenotypes and clinical behavior. Often, the clinical behavior of these tumors corresponds with their underlying pathologic features. For example, in those tumors deemed as "typical carcinoid/NETs", clinical behavior

is often very indolent. At the other end of the spectrum, NETs can present as small cell lung cancer (SCLC) which is characterized by virulent and highly metastatic behavior. Those tumors deemed as "atypical carcinoid/NETs" usually have an intermediate clinical phenotype. Lung NETs are rare: the annual incidence rate is estimated to be approximately 1 in 100,000. In those patients whose lung NETs are no longer surgically resectable and/or have metastasized distantly, the treatment goals are principally disease control and symptom palliation. Because of their rarity, there are very limited prospective Level 1 data to guide optimal management of lung NETs. Treatment recommendations are often based on extrapolation from clinical experience in gastrointestinal NETs (specially pancreatic NET), subset analyses from other NET trials, anecdotal reports (case series), and expert opinion (e.g., consensus panels). Thus, the optimal management strategy for Lung NETs is not yet fully defined. Systemic therapy options range from somatostatin analog therapy, mTOR inhibitor therapy, and cytotoxic chemotherapy. Somatostatin analog therapy is offered in selected patient subsets that have slowly progressing disease and whose tumors express somatostatin receptors as detected by nuclear medicine scanning (Octreoscan). Somatostatin analog therapy is only modestly efficacious, with disease stabilization as the expected clinical benefit. Inhibition of the mTOR with everolimus has demonstrated efficacy in randomized trials. In the RADIANT-2 trial of everolimus+octreotide vs. placebo+octreotide in NETs, a small subset of patients with lung NETs (n=44) was analyzed. This showed an improvement in progression free survival with everolimus+octreotide vs. the control arm (median PFS 8.8 months vs 2.8; Hazard Ratio (HR) = 0.62; p=0.1). Subsequently, the phase III RADIANT-4 trial of everolimus vs placebo in non-functional lung and GI NETs was conducted. In this trial, approximately 30% of the 302 randomized patients had lung NETs. RADIANT-4 showed a PFS and overall survival (OS) benefit in favor of everolimus (PFS HR=0.39, p<0.0001; OS HR=0.64, p=0.037). More recently, a randomized phase II trial (LUNA) of pasitreotide alone, everolimus alone, or the combination showed a trend for improved PFS for the combination arm (PFS at 9 months was 39.0% for pasitreotide alone, 33.3% for everolimus alone, and 58.5% for the combination). In patients who are not candidates for somatostatin analog therapy or everolimus, or have failed these therapies, cytotoxic chemotherapy is often considered. The most commonly used regimens include platinum-etoposide (similar to that employed for SCLC) and temozolomide. Response rates to chemotherapy are reportedly much lower in lung NETs (vs SCLC) in retrospective studies; for example, platinum-etoposide is reported to yield response rates of 20-30% in lung NETs compared to rates greater than 50% in SCLC. It is thought that tumor responses are possibly influenced by the degree of tumor de-differentiation. Other agents with anecdotal activity include 5FU, capecitabine, oxaliplatin, and anthracyclines. Prospective trials of systemic therapy in lung NETs are essential to define the optimal standards of care. Selected References: 1. Hendifar, AE et al. J Thor Oncol 2016; 12(3):425-436 2. Yao, J. et al. Lancet 2016; 387: 968-77 3. Fazio N, et al. Chest 2013; 143(4):955-962

Keywords: carcinoid, neuroendocrine tumors, NETs

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MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 07.04 SURGICAL TREATMENT FOR NEUROENDOCRINE TUMORS OTHER THAN SCLC

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In the 1970s, pulmonary neuroendocrine tumors were classified into three histologically defined categories: typical carcinoid (TC), atypical carcinoid (AC) and small cell lung carcinoma (SCLC) [1]. In 1999, the World Health Organization (WHO) classified large cell neuroendocrine carcinoma (LCNEC) as a fourth neuroendocrine tumor of the lung. Although LCNEC was classified as a variant of large cell carcinoma in 1999 [2], it was classified as a neuroendocrine tumor in 2015. To date, for neuroendocrine tumors of the lung, the major categories of morphologically identifiable neuroendocrine tumors are TC, AC, LCNEC, and SCLC. Analyses of molecular markers revealed that low-grade TC and intermediate-grade AC exhibit a low proliferative rate compared with high-grade LCNEC and SCLC [3], and TC and AC have different genetic alterations from high-grade LCNEC and SCLC [4]. Analyses of their genetic alterations show that neuroendocrine lung tumors may represent a spectrum ranging from low-grade TC and intermediate-grade AC to highly malignant LCNEC and SCLC tumors [4]. TC is classified as a malignant epithelial tumor of the lung [2, 5]. However, the overall survival rate is better for TC than for AC [5, 6], and the frequency of lymph node metastases in TC is lower than in high-grade LCNEC and SCLC [6]. Therefore, some investigators have advocated limited resection in patients with TC [7]. Some reports revealed that sublobar resection was noninferior to lobectomy for survival in patients with TC tumor [7]. However, other reports advised that radical oncologic surgery with radical node dissection was needed, and segmental and other limited procedures had to be avoided because of the high frequency of lymph node involvement and multicentric forms [8]. Moreover, preoperative diagnoses and/or diagnoses from intraoperative frozen sections are often difficult for differentiating AC from TC, because small amounts of necrosis or few mitoses are sometimes unclear in those specimens. A randomized controlled trial is the best method to compare surgical efficacy. However, it may be impractical due to the rarity of carcinoid tumors. Moreover, AC has a poorer prognosis and a higher frequency of lymph node metastases than TC. Therefore, sublobar resection for TC might be the optimal surgical method because of lung preservation and lower mortality than lobectomy; however, limited resection for TC remains an area of controversy. Several reports [9] revealed that the clinical behavior, morphology, and prognosis of LCNEC were similar to those of SCLC, even though there might be several clinicopathological differences between SCLC and LCNEC in peripheral, small-sized, and high-grade neuroendocrine tumors [10]. Because it is difficult to diagnose patients with LCNEC pre-operatively, and most cases have been diagnosed postoperatively from surgically resected specimens, many reports on LCNEC have referred to surgical cases, of which the majority [9] revealed that patients with LCNEC had poor prognoses. Even patients with pathological stage I LCNEC have had poor prognoses, with five-year survival rates of 27-67% [9]. In patients with LCNEC who underwent radical surgery and complete resection, many recurrent tumors were observed as distant metastases [10]. Therefore, surgery alone is not sufficient to treat patients with LCNEC, and subsequent adjuvant therapy may be necessary [10]. Although there were high response rates with platinum-based and SCLC-based chemotherapies in patients with LCNEC, almost all patients had only partial responses [9, 10]. Patients with LCNEC may not be able to expect complete responses with platinum-based and SCLC-based chemotherapies compared with patients with SCLC, even though these chemotherapies are as effective as adjuvant treatment. Therefore, patients with advanced-stage LCNEC had a poor prognosis because they could not always achieve a complete response. Although the indication for surgery is limited to stage I in patients with SCLC, surgery and adjuvant chemotherapy may achieve satisfactory results in terms of survival for patients with LCNEC with not only stage I but also stage II/III [10]. Therefore, surgical indications for patients with LCNEC may not be limited to clinical stage I cases, and surgery with adjuvant chemotherapy should be attempted for resectable LCNEC. References [1] Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg*. 1972;64:413-21. [2] Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E, editors. 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Keywords: carcinoid, Surgery, neuroendoctine

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MS 07.05 ESTS REGISTRATION FOR NEUROENDOCRINE TUMORS

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Lung Neuroendocrine Tumors (NETs) are rare neoplasms derived from the neuroendocrine cells of the bronchopulmonary epithelium. They represent about 25% of all the neuroendocrine tumors, and no more than 2%-3% of all the primary tumors of the lung. Their incidence has recently increased by approximately 6% per year, probably due to the improved awareness as well as for the diffusion of lung cancer screening programs worldwide. NETs' incidence now ranges from 0.2 to 2 per 100,000 individuals per year in the United States. Their rarity, along with the lack of randomized clinical trials, make lung NETs' global management still questioned, especially in case of advanced diseases, and only few clinical recommendations currently exist. In 2012, during the Annual Meeting in Essen (Germany), the European Society for Thoracic Surgeons (ESTS) created a new Working Group (WG) specifically dedicated to the Lung NETs. The Steering Committees was composed by the following Thoracic Surgeons: Pier Luigi Filosso (Torino, Italy-Chair), Pascal Alexandre Thomas (Marseille, France), Mariano Garcia-Yuste (Valladolid, Spain), Eric Lim (London, UK), Federico Venuta (Rome, Italy), Alessandro Brunelli and Konstantinos Papagiannopoulos (Leeds, UK), Hisao Asamura (Tokyo, Japan). The aim of this WG was to create a group of physicians expert on Lung NETs in order to improve scientific knowledge on such rare neoplasms, and disseminate it among the scientific community. A specific database was rapidly designed, to retrospectively collect data of patients operated for lung NETs, and it was sent to all the ESTS Members who expressed their interest to this project. Moreover, a survey concerning lung NETs'clinical management was prepared and its results were recently published (Future Oncol. 2016;12:1985-1999). Up to now, 2040 operated NETs patients have been collected amongst 17 high-volume International Thoracic Surgery Institution worldwide. This retrospective database was used for several studies about lung NETs clinical behavior and outcome. In particular, the outcome and prognostic factors of two aggressive lung NETs: atypical carcinoids (ACs) and

large-cell neuroendocrine carcinomas (LCNCs) were the object of the first publication (Eur.J.Cardiothorac Surg. 2015;48:55-64). For ACs, age (P<0.001), tumour size (P=.015) and sub-lobar resections (P=0.005) were independent negative prognostic factors; for LCNCs, only pTNM stage III tumors (P=0.016) negatively affected outcome in the multivariate analysis. Local recurrences and distant metastases were statistically more frequent in LCNCs (P=0.02), as expected. A prognostic model of survival for typical carcinoids (TCs) was the matter of the second publication (Eur.J.Cardiothorac Surg. 2015;48:441-447): an analysis of 1109 TC patients was performed. A prediction model for mortality, evaluating age, gender, previous malignancies, peripheral tumour location, TNM stage and ECOG PS was elaborated, and the final model showed a good discrimination ability with a C-statistic equal to 0.836 (bootstrap optimism-corrected 0.806). Moreover, this model has been recently validated by *Cattoni and Coll*. The treatment of biologically aggressive/advanced lung NETs was recently investigated in a paper published by the Journal of Thoracic Disease (J.Thorac. Dis. 2015;7:S163-S171). Surgery, whenever feasible, remains the mainstay of treatment, and chemo/radiotherapy should be reserved to progressive diseases. In case of resected N1-N2 carcinoids, a "watch and see" policy and a close clinical/radiological follow-up is also recommended. Surgery alone is not sufficient to treat high-grade NETs (e.g.: LCNC): adjuvant CT is suggested even in early stages. Platinum-Etoposide regimen demonstrated to be the most effective; Irinotecan and other biological drugs are also regarded to be very promising. The management of advanced lung NETs should be tailored by multidisciplinary teams including Medical and Radiation Oncologists, Surgeons, Pathologists, Pulmonologists, Endocrinologists, Interventional Radiologists; patients' prognosis is mainly dependent on tumor grade and its anatomical extent. Large-cell neuroendocrine carcinoma (LCNC) is a rare tumor characterized by an aggressive biological behaviour and poor prognosis; its optimal treatment is still under debate. Some recent reports indicate that adjuvant chemotherapy (CT) may have a beneficial effect on survival. Data from 400 patients with resected LCNC were analyzed. The 3- and 5-year survival rates were 54.1% and 45%, respectively. With the multivariable model, increasing age, ECOG ≥2 and advanced TNM stage were indicators of poor prognosis. Weak evidence of a higher overall survival in patients receiving adjuvant CT (adjusted hazard ratio 0.73; 95% confidence interval: 0.56-0.96, P =0.022) was also observed (Eur.J.Cardio-Thorac. Surg. 2017;52:339-345). In Stage I TCs (SITCs) non-anatomical resections (wedge) are sometimes advocated because of their indolent behavior. An analysis on effect of surgical procedure on SITC patients' survival was therefore done (Eur.J.Cardiothorac. Surg. 2017 *submitted paper*). Eight-hundred seventy-six SITC patients (569 females,65%) were included in this study; the 5-year OS rate was 94.3% (95%CI:92.2 –95.9). At univariable analysis, wedge resection resulted to be associated with a poor prognosis (5-year OS 82%,95%CI:0.71-0.89,P<.001) compared to other anatomical resections. At multivariable score-adjusted analysis, wedge resection confirmed to be an independent predictor of poor prognosis (HR2.17,95%CI: 1.19-3.96,P=.012). Since 2106, a lung NETs *prospective* database is active through the official ESTS European Database, and up to now, more than 150 new cases have been collected. Through this new platform, very easy to be used, we are confident to collect, in few years, more data especially on possible tumor recurrences and their treatment, as well as on the role of emerging biological drugs used in the adjuvant setting in advanced diseases. An active participation of Medical/Radiation Oncologists to this scientific project would be also desirable. The active role of the most important Scientific Societies could strongly support the success of this scientific project.

Keywords: Surgery, registry, Lung neuroendocrine tumors

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MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 07.06 WHICH CHEMOTHERAPY OR TARGETED THERAPY IS BETTER FOR TREATMENT OF LCNEC PATIENTS: SCLC-BASED VERSUS NON-SCLC-BASED REGIMENS?

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Staging of large cell neuroendocrine carcinoma (LCNEC) was classified based on non-small cell type (TNM stage). The treatment of early stage (I, II) was mainly surgery; the use of neo - adjuvant and adjuvant chemotherapy are in consideration but there's not a standard approach; for stage III which limited to the thoracic area, the role of concurrent chemotherapy and radiotherapy is one of the options. Whether the regimen of chemotherapy should be similar to small cell lung cancer (SCLC) or the regimen of non -small cell lung cancer (NSCLC) is not clear. Most of the data are in favor of SCLC regimen which is Cisplatin plus etoposide; however the data came from retrospective and small numbers of patients, thus there's an unmet need to improve the treatment of LCNEC. Large Cell Neuroendocrine Carcinoma and Small Cell Lung Cancer are both consider high grade neuroendocrine carcinoma of the lung. Small cell is the most frequent type of lung neuroendocrine tumor, occurs around 15% of lung cancer while Large Cell neuroendocrine carcinoma was only about 3% of lung cancer. According to WHO classification in 2004 LCNEC was classified as a variant of large-cell carcinoma; however in 2015 WHO classification LCNEC was classified into a group of neuroendocrine tumor which includes SCLC, typical carcinoid, atypical carcinoid and LCNEC. According to genomic analysis, LCNEC was separated into two groups. Some have genomic characteristic of SCLC and some have genomic characteristic of NSCLC. The new modalities such as anti-angiogenesis and in the case of EGFR mutation the treatment with EGFR inhibitor should be considered. The role of met inhibitors in LCNEC should be explored. Thus there is a long way to go in order to improve the outcome of this rare lung cancer type.

Keywords: large cell neuroendocrine carcinoma, chemotherapy regimen

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MS 08.02 CURRENT ROLE OF RT IN MPM

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Local therapy as the primary treatment modality of early malignant pleural mesothelioma (MPM) remains highly controversial due to lack of clear benefit in comparative clinical trials. In specialized experienced centers, the initial approach is usually surgical resection - extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D). No consensus exists with regard to the optimal use of radiotherapy (RT) in MPM. At the present time, there is no evidence to support the use of radical RT as a single modality in MPM, because of the inability to deliver a therapeutic high dose of radiation (e.g. 60Gy in 30 fractions) to the entire pleura without overdosing the surrounding organs at risk. However, RT has been used in the management of MPM in three indications: as prophylaxis to reduce the incidence of recurrence and pain at sites of diagnostic or therapeutic instrument insertion, as part of multimodal definitive treatment (following induction chemotherapy and surgical resection) to improve locoregional control in early-stage disease and for palliation of symptoms (mainly chest wall pain) in patients with advanced disease. During thoracoscopy, thoracocentesis or needle biopsy in patients with MPM, the seeding of tumor cells along the needle tract may occur, leading to painful metastases at the intervention sites in 20-50% of cases [1]. Prophylactic radiotherapy to chest wall sites of invasive procedures has previously been recommended. However, recent randomized studies (e.g. SMART trial) have shown that prophylactic RT should not be routinely used to prevent procedure tract metastases (PTMs) in MPM, as it confers no benefits in terms of chest pain control, analgesia use, survival, QoL and the data on the potential effect on PTMs' incidence reduction are discrepant [1]. Instead patients should undergo careful clinical follow-up allowing the immediate detection and treatment of PTMs. Surgical resection alone in early MPM is associated with high local recurrence rates (69% after P/D and 38% after EPP) [2]. Therefore, to reduce local failure rate conventional RT has been used as a component of potentially curative trimodality treatment. Adjuvant RT was first used in patients after EPP and was delivered with anterior posterior photon fields matched with electron boost fields. A similar hemithoracic RT technique was explored after P/D, but additional block for central part of the lungs was required. The population based studies data on the potential role of adjuvant RT in improving overall survival (OS) are conflicting [3]. However, a subsequent analysis utilizing the National Cancer Database (NCDB) revealed the improvement of the 2-year rate of OS from 20% to 34% in patients with MPM receiving conventional RT after surgery [3]. Without significant improvement in local control and overall survival after P/D, conventional RT has been shown to decrease local recurrence after EPP to 13% and result in a median survival of 17 months [3]. The benefit in local control was strongly dose-dependent and obtained with a median dose of ≥54Gy [3]. Subsequently, the IMRT technique was implemented to improve adjuvant RT outcomes after P/D (IMPRINT approach). This novel method offers better coverage of the extensive, irregularly shaped target, safer dose escalation in the target volume and optimal sparing of OARs, but results in more heterogenous dose distribution, with a larger volume of normal tissue receiving low-dose radiation than in conventional techniques. IMRT was shown to be associated with a lower incidence of local recurrence (14% vs 42%), improved overall survival (median 20 vs 12 months) and lower rates of grade ≥2 esophagitis (23% vs 47%) when compared with conventional techniques [4]. A potential disadvantage of IMRT is the dose delivered to the contralateral lung that is associated with higher risk of pneumonitis (up to 46% of fatal pneumonitis in early series) [5]. Mean contralateral lung dose >8,5Gy and higher percentage (>80%) of the contralateral lung receiving dose >5Gy were significantly associated with higher risk of pulmonary toxicity. Strict dosimetric constraints, particularly on the contralateral lung (MLD<8,5Gy, V20<10%, V5<60%) and optimal algorithms in treatment planning (e.g. accurate measurement of volumes receiving low radiation doses on the basis of Monte-Carlo algorithm), are critical for radiotherapy planning [4]. Another novel approach employs the combination of IMRT and electrons, that offers better sparing of heart, liver and kidneys [6]. The technical aspects of adjuvant IMRT for MPM can further be improved. When compared to step-and-shoot linac-based IMRT, the use of helical tomotherapy significantly improved target coverage, homogeneity index, lowered average V5<40% and MLD<5Gy for the contralateral lung [7]. Intensity-modulated arc therapy also demonstrated superior V20 and better target coverage in addition to shorter treatment delivery time [8]. Proton therapy was also evaluated in the mentioned setting, offering better sparing of OARs and possibility of further dose escalation to improve target coverage [9]. Whether these dosimetric advantages will translate into clinical benefit, should be assessed in future prospective studies. The trimodality treatment of MPM consisting of induction chemotherapy (pemetrexed+cisplatin), surgical resection and adjuvant radiation has resulted in the best survival outcome thus far in non-randomized cohorts. Accelerated hemithoracic radiation (25Gy in 5 daily fractions), followed by EPP, was evaluated as an alternative. This approach is feasible and associated with encouraging overall survival (median of 51 months) and disease-free survival (47 months) in patients with epithelial cT1-3N0M0 MPM [10]. These promising results should support further studies to clarify the role of hypofractionated pre-operative RT in the management of MPM. Radiotherapy can provide palliation of chest pain in the course of MPM in 50-60% of cases, although the duration of response is often disappointing (2-3 months) [11]. An effective palliation was observed after the dose ≥40Gy and a higher local response rate for patients treated with a 4Gy per fraction regimen compared with those receiving fractions lower than 4Gy was reported (50% vs 39%) [11]. Many aspects of RT for patients with

MPM are still not standardized and warrant further investigations. Clinical trials designs will require integration of new systemic therapies, immune modulation and novel technology advances in RT, with the guidance of predictive and prognostic biomarkers, as well as genetic profiling. MPM patients with resectable disease should be encouraged to participate in clinical trials. Bibliography: 1. Arnold DT, Clive AO: Prophylactic radiotherapy for procedure tract metastases in mesothelioma: a review. *Curr Opin Pulm Med* 2017, 23(4):357-364. 2. Pass HI, Kranda K, Temeck BK, Feuerstein I, Steinberg SM: Surgically debulked malignant pleural mesothelioma: results and prognostic factors. *Ann Surg Oncol* 1997, 4(3):215-222. 3. Rosenzweig KE: Malignant pleural mesothelioma: adjuvant therapy with radiation therapy. *Ann Transl Med* 2017, 5(11):242. 4. Shaikh F, Zauderer MG, von Reibnitz D, Wu AJ, Yorke ED, Foster A, Shi W, Zhang Z, Adusumilli PS, Rosenzweig KE et al: Improved Outcomes with Modern Lung-Sparing Trimodality Therapy in Patients with Malignant Pleural Mesothelioma. *J Thorac Oncol* 2017, 12(6):993-1000. 5. Allen AM, Czerminska M, Janne PA, Sugarbaker DJ, Bueno R, Harris JR, Court L, Baldini EH: Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006, 65(3):640-645. 6. Chan MF, Chui CS, Song Y, Burman C, Yorke E, Della-Biancia C, Rosenzweig KE, Schupak K: A novel radiation therapy technique for malignant pleural mesothelioma combining electrons with intensity-modulated photons. *Radiother Oncol* 2006, 79(2):218-223. 7. Sterzing F, Sroka-Perez G, Schubert K, Munter MW, Thieke C, Huber P, Debus J, Herfarth KK: Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma: helical tomotherapy compared with step-and-shoot IMRT. *Radiother Oncol* 2008, 86(2):251-257. 8. Scorsetti M, Bignardi M, Clivio A, Cozzi L, Fogliata A, Lattuada P, Mancosu P, Navarria P, Nicolini G, Urso G et al: Volumetric modulation arc radiotherapy compared with static gantry intensity-modulated radiotherapy for malignant pleural mesothelioma tumor: a feasibility study. *Int J Radiat Oncol Biol Phys* 2010, 77(3):942-949. 9. Krayenbuehl J, Hartmann M, Lomax AJ, Kloeck S, Hug EB, Ciernik IF: Proton therapy for malignant pleural mesothelioma after extrapleural pleuropneumonectomy. *Int J Radiat Oncol Biol Phys* 2010, 78(2):628-634. 10. de Perrot M, Feld R, Leighl NB, Hope A, Waddell TK, Keshavjee S, Cho BC: Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 2016, 151(2):468-473. 11. Davis SR, Tan L, Ball DL: Radiotherapy in the treatment of malignant mesothelioma of the pleura, with special reference to its use in palliation. *Australas Radiol* 1994, 38(3):212-214.

Keywords: malignant pleural mesothelioma, Radiotherapy

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MS 08.04 IMMUNOTHERAPY IN MPM

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The recent success of checkpoint blockade in other malignancies has led a resurgence of interest in this modality for mesothelioma. Historically, occasional responses were seen with cytokine therapy, immunomodulatory gene therapy, and vaccination incorporating suicide genes or immunological adjuvants. However, the availability of checkpoint blockade and identification of mesothelioma tumour antigens has opened the field to a plethora of multicentre clinical trials and to interest in developing immunotherapy for this indication. The cytotoxic T-lymphocyte Antigen 4 (CTLA-4) blocking antibody tremelimumab was the first checkpoint blockade treatment trialled in mesothelioma, with two single arm phase II clinical trials reporting modest objective responses and encouraging stable disease(1, 2). Unfortunately, the subsequent randomised phase IIb study of tremelimumab versus placebo as second-line treatment for pleural mesothelioma, the DETERMINE trial, did not reach its primary endpoint (Kindler et al. in press). The next reported trials examined the efficacy of PD pathway blockade. Results from the phase I KEYNOTE 028 study mesothelioma cohort of 25 pre-treated patients were recently published. Using single agent pembrolizumab, the partial response (PR) rate of 20% was lower than originally reported, although a 72% disease control rate (DCR) was observed(3). All patients were selected for >1% tumour PD-L1 expression. The median duration of response was 12.0 months, with no new safety concerns. Three other trials of single-agent PD-pathway inhibition have been reported subsequently. Preliminary results have been reported from a second study of pembrolizumab as second line therapy, with PR of 21%, DCR of 80%, and median progression free survival (PFS) of 6.2 months(4). The NivoMes study of second-line single agent nivolumab reported a PR rate of 15%, with stable disease rates of 35% and a median PFS of 3.6 months(5). Neither of these studies selected for PD-L1 expression. Finally, the JAVELIN study of Avelumab, a PD-L1 inhibitor, in patients with prior therapy reported a PR rate of 9.4% and DCR of 57%(6). There is no clarity on the importance of PD-L1 expression as a predictor of response. As with other cancers, pseudoprogression and subsequent response can be seen in some patients with the use of checkpoint blockade in mesothelioma. Whilst the results of single-agent therapies have been hailed as promising, only a minority of patients derive durable benefit, and as yet there is no clear predictive biomarker. The current generation of clinical trials are focusing on a. evaluating single agent checkpoint blockade in randomised trials; b. combining immunotherapies; and c. combining checkpoint blockade with existing therapies. The MAPS-2 study recently reported on combination ipilimumab and nivolumab as second or third line treatment(7). 125 participants were rapidly recruited to this phase IIb clinical trial, and were randomised to receive either nivolumab alone, or nivolumab with ipilimumab. In the intention to treat population, the disease control rate was 51.6% for the combination and 39.7% for nivolumab alone, with PR rates of 24.2% and 17.5% respectively. PFS was 5.6 months in the combination arm vs. 4.0 months in the nivolumab arm, and there was a promising survival signal in the combination arm. Nevertheless, as with this combination in other settings, toxicity was substantial (although manageable) and three treatment-related deaths were reported. Further maturity of these data is awaited. Ongoing clinical trials of single agent checkpoint blockade included the randomised phase III CONFIRM trial, comparing nivolumab with placebo in 336 previously treated patients (NCT03063450), and the randomised phase III PROMISE-Meso study, comparing pembrolizumab with chemotherapy in the second line (plus) setting in 142 patients (NCT02991482). These studies should be sufficient to confirm results of the previous single agent/single arm trials, with further single agent studies of PD1 blockade in the second/third line setting unlikely to move the field forward substantially unless they are focussed on biomarker questions. The successful rapid recruitment of MAPS-2 augurs well for rapid completion of other combination immunotherapy studies. The CA-209-743 (CheckMATE 743) trial is comparing platinum based chemotherapy to combination nivolumab and ipilimumab in 600 patients (NCT02899299). The INITIATE trial (NCT03048474) is testing nivolumab and ipilimumab in just 33 patients, but with a biomarker focus. The completed NIBIT-Meso 1 trial is a phase II study of tremelimumab and durvalumab for which results are likely to be available soon (NCT02588131), with a further phase II trial of the same agents and similar design open in the USA (NCT03075527). Finally, in combinations of checkpoint inhibitors with conventional therapies, the most mature concepts are combinations with chemotherapy in the first line setting. Two single arm phase II clinical trials of identical design are combining cisplatin and pemetrexed first line chemotherapy with durvalumab, one Australian (ACTRN 12616001170415) and one in the USA (NCT02899195). A randomised phase II study in Canada is comparing first line cisplatin/pemetrexed with either pembrolizumab or chemotherapy plus pembrolizumab (NCT02784171). The Australian 'DREAM' study has completed recruitment. All trials are incorporating biomarker studies, which may prove particularly challenging in the context of concurrent chemotherapy. No discussion on immunotherapy in mesothelioma would be complete without comment on anti-mesothelin strategies. The anti-mesothelin immunotoxin SS1P has undergone phase I testing, however neutralising antibody development mandated combination with immunosuppressive pre-treatment moving forward. Durable responses have been seen in small numbers of patients(8). The chimeric monoclonal mesothelin antagonist MORAb-009 (Amatuximab) has completed early phase testing and is now in phase III combined with cisplatin and pemetrexed (NCT02357147). Mesothelin is also being used as the target antigen in Chimeric Antigen Receptor (CAR) T cell therapy in pilot testing. Finally, anetumab ravtansine is an antibody drug conjugate linking a human anti-mesothelin monoclonal antibody to the spindle poison DM4(9). Results have recently been released suggesting no benefit over single agent vinorelbine in a second-line phase IIb study (NCT02610140). This abstract is not exhaustive, with other immunotherapies under investigation including dendritic cell therapy, CAR-T cell therapy, and allogeneic tumour cell vaccine therapies amongst others. It remains unclear which immunotherapies, in which combinations, and at which point in the disease trajectory will be permanently integrated into management. Biomarker studies to predict both toxicities and outcomes are likely to be critical to guide patient selection. REFERENCES 1. Calabro L, *et al.* (2013) Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *Lancet Oncol* 14(11):1104-1111. 2. 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Keywords: Checkpoint blockade, Mesothelioma, Immunotherapy

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MS 08.05 NEW BIOLOGICAL INSIGHTS

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Malignant mesothelioma (MM) is a mesodermally derived, primarily pleural or peritoneal tumor with aggressive behavior. The incidence of this once-rare tumor is increasing rapidly because of the widespread use of asbestos. In Japan, the annual number of MM-related deaths in 2015 was approximately 1,400, which is 3-fold higher than that observed 20 years ago. The median survival of patients with malignant pleural mesothelioma is 9 to 18 months after diagnosis, which necessitates urgent

development of more effective new therapeutic modalities against this aggressive disease. Neuro bromatosis type 2 (NF2) is a tumor suppressor gene that is deleted or mutated in approximately 40% of MM tumors. The gene product of NF2, Merlin, suppresses MM cell proliferation, at least in part, by regulating the Hippo signaling pathway. Hippo signaling is a tumor-suppressive pathway, and alterations in the components of this pathway, including LATS2, SAV1, and AJUBA, have been detected in MM cells. Inactivation of the Hippo signaling pathway leads to the constitutive activation of YAP and TAZ, downstream transcription coactivators that are regulated by this pathway. We previously reported that inhibition of YAP in Merlin-deficient MM cells reduces cell proliferation and inhibits anchorage-independent growth, whereas expression of an active YAP mutant in immortalized mesothelial cells induces oncogenic transformation. While the oncogenic roles of YAP has been extensively studied in MM cells, the possible pro-oncogenic functions of TAZ, a homolog of YAP, is not well understood. Using a panel of MM cell lines, we observed that approximately 65% of these cell lines show activation (underphosphorylation) of TAZ. We knocked down TAZ with shRNA-TAZ in MM cells with high TAZ activation and detected strong inhibition of cell proliferation, anchorage independent growth, cell motility, and invasion in vitro. Meanwhile, immortalized mesothelial cells transduced with a constitutive activated form of TAZ (TAZ S89A mutant) showed enhancement of these in vitro phenotypes and tumorigenicity in nude mice. Using microarray analyses, we identified that while most upregulated genes were common between the TAZ and YAP activated cells, TAZ induced transcription of genes encoding cytokines and their receptors more than YAP. Among the upregulated cytokines, we observed that TAZ binds to the promoter region of the gene encoding IL1-beta along with TEAD transcription factors, which increased IL1-beta transcription and subsequently cell proliferation of immortalized mesothelial cells. In contrast, IL1-beta knockdown or an IL1 receptor antagonist inhibited cell proliferation of MM cells, suggesting that IL-beta signaling suppression may have stronger inhibitory effects on MM cells with TAZ activation. The mevalonate pathway has recently been reported to play a pivotal role in regulating the downstream events of the Hippo pathway. We identified antitumor effects of statin on MM cells with Hippo signaling pathway inactivation. Statin attenuated proliferation and migration of MM cells harboring a NF2 mutation by accelerating YAP phosphorylation/inactivation. Interestingly, not all MM cells with NF2-Hippo pathway inactivation exhibited statin sensitivity. All the statin high-sensitive MM cell lines had increased p-YAP/YAP ratios (inactivation) after statin exposure, whereas in statin low-sensitive cells, the p-YAP/YAP ratio was generally low or unchanged. Genetically, the statin high-sensitive MM cells harbored NF2 and/or LATS2 mutations without BAP1 mutation, whereas BAP1 mutations were frequently identified in statin low-sensitive cells. Indeed, the Y-MESO-25 cell line, carrying both NF2 and BAP1 mutations, regained moderate statin-sensitivity after transfection with a wild-type BAP1 plasmid, indicating that BAP1 mutations interfered with the anti-proliferative effects of statins on MM cells with Hippo pathway inactivation. However, the interactions between BAP1 and the Hippo pathway remain to be elucidated. In conclusion, YAP and TAZ activation via NF2-Hippo pathway inactivation is essential for MM cells to acquire more malignant phenotypes, and therefore, detailed understanding of the biology of this pathway is required to develop new therapeutic modalities against MM based on dysregulation of this pathway.

Keywords: Hippo pathway, mevalonate pathway, NF2

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MS 08.07 ACHIEVING EQUITABLE ACCESS TO NOVEL TREATMENTS FOR ALL PATIENTS

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The UK has the highest incidence of Mesothelioma in the world with over 2700 cases diagnosed in 2014 (Cancer Research UK 2017). Data for 80% of these patients was submitted and analysed as part of the UK's National Lung Cancer Audit Mesothelioma Report (NLCAMR) 2016 (Royal College of Physicians [RCP] 2016). The report confirmed that an increasing number of patients are receiving chemotherapy in the UK particularly patients with a good performance status; 53% compared to 41% in the audit's 2014 report. The current audit does not identify the proportion of patients who receive their treatment as part of a clinical trial however the report recommends "All patients should be offered access to relevant clinical trials even if this requires referral outside of their network" (RCP 2016). With an increasing number of mesothelioma clinical trials now available in the UK, and more in development, facilitating seamless movement of patients from one specialist clinical team to another is essential. Mesothelioma UK, a national charity dedicated to improving outcomes for those affected by Mesothelioma, is establishing a comprehensive package of services and resources specifically to support this. The charity's vision, for ensuring equitable access to treatment and trials is outlined in the charity's 2016-2021 Strategy, The Next Five Years (Mesothelioma UK 2016). This presentation provides insight into readily transferable measures Mesothelioma UK has developed to support equitable access to treatment and care across the UK. References Cancer Research UK 2017 (Last viewed August 4th 2017).

Keywords: Equitable Treatment Access

MS 09 GLOBAL PERSPECTIVES IN ELIMINATING THE MAJOR CAUSE OF LUNG CANCER
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MS 09.01 GLOBAL TOBACCO CONTROL

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The history of global tobacco control starts at the beginning of the twentieth century with early data linking the smoking of tobacco with the risk of lung cancer, a previously rare disease. The build up of scientific evidence for the link gained pace toward the middle of century when landmark publications brought more widespread recognition of the phenomenon[1,2]. The pivotal US Surgeon General Report from 1964 gave a clear message that tobacco smoking was unequivocally associated with an increased risk of developing lung cancer[3]. Over the following decades the paradigm of tobacco control recognizable today culminated in the development the first global public health treaty, the World Health Organization Framework Convention on Tobacco Control (WHO FCTC), which came into force in 2005 and currently lists 181 countries as Parties to the Convention[4]. In 2008, the FCTC launched the MPOWER measures (Table 1.), six steps proven to lead to reduction in tobacco use around the world[5] and that provide the ability to benchmark the effects of tobacco control strategies between countries[6]. In countries with robust implementation, these measures have achieved what may have once been unthinkable, the saving of millions of lives[6] and the reduction in smoking rates to historic post-WWII lows[6]. There have been enormous benefits, with a reduction in cigarette consumption, altered rates of disease and a reduction in smoking uptake. But the inconsistencies in regulation and in MPOWER implementation around the world have led to problems with the shifting of tobacco industry efforts to the developing world[7], the targeting of vulnerable groups for new market share[7] and the entrenchment, in some countries, of the tobacco industry in the halls of government. New threats to global tobacco control are starting to appear from the impacts of globalization of trade[7], newer products whether "low-harm" or otherwise and from focused, covert attacks by the tobacco industry itself. This presentation aims to review the development and impact of current tobacco control policy, to examine emerging threats to tobacco control, to focus on evasive manoeuvres of the globalizing tobacco industry and to discuss possible future tobacco control strategies that these developments will require. Over the last half century the tobacco industry in the developed world has become globalized. Four companies have come to dominate the global tobacco trade, Philip Morris International, British American Tobacco, Japan Tobacco International and Imperial Tobacco[8]. This has given companies such as PMI the economic clout to oppose, delay and threaten tobacco control strategies such as plain packaging and smoking bans[9]. The tobacco industry in Asia, a region of the world with very high smoking rates, is heading towards globalization. Companies such as Korean Tobacco and Ginseng (KT&G) and the China National Tobacco Corporation (CNTC) have developed foreign exports with government support[8] and have strengthened their domestic operations with consolidation and restructuring[8]. New global tobacco players have the potential to generate new competition, innovation and price reduction, all with detrimental impacts on public health[8]. The development of "low-harm" products such as electronic nicotine delivery systems (ENDS), including e-cigarettes, has opened new frontiers in regulatory control with concerns that such products may open new developed world markets for tobacco companies that otherwise continue to sell tobacco cigarettes in low and middle-income countries[7]. Tobacco companies use international trade relations to oppose the implementation of tobacco control measures; in the fight against plain packaging in Australia, the tobacco industry invoked trade treaties and the possibility of unfair trade restrictions. The tobacco industry holds to a culture of political sabotage that includes infiltration of government by lobbyists and open recognition of the value of political skills in undermining public health initiatives in tobacco control All of these developments call for a modernization of the tobacco control paradigm. This may include financial pressures such as disinvestment in the tobacco industry by pension funds[10], staunch regulatory approaches to ENDS and perhaps the development of finely honed political skills to match or surpass those of the tobacco industry. Even creative approaches to the dissemination of data, such as maps showing countries moving towards plain packaging or graphical presentation of the country-by-country distribution of tobacco factories may help inform the community and subvert the newer "low-harm" messages of the large tobacco companies. Many successes over many years can be attributed to traditional tobacco control, the emphasis on the science and the FCTC and MPOWER measures. However, the tobacco industry has very strong drive for survival with multiple strategies for evasion of control. The scientific arguments are irrefutable but are not enough to overcome an industry prepared to either deny the science, to ignore it while developing market share where regulations are weak or to espouse overt evasion techniques in company documents. MPOWER is no longer enough as the opposition does not play by the rules. Effective long-term global tobacco control will need to draw upon many resources including scientific evidence, economic pressure, the ability to avoid distractions and delaying tactics, resolute evaluation and regulation of ENDS and, ultimately, political dexterity in dealing with an industry prepared to do just about anything to maintain profit.

Table 1. MPOWER Measures
MPOWER Measures
Monitoring tobacco use and prevention policies **Protecting** people from tobacco smoke **Offering** help to quite tobacco use **Warning** about the dangers of tobacco **Enforcing** bans on tobacco advertising, promotion and sponsorship **Raising** tobacco taxes

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Keywords: Tobacco Control, Tobacco industry, Globalization

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MS 09.03 COST EFFECTIVENESS OF SMOKING CESSATION

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Cost Effectiveness of Smoking Cessation WHO estimates that tobacco kills more than 7 million people each year. More than 6 million of these deaths are the result of direct tobacco use while around 890,000 deaths are the result of non-smokers being exposed to second-hand smoke. Around 60-70% of smokers want to quit smoking. However, the success rate for quitting smoking is quite low without a systematic approach. Counselling and medication can help increase the success rate. Only 24 countries provide national comprehensive cessation services with full or partial cost-coverage to assist tobacco users to quit. This represents merely 15% of the world's population. FCTC article 14 concerns the provision of support for reducing tobacco dependence and cessation, including counselling, psychological support, nicotine replacement, and education programs. Parties are required to develop and disseminate national guidelines on tobacco cessation and are encouraged to establish sustainable infrastructure for such services. Tobacco use treatment are not only clinically effective, but are cost-effective as well. Tobacco use treatments, ranging from clinician advice to medication to specialist-delivered intensive programs, are cost-effective in relation to other medical interventions such as treatment of hypertension, hyperlipidemia and to other preventive interventions such as periodic mammography. Even though a single application of any effective treatment for tobacco dependence may produce sustained abstinence in only a minority of smokers, tobacco use treatment remains highly cost effective. For example, Fiore and colleagues estimate the cost per life-year saved of tobacco dependence treatment to be $3,539. These estimates compare favorably with other health interventions in the U.S. like statins (which costs $50,000 per life-year saved), and diabetes treatment ($34,000 per life-year saved). Most effective way for more clinicians to intervene is to provide them with information regarding multiple effective treatment options and to ensure that they have ample institutional support to use these options. Clinicians, administrators, insurers, and purchasers can cooperate to encourage a culture in which intervention for smokers is an essential part of standard care. Korea is one such successful example. Eighty percent increase of price for a pack of cigarette since 1st of Jan, 2015 provided the momentum for other kinds of tobacco control activities. Even though only a small portion of increased tobacco tax was distributed to tobacco control activity, the tobacco control budget in 2015 has jumped by 13 times compared to previous year. 1. 246 Smoking Cessation Clinic in Health centers : All the health centers in Korea have smoking cessation clinic and gives counselling and NRTs for free. 2. Quitline : Nationwide quitline service is located in National Cancer Center. It gives counselling over the phone with proactive service for free. 3. Hospital based smoking cessation service : If a smoker visits hospital and gets counselling and medication(NRTs, bupropion, and varenicline) the fees for counselling and medication is actually free. National Health Insurance Foundation supports this program. 4. Community Smoking Cessation Center: There are 18 community smoking cessation centers in Korea. They provide three different services. 1) Residential 5 days smoking cessation program : intensive program which gives counselling, medication, etc. for free. 2) Residential 2 days smoking cessation program : short-term education program for free 3) Visiting program : Some underprivileged smokers, such as female smokers or adolescents who does not go to school, disabled smokers, or college students tend to not use smoking cessation programs due to various reasons. So community smoking cessation centers visit those special underprivileged populations. This service gives counselling and NRTs for free. References Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008. Cromwell J, Bartosch WJ, Fiore MC, et al. Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. 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Keywords: cost effectiveness, Smoking Cessation, Korea, Cost Effectiveness, Smoking Cessation, Korea

MS 09 GLOBAL PERSPECTIVES IN ELIMINATING THE MAJOR CAUSE OF LUNG CANCER
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 09.04 NICOTINE DEPENDENCE AND CESSATION IN LUNG CANCER PATIENTS

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Tobacco use is well known as a carcinogen linked to many malignacies and also linked to non-oncologic diseases such as cardiovascular disease, chronic lung disease, and respiratory infections. The majority of lung cancer patients do have a history of smoking; often many are actvely smoking at the time of diagnosis and many struggle with cessation during treatment and through survivorship. Patients may have a perception of futility and lack of perceived benefit regarding cessation, and some clinicians may view tobacco cessation with a pessimistic perspective in that "the damage is already done." One of the first steps toward cessation in lung cancer patients is to make patients, families, and physicians aware of the continued harms of smoking, the negative impact on efficacy of treatment, and for those who may be treated with curative intent, the potential for development of malignacy in the future. As the potential benefits range widely and may apply differently to different patients, the ability to individualize a message regarding relevant positive impacts of cessation is crucial. For cancer patients overall, there is survival advantage in those who are able to quit, compared to continued smoking. Nicotine and its metabolic products can promote tumor growth through increased proliferation, angiogenesis, and other pathways. Furthermore, nicotine can decrease the biologic effectiveness of conventional cancer treatments such as chemotherapy and radiotherapy. For patients undergoing surgery, smoother recovery and avoidance of perioperative complications such as respiratory infection, wound complications, and perioperative cardiovascular events is critical. For those treated with curative intent, continued smoking can clearly be a significant risk factor for metachronous lung cancer, or development of different primary tumors. Even in those with incurable disease, overall survival benefit of cessation has been demonstrated. In addition, many patients with lung cancer and a smoking history have significant burden of respiratory symptoms, including dyspnea, wheezing, exercise intolerance, cough, pneumonia, etc. From a palliative standpoint, cessation can ameliorate some of the respiratory symptoms, and improve quality of life. Physician advice is a powerful tool and should be part of every encounter. Ask-Advise-Refer is a simple standard strategy which can be integrated into even the busiest of workflows. This involves asking every patient about tobacco use, advising cessation and referral to a tobacco treatment resource. That resource may be a Certified Tobacco Treatment Specialist, a telephone counseling service (such as a 'quitline'), a group counseling setting or other specialist. A more indepth cessation strategy involves the "5 As": Ask, Advise, Assess, Assist, Arrange. In addition to asking every patient about use and advising them to stop, a physician should Assess their use, prior quit attempts, and willingness to make a quit attempt. Then a provider should Assist the patient with their quit attempt with counseling and pharmacotherapy. Motivational interviewing is a standard counseling strategy in which a process of questioning and interviewing which strengthens and engages intrinsic motivation within the patient in order to change behavior. Pharmacotherapy consists of nicotine replacement therapy, varenicline, and/or buproprion. Previous concerns regarding severe psychiatric side effects such as suicidal ideation with varenicline have made some patients and physicians wary to use it; however, a recent trial shows varenicline to be very safe with no higher incidence of psychiatric side effects than placebo. Nicotine replacement therapy (NRT) can be delivered in a slow continuous format via a nicotine patch, and/or via short acting NRT such as gum, lozenges, nasal spray, or prescription inhaler. Often times a long acting modality (nicotine patch) can be used in combination with a short acting NRT as combination therapy. Overall pharmacotherapy increases success of quit attempts, and should be integrated as a part of the patient's overall healthcare plan. Often times the choice of pharmacotherapy is guided by what has or has not worked for that patient in the past. Electronic Nicotine Delivery Systems (ENDS) or e-cigarettes have recently become widespread and commonly available in many countries. The nicotine content is widely variable, and other componenets of the vaporised liquid make comparison and quantification much more difficult than that for approved pharmacotherapy where dosing is consistent and predictable. It is true that ENDS may not contain the same level of carcinogens as cigarettes, but in reality many users of ENDS are not able to quit conventional cigarettes, but use ENDS when not able to smoke and then use conventional cigarettes when they can smoke. At current, data is lacking and does not support e-cigarettes above approved pharmacotherapy. For those patients who are using e-cigarettes, the primary goal to complete cessation of conventional cigarettes. Patients who are using e-cigarettes and unable to quit smoking should be steered toward approved pharmacotherapy. Multiple different strategies exist to support patients during cessation attempts. There is no universally applicable single way to approach cessation. Counseling and pharmacotherapy are mainstays of cessation support and best outcomes result from using them together. A concerted, consistent message combined with appropriate pharmacotherapy and counseling may help many patients with lung cancer to quit smoking and gain the benefits of cessation.

Keywords: tobacco, Smoking Cessation, outcomes

MS 09.06 TOBACCO INDUSTRY INTERFERENCE IN LOW AND MIDDLE INCOME COUNTRIES

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The 2016 FCTC Report of the Conference of Parties (COP 2016) alerts that tobacco is the only legal non-prescription product that can kill between 33% and 50% of consumers when used as recommended by the tobacco industry[1]. The tobacco industry is also the only industry that, due to the potential lethality of its products and their impact on public health, has elicited a legally-binding intergovernmental treaty for protecting public health policies from the interference by the industry and by those who act to protect their interests. Besides the heavy political lobbying for blocking, delaying or weakening public health policies on tobacco control, the industry frequently resorts to legal disputes on the basis of international free trade agreements and bilateral agreements to revert governmental policies1. During the 6th COP, in 2014, the FCTC adhering State Parties have declared that the tobacco industry interference in public health policy for tobacco control continues to represent the main hindrance for full implementation of FCTC articles[2,3]. According to the WHO's global report on tobacco industry interference of 2012, the most common tactics used by the industry are[4]:

• maneuvering to hijack the political and legislative process;

• exaggerating the economic importance of the industry;

• manipulating public opinion to gain the appearance of respectability;

• fabricating support through front groups;

• discrediting proven science;

• intimidating governments with litigation or the threat of litigation.

Despite the tobacco industry claiming otherwise, the Director-General of the World Trade Organization (WTO) has declared that there is no inherent conflict between FCTC implementation by the ratifying countries and the WTO rules[5]. He enlightens that there are two WTO principles that should be respected: the non-discrimination and the necessity principles. The first one implies that the implemented tobacco-control policy does not treat an imported product differently than its domestic equivalent; whereas the necessity principle states that such measure, law or provision "must be necessary for complying with the proposed health goal and that it should not be more restrictive than necessary on trade in order to achieve this goal"[6]. Furthermore, according to the WTO, a "Member States have the right to determine the level of health protection that they wish to promote..." and, "when considering the less restrictive alternatives, these must meet the regulatory goal and be reasonably available, as well as genuinely alternative and not complementary measures"[6]. As far as bilateral agreements are concerned, the industry has used them in some countries to revert or impede the FCTC provision on cigarette packaging and labeling, by claiming that it breaches bilateral trade provisions that protect trademark and property rights[6]. Therefore, legislators should consider four basic principles when implementing tobacco control regulations: 1), to make sure that the law "only restricts property rights to the extent of achieving a public health objective"; 2), to avoid raising expectations of tobacco-industry investors that they will not be subjected to the regulation in question; 3), to ensure legislation's compliance with the principles of due process and natural justice; and 4), to make sure that the new regulation will not be discriminatory. The careful application of these principles in the legislation wording and form will not only reduce international litigation but also protect the FCTC-ratifying Party from having to pay the tobacco industry compensation for damages[6]. In 2014, the COP participants unanimously decided to accelerate the full implementation in all public administration sectors and diplomatic missions of Article 5.3 and its guidelines[3]. Article 5.3 of the Framework Convention for Tobacco Control (FCTC) offers essential guidelines that were unanimously approved by the FCTC-ratifying countries in 2008. Article 5.3 thereby obligates ratifying countries to protect their health policies from tobacco manufacturers' interference and to recognize that the tobacco industry bears fundamental and irreconcilable conflict of interests with public health and the FCTC implementation. In fact, Article 5.3 guidelines are the backbone of the FCTC treaty and help to prevent and reduce litigations aiming at reversing or halting the implementation of further anti-tobacco policies[1]. According to Article 5.3, countries should refuse to treat tobacco companies as "collaborators" in public health policy making; should not invest in the tobacco industry; should not receive contributions or grants from the tobacco industry; should not partner with tobacco industry either for health or other purposes – including their so-called social responsibility programs; should not celebrate non-binding or non-enforceable agreements; nor admit tobacco industry representatives on FCTC delegations or on other tobacco-control administrative agencies. Another relevant provision of Article 5.3 concerns transparency[7] in the interactions between government agencies and the tobacco industry by promoting afore public notices and free public access to reports, records, and documents about such interactions, besides promoting public hearings about the meetings. Moreover, it recommends the disclosure or registration of tobacco-affiliated organizations, advocacy groups and lobbyists; legal penalties on tobacco business for disseminating false or misleading information or propaganda; disclosure of tobacco industry business, such as market share, revenues, production, manufacture, relationship with tobacco farmers, investments in marketing, analysis of tobacco products chemical contents, and "social responsibility" actions and related activities; obligatory disclosure of current or past work with tobacco industry by applicants to jobs in governmental bodies involved in health policy-making, policy execution or surveillance[7]. The 2016 PAHO Report for the Region of Americas alerts that there are more than one billion smokers in the world and that 11.4% of them live in the Region of the Americas, which represents a population of 127 million smokers in our continent[1]. Prevalence shows that 21.2% of adults or teenagers older than 15 are smokers[1], which poses a heavy burden on public health, especially because it is among the youth and the lower income segments that the prevalence is higher. However far we had already progressed in fighting smoking and the consumption of other tobacco products, we are still very far from eradicating this addiction that responds for the vast majority of lung cancer cases, not to mention Head & Neck tumors and cardiovascular diseases. The implementation by all ratifying Parties of the FCTC six provisions that comprise the MPOWER package may drastically reduce in the coming two decades the morbidity and mortality associated with tobacco consumption. Our struggle is just beginning. **References** Pan American Health Organization. WHO FCTC. *Report on Tobacco Control for the Region of the Americas. Who Framework Convention on Tobacco Control: 10 Years Later.* Washington DC: PAHO, 2016. World Health Organization. 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Keywords: anti-tobacco policies, tobacco legal issues, FCTC articles

MS 10.02 INTERPRETING PUBLISHED RESEARCH

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Background The Evidence-Based Practice (EBP) or Evidence-based Healthcare (EBHC) movement has revolutionised health care in the last 20 years by promoting research appraisal, interpretation and implementation.[1] EBP has been the cornerstone of practice development and service improvement. The most common definition of EBP is "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research."[2] This presentation will reflect on EBP relating to interpreting published research to enhance practice. In lung cancer this is an opportune time as evidence regarding new treatments, services and professional roles is growing. Some of the recent changes and challenges to EBP that influence how we interpret research will first be considered. Second, tools that can support lung cancer practitioners in interpreting published research will be discussed. Finally the presentation will reflect on the contribution of creative, methods of co-production to mobilize knowledge and published evidence to improve practice. The future application and contribution of these methods is considered **Evidence-Based Practice: Changes and Challenges** Much has changed since 1996 in terms of EBP and the environment in which it operates. Now EBP is considered to comprise 3 components, 'Best Research Evidence', 'Clinical Expertise' and 'Patient Values, Experience and Preferences'.[3] Critically, the much quoted definition Sacket definition of EBP[1,2] misses the third vital element, which is, the integration of patient values, experiences and preferences. In addition, the initial emphasis in EBP was on medicine and applying evidence to practice regarding individual patients care and treatment. However, EBP has now evolved into Evidence-Based Healthcare (EBHC), where evidence is mobilized to change practice at a policy, organisation or service level. To address this change in emphasis a change to research methodologies is required, as well as a rethink regarding the hierarchy of evidence. The Randomised Controlled Trial is not always adequate. Mixed-methods approaches are more commonly employed and the value placed on qualitative, patient experience methods has increased. Whilst meta-analysis and randomised controlled trial methodologies remain the gold standard to generate evidence of effectiveness, EBH questions have become more complex and diverse. These questions require different research approaches and tools to generate answers. Finally, EBP is only as good as the evidence it's based on.[4] We therefore need to be aware of the limitations of current evidence, for example, the influence of vested interest (e.g. industry and managers), not publishing negative trial results, cherry picking findings to report, over-inflation of claims from trials, the overwhelming volume of evidence, and the critical gaps in evidence.[4,5,6] In addition, policy across the globe demands more patient and public involvement in the identification of research priorities and the conduct of research. There have also been huge methodological developments in terms of applying research to practice for example, service improvement and quality improvement methodologies, such as Microsystems. More recently there has also been a growth in interest in knowledge mobilisation, co-production and co-design. These enable people working in health care to work in equal partnership with people receiving healthcare in order to generate, appraise and use research to develop creative solutions to current problems with health services, care and treatment.[7,8] **Tools to support research interpretation and application** A key task in EBP is to interpret published research. Over the years a proliferation of strategies, tools and resources have been developed to support clinicians, researchers and academics in appraising, interpreting and applying evidence to enhance practice.[3,5] Broadly a 5 stage EBP process is advocated, Ask, Acquire, Appraise, Apply, Assess, each with its own strategies and tools. The purpose of each of these stages will be explained and implications for interpreting research will be summarised. A brief summary of some of the current tools will be presented

including online training courses, critical appraisal tools and quality assurance criteria. **The role of co-production in interpreting and applying research** The recent interest in co-production and knowledge mobilisation (KM) will potentially change how we interpret and use published research. Greater emphasis has been placed on creative approaches to knowledge generation through co-production, co-creation and co-design.[7] These approaches change the role of traditional published evidence in changing practice and service development. This change raises the importance of "blurring the boundaries between knowledge creation and knowledge use through integrating multiple stakeholders' perspectives in research and implementation activity. It also supports the notion that such approaches should be iterative and incremental."[8] Embracing a co-production approach to research generation, interpretation and application means rejecting a reliance on Mode 1 knowledge, where research knowledge is created by university-based scientists and *then interpreted* packaged and processed in a way that makes it accessible and usable to non-academics. In preference Mode 2 knowledge is espoused, where knowledge and research is collaboratively generated in its field of application with a range of stakeholders.[7] The co-production process in healthcare will be summarized with reference to key literature, examples[7-10] and evidence of impact.[10] Finally the relevance of this for research interpretation in lung cancer is considered. **Conclusion** There are limitations to published research to inform lung cancer treatment and practice. Published research is never going to tell you enough to support change. Need to incorporate patient and public view. Co-production in KM provides a way forward to think differently in interpreting evidence and developing services and care.

Keywords: Critical appraisal, Research, Evidence Based Practice

MS 10 EVIDENCE BASED CARE: INTERPRETING THE RESEARCH AND ENHANCING PRACTICE
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 10.03 COMMUNITY OUTREACH - ENGAGING IN PRIMARY CARE

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Background/Objective: Lung cancer clinical trials are critical to advancing our understanding of disease characteristics, diagnostic criteria and treatment options. With evolving molecular testing and immunotherapies, clinical trials are increasingly complex and challenging to conduct at the site level. This report highlights the role of the Lung Cancer Clinical Research Nurse (LC-CRN) as vital to supporting patient participation and physician involvement for lung cancer trials. We also review new challenges with immunotherapies, nuances of sending tissue for molecular testing and importance of managing patient and family expectations. Methods: The St. Joseph community hospital multidisciplinary Thoracic Oncology Program was established in 2004, averaging 150 lung cancer patients annually. Since 2013, we facilitated efforts to increase participation in research studies. Strategies included (1) streamlining practices within the internal program structure and catalyzing efforts to acquire novel trials, (2) training a specialized LC-CRN to efficiently screen patients to exclusion criteria, and (3) enhancing enrollment and retention practices. Results: To streamline our portfolio, we closed stagnant trials and prioritized non-competing trials with novel agents of interest to our providers that address particular needs of our community population. Since 2013, lung studies open to accrual have tripled and patient enrollment continues to increase in both clinical trials and donations to our tissue biorepository. Current lung trials include diverse standard-of-care options alongside immunotherapies, genomic profiling, tissue biorepository, a tumor device and liquid biopsy trial. Responsibilities of the LC-CRN are to engage physicians, identify and accrue patients, coordinate specimen requirements, ensure protocol and ethics compliance, and communicate readily with study team and sponsors. At our site, specialized LC-CRN training included NCCN guideline review, sponsor visits for protocol training, creating and utilizing simple recruitment and screening tools, flyers and worksheets. The LC-CRN provides routine education about available and upcoming trials at weekly thoracic tumor boards, using visual aids to simplify comparisons of patient entry criteria across multiple studies. In partnership with study investigators, LC-CRNs are uniquely skilled to simplify clinical trial summaries to patients and communicate study content and patient commitment. LC-CRNs must have a robust understanding of disease processes and standard oncology treatment guidelines, including mutation testing. The LC-CRN must also be well acquainted with lung research protocols to advise providers of required tests/procedures, treatment/dosing, and management of adverse reactions. During the consent review, study visits and follow-ups, the LC-CRN must address patient concerns and assess key areas for further education. Effective communication with study sponsors include proper charting and documentation, data entry and responses to queries, as well as record submissions for billing/insurance processes unique to the study or healthcare setting. We implemented recruitment and retention processes supported by literature to ensure a majority of new and recurrent lung cancer patients are considered for clinical trials. Patient cases are presented at multi-disciplinary tumor boards and lung program meetings for group discussions. A recent publication noted higher physician engagement at tumor boards correlated with increased patient accrual and satisfactory prognostic outcomes (Kehl et al., 2015). The LC-CRN also cross-collaborates with navigators, genetics counselors, infusion nurses, radiation staff and others to identify and manage study patients. Literature noted early and repeated presentation of trial information during patient visits boosted trial participation to over 50% of 309 patients with thoracic malignancies (Logan et al., 2017). The close relationship of the LC-CRN to patients and their care team may avoid patient dropout, which often occurs due to misinformation or non-compliance to complex oncology study protocols (McCarthy-Keith et al., 2010). Routine clinical guidance throughout treatment remains important for research engagement and addressing specialized needs of lung cancer patients (Islam et al., 2014; Mosher et al., 2017). Common challenges with immunotherapies include identifying immunotherapy adverse events (IrAEs), fulfilling tissue requirements for molecular testing, and managing patient/family expectations. Research teams ensure ongoing dialogue and education with patients to promptly address IrAEs. We conduct a protocol "dry run" with the clinic staff, pharmacist, hospital facilities director and safety manager to ensure compliance of agent preparation, delivery, spill preparedness and IrAE management. We also oversee tissue acquisition and processing, as it can be a significant barrier to enrollment and retention (Lim et al., 2016). Fresh tissue, via core or excisional biopsies, is often required over archived tissue at study entry, progression or change of treatment. Collaborations with our pathologist, interventional radiologist, finance team and technicians ensure timeliness and correct acquisition methods over multiple time points. With the emergence of personalized immunotherapies come high hopes, but also fears and misconceptions about drug capabilities and efficacy in treatment regimens. The LC-CRN can readily distinguish and manage family and patient expectations by conducting extensive and ongoing teaching about medical use, potential benefits and dangerous side effects. In one setting, 85% of 40 lung and esophageal cancer patients were satisfied with trial participation following a positive experience with a study navigator (Cartmell et al., 2016). Strategies utilizing dedicated staff members, such as a LC-CRN, are necessary in guiding and educating patients about research concerns and processes. Overall, the LC-CRN and thoracic oncology care team are intimately involved in addressing patient expectations and care management to maximize research participation and patient outcomes in oncology care. Conclusion: The landscape of lung cancer diagnosis and treatment is quickly shifting. A durable and flexible research infrastructure includes having an active multidisciplinary thoracic team with dedicated staff advocating for patient access to clinical trials. The role of the LC-CRN in supporting participation in lung cancer trials is vital. With proper education and training, the LC-CRN is best positioned to support patient participation, physician involvement and patient/sponsor expectations in lung cancer trials. REFERENCES Cartmell KB, Bonilha HS, Matson T, Bryant DC, Zapka JG, Bentz TA, Ford ME, Hughes-Halbert C, Simpson KN, Alberg AJ. Patient participation in cancer clinical trials: A pilot test of lay navigation.<https://www.ncbi.nlm.nih.gov/pubmed/27822566> Contemp Clin Trials Commun. 2016 Aug 15;3:86-93. PMID: 27822566 Islam KM, Opoku ST, Apenteng BA, Fetrick A, Ryan J, Copur M, Tolentino A, Vaziri I, Ganti AK. 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Keywords: Clinical Research Nurse, Trial enrollment, clinical trials

MS 10 EVIDENCE BASED CARE: INTERPRETING THE RESEARCH AND ENHANCING PRACTICE
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MS 10.05 IMMUNOTHERAPY: THE LATEST

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The Latest Immunotherapy agents are now a prominent drug class in the management of NSCLC. It is important for oncology nurses to understand the drugs that are approved as well as the management of the toxicities. There are currently 3 drugs approved for use in several scenarios for NSCLC, listed in table1.

DRUG	INDICATION	TYPE IMMUNOTHERAPY
Atezolizumab	2nd line NSCLC	PD-L1 inhibitor
Nivolumab	2nd line NSCLC	PD-1 inhibitor
Pembrolizumab	1st line NSCLC -single agent in PD-L1 ≥ 50% -in combination with pemetrexed and carboplatin regardless of PD-L1 expression 2nd line NSCLC in patients with PD-L1 ≥ 1%	PD-1 inhibitor

Table 1. Immunotherapy drugs still under investigation for NSCLC include durvalumab, another PD-L1 inhibitor. Also, anti-CTLA 4 drugs such as ipilumumab

and tremelimumab are being studied in combination with PD-1 or PD-L1 inhibitors. Finally, early stage studies are beginning to look at the utility of CAR-T cell therapy in NSCLC. Follow up data from the Checkmate studies in NSCLC as well as the Keynote trials will give more up to date survival statistics for nivolumab and pembrolizumab, respectively. Toxicity management for these immunotherapy drugs has been at time challenging. The toxicities are very different from traditional chemotherapy used in NSCLC. When caught early, these toxicities can be managed and many times, treatment can be continued. However, if severe or identified late, toxicities from immunotherapy can be life-threatening. Immune-mediated toxicities reported in trials of NSCLC such as pneumonitis, colitis, endocrinopathies, nephritis, hepatitis are some of the toxicities that can become life-threatening if not managed properly. Other than the endocrinopathies, most of these toxicities must be managed with high dose corticosteroids and tapered slowly under close supervision. More common adverse events of the immunotherapies such as fatigue, rash, nausea, diarrhea, arthralgia can be expected and managed without using corticosteroids, instead, using more standard supportive care medications.

Keywords: Immunotherapy, toxicity

MS 11 COMBINED MODALITY TREATMENT FOR SUPERIOR SULCUS TUMORS
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 11.01 PREOPERATIVE CHEMORADIOTHERAPY FOLLOWED BY SURGICAL RESECTION

H. Kunitoh

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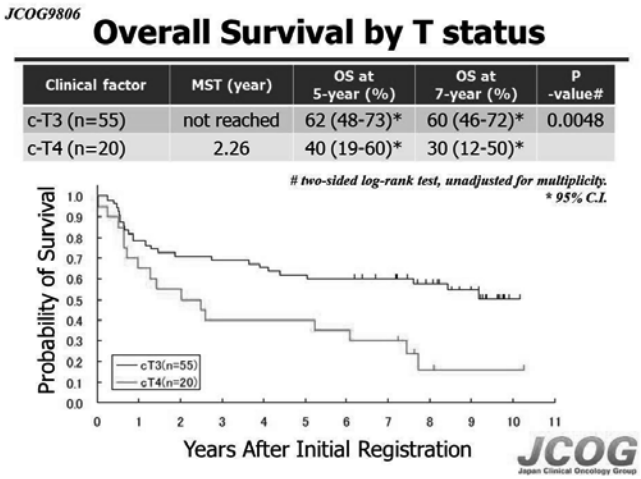
Superior sulcus tumors (SSTs), involving structures at the thoracic inlet, have posed a challenging problem for surgeons, radiation oncologists and medical oncologists alike, ever since they were first described[1]. Pre-operative radiotherapy had long been the community standard in the management of SSTs. However, both the complete resection rate (approximately 50%) and long-term survival (approximately 30%) rate had remained poor and unchanged over 40 years, since the first treatment strategy was reported in the 1960's. Local control had remained the main problem, adversely affecting the quality of life as well as the survival of the patients[2]. Encouraged by the promising data of concurrent chemoradiotherapy for mediastinal node-positive N2 NSCLC, two prospective studies applied this modality as preoperative therapy for patients with SSTs; one from the US (led by the Southwest Oncology Group SWOG9416-Intergroup Trial 0160[3]), and the other from Japan (by the Japan Clinical Oncology Group, JCOG 9806[4]). In both trials, patients with SSTs received two cycles of cisplain-based chemotherapy (etoposide-cisplatin in US, mitomycin-vindesine-cisplatin in Japan), concurrently given with thoracic radiotherapy 45Gy/27fr. Then they underwent surgical resection. Boost radiotherapy was given to unresected/imcompletely resected tumors. In spite of minor differences, the results of the two trials were strikingly similar (Table). The intensive trimodality approach was found to be feasible in both reports, with a reasonably low toxic death rate of 4%. The resection rate, which had remained unchanged at about 50% for almost 40 years with conventional preoperative radiotherapy, was approximately 70% in both studies. Particularly noteworthy was the reproducibility of the favorable survival data, with a 5-year OS of 44% in the US trial and 56% in the Japanese trial, which were clearly superior to the historical value of 30%. Although T factor (T3 vs. T4) was not a significant prognostic factor in the US trial, T3 patients did far better than T4 in the Japanese study (Figure), reflecting lower resection rate (78% vs. 40%).



A shift in the trend of clinical problems also became clear. The relapse patterns changed from predominantly locoregional to mainly distant recurrences in cases with complete resection, and a significant number of such patients suffered from metastasis in the brain as the initial site of relapse. In the JCOG study, 7-year follow-up data[5] revealed that 21 (41%) of the 51 patients who underwent R0 resection relapsed; initial site of relapse included locoregional only in 1, distant metastasis only in 14 (5 were "brain only"), and both in 6. In contrast, out of the 24 patients who failed to get R0 resection, 18 got tumor recurrence, with 13 locoregional relapses. In order to improve the outcome, SWOG subsequently launched another trial, S0220, with docetaxel consolidation after the induction therapy[6]. However, the overall survival was no better than the initial two reports, with the 3-year OS of 61%. The relapse pattern remained predominantly distant. Preoperative chemoradiotherapy was compared to conventional pre-operative radiotherapy in the Massachusetts General Hospital. In their retrospective analysis, Wright et al[7] did show that pre-op chemoradiotherapy was better that pre-op radiotherapy, with 4-year OS of 84% vs. 49%. In their single-institute trial (#92-038) at the MD Anderson Cancer Center, Gomez et al reported[8] the results of initial surgery followed by chemoradiotherapy in "resectable" SST. The result was comparable with those of the multi-institutional studies (Table), which included many "marginally resectable" tumors. Given the potential selection biases, the evidence would favor pre-operative chemoradiotherapy strategy.

Trial	JCOG9806	SWOG9416	MDA92-028
Patient accrual	76/ 3.6 years	116/ 4.3 years	32/ 13 years
No. institutions	19	NR (5 groups)	1
Chemotherapy	Pre-op	Pre- & post-op	Post-op
Chemotherapy	MVP	EP	EP
Radiotherapy	Pre-op	Pre-op	Post-op
Radiotherapy	45Gy/25fr	45Gy/25fr	60Gy/50fr
%T4 disease	26%	29%	22% (pathological)
Radiological ORR	61%	42%	N/A
Resection rate	75%	80%	100%
Complete resection rate	68%	76%	72%
Pathological CR rate	16%	29%	N/A
Toxic death rate	4%	4.5%	0
OS at 3-years	62%	NR	NR
OS at 5-years	56%	44%	50%
OS at 7-years	52%	41%	50%

In summary, preoperative chemoradiotherapy is the current standard of care for patients with SSTs. Several critical questions remain unsolved, however, including effective suppression of micrometastases in cases with R0 resection, prevention of brain metastases, and management of N2 SSTs, which were excluded from the hitherto reported trials. References 1) N Engl J Med 337: 1370-1376, 1997 2) J Thorac Cardiovasc Surg 119: 1147-1153, 2000 3) J Clin Oncol 25: 313-318, 2007 4) J Clin Oncol 26: 644-649, 2007 5) Proc Am Soc Clin Oncol 28 suppl: 2010, (abstr 7025) 6) Ann Thorac Surg. 98: 402–410, 2014 7) Ann Thorac Surg 73:1541-4, 2002 8) Cancer 118: 444-51, 2012

Keywords: preoperative chemoradiotherapy, superior sulcus tumor, Surgical resection

MS 11 COMBINED MODALITY TREATMENT FOR SUPERIOR SULCUS TUMORS
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 11.02 PROBLEMS IN THE MANAGEMENT OF SUPERIOR SULCUS TUMOR

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Pancoast tumors or superior pulmonary sulcus tumors (SSTs) are a rare subgroup of non-small cell lung carcinomas and occur in about 3-5% in patients with lung cancer. It is one of the most challenging thoracic malignancy to treat because of their proximity to vital structure in the thoracic inlet. In the last two decades improvements in appropriate preoperative staging, in multimodality treatment and development of new operative techniques have resulted in more curative treatment and better long-term results. However, in the preoperative assessment the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) has not been studied specifically in SSTs, also imaging methods to access pathological response after induction treatment is not clearly defined. Furthermore, management of STSs with invasion of spine or subclavian vessels remains controversial. Invasion of these structures was traditionally considered as a contraindication to surgery because of technical difficulties and poor long-term results. Also, patients with SST and N2 or N3 disease had an extremely poor prognosis due to loco regional recurrences, so that due to previous recommendations, this group of patients should not be treated surgically except in a protocol setting. The surgical approach (anterior/posterior/combined) varies dependent on tumor spread and although lobectomy is recommended as the standard type of pulmonary resection, many authors reported no significant different survival rates after sublobar operations. Finally, brain metastases remain the most common form of distant relapse, the use of prophylactic cranial irradiation is not generally accepted. Clinical diagnosis and appropriate staging has to be conducted. SSTs are well accessible by transthoracic fine-needle aspiration. MRI is the modality of choice for imaging structures of the thoracic inlet, including the brachial plexus, subclavian vessels, spine and neural foramina. It shows local extent of the disease and is important for preoperative planning. EBUS-TBNA and

PET is recommended for evaluation of mediastinal disease and distant metastasis before starting the induction treatment, mediastinoscopy is indicated to access pathological nodal response before surgery. A prospective phase II trial (SWOG INT 0160) showed that induction treatment with preoperative two cycles chemotherapy and concurrent radiotherapy with 45 Gy followed by surgery resulted in better tumor response and local control, higher rates of R0 resections and improved long-term overall survival, by low perioperative morbidity and mortality. Today, induction chemo radiotherapy followed by surgery has been established as standard treatment regimen for SSTs. Although vertebral body invasion and subclavian artery involvement are declared as negative prognostic factors, improvement in surgical techniques and cooperation of different surgical specialists, resulted in promising results for these difficult group of patients. Several authors described surgical techniques for tumor resection involving the transverse process only, or the intervertebral foramina, requiring hemivertebrectomies with spinal fixation, or the vertebral body, requiring total vertebral body resection with spinal fixation. In highly selected patients these extensive resections could be performed with acceptable morbidity and mortality in specialized centers with interdisciplinary teams of thoracic and spine surgeons. The en bloc resection technique provided acceptable recurrent rate (local 15%, distant 45%) and good long-term survival (25%-30% at 5-years). The introduction of the anterior approach made the resection of SSTs with subclavian artery involvement easier. After resection, the subclavian artery was reconstructed either with a ring supported polytetrafluoroethylene (PTFE) graft or direct by end-to-end anastomosis. Some authors reported about resection along the subadventitial plane to obtain tumor free margins or the use of autologous grafting. Five-year survival rates range between 25% and 32%. Extrapolating from the favorable results in other lung cancers, investigators have also considered induction chemoradiation for SSTs with mediastinal lymph node involvement (N2 disease), a group of patients previously considered hopeless. It is noteworthy that in two studies, no difference in median and overall survival was found between positive or negative pretreatment mediastinal N2 disease. Although these data should be interpreted with caution because they are liable to selection, they show that surgery is feasible with an acceptable outcome. Another important issue is that some authors found that ipsilateral supraclavicular lymph node is a local lymph node, so that patients with SSTs and N3 status (ipsilateral supraclavicular node involvement) showed a better prognosis than patients with N2 status (ipsilateral mediastinal node involvement). This have been confirmed in two larges and a few small series and underlines that ipsilateral supraclavicular N3 involvement could represent only local extension and may have a prognostic importance near to that of N1 disease. The influence of the type of lung resection, lobectomy versus sublobar resection, on the survival rates remains controversial. Lobectomy was associated with better survival compared with patients with wedge resections, but these data came predominantly from the pre-induction era with trimodality treatment. One important question is the necessity of lobectomy in patients with SSTs and pathological complete response (pCR). Some authors reported no significant different survival rates after sublobar operations in pCR patients and a higher incidence of wedge resection was found using the anterior approach only. Infiltration of the thoracic inlet increases the technical complexity of surgery, requiring extended resections and demanding reconstructive procedures. Completeness of resection represents one of the main factors influencing the long- term outcome of patients, pointed out in all publications about SSTs. Brain metastases remain one of the most common forms of relapse, prophylactic cranial irradiation (PCI) may be useful addition to preoperative chemoradiotherapy. Improvements in the combined preoperative treatment and surgical approach have significantly influenced local control and survival rates of SSTs. Further refinement of these techniques, also the addition of other chemotherapy agents or biologic agents as angiogenetic inhibitors or tyrosine kinase inhibitors could give some new perspectives in the treatment of SSTs. Further studies are needed to examine the effect of PCI on the survival after relapses in the brain. I declare no conflicts of interest.

MS 11 COMBINED MODALITY TREATMENT FOR SUPERIOR SULCUS TUMORS
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MS 11.03 SURGICAL APPROACHES IN SUPERIOR SULCUS TUMOR

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Complete en bloc resection is the corner stone of the treatment of solid tumors. Those located in the superior sulcus (SS) or thoracic inlet are known to have bad reputation because their resection represents a real technical challenge. The complexity of such surgery is due to the congestion of a very tight space (SS) by major neurovascular structures as well as to the proximity of the esophagus, the trachea and the spine. The preoperative work-up, in order to assess the involvement of such structures by SS tumors, may include, further to the routine bronchoscopy and cervico thoracic CT scan, an MRI to rule out spinal extension, venous angiography, subclavian arteriography or esophagoscopy. Many surgical approaches to remove SS tumors and many anatomical classifications have been reported during the last 6 decades. The goal of the surgical approach is to allow a wide and safe exposure of the SS, complete en-bloc resection of the tumor and all the involved structures and a potential arterial or spinal resection and reconstruction. The main goal of an anatomical classification is to facilitate the choice of the most appropriate surgical approach according to the extension of the tumor. After an anatomical description of the SS, we will review all the surgical approaches described in the literature to remove benign or malignant tumors developed in the SS. The emergence of new surgical techniques during the last 2 decades, such video-assisted and robotics surgeries had modify the surgical approaches in thoracic surgery. We will describe all the surgical approaches currently available to resect SS tumors with their advantages and their limits. Based on our experience we will describe a simplified anatomical classification of SS tumors. After identification of all contra-indications to SS tumor resection, we will describe the surgical approaches we use currently allowing when needed arterial and spinal resections and reconstructions.

Keywords: surgical approaches, Superior sulcus

MS 11 COMBINED MODALITY TREATMENT FOR SUPERIOR SULCUS TUMORS
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MS 11.04 RADIATION THERAPY FOR SUPERIOR SULCUS TUMOR

S. Senan

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In 2003, an IASLC Consensus Report recommended that 'superior sulcus tumors (Pancoast tumors, T3 or T4) should preferentially undergo trimodality treatment, including chemoradiation and surgery' [Eberhardt WE, Lung Cancer 2003]. This recommendation was based on the early results of the phase II Intergroup Trial 0160) trial, findings which have been subsequently updated [Rusch VW, J Clin Oncol 2007]. Results of two other prospective phase II trials, namely the JCOG 9806 and the SWOG-Intergroup Trial S0220, support the use of the trimodality approach in superior sulcus tumors [Kunitoh H, J Clin Oncol 2008; Kernstine KH, Ann Thorac Surg 2014]. Between 30-40% of patients with a locally-advanced NSCLC can develop local disease recurrence following full-dose chemoradiation [Baker S, Radiat Oncol 2016]. As the impact of a local recurrence for patients with superior sulcus tumors can be great, the role of surgery remains relevant for this site. Recent ESMO guidelines have identified this patient subgroup as having an increased risk of an incomplete resection [Eberhardt WE, Ann Oncol 2015], and consequently, the role of concurrent CT-RT as an induction scheme is considered standard at centers with the available surgical expertise. This overview will address radiation-related topics such as dose and fractionation schemes, treatment fields, newer radiation delivery techniques (MRI-guided radiotherapy, protons), salvage radiotherapy for small volume recurrences, and the treatment of second primary lung tumors.

MS 11 COMBINED MODALITY TREATMENT FOR SUPERIOR SULCUS TUMORS
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 11.05 DEFINITIVE CHEMORADIOTHERAPY IN SUPERIOR SULCUS TUMOR

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Superior sulcus tumors have been long defined as a distinct clinical entity. Symptoms including Horner's syndrome and other neurologic findings as well as severe shoulder pain and SVC syndrome characterize this disease. Early on, the use of preoperative therapy was recognized as potentially useful. Over time, initial chemoradiotherapy followed by surgery has emerged as standard of care for patients with T3 or T4 lesions and N0 or N1 disease. 3-year survival rates of approximately 60% have been reported for surgically resectable patients with advanced disease. More recently, the addition of consolidation chemotherapy following subsequent surgery was evaluated, but its exact contributions to increasing survival remain unclear. The majority of patients will progress, usually with systemic disease and a large fraction of patients develop brain metastases. Patients with unresectable disease receive concurrent chemoradiotherapy as definitive therapy. Here, commonly used regimens such as the combination of cisplatin/etoposide, carboplatin/paclitaxel, and cisplatin/pemetrexed are utilized. However, more effective therapies are needed and special emphasis on increasing the systemic antitumor activity against micrometastatic disease will be required. The use of targeted therapies such as erlotinib or crizotinib for EGFR mutated or ALK fusion-related adenocarcinomas is currently under investigation. Of high recent interest is the possible addition of immune oncology agents such as the PD-1 or PD-L1 inhibitors. A recent report on the use of the PDL1 inhibitor durvalumab after completion of concurrent chemoradiotherapy in patients with unresectable stage IIIB disease has been reported as meeting its primary endpoint. It is likely that this and other studies will be relevant for superior sulcus tumors as well. Currently ongoing trials of increasing progression-free survival and their scientific basis will be reviewed.

Keywords: superior sulcus tumor, concomitant chemoradiotherapy

MS 12 SUSTAINABLE CARE SYSTEM IN EACH REGION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 12.04 SUSTAINABLE CARE SYSTEM IN PHILIPPINES

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The Philippines is an archipelago composed of more than 7000 islands and is considered one of the emerging economies in Asia. Hence, it is not a surprise that although there is a huge improvement seen in the country, providing sustainable healthcare, even though it is in the list of the government's priorities, is still a major problem. Cancer, as reported by the Philippine's Department of Health (DOH) is the third leading cause of mortality behind Infectious and Cardiovascular Diseases. The top malignancy cases reported by the DOH involve the Breast, Lung, Prostate, Cervical and Colorectal. Incidence rates are highest in more developed countries

due to early detection of the disease therefore in areas like the Philippines, which lacks access to early diagnosis and treatment, mortality rates remain high. One reason surmised besides lack of financial back up is the geography of the country. With more than 7107 and rising islands, health care delivery is more challenging due to most towns, especially in the southern parts of the country, are difficult to go to or inaccessible by land, air and/or sea. However, in spite of lack thereof, the Department of Health – Philippine Cancer Control Program established in 1990, with Administrative Order 89-A, continue to work hard to bridge the gap. Its mission is to reduce cancer morbidity and mortality in the country operating in a systematic and organized approach utilizing primary and secondary prevention at the community level and tertiary prevention in the different regions of the country through hospitals and community levels. By means of the 6 pillars namely, Epidemiology & Research; Public Information & Health Education; Prevention & Early Detection; Treatment; Training; and Pain Relief (focusing on subprograms involving breast, lung and cervical cancer control, cancer pain relief), a healthcare system that is sustainable was hoped to be established. There are numerous projects formulated using the 6 pillars however due to lack of financial support, stricter implementations of guidelines and slow government approvals into law, mortality from cancer continues to rise. Nonetheless, the program as well as medical societies such as the Philippine Society of Medical Oncology, Philippine Cancer Society, Philippine Society of Oncology, Philippine College of Surgeons and so on, remain confident and continue to work towards the goal. Programs, such as the Philippine Medicines Policy of 2011 employed strategies that would provide free medicines in the hope to address priority diseases such as TB, HIV, Malaria and Cancer. The Philippine Health Insurance Corporation in 2012 provided Benefit Packages in the aim of giving assistance to marginalized sectors of society afflicted with certain malignancies and promote patient empowerment to become active participants in healthcare decision-making by being informed and educated about their illness and adhering to treatment plans. Republic Act 10606 (The Universal Health Care Act of 2013), ensures that all Filipinos, especially the poorest of the poor, will receive health insurance coverage from the Philippine Health Insurance Corporation. The National Center for Disease Prevention and Control-Degenerative Disease Office (2014), developed clinical pathway guidelines for selected non-communicable diseases including cancer in the hope to manage these cases systematically in the country. All these policies and laws are meant to provide a sustainable healthcare in the Philippines but unless properly implemented, followed and financed, the realization of these dreams will remain elusive. There is nevertheless a glimmer of hope with the newly signed law last July 23, 2017, the Executive Order 26, known as the National Tobacco Ban which prohibits smoking in all public places and utility vehicles nationwide. If implemented properly, it would significantly decrease lung cancer incidence and mortality in the country.

Keywords: Philippines, Healthcare Policy, Sustainable Care

MS 13 HOW TO DEAL WITH CNS METASTASES
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 13.01 STRATEGIC APPROACH TO CNS METASTASIS

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Brain metastases (BMs) concern more than 10-15% of patients with stage IV NSCLC at baseline and more than 40% during the disease course. The wider use of MRI and improvement of extra-cranial systemic disease control contribute to increase the BMs incidence. The issue of BMs is critical in the management of NSCLC patients in the perspective of the neurological consequences of brain lesions. BMs occurrence is synonymous of a poor outcome in NSCLC but reflects in fact many different situations. Establishing a therapeutic strategy needs first to assess their prognosis; the most appropriate scale is the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers including as prognostic factors *EGFR* mutations and *ALK* rearrangement in addition to age, number of BMs, extra-cranial disease and Karnofsky status, with a median survival varying from 3.0 months for the worse subgroup (GPA 0.5-1) to 46.8 months for patients with oncogene addiction and good prognostic factors (GPA 3.5-4). The second step is to evaluate the indications, efficacy and side effects of available therapeutic «weapons». Corticosteroids are active against cerebral edema and improve symptoms. Whole brain radiotherapy (WBRT) has been for decades the treatment «reflex» of BMs but the emergence of stereotactic radiosurgery (SRS) or radiotherapy (SRT) and the issue of neurocognitive complications led to deferral or omission of WBRT in an increasing number of patients. WBRT remains indicated in patients with symptomatic, large (≥3 cm) and numerous BM. However, palliative WBRT did not provide any benefit in terms of survival, quality of life and QUALYs compared to supportive care alone in the Quartz trial; the subgroup analysis suggests a benefit only in patients with better prognostic factors. Neuroprotective strategies as sparing hippocampi during WBRT are currently evaluated. SRS defined by invasive contention with sub-millimeter accuracy or noninvasive SRT with millimeter accuracy are indicated in case of 1 to 3 BMs (but now up to 10 lesions) with a diameter <3 cm, alone or as a boost on the top of WBRT. SRS/SRT alone avoids neurocognitive toxicity of WBRT and provides a similar OS to that of surgical resection when using SRS/SRT for patients with operable lesions. Radionecrosis is observed in 10-17% of patients treated with SRS/SRT, making difficult the distinction with a tumor relapse. In spite of reduction in local and distant brain failures or in death from neurological causes, adjuvant WBRT after SRS/SRT does not improve overall survival and has a detrimental effect on neurocognitive functions and quality of life. Surgical resection of BMs achieves survival and functional benefit in addition to WBRT. Surgery is indicated in case of a symptomatic lesion, larger than 2 cm, with a mass effect, allowing fast improvement of symptoms. The invasive edge of BMs explains the high local recurrence rate after resection and the need for adjuvant radiotherapy. WBRT is progressively less used in favor of SRS/SRT despite a better intracranial control rate because of a higher rate of cognitive deterioration. Systemic treatment remains critical for extracranial systemic control of the disease. Brain-blood barrier limits the brain penetration of systemic agents, especially with efflux transporters as P-gp, for which many TKIs and cytotoxic agents are substrates. BMs usually cause brain-blood barrier disruption with heterogeneous drug penetration. Cytotoxic chemotherapy provides similar response rates in BMs to those of extracranial disease. Anti-PD-1 antibodies seem to be active in the brain but available data are scarce. First and second-generation EGFR TKIs have a low brain penetration but sufficient to obtain response rates similar to those achieved for systemic disease; duration of response might be inferior. Osimertinib has a better CNS penetration. For ALK+ disease, crizotinib is a P-gp substrate with a low blood/CSF concentration ratio and brain is the most frequent site of progression. Next-generation ALK TKIs have a better CNS diffusion; alectinib largely decreases the cumulative incidence of BMs compared to crizotinib. Concurrent administration of TKIs with brain radiotherapy is controversial and is not recommended outside of a clinical trial. Defining an optimal multidisciplinary strategy needs to take into account many parameters, including number, location and size of brain metastases, leptomeningeal lesions, neurological symptoms, risk factors for neurocognitive alteration, extracranial metastases and their control, primary lung tumor control, and identification of a targetable oncogenic addiction. In absence of a targetable genomic alteration, BMs at baseline can benefit from systemic treatment alone in selected patients with no neurological symptoms, small intracranial tumor burden, low risk of impending neurologic issues, on the condition that they are closely monitored; brain radiotherapy can be safely deferred to intracranial progression. Symptomatic BMs require local treatment, by favoring SRS/SRT rather than WBRT; adjuvant WBRT is not recommended but further close monitoring is mandatory to detect new intra-cranial lesions. Surgery is preferred for large lesions, posterior fossa location or diagnosis; adjuvant SRS/SRT is mandatory to avoid local recurrences. WBRT remains indicated for multiple symptomatic lesions not eligible for SRS/SRT except in poor PS patients. In case of *EGFR* mutations, asymptomatic patients with BMs are treated with first or second-generation EGFR TKIs but must be closely watched with repeated brain imaging. A recent retrospective study suggests that front-line SRS/SRT might improve overall survival as CNS remains a sanctuary site in oncogene-addicted disease. Symptomatic patients are locally treated, favoring SRS/SRT requiring only a short interruption of systemic treatment. For patients with *ALK+* disease, the advent of alectinib as standard front-line treatment should change the management approach to BMs: the low incidence of BMs should allow spacing brain monitoring while the high intra-cranial response rate should permit to delay local treatment. For *ALK+* patients developing BMs on ALK TKI, local treatment with SRS/SRT or surgery if necessary is the first option; switching to another TKI with a better brain penetration is another option for patients candidates to WBRT. The longer life expectancy of *ALK+* patients leads to defer as far as possible the use of WBRT. However, improvement of intracranial control should be considered in patients at preferential risk of dying from intracranial progression, independently on mutational status.

Keywords: non-small cell lung cancer, brain metastases

MS 13 HOW TO DEAL WITH CNS METASTASES
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MS 13.02 SBRT VS. WBRT

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The management of brain metastases remains a challenging issue due to the detrimental impact on the patient quality of life and the wide range of clinical situations. The question is not a local treatment or WBRT but when and how to use the different modalities for each patient. Survival, an endpoint often used, is probably not the best way to evaluate the local efficacy: most patients will died from progressive extracranial disease. The brain tumor control (local or freedom from new brain metastases) is a better way to assess the impact of WBRT or SBRT. Another major problem is the great heterogeneity of the primary tumors and clinical situations. First, we should remember that most patients are not candidate for a local treatment (SBRT or surgery (S)) due to the number of lesions, locations, performance status, meningeal infiltration…and WBRT remains the standard treatment if a brain irradiation is needed. For patients with an "oligo metastatic disease", many studies have clearly showed the superiority of a form of local treatment (S or SBRT) compared to WBRT at least in term of progression or control at the primary brain site (table1) (1-5). Another issue is to control the disease within the brain: new brain metastases are very common. WBRT has been tested either after S or SBRT to prevent the development of those new lesions: indeed adding WBRT let to a better brain tumor control but this did not translate in any major survival benefit. One major drawback of WBRT is its possible toxicity: the impact on the quality of life, the neurocognitive toxicity, the fatigue and the hair loss. In the EORTC trial, WBRT had a transitory negative impact on the physical or cognitive functioning and more fatigue in the early period of observation compared to the group of patients in the observation arm (6.). A current approach is to follow the patient after SBRT and in case of relapse to propose a salvage treatment which may be a new course of SBRT or even WBRT. Another question was to improve the local control after S adding SBRT. Postoperative SBRT has been proposed and several retrospective studies have shown the feasibility results. Two recently published randomized trials have compared postoperative SBRT to either WBRT or observation. The two main conclusions were less cognitive deterioration with SBRT compared to WBRT(15% vs 48%) and less local relapse at the primary site compared to no treatment (at 1 year 43% vs 72%) but no difference in overall survival (4,5). An intriguing observation was the better local control at one

year after postoperative WBRT compared to SBRT (4). Is there a group of patients benefiting from WBRT? In a new analysis of the Aoyama trial, patients with NSCLC were divided according to a graded prognostic assessment: a statistically significant benefit was observed only in the favorable group with a 6 months gain in median survival (7). A similar observation was reported in the RTOG trial testing the role of adding SBRT to WBRT with a median survival of 14 vs 21 months (8). Is it possible to reduce WBRT toxicity? The hippocampus region play an important role in the preservation of the neurocognitive functions: techniques have been developed to spare the hippocampus region keeping the dose below 7 Gy with a better quality of life and a very low risk of new brain metastases occurring in this spared regions (9). This approach should be tested in large scale phase III trial. Last but not least, the timing of the treatment should be individualized based on the patient needs, and in asymptomatic patients, SBRT may be safely postponed if a systemic treatment is to be administered.

Authors	Treatment	Evaluation Time	Local Control	Brain Tumor Control
Aoyama Kocher Andrews Brown Mahajan	SBRT SBRT+WBRT Surgery Surg+WBRT SBRT SBRT+WBRT WBRT WBRT+SBRT Surg+WBRT Surg +SBRT Surg SURG. SBRT	1 Y 2 Y 1Y 1Y 1 Y	72% 88% 41% 73% 69% 81% 60% 74% 78% 55% 45% 72%	23% 53% 58% 77% 52% 67% 51% 62% 69% 32% 33% 43%

· Estimated from figures References 1.Aoyama H., Tago M., Shirato H. for the Japanese Radiation Oncology study Group 99-1 (JROSG 99-1) investigators Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases. Secondary analysis of the JROSG-99 randomized clinical trial JAM Oncol. 2015; 1: 457-464 2.Kocher M., Soffietti R., Abacioglu U., et al Adjuvant whole-brain radiotherapy versus observation after surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J.Clin.Oncol. 2011; 29:131-141 3.Andrews D.W., Scott C.B., Sperduto D.W. et al Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial Lancet 2004; 363:1665-72 4.Brown PD, Ballman KV, Cerhan JH,et al Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial.Lancet Oncol. 2017 Jul 4. pii: S1470-2045(17)30441-2. doi: 10.1016/S1470-2045(17)30441-2. [Epub ahead of print] 5.Mahajan A, Ahmed S, McAleer MF, et al Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017 Jul 4. pii: S1470-2045(17)30414-X. doi: 10.1016/S1470-2045(17)30414-X. [Epub ahead of print) 6.Soffietti R., Kocher M., Abacioglu U., et al A European Organiszation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation after surgical resection of one to three cerebral metastases: quality of life results J.Clin.Oncol. 2011; 31:65-72 7.Aoyama H., Tago M., Shirato H. et al Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial JAMA 2006; 295: 2483-91 8.Sperduto P.W., Shanley R., Luo X., et al Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation verus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). Int.J.Radiat.Biol.Phys. 2014; 90: 526-531 9.Gondi V., Hermann B.P., Mehta M.P., Tome W.A. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int. J. Radiat. Oncol. Biol. Phys. 2012 ; 83 : 487–93

Keywords: brain metastases, Radiotherapy, SBRT

MS 13 HOW TO DEAL WITH CNS METASTASES
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 13.04 THE ROLE OF CHEMOTHERAPY IN THE MANAGEMENT OF CNS METASTASIS

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The optimal management of patients with CNS metastases from lung cancer should be a multidisciplinary approach which encompasses supportive therapy, local CNS-directed therapies including surgery, stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT), and most importantly systemic therapy. In the case of patients with **small cell lung cancer** (SCLC), both the primary tumour and systemic metastases are generally chemosensitive, at least initially. Most studies suggested that brain metastases are as sensitive to systemic chemotherapy as extracranial disease. The concept of the brain as a pharmacologic sanctuary site for established metastases is in contrast with clinical observations of frequent responses in brain metastases to systemic chemotherapy. Response rates (RRs) of brain metastases from SCLC to systemic chemotherapy in treatment naive patients have been reported to range from 27% to 85%. RRs in previously treated patients with brain metastases range from 22% to 50% and are comparable to the RRs with second-line chemotherapy observed in extracranial disease. A meta-analysis of five studies with a single chemotherapy for pretreated patients showed RRs ranging from 33% to 43%.[1] Adding WBRT to chemotherapy increases the RR of the brain metastases, but does not appear to improve survival as shown in a phase III trial by the European Organization for Research and Treatment of Cancer.[2] For patients with advanced non-small cell lung cancer (NSCLC) without molecular drivers, chemotherapy is the mainstay of treatment. Although NSCLC is less responsive to systemic chemotherapy than SCLC, results of combining platinum compounds and third generation agents are substantially better than with earlier regimens. Platinum-based doublets are the cornerstone treatment in the first-line setting for metastatic NSCLC.[3] There is a presumed lack of effectiveness of systemic chemotherapy in CNS metastases from NSCLC because of the belief that chemotherapeutic drugs cannot cross the blood-brain barrier (BBB).[4] However, there is increasing evidence that the integrity of the BBB is impaired and disrupted in the presence of macroscopic CNS metastases. Despite a low penetration of the CNS, chemotherapy drugs have demonstrated encouraging activity against CNS metastases from NSCLC. A number of phase II studies reported RRs to cisplatin-based combination chemotherapy regimens ranging from 35% to 50%. Several clinical trials with upfront platinum-based chemotherapy have shown intracranial RRs ranging from 23% to 50% which correlated with and almost comparable to systemic RRs.[5] These data suggest that the intrinsic sensitivity of the tumour to the cytotoxic drug is more important in predicting response to the chemotherapeutic drug than the theoretical expected ability of the drug to penetrate the BBB. There are few randomised phase III trials of advanced or metastatic NSCLC evaluating different kinds of treatment in patients with brain metastases because generally, such patients have been excluded from clinical trials because of poor prognosis. Despite a penetration of CNS of less than 5%, pemetrexed demonstrated a consistent activity against brain metastases from NSCLC. One of the first evidence of pemetrexed activity against brain metastases came from a retrospective Italian study by Bearz and colleagues on 39 NSCLC patients with CNS metastases treated with pemetrexed as second or third line.[6] Although the patients were unselected for histology, the study reported an intracranial RR of 30.8%, with clinical benefit obtained in 69% of patients. All patients who had an overall response (i.e., partial response and stable disease) to pemetrexed had a benefit over cerebral metastases as well with partial response in 11 patients (28.2%) and stable disease in 21 (53.8%), with a clinical benefit rate of 82% for CNS metastases and an overall survival (OS) of 10 months. The addition of platinum compounds to pemetrexed slightly improved the outcome as shown in subsequent studies. In a phase II trial on 43 chemotherapy naïve NSCLC with brain metastases (93% with non-squamous histology) treated with pemetrexed and cisplatin for six cycles, the intracranial RR was 41.9%.[7] A comparable intracranial RR of 40% was observed when pemetrexed was combined with carboplatin in an observational study on 30 patients with adenocarcinoma and brain metastases.[8] These clinical trials showed that platinum-based regimens are active against brain metastases from NSCLC and high RRs can be achieved with pemetrexed-containing regimens in patients with non-squamous NSCLC. A *post-hoc* analysis of a large prospective observational European study on 1,564 patients with newly diagnosed advanced NSCLC receiving first-line platinum-based regimens showed that in the subgroup of 263 patients with brain metastases the median OS was 7.2 months which ranged from 5.6 months for patients treated with cisplatin/gemcitabine up to 9.3 months for those treated with platinum/pemetrexed.[9] In conclusion, systemic chemotherapy is an important part of the multidisciplinary managment of CNS metastases. Patients with small asymptomatic brain metastases from SCLC and NSCLC should be treated with the most active platinum-based combination chemotherapy upfront. Radiation therapy and other CNS-directed treatment may be deferred until the effects of the systemic chemotherapy on the CNS metastases can be determined. **References** 1. Grossi F, Scolaro T, Tixi L, et al. The role of systemic chemotherapy in the treatment of brain metastases from small-cell lung cancer. 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Keywords: chemotherapy, CNS, Metastases

MS 13.05 TARGETED THERAPY FOR EGFR POSITIVE MUTANT NSCLC WITH CNS METASTASIS

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Central nervous system (CNS) metastases including brain metastasis (BM) and leptomeningeal metastasis (LM) are associated with poor prognosis in non-small cell lung cancer (NSCLC). The epidermal growth factor receptor (*EGFR)* mutations were initially reported in 2004 and currently defined the most prevalent actionable genomically classified subgroup of NSCLC, which account for 40% of Asian patients and 10-15% of White or African American patients. Patients with *EGFR* mutant NSCLC may have a higher incidence of CNS metastases due to prolonged survival with targeted agents and the increased quality of CNS imaging. More than 50% of NSCLC patients with *EGFR* mutation develop CNS metastases during their lifetime (1). The median overall survival (OS) for patients with BM is around 16 months (2) and 4.5-11 months for those with LM (3). Whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or surgery is widely used for BM, whereas no standard therapy is available for LM. Moreover, the benefit of radiotherapy is limited due to toxicities and long term sequelae. Brain is a privileged site, sheltered from the systemic circulation by the blood-brain-barrier (BBB), which is highly specialized structure with tight junctions created by the interaction between astrocytes, pericytes and endothelium. In addition, numerous efflux transporters (e.g. P-glycoprotein) have been identified, leading to prevent many traditional drugs from the circulation into the brain parenchyma. Although the permeation of EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib or erlotinib across the BBB has been reported, the cerebrospinal fluid (CSF) concentrations of TKIs at standard doses comprise only small fraction of the plasma concentration indicating the limited ability to permeate into the CSF (4). Several small series of phase II studies reported that EGFR TKIs, gefitinib, erlotinib or afatinib show CNS response rate of 55 to 89%, median PFS of 5.8 to 14.5 months and median OS of 15.9 to 22.9 months in patients with brain metastases. Recently, new generation EGFR TKI, AZD 3759 which is designed to effectively penetrate BBB demonstrated profound anti-tumor activity in preclinical models. Phase I study showed the free plasma concentration of AZD 3759 was approximately at the same range as that in CSF and yielded $K_{p,uu,CSF}$ values of 1.18 and 1.00 for 200mg and 300mg, respectively. Tumor responses were observed in 83% and 72% of the patients with CNS and extracranial disease respectively in EGFR TKI naïve NSCLC (5). Osimertinib, a third generation EGFR TKI designed to target both activating *EGFR* mutation and T790M but sparing wild type *EGFR*, distributed into mouse brain to a greater extent than gefitinib (brain/plasma ratio 3.4 for osimertinib *vs* 0.21 for gefitinib). Osimertinib showed significant brain exposure and tumor shrinkage in preclinical brain metastases model. In 50 of 411 evaluable for CNS response in pooled AURA phase II study, osimertinib showed 53% of response rate and the median CNS PFS has not been reached (6). Confirmatory phase III study comparing osimertinib with platinum-doublets in T790M positive patients demonstrated significant improvement of PFS regardless of CNS metastases suggesting this agent has benefit in patients with CNS metastases. Recently released press showed that first-line osimertinib comparing with gefitinib/erlotinib (FLAURA) met the primary endpoint of PFS. It would be interesting to evaluate whether upfront use of osimertinib in *EGFR* mutant NSCLC can delay CNS metastases. Given the relatively high response rate in brain metastasis with EGFR TKI, the upfront use of EGFR TKI can delay other local therapies such as WBRT, SRS or surgery, leading to reduced side effects related to local therapy. However, the retrospective multi-institutional analysis demonstrated that the use of upfront EGFR TKI and deferral of radiotherapy is associated with inferior OS in patients with *EGFR* mutant NSCLC who developed brain metastases (7). Based on the potential synergistic effects of the combination of EGFR TKIs and radiotherapy due to opening of BBB by radiotherapy, several prospective trials were conducted. A phase II study of erlotinib combined with WBRT in 40 patients with NSCLC achieved 86% of response rate, 11.8 months of overall survival, whereas 19.1 months in patients with *EGFR* mutation (8). The Radiation Therapy Oncology Group conducted a phase II trial of WBRT and SRS alone or with either temozolomide or erlotinib for NSCLC patients with one to three brain metastases (*EGFR* mutation status was not tested). This study was closed early due to slow accrual and three arms did not show any differences in terms of efficacy. However, grade 3 to 5 toxicities were 41-49% in two concurrent drug combination arms. Thus, prospective randomized trial of SRS followed by EGFR TKI *vs* EGFR TKI followed by SRS at CNS progression is needed. Leptomeningeal disease (LM) is a fatal manifestation and its incidence is increasing in *EGFR* mutant NSCLC up to 10%. The prognosis remains very poor despite systemic treatment, intrathecal chemotherapy, radiotherapy and even molecular targeted therapy. Although EGFR TKIs have shown promising efficacy in the treatment of LM, especially with high dose or pulsatile dosing, the duration of efficacy is still limited with lack of survival improvement (9). Compared to gefitinib, erlotinib showed higher CSF concentrations (28.7 *vs* 3.7 ng/ml) and retrospective analysis showed promising activity with erlotinib in LM. It is not clear whether combination of intrathecal chemotherapy or WBRT can be applied to *EGFR* mutant NSCLC patients. Given the significantly higher penetration across the BBB ($K_{p,uu,brain}$ =0.86) of AZD 3759, AZD3759 showed 28% of response rate (5/18) in TKI pretreated LM patients and 75% (3/4) in TKI naïve patients suggesting promising efficacy. The mean osimertinib concentration in CSF was 7.5nM in the T790M unselected cohort and AZD 9291 at 160mg once daily demonstrated encouraging activity with 43% of LM disease response and manageable tolerability (10). Both agents are currently being investigated in a larger cohort of patients with brain metastasis and leptomeningeal disease. Another challenge of conducting clinical trial in patients with LM is lack of standardized response evaluation method. Combinational measurements including neurological sign, CNS imaging and CSF cytology have been proposed, but further validation is warranted. In conclusion, CNS metastases in *EGFR* mutant NSCLC are increasing. Although EGFR TKI has been reported to improve clinical outcome, isolated or pre-dominant progression of CNS metastases remains a major issue in patients on EGFR inhibitors due to relative low penetration to BBB. New generation EGFR TKIs with better BBB penetration might have an impact on therapeutic strategies. Further studies are required to evaluate the optimal sequence of EGFR TKI therapy and radiotherapy. References Rangachari D, , et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015; 88: 108-11. Fan Y, Xu X, Xie C. EGFR-TKI therapy for patients with brain metastases from non-small-cell lung cancer: a pooled analysis of published data. Onco Targets Ther 2014; 7: 2075-84. Umemura S, Tsubouchi K, Yoshioka H, et al. Clinical outcome in patients with leptomeningeal metastasis from non-small-cell lung cancer: Okayama Lung Cancer Study Group. Lung Cancer 2012; 77: 134-9. Togashi Y, Masago K, Masuda S, et al. 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MS 14.01 ELEMENTS TO REACH THE TREATMENT GOAL OF PALLIATION

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Despite fast growing information of tumor molecular biology, the increase in the therapeutic portfolio, and a significant improvement in diagnostic radiology, treatment of advanced NSCLC in 2017 remains palliative with still no curative perspective for the vast majority of patients. Therefore, the main treatment goals include the change from an acute into a chronic disease, extending survival times as well as improving or just maintaining quality of life. In order to assure an optimal palliation the majority of patients with advanced NSCLC – considering the high age and concomitant comorbidities - frequently may require modifications of the treatment standard. Furthermore, it can also not be ignored that recently approved novel agents and innovative diagnostic technology represent a growing burden of financial toxicity leading to regional differences in the availability of modern therapy and in the access to molecular testing and modern imaging. Nonetheless, treatment algorithms for advanced NSCLC have over the last decade gradually gained in complexity by incorporating a number of diagnostic and therapeutic achievements allowing personalization, individualization, and precision of therapy. Not only patient factors such as performance status (PS), comorbidity, and patients' treatment expectation must lead to treatment differentiation and modification but also disease characteristics such as tumor stage, tumor load, histological type (squamous vs non–squamous) and the molecular profile of the tumor (mutant vs wild type) influence the process in reaching the goal of optimal sustainable palliation. Other critical elements in realizing personalized therapy and precision medicine within the process of optimal palliation consist in a rational selection of anti-cancer agents (predictive factors, mode of action, toxicity profile) and their appropriate application (single agent, concomitant combinations, drug sequencing) as well as other novel therapeutic actions such as interventional radiology, modern radio therapy, and minimal surgery. Optimal therapeutic management for sustainable palliation should definitely be based on clinically reliable evidence presented by frequently updated treatment recommendations: Today's treatment algorithm for advanced NSCLC is challenged by a number of newer agents, such as tyrosine kinase inhibitors, monoclonal antibodies, checkpoint inhibitors (Table 1),

2nd-line	Docetaxel, Pemetrexed, EGFR-TKI	**1st-line**	Bevacizumab - non-squamous NSCLC
I	Ramucirumab / Doc - NSCLC	I	Bevacizumab/Erl. – EGFRm NSCLC
I	Nintedanib / Doc - non-squamous	I	Pemetrexed - non-squamous NSCLC
I	Nivolumab - NSCLC	I	Pemetrexed, Erlotinib - maintenance
I	Osimertinib - EGFRmT790M	I	Gefitinib, Erlotinib, Afatinib - EGFRm
I	Crizotinib, Ceritinib – ALK	I	Necitumumab - squamous NSCLC
I	Alectinib - ALK	I	Crizotinib - ALK/ROS
I	Pembrolizumab – PD-L1-low	I	Ceritinib – ALK
I	Atezolizumab - NSCLC	I	Alectinib -ALK
		I	Pembrolizumab - PD-L1-high

Table 1 and the incorporation of new treatment strategies such as continuation or switch maintenance therapy (Figure 1).

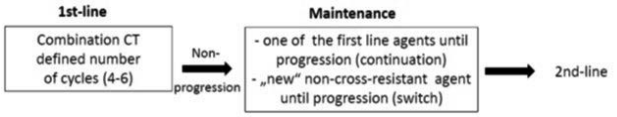

Figure 1 For advanced NSCLC (Figure 2) it is generally accepted that platinum based doubled chemotherapy remains the backbone for the majority of our patients with good PS and this combination therapy should be modified according to feasibility and tolerability, comorbidity, patients' age over 70 years, PS.

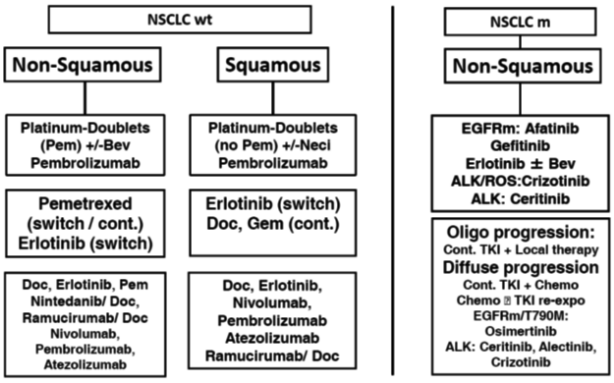

Figure 2 For wild type non-squamous NSCLC there is pemetrexed which has been shown to be favorable over older cytotoxic agents if combined with platinum based components. In addition, pemetrexed has also sufficiently demonstrated that if it is continued in case non-progression under four cycles of standard platinum based doublet chemotherapy not containing pemetrexed (switch maintenance) or containing pemetrexed (continuation maintenance) prolongs survival. Another agent, the small molecule and EGFR-tyrosine kinase inhibitor erlotinib also prolongs survival if used in the switch maintenance setting but its benefit depends on the quality of response to the chemotherapy and is restricted to patients which have experienced disease stabilization only. The VEGFR-targeting antibody, bevacizumab, if added to platinum based doublet therapy, specifically to carboplatin/paclitaxel significantly improves response rate, duration of response, progression free survival, as well as overall survival in eligible patients. Human immune checkpoint inhibitor-antibodies inhibiting the PD-1 receptor or PD-1 ligand have recently been integrated into the treatment algorithms of wild type NSCLC. Pembrolizumab is currently the only checkpoint inhibitor approved and recommended for first line therapy in patients with a PD-L1 expression level ≥ 50 % and with negative or unknown EGFR/ALC/ROS1 testing. In wild type squamous NSCLC the given treatment options are still limited and platinum based therapy (no pemetrexed, no bevacizumab) remains the recommended treatment standard. Nonetheless, just recently the EGFR-targeting monoclonal antibody necitumumab has shown to significantly improve survival if combined with the standard doublet regimen cisplatin/gemcitabine in comparison to cisplatin/gemcitabine only and therefore, has just recently approved. Maintenance therapy in squamous tumors with docetaxel or erlotinib (switch) or gemcitabine (continuation) may be justified in some patients even here the statistical evidence is weak. For about 10-30% of NSCLC (in Europe < 15%) non-squamous tumors expressing specific molecular features first-line treatment by genotype has been established. Tumors with sensitizing EGFR mutations have been exposed by gefitinib, erlotinib, and afatinib and have shown to prolong progression free survival over standard platinum based doublet standard therapy. In tumors bearing ALK-/ROS1-gene-rearrangements crizotinib and ceritinib have also shown to prolong progression free survival if compared to platinum based / pemetrexed doublet chemotherapy. Therefore, EGFR-TKI therapy (erlotinib, gefitinib, afatinib) should be prescribed for patient with tumors bearing sensitizing EGFR-mutations and for patients with tumors bearing ALK-/ROS1-gene-rearrangements ALK-/ROS1-targeted therapy (crizotinib, ceritinib) should be prescribed. However, for these patients molecular testing is critical and should be used to select patients for EGFR/ALK/ROS1 targeted therapy. Patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics (ethnicity, gender, smoking status). Last but not least, second-/subsequent-line therapy is another strong element contributing to sustainable palliation in patients with advanced NSCLC. For tumor without driver mutations agents available before 2014 include docetaxel, pemetrexed (for non-squamous cell tumors only) and erlotinib. In recent years the two antiangiogenic agents nintetanib and ramucirumab (both in combination with docetaxel) and three immune checkpoint inhibitors (nivolumab, pembrolizumab, azetolizumab) have been added to the armentarium to treat patients with advanced non-mutated NSCLC who have progressed on or after first-line therapy (Figure 2). In mutated NSCLC several therapeutic options for second-/subsequent line-therapies are recommended depending on the type of progression and the molecular profile of the tumor. Osimertinib has been just recently approved for EGFRm/790M expressing tumors. For ALK-positive tumors ceritinib, alectinib, and crizotinib can be prescribed. In general, selection of agents for second-/subsequent-line therapies is based on whether the drugs have been used earlier, or toxicity or patients view. References are available by the author.

Keywords: sustainable palliation, recommendations, advanced NSCLC

MS 14 QOL EVALUATION IN PRACTICE FROM THE VIEWPOINT OF PHYSICIANS AND NURSES
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 14.02 DIMENSIONS OF QUALITY OF LIFE IN LUNG CANCER

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Lung cancer is the leading cause of death in the world. Approximately 85% of patients are diagnosed with advanced disease, associated with high morbidity and mortality. Lung cancer is associated with a higher burden of symptoms compared to other cancers. Patients may experience symptoms from disease such as cough, dyspnea, anorexia, malaise, pain and anxiety. Lung cancer patients often report symptom clusters (2 or more symptoms occurring simultaneously). Patients may also experience symptoms secondary to immediate and chronic side effects of treatment. Treatments for lung cancer include surgery, radiation therapy, chemotherapy, targeted therapy and immunotherapy. Patients may receive a combination of these therapies either concurrently or sequentially. Each therapy is associated with a unique adverse symptom profile. Collectively these symptoms negatively impact clinical outcomes. High symptom burden is associated with poorer clinical outcomes such as survival and health related quality of life (HRQOL). HRQOL is the evaluation of the patients own life situation from their perspective. HRQOL may also be referred to as patient reported outcomes (PROS) and the measurement referred to as patient reported outcome measures (PROMs). HRQOL is subjective and multidimensional. HRQOL measures include physical, psychological, cognitive, social and life roles. Quality of life may be negatively influenced by risk factors such as co-morbid medical conditions, poor nutritional status, emotional distress, sleep disturbances, poor pulmonary function, poor financial resources, poor social support and past family history. Poor nutritional status, including malnutrition, sarcopenia and cachexia, is associated with poor quality of life, poor response to treatment and decreased survival. Emotional distress, anxiety and depression, is linked to lower HRQOL, increased symptom burden and poorer prognosis. Previous experience with family cancer and perceived risk of cancer, specifically among women, is associated with poorer reported HRQOL. Caregivers of patients with poorer HRQOL have a greater caregiver burden. This in turn negatively impacts the patients HRQOL further. Maximizing quality of life is an essential component of lung cancer management. Pre-diagnosis HRQOL and HRQOL at diagnosis are a strong prognostic factor for survival in lung cancer. HRQOL measurements are useful to evaluate treatment efficacy. HRQOL is an important clinical outcome measure to consider as newer treatments and improved therapeutics are providing the opportunity for long term survival for some patients. It is especially important in cases when therapy is unlikely to be curative, as patients often report that HRQOL is more important than short term survival benefits. Several instruments have been developed to assess HRQOL (Table 1). Some of the tools are generic, some specific to cancer and others that specifically focus on lung cancer. Most of the instruments are questionnaires. Several tools developed demonstrate correlation with performance status, symptoms and survival. Studies suggest that disease specific instruments may enhance outcome measures and be more useful in predicting outcomes. The tools specific to lung cancer include: The Lung Cancer Symptom Scale (LCSS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTIC-QLQ), Functional Assessment of Cancer Therapy-Lung (FACT-L) and the Short Form Health Survey (SF). The City of Hope Quality of Life Family Care Giver Tool (COH-QOL-FCG) focusses specifically on the quality of life impacted by the family care giver.

Table 1

Tool	Questions	Context Areas
The Lung Cancer Symptoms Scale (LCSS)	15	Patient and observer (healthcare professional) forms. Measures physical and functional dimensions
EORTC-QLQ C30	30	Cancer symptoms, physical symptoms, 5 functional areas (physical, role, cognitive, emotional, social), overall financial impact.
EORTC-QLQ-LC 13	13	Developed as supplement to the QLQ-C30 above. 13 items assess lung cancer symptoms, treatment related side effects (chemotherapy specific) and pain
Functional Assessment of Cancer Therapy-Lung (FACT-L)	37	Combination of the FACT-generic 27 questions on general QOL (physical, social and family, emotional, functional well-being and relationship with physician), and 10 items on lung cancer specific symptoms.
Short Form Health Survey (SF-36)	36	General health (physical function, role physical function, bodily pain, general health perception, vitality, social functioning, role emotional, mental health) with 2 summary scales measuring physical and mental component scales.
City of Hope Quality of Life Family Care Giver Tool (COH-QOL-FCG)	37	Measures physical, psychological, social and spiritual

There are some inherent limitations of the instruments. The scales have been developed by health care providers who may have different biases on what defines HRQOL. Therefore, there are likely metrics that are missing from the measures obtained. Accurate and consistent data collection may be influenced by fluctuations in the patients' health status and symptom burden, making it difficult for them to complete questionnaires. If instruments are completed by a caregiver or healthcare provider, performance status may be used as a proxy for overall HRQOL. While performance status is correlated with HRQOL, it does not include all parameters. Operational barriers may be time demands on the health care provider, space limitations or technology breakdown when using online access. Other barriers may be the influences of language, culture, religion, age and educational level. Health care providers should continue to explore other strategies for capturing HRQOL data. The overall goal of health care providers is to improve the lives of patients. Better HRQOL is associated with better performance status, less frequent symptoms, lower anxiety, and improved response to treatment. Therefore, health care providers should continue to develop strategies that enhance HRQOL. HRQOL assessment provides an opportunity to assess for symptoms and potentially modifiable risk factors that negatively impact HRQOL and long term outcomes. This provides the bases for designing interventions that enhance HRQOL. Ongoing efforts include: refining surgical procedures, radiation techniques, selection of systemic therapeutics (chemotherapy, targeted therapy and immunotherapy) and combinations, with on maintaining efficacy with improved HRQOL outcomes. Focused interventions on modifiable factors may include: aggressive symptom management, structured supportive and palliative care, structured distress screening, resilience building, nutritional support, physical therapy and activity, family caregiver support. Consideration of HRQOL is an integral responsibility of all members of the healthcare team. References Borges, E.L., Franceschini, J., Costa, L.H.D., Gernandes, A.L.G., Jamnik, S. & Santoro, I.L. (2017). Family caregiver burden: the burden of caring for lung cancer patients according to stage and patient quality of life. *J. Bras Pneumol.* 43 (1): 18-23. Bye, A., Sjøblom, B., Wentzel-Larsen, T., Grønberg, B.H., Baracos, V.E…… Jordhøy, M. (2017). Muscle mass and association to quality fo life in non-small cell lung cancer patients. *Journal of Cachexia, Sarcopenia and Muscle.* May 10. doi: 10.1002/jcsm.12206. [Epub ahead of print] Chabowksi, M, Polanski, J, Mazur, G, Janczak, D. & Rosinczuk, J. (2017). Sociodemographic and clinical determinants of quality of life of patients with non-small cell lung cancer. *Advs Exp Medicine, Biology-Neuroscience & Respiration.* Jun 2. doi: 10.1007/5584_2017_36. [Epub ahead of print] Delibegovic, A., Sinanovic, O., Galic, G., Sabic, A. & Sabic, D. (2016). The influence of palliative care on quality of life in patients with lung cancer. *Mater Sociomed.* 28 (6): 420-423. Eser, S., Göksel, T., Erbaycu, A.E., Baydur, H., Başank, B….Eser, E. (2016). Comparison of generic and lung cancer-specific quality of life instruments for predictive ability of survival in patients with advanced lung cancer. Springer Plus.5: 1833. Lou, V.W.Q., Chen, E.J., Jian, H., Zhou, Z., Zhu, J, Li, G. & He, Y. (2017). Respiratory symptoms, sleep, and quality of life in lung cancer. *Journal of Pain and Symptom Management*. 53 (2): 250-256. Morrison, E.J., Novotny, P.J., Sloan, J.A, Yang, P., Patten, C.A., Ruddy, K.J. & Clark, M.M. (2017). Emotional problems, quality of life, and symptom burden in patients with lung cancer. *Clinical Lung Cancer.* Mar 2. pii: S1525-7304(17)30051-7. doi: 10.1016/j.cllc.2017.02.008. [Epub ahead of print] Pinheiro, L.C., Zagar, T.M. 7 Reeve, B.B. (2017). The prognostic value of pre-diagnosis health related quality of life on survival: a prospective cohort study of older Americans with lung cancer. *Qual Life Res.* 26: 1703-1712. Polanski, J, Jankowska-Polanska, B., Rosinczuk, J., Chabowski, M & Szymanska-Chabowska A. (2016). Quality of life of patients with lung cancer. *Onco Targets Ther.* 9:1023-8.

Keywords: HRQoL, HealthOutcomes, quality of life

MS 14 QOL EVALUATION IN PRACTICE FROM THE VIEWPOINT OF PHYSICIANS AND NURSES
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 14.03 ESTIMATING PROGNOSIS - HOW ACCURATE CAN WE BE?

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In the lung cancer field, several studies have described the relationship between prognosis and quality of life (QoL), with most reports (Table 1), concluding a QoL evaluation of patients with advanced lung cancer before the start of chemotherapy could predict a patient's prognosis. Such reports described common features: a poor prognosis for investigated patients whose disease was at an advanced stage and/or who were elderly, and the use of cytotoxic agents or irradiation, with poor efficacy. Molecular targeted drugs for epidermal growth factor receptor (*EGFR*) mutations and the anaplastic lymphoma kinase (*ALK*) fusion gene have recently been used in clinical practice. Such agents have led to dramatic improvements in patients with driver mutations. Indeed, we witnessed a "Lazarus response" during the NEJ001 study [1], which investigated the efficacy of an EGFR–tyrosine kinase inhibitor (TKI), gefitinib, for advanced non-small cell lung cancer (NSCLC) patients harboring *EGFR* mutations with a poor performance status (PS): The PS improvement rate was 79% (p<0.00005); in particular, 68% of 22 patients improved from ≥PS 3 at baseline to ≥PS 1. And median survival time of the *EGFR*-mutated patients was 17.8 months, while that of the patients without *EGFR* mutations was 3.5 months. Unfortunately, following the introduction of "precision medicine" for lung cancer, few reports have described the relationship between prognosis and QoL. Herein, we describe NSCLC patients with an *EGFR* mutation treated with gefitinib or chemotherapy as first-line treatment in a randomized phase III study, termed NEJ002 [2]. The patients' QoL was assessed prior to treatment and, thereafter, weekly by the Care Notebook [3]. The relationship between prognosis and QoL data, employed before and 4 weeks after the initiation of treatment, was analyzed by univariate and multivariate Cox regression. QoL data from 148 patients (72 in the gefitinib arm and 76 in the chemotherapy arm) were analyzed. Multivariate Cox regression showed that only a fatigue score on the Care Notebook assessed 4 weeks after the start of gefitinib could predict a patient's prognosis. Other QoL scores, including those before starting not only gefitinib but also chemotherapy, did not affect survival. Estimating Prognosis - How Accurate Can We Be *as the QoL Researcher*? We hypothesize answers fall into two patterns: In the case of employing agents with a poor efficacy, such as cytotoxic agents, the QoL score before treatment should be evaluated as done previously. However, when treating with a very effective agent, the QoL score *under* treatment should be employed because any improvement in prognosis and QoL is strongly dependent on the efficacy of the agent. The next theme is "Estimating Prognosis *of the Patient* - How Accurate Can We Be *as the Attending Physician*? Unfortunately, we do not have rigid evidence for employing QoL assessments. Measuring QoL can have clinical benefits as well as research benefits. These include fostering patient–provider communication, helping clinicians and patients to identify problems and set priorities, and to assess therapy, palliative care, and rehabilitation. However, in my experience of validating the Japanese version of the EORTC QLQ-C30 [4], the answering rate for PS 0–2 patients was over 99% (225/228), but the corresponding rates for PS 3 and PS 4 patients were 81% (38/47) and 13% (9/69), respectively. Furthermore, multiple regression analyses showed that Symptom scale (coefficient: 0.188, p=0.001) and Emotional functioning (coefficient: 0.156, p=0.004) significantly related to Global QoL functioning in patients with PS 0-2; however, Symptom scale alone (coefficient: 0.220, p=0.042) significantly correlated to it in those with PS 3-4. Thus, when the patient concentrates on his/her symptoms and/or fails to respond a QoL questionnaire due to poor PS, a known adverse prognostic factor in advanced cancers, the attending doctor could recognize the patient's short survival. Two studies have succeeded in showing the prolongation of patients' survival under palliative care. Jennifer et al. [5] randomly assigned patients with newly diagnosed metastatic NSCLC to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone. The FACT-L scale, including the lung cancer subscale (LCS) and Trial Outcome Index (TOI), measured at 12 weeks revealed that patients assigned to early palliative care had a better QoL than did patients assigned to standard care (p = 0.03). In addition, median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, p = 0.02). Basch et al. highlightened the importance of monitoring symptoms at ASCO 2017 [6]. Patients receiving routine outpatient chemotherapy for metastatic solid tumors, including lung cancer, were randomly assigned to self-report 12 common symptoms via tablet computers ("PRO intervention"), or to usual care. Median overall survival in the PRO intervention arm was 5 months longer than the control arm (31.2 vs. 26.0 months, HR, 0.832, p = 0.03). These two studies indicate that symptomatic QoL monitoring is critical for clinical practice and for predicting prognosis.

Table 1 Studies on relationship between baseline QoL score and survival in advanced NSCLC patients

Reference	Therapy type	Number of patients	Questionnaire	Prognostic, baseline scale/item
Herndon et al. Cancer 1999, **85:**333-340.	Cisplatin/vinblastine	206	EORTC QLQ-C30	Pain
Langendijk et al. Radiother Oncol 2000, **55:**19-25.	External irradiation (>/=60 Gy)	198	EORTC QLQ-C30	Global QOL
Moinpour et al. Qual Life Res 2002, **11:**115-26.	Cisplatin+vinorelbine or Carboplatin+paclitaxel.	222	FACT-L	Total FACT-L score
Eton et al. J Clin Oncol 2003, **21:**1536-1543.	Cisplatin+etoposide or Cisplatin+paclitaxel	573	FACT-L + TOI	Physical well-being and TOI
Maione et al. J Clin Oncol 2005, **23:**6865-6872.	Vinorelbine+gemcitabine, Vinorelbine alone, or Gemcitabine alone	566	EORTC QOL-C30	Global QOL
Sundstrøm S, et al, J Thorac Oncol. 2006; 1(8):816-24.	Palliative radiotherapy	301	EORTC QOL-C30	Appetite loss
Efficace et al. Ann Oncol 2006, **17:**1698-1704.	Paclitaxel+cisplatin Gemcitabine+cisplatin Paclitaxel+gemcitabine	391	EORTC QLQ-C30 + QLQ-LC13	Pain, and dysphagia

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MS 14 QOL EVALUATION IN PRACTICE FROM THE VIEWPOINT OF PHYSICIANS AND NURSES
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MS 14.05 QUALITY OF LIFE IN WOMEN WITH LUNG CANCER AND EFFECT OF INNER STRENGTH IN MOOD AND QOL

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The incidence rate of lung cancer has declined in males and increased in females in Korea (Jung et al., 2017). In the United States, lung cancer incidence rates began declining in the mid-1980s in men and in the mid-2000s in women because of reductions in smoking prevalence that began decades earlier. Contemporary differences in lung cancer incidence patterns between men and women reflect historical differences in tobacco use (Siegel, Miller, & Jemal, 2016). Women took up smoking in large numbers decades later than men, first initiated smoking at older ages, and were slower to quit, including recent upturns in smoking prevalence in some birth cohorts (Giovino, 2002; Jemal, Ma, Rosenberg, Siegel, & Anderson, 2012). In the United States, the 3 most commonly diagnosed cancers are breast, lung and bronchus, and colorectum, representing one-half of all cases for women (Siegel et al., 2016). The purpose of this study is to analyze the correlation among mood state, distress, symptom experience, inner strength, and quality of life(QoL) in female patients with lung cancer. Also, this study includes descriptive research regarding the influence factors on QoL in them. A total of 206 research subjects who diagnosed with primary lung cancer at a cancer hospital in Gyeonggi, Korea were examined from 1 July 2016 to 31 October 2016. Several instruments were used for research methods: K-POMS-B for mood state, NCCN Distress Thermometer for distress, NCC for understanding aspect of distress, MDASI-LC for symptom experience, ISQ for inner strength, and FACT-G for QoL. Data of this study was analyzed by using SPSS Ver. 23.0 for Windows. The general and diseased characteristics of patients were analyzed through descriptive statistics, frequency, percentage, average, and standard deviation. Independent t-test and One-way ANOVA were used to examine differences according to their characteristics. Bonferroni correction, Pearson correlation coefficient, and hierarchical multiple regression for impact factors of QoL were also used. For reliability, Cronbach's α was calculated. The results of this study are as fellows; 1. The mean score of the mood disorder was 20.74, symptom experience was 2.88, symptom degree was 2.76, disturbance of daily life was 3.01. The mean score of the inner strength was 97.98. Among sub-categories, the mean score of the searching for meaning on disease was 18.53, fellowship was 27.0, self-determination was 25.2, activity and rest was 27.1. The total mean score of QoL was 66.69, physical stability was 19.13, social stability was 18.04, emotional stability was 16.19, function status was 13.32. The highest result was in physical stability, whereas function status gained the lowest result. The mean score of distress was 4.19, sleep disorder was 3.2, insomnia affecting daily life was 2.45, anxiety symptom was 2.79, anxiety symptom affecting daily life was 2.25, depression was 1.92, depression affecting daily life was 1.68. In categories asking the needs of medical care, it was measured that insomnia was 38.5%, anxiety was 41,7%, depression was 19.9%. 2. The factors affecting in QoL were occupation, expectation of treatment outcome, activity ability, inner strength, symptom experience (the severity of symptom, the severity of disturbance of daily life), and mood state. 3. Higher scores in symptom experience, distress, and mood disorder categories have lower quality of life than those with higher scores of inner strength. 4. As a result of hierarchical analysis, these suggested that occupation status, expectation of treatment outcome (life extension), activity ability, inner strength, and symptom experience (the severity of symptom, the severity of disturbance of daily life) can be beneficial variables of QoL. The model was explained 70.7% of the total variance of quality of life. Cancer as a chronic illness places new demands on patients and families to manage their own care, and it challenges old paradigms that oncology's work is done after treatment. Therefore, to improve the quality of life in women survivors with lung cancer, we need to apply nursing interventions strengthening inner strength, activity ability, performance status, and symptom control.

Keywords: quality of life, Inner strengh, Women

MS 15 MOLECULAR TESTING
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 15.02 MOLECULAR TESTING USING NGS

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Lung cancer has shown a decrease in incidence and mortality in recent decades; however, it remains one of the cancers with the highest incidence and ranks first in cancer-related deaths in the United States. Despite advances in early detection and standard treatment, most patients are diagnosed at an advanced stage and have a poor prognosis, with an overall 5-year survival rate of 10% to 15%. Lung cancer is a heterogeneous disease comprising several subtypes with pathologic and clinical relevance. The recognition of histologic subtypes of non-small cell lung carcinoma (NSCLC), namely adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma as the most frequent subtypes, has become important as a determinant of therapy in this disease. In addition, in recent years, the identification of molecular abnormalities in a large proportion of patients with lung cancer has allowed the emergence of personalized targeted therapies and has opened new horizons and created new expectations for these patients. The use of predictive biomarkers to identify tumors that could respond to targeted therapies has meant a change in the paradigm of lung cancer diagnosis. This paradigm change affects all stakeholders in the fight against lung cancer including pathologists. Currently, several multiplex genotyping platforms for the detection of oncogene mutations, gene amplifications and deletions, and rearrangement are moving to the clinical setting. Genome-wide molecular investigations using next-generation sequencing (NGS) technologies have been evaluated in the research setting, with promising results. Further investigations in NSCLC are required for a better understanding of the implications of intratumor heterogeneity and the roles of tumor suppressor genes and epigenetic events with no known driver mutations. NGS in the clinical setting will provide comprehensive information cheaper and faster by using small amounts of tissue. Recently, NGS genotyping platforms utilization has extended to liquid biopsy (cell free DNA). Pathologists should be able to precisely handle tissue adequacy in terms of quantity and quality and maintaining tumor cells for detection of molecular alterations. The clinical successes of targeted therapy and immunotherapy approaches to lung cancer have posed additional challenges to the scientific community and pathologists to develop predictive biomarkers of response to these therapies and have highlighted the need for proper procurement and processing of tissue specimens from patients with lung cancer.

Keywords: next generation sequencing, mechanisms of resistance, targeted therapy

MS 15 MOLECULAR TESTING
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 15.03 MOLECULAR TESTING USING BLOOD (LIQUID BIOPSY)

C. Dive

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Tumour biopsies are the 'gold standard' with which to interrogate a patient's tumour biology and assess biomarkers useful for treatment decision making. However, for longitudinal monitoring of disease in certain cancer types (e.g. lung) and particularly in patients with multiple metastatic lesions), serial biopsies may not be readily acquired and easily repeatable and a less invasive tumour sample is required. Liquid biopsies are beginning to gain acceptance as a surrogate for tumour profiling and in NSCLC, regulatory approval has been given for EGFR mutation testing in circulating tumour DNA (ctDNA) where biopsies are not available. My presentation will cover the development and utility of liquid biopsies in lung cancer, focusing on both ctDNA and circulating tumour cells (CTC). An avalanche of new technology platforms for circulating tumour cell (CTC) analysis is arriving in translational research laboratories, employing different approaches to CTC enrichment, purification and molecular characterisation. The semi-automated, robust and validated CellSearch platform (Menarini) remains the only technology that is FDA approved to determine patient prognosis (in breast, prostate, and colorectal cancers) by enumeration of EpCam expressing CTCs. CellSearch CTC count is also prognostic in both SCLC and NSCLC. The the ability to preserve CTCs for analysis 96h after blood draw is a major advantage for multicentre clinical trial scenarios. However, since CTCs are heterogenous and may downregulate epithelial markers during epithelial to mesenchyme transition (EMT) it is critical that marker independent CTC technologies are adopted to better explore CTC biology and heterogeneity, and the potential for a wider range of CTC based biomarkers is becoming apparent. I will review a range of CTC enrichment and isolation approaches and discuss our data on single CTC molecular profiling. I will compare and contrast the challenges for CTC profiling in small cell lung cancer (where EpCam positive CTCs are prevalent) and NSCLC (where EpCam positive CTCs are rare). I will also discuss the development of CTC patient-derived explant models (CDX) from SCLC and NSCLC patients and the advantages these may provide over conventional PDX models generated from a tissue biopsy. I will describe the utility of CDX models in drug development and in exploring the biology of progressing lung cancers, including vasculogeneic mimicry whereby SCLC cells adopt endothelial characteristics that may facilitate tumour growth and metastasis. I will present our ctDNA profiling approaches for selection of patients to early clinical trials and finally I will scan the horizon to the potential use of CTC and ctDNA as potential early detection biomarkers that complement CT scans. 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MS 16 FUTURE DIRECTION OF CHEMORADIOTHERAPY FOR INOPERABLE NON-SMALL CELL LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 16.03 MANAGEMENT ACCORDING TO THE HISTOLOGIC SUBTYPES

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The suitable characteristics of the carcinoma for definitive radiotherapy (RT) are that (a) involved areas of the disease can be covered by adequate planning target volume (PTV), and that (b) the tumor cells can be sterilized with under tolerable doses for the surrounding normal tissues. Among non-small cell lung cancer (NSCLC), squamous cell carcinoma (SQ) has the characteristics to grow locally, to spread proximally along the trachea-bronchial trees and to develop regional nodal metastases. In SQ, furthermore, surgical resection is well known to be effective even for locally advanced disease. On the other hand, non-SQ has the tendency to develop distant metastases at early T-stage. In a randomized controlled trial comparing continuous, hyperfractionated, accelerated radiotherapy (CHART) (54Gy/36fr in 12 consecutive days) with conventional RT (60Gy/30fr in 6 weeks), the SQ patients had absolute advantages of CHART in both local progression-free survival (LPFS) and overall survival (OS). Therefore, SQ is considered to be a good candidate for intensive loco-regional treatment. In RTOG 0617 trial of standard-dose versus high-dose conformal RT with concurrent and consolidation carboplatin + paclitaxel with or without cetuximab for patients with stage IIIA/B NSCLC, an EGFR H-score less than 200 (low EGFR expression) was noted more commonly in non-SQ patients whereas an EGFR H score of 200 or more (EGFR-overexpression) was more common in SQ patients (p=0.0003). In patients with an H score of 200 or higher, median OS for the cetuximab group was 42.0 months (95% CI 20.6–not reached) versus 21.2 months (17.2–29.2) for the no-cetuximab group. These results suggested that SQ patients might benefit from the addition of cetuximab to chemoradiation like SQ of the head and neck. Furthermore, on phase II study of nimotuzumab in combination with concurrent chemoradiotherapy for Japanese patients with locally advanced NSCLC, the LPFS was significantly better for SQ patients than for non-SQ patients. The results also suggested that the low in-field relapse rates might be attributed to the radio-sensitizing effect of nimotuzumab and contribute to the improved OS of SQ patients. By contrast, non-SQ patients did not benefit from nimotuzumab because the distant relapse rate was significantly higher for non-SQ than that for SQ. In non-SQ histology, EGFR mutations are well known to often appear especially in adenocarcinoma. Some clinical trials of EGFR-TKI combined with standard platinum-based chemoradiotherapy for EGFR-mutant locally advanced NSCLC are ongoing in Japan. In the future direction, the locally intensified chemoradiotherapy using high-precision RT techniques and advanced radiation sensitizers including molecular targeting drugs may be more important for SQ and newly developed systemic therapies with powers of sterilizing subclinical distant metastases may be more effective for non-SQ among locally advanced NSCLC.

Keywords: non-small cell lung cancer, Chemoradiotherapy, molecular targeting drug

MS 16 FUTURE DIRECTION OF CHEMORADIOTHERAPY FOR INOPERABLE NON-SMALL CELL LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 16.04 FUTURE DIRECTION OF IMMUNO-RADIOTHERAPY

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Introduction: Recently, systemic approaches to inperable non-small-cell lung cancer (NSCLC) in stage IV disease have been significantly improved by the introduction of a new treatment modality: immunotherapy with PD-1 antibodies. Currently, nivolumab is registered for the second-line therapy of NSCLC without prerequisite of PD-L1 expression in tumor tissue. Pembrolizumab has been registered for PD-L1 positive (> or = 1% TPS) patients in second-line and for high expressors (> or = 50% TPS) also in the first-line setting. In some countries already platinum-based combination chemotherapy (CTx) plus pembrolizumab is accepted for first-line therapy of medium expressors (1-49% TPS) and also for high expressors. Other PD-L1 antibodies have already achieved positive phase-III results (atezolizumab) or large phase-III trials have finished accrual and final results are awaited (eg. durvalumab). Based on these paradigms, the rationale for combinations with radiotherapy (RTx) in NSCLC is analyzed and trial design of currently ongoing studies as well as reported signals of first results are summarized. **Material and Methods:** Clinicaltrials.gov has been searched for ongoing and active clinical trials with immmunotherapy and RTx. We divided NSCLC strategies into a) locally advanced and inoperable NSCLC stage III b) advanced and inoperable stage IV NSCLC (episcopal effect) c) combinations of immunotherapy and stereotactic RTx in early disease NSCLC d) oligometastatic disease. **Results:** a) introduction of PD-1 antibodies into treatment strategies of inoperable stage III NSCLC will get a significant booster efffect by the recently reported outcome signals of the Pacific Trial looking at durvalumab consolidation therapy versus placebo following concurrent CTx/RTx in stage III NSCLC (press release, AZ, May 2017). PFS was signifcantly longer for the administration of durvalumab as maintenance in this situation. We expect presentation of the final results at an important Lung Cancer conference during this fall. Theroretically, intoduction by DNA double-strand breaks in patients following concurrent CTx/RTx or RTx alone could lead to an increase in tumor mutational load and could potentially enhance the efficacy of any PD-1- or PD-L1-antibody therapy. A consolidation therapy of PD-1-antibody treatment following concurrent chemoradiotherapy aiming at cure was found to be a rational strategy to improve long-term survival results in inoperable stage III NSCLC. Other trials ongoing are looking at combinations of RTx with concurrent PD-1 immunotherapy or concurrent CTx/RTx combined with concurrent adminstration of PD-1 antibody therapy.Trials outlines will be summarized and presented. Only one phase-II study including pembrolizumab has maintenenance has already been presented with ist results at ASCO 2017. Treatement was manageable and toxicity acceptable. First signals shown efficacy of this strategy but final survival data are pending. Other clincial trials are currently also looking at combinations of CTx and PD-1-immunotherapy and concurrent RTx. Also other immunotherapy drugs such as CTLA4-antibodies or combinations of both PD-1(eg. nivolumab, pembrolizumab, atezolizumab, durvalumab) and CTLA4-antibodies (ipilimumab, tremelimumab) are also being investigated in stage III NSCLC. b) few trials are also looking to enhance

systemic effects of immunotherapy (PD-1/PD-L1 and CTLA-4) and concurrent RTx of tumor lesions. The so called "episcopal effect" is being investigated within several clinical studies. Theoretically, the release of tumor associated antigens (TAA) by RTx given to specific tumor lesions leading to tumor lysis including the release of antigens into the circulation could potentially enhance the systemic immunological effects of checkpoint-inhibitor therapies. Well-selected case reports have given hints to support such thesis but only randomized trials will finally verify if this approach is really valid and worthwhile. c) the stereotactic and, therefore, locally ablative RTx techniques also aiming at early inoperable NSCLC patients could also potentially benefit from combinations with new immunotherapy. Several trials are underway for combinations with nivolumab, pembrolizumab, atezolizumab and durvalumab. Finally, for all mentioned treatment strategies concurrent versus sequential administration of immunotherapy and RTx is a complete open issue. Also, permutations including combinations together with platinum-based CTx and immunotherapy together with RTx have recently become very attractive. d) Last but not least, the patient group of oligometastatic patients (M1a, M1b, M1c with less than four lesions in one organ, eg. brain) seems to be a very interesting group of patients to increase both local as well as systemic control of the treatment. **Conclusions:** Consolidation durvalumab may potentially become the first strategy to become a new paradigm of treatment for stage III NSCLC. We will have to wait for the final results of that trial to draw more valid conclusions for future treatment strategies. However, based on the inclusion of new immunotherapy with checkpoint inhibitors already into the standard treatment algorithms of stage IV disease in NSCLC it can be predicted that also in other disease settings these innovative approches may finally extend our potential treatment options - at least for well selected patient subsets. Referrences: Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65. doi: 10.1056/NEJMoa1200694. Epub 2012 Jun 2. Rizvi NA, Mazières J, Planchard D,et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015 Mar;16(3):257-65. doi: 10.1016/S1470-2045(15)70054-9. Epub 2015 Feb 20. Brahmer J, Reckamp KL, Baas P, et al. 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Keywords: Immunotherapy, non-small cell lung cancer, Radiotherapy

MS 16 FUTURE DIRECTION OF CHEMORADIOTHERAPY FOR INOPERABLE NON-SMALL CELL LUNG CANCER
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 16.05 HIGH-DOSE BOOST RADIATION USING SBRT/ IMRT

J. Cox
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Chemotherapy combined with radiation therapy has become standard treatment for inoperable non-small cell lung cancer (NSCLC). The combination was first proposed in the 1970s. Although induction (neoadjuvant) chemotherapy followed by radiation therapy was initially considered preferable owing to concerns about toxicity, it eventually became clear that concurrent treatment was more effective. Similarly, low-dose radiation therapy was thought to be the safest, and radiation oncologists were loath to use any dose/fractionation regimen that exceeded standard approaches with radiation therapy alone. Chemotherapy evolved in a similar fashion. At first, single agents were used, followed by tests of various combinations of different drugs, with eventual acceptance of 2-drug combination regimens, usually consisting of a platinum compound with another agent. These regimens were combined with standard radiation therapy, usually to a dose of 60 Gy in 30 fractions using three-dimensional conformal radiation therapy (3D CRT), planned on the basis of computed tomography (CT); this combination produced tolerable adverse effect profiles that were less severe than those after the previous standard of 2D treatments based on plane radiography. The next iteration of external-beam radiation therapy was intensity-modulated radiation therapy (IMRT), which involves directing multiple beamlets at the tumor while limiting the doses to surrounding critical structures. IMRT, which depends on CT imaging for staging and treatment planning, also allowed higher fraction sizes and total doses to be tested in attempts to increase tumor control. However, use of higher total doses has had potentially intimidating results in clinical trials. In a recent prospective clinical trial of the Radiation Therapy Oncology Group (RTOG 0617) in which standard-dose 60 Gy in 30 fractions given over 6 weeks was compared with high-dose 74 Gy in 37 fractions over 7 1/2 weeks, the higher total dose actually led to poorer local control. It has been hypothesized that failure to adequately cover the gross tumor volume in the high-dose arm resulted in the higher local failure rate. For small (T1 or T2) tumors of the lung, investigators have tested very-high-dose treatments based on 3D targeting of every fraction, an approach that requires 3D imaging capability. In the United States, achieving such precise targeting has required collaborations with medical physicists in the delivery of each fraction. The next generation of radiation therapy, stereotactic body radiation therapy or SBRT, began as a treatment for lesions in the brain. In Sweden, Leksell and colleagues developed an approach that came to be known as stereotactic radiation therapy. Considered an alternative to surgical resection, stereotactic radiation therapy was predicated on immobilizing the patient with a stereotaxic frame, using multiple cobalt-60 sources in a helmet-like configuration, and administering the radiation in a single fraction. Because the goal of this approach was controlled necrosis rather than a surgical defect, this approach also came to be known as stereotactic radiosurgery. Approximately 25 years later, a similar approach was developed in which linear accelerators were used to deliver SBRT. Similar principles were used: precise imaging with of the tumor with CT and, more recently, with fluorodeoxyglucose positron emission tomography; careful and secure immobilization with various body frames; management of respiratory motion for lesions in the thorax; intensity-modulated treatment planning; and image-guided targeting. From 1 to 5 or even 10 fractions are delivered in this manner, with both the treating physician and collaborating physicist attending each treatment to ensure consistent image guidance. This approach allows the delivery of very high biological doses. SBRT has been shown to result in local control rates of 85% to 95% for tumors up to 4 cm in diameter. Proton beam therapy is the latest means to control NSCLC, particularly for tumors that are larger than the T1 or T2 tumors usually treated with SBRT. Protons differ from photons in their interactions with tissues in the body; protons are heavy particles that produce different ionization tracks and deposit most of their energy at the end of their range. Where they come to a stop is a function of their energy when they enter the body. Protons have lower energy than photons until they reach their prescribed depth, at which point they produce a peak of ionizations, the Bragg peak. This Bragg peak can be spread out to cover the tumor in depth, and the beam can be shaped in the other two dimensions by electronic or physical means to achieve a high-dose volume that has the same size and shape of the tumor. Properly directed proton therapy essentially delivers no dose beyond the gross tumor volume. The relative biologically effective dose (RBE) of proton beam therapy is approximately the same as that of x-rays, so the effects of the doses in the tumor and the surrounding normal tissues (organs at risk) are well understood. Proton beam therapy and chemotherapy interact in predictable ways, and so the toxicity patterns are similar to those with chemotherapy and photons. However, proton therapy seems to have less severe effects on blood counts. In clinical trials to date, whether with IMRT, SBRT, or protons, the greatest need seems to be to enhance the effectiveness of the systemic treatment. Considerable interest has been expressed in combining each of these radiation delivery methods with immunotherapy. The occurrence of an occasional abscopal effect with radiation therapy has given rise to cautious enthusiasm for further exploration of this area.

Keywords: IMRT; SBRT; stereotactic ablative radiation therapy; proton beam therapy

MS 17 LESSONS LEARNED FROM NEGATIVE TRIALS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 17.02 MAGRIT

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Antigen-specific immunotherapy or cancer vaccination has been studied in several large phase III trials in NSCLC in different stages [1]. Agents consisted of two major components: immunogenic tumor-associated antigens, combined with a strong adjuvant to generate the tumor directed attack. Overall, the results of these trials have been disappointing. One of these phase III trials was MAGRIT, the largest therapeutic clinical trial ever performed in NSCLC. The MAGRIT trial (*MAGE-A3 as Adjuvant Non-Small Cell Lun*G Cance*R Immuno*T*herapy*[2]. Other major trials in this setting, such as RADIANT, studying adjuvant erlotinib [3], and ECOG 1505, studying the addition of bevacizumab cisplatin-based adjuvant chemotherapy [4], proved to be negative. As adjuvant cisplatin-based chemotherapy can be hard to tolerate for many patients [5], a less toxic and effective therapy to improve the outcome in this group was of great interest. Melanoma associated antigen (MAGE)-A3 was an interesting target because it is almost exclusively expressed on tumor cells, and not expressed in normal tissue (except in male germline cells, which however do not present the antigen). The MAGE-A3 vaccine was a recombinant protein antigen-based vaccine, containing the recombinant fusion protein (MAGE-A3 and protein D of Haemophilus Influenzae) in combination with an immune response enhancing adjuvant. Clear responses to this compound had been noted in early experience in patients with

metastatic melanoma [6]. For NSCLC, the proof of concept study was a double-blind, placebo-controlled, randomized phase II trial [7]. Patients with completely resected MAGE-A3-positive stage IB-II NSCLC were randomly assigned to either MAGE-A3 vaccine (N=122) or placebo (N=60), 5 administrations q3 weeks followed by 8 administrations q3 months. No adjuvant chemotherapy was given, as this therapy was not established in the study interval. Disease-free interval (DFI) was the primary endpoint. After a median post-resection period of 70 months, there was a trend in favor of MAGE-A3, with a Hazard Ratio (HR) for DFI 0.78 (95%CI 0.49-1.24; two-sided *P*=0.295). No significant toxicity was observed, resulting in very high therapy compliance. Furthermore, a possible gene signature (GS), predictive of clinical activity of the MAGE-A3 vaccine in previous metastatic melanoma experience [6], could be validated in early-stage NSCLC [8]. Actively treated GS-positive NSCLC patients showed a favorable DFI compared with placebo-treated (HR 0.42, 95% CI 0.17-1.03; *P*=0.06), whereas among GS-negative patients, no such difference was found (HR 1.17, 95% CI 0.59-2.31; *P*=0.65). This led to the large double-blind, randomized, placebo-controlled phase III trial MAGRIT (ClinicalTrials.gov, number NCT00480025) [9]. MAGE-A3 positive patients with completely resected stage IB, II or IIIA NSCLC, and adjuvant chemotherapy as clinically indicated, were 2:1 randomly assigned to the MAGE-A3 vaccine or placebo. Randomization and treatment allocation was done centrally via internet with stratification for chemotherapy versus no chemotherapy. A minimization algorithm accounted for the number of chemotherapy cycles received, disease stage, lymph node sampling procedure, performance status score, and lifetime smoking status. The primary endpoint was broken up into three co-primary objectives: disease-free survival in the overall population, the no-chemotherapy population, and patients with a potentially predictive gene signature. Between Oct 18, 2007, and July 17, 2012, a total of 13,849 surgical patients in 443 centers in 34 countries were screened for MAGE-A3 expression, 4210 had MAGE-A3 expression, and 2,272 were treated (active vaccine 1,515; placebo 757). 784 patients in the MAGE-A3 group also received chemotherapy, as did 392 in the placebo group. At the time of the report, median follow-up was 38.1 months in the MAGE-A3 group and 39.5 months in the placebo group. In the overall population, median disease-free survival (DFS) was 60.5 months (95% CI 57.2–not reached) in the MAGE-A3 vaccine group and 57.9 months (55.7–not reached) in the placebo group (hazard ratio 1.02, 95% CI 0.89–1.18; *P*=0·74). In the predefined subgroup patients who did not receive chemotherapy, median DFS was 58.0 months (95% CI 56·6–not reached) in the MAGE-A3 group and 56.9 months (44.4–not reached) in the placebo group (hazard ratio 0.97, 95% CI 0.80–1.18; p=0·76). Because of the absence of treatment effect, the predictive gene signature could not be further studied. The frequency of grade 3 or worse adverse events was similar: 246/1515 (16%) in the MAGE-A3 group and 122/757 (16%) in the placebo group. It was concluded that adjuvant treatment with the MAGE-A3 vaccine did not increase DFS compared with placebo in patients with MAGE-A3-positive surgically resected NSCLC, and the further development of the MAGE-A3 vaccine for NSCLC was stopped. REFRERENCES 1. Decoster L, Wauters I, Vansteenkiste J. Vaccination therapy for non-small cell lung cancer: Review of agents in phase III development. *Ann Oncol* 2012; 23: 1387-1393. 2. 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Keywords: Immunotherapy, Cancer vaccines, MAGE-A3

MS 17 LESSONS LEARNED FROM NEGATIVE TRIALS
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 17.04 MET-LUNG: A PHASE III TRIAL OF ONARTUZUMAB (METMAB) PLUS ERLOTINIB VS ERLOTINIB IN PREVIOUSLY TREATED STAGE IIIB OR IV NSCLC

K. Kelly

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A well-known mechanism of resistance to EGFR-TKIs is MET upregulation. MET inhibitors were developed to overcome and prevent this resistance mechanism. Onartuzumab is a monoclonal antibody that binds the extracellular domain of MET. By blocking the interaction with its HGF ligand, activation of the MET signaling pathway does not occur and tumor growth is halted. The clinical evaluation of onartuzumab followed the traditional phase I, II and III registration pathway. In the randomized Phase II trial of erlotinib and placebo versus erlotinib and onartuzumab the trial failed to meet the co-primary endpoint of PFS in the intent to treat population but was positive for the co-primary endpoint of PFS in 66 patients with MET positive tumors defined as IHC > 2+ expression (HR, .53; P .04) (1). Overall survival was also significant (HR, .37; P .002). Objective response rate (ORR) was reported as 8.6% and 3.2% for onartuzumab versus placebo, respectively. Based on these results a randomized placebo controlled phase III trial was launched in patients with MET expressing tumors (2). Surprisingly this trial did not meet its OS primary endpoint and numerically favored the placebo arm. A total of 499 patients were enrolled. The median OS was 6.8 months for onartuzumab versus 9.1 months for placebo (HR, 1.27; 95% CI, 0.98 to 1.65; P = .067). Median progression-free survival was 2.7 months versus 2.6 months (HR, 0.99; 95% CI, 0.81 to 1.20; P = .92) and the ORR was 8.4% compared with 9.6% respectively. When a trial is negative scrutinizing all aspects of the trial and its predecessor trial to determine if there were instructive signals is needed. In this case, reported patient characteristics were similar between the two trials but other patient variables such as the frequency of patients with brain metastases, sites of metastases, and time from previous therapy were not provided. However a large magnitude of difference would be required to significantly alter the results which is unlikely. Adverse events profiles were unrevealing. There were differences related to the MET biomarker that may have influenced the phase III results. In the phase II trial MET IHC expression was retrospectively determined compared to its prospective determination in the phase III trial and its use as a stratification factor. Although the frequency of MET 2+ versus 3+ IHC expression was similar in the two trials, the retrospective nature of the analysis in the phase II trial with its inherent imbalance in patient characteristics may have been misleading especially in the context of the small sample size. Had this been a randomized biomarker selected Phase II trial with a larger sample size we might have seen a different outcome. The assay itself was not a factor. Rigorous validation of the MET IHC assay was conducted. The assay was performed at Genentech for the phase II study and these investigators carefully trained the central laboratories personnel performing the assay for the phase III trial. A robust quality check and audit program was followed. A frequently asked question is whether IHC accurately characterize drivers of MET dysregulation that would result in EGFR tyrosine kinase inhibitor (TKI) resistance and onartuzumab responsiveness. In an exploratory biomarker analysis from the Phase II study MET IHC remained the most robust predictor of efficacy for the combination (3). In the phase III trial a detailed EGFR and MET pathway analysis that included MET and EGFR FISH, EGFR amplification and EGFR, KRAS BRAF, PIK3CA mutational analysis failed to find a biological explanation for onartuzumab inactivity (3). An analysis of MET Exon 14 splicing mutations was not conducted because these mutations had not been discovered at the time of study conduct. Although it would be intriguing to know the frequency of these mutations and their association to onartuzumab activity this is unlikely to be performed. The subgroup results supported further investigation of onartuzumab in a MET positive population but the results were modest. The statistically significant 1.4 month improvement in median PFS is not clinically significant and objective response rates were similar between the arms. Driving the phase III design was the impressive 8.8 month improvement in median OS for the combination but without strong efficacy signals in ORR and PFS to account for this survival outcome suggests other factors were at play such as subsequent therapies and warrants caution. The dilemma with encouraging preliminary data is what is the optimal next study design especially in this instance where the findings were modest? Too many times we have seen positive phase II trials lead to negative phase III results. While a phase III trial is the quickest route to a definitive answer it is done at the price of hundreds of patients. This is particularly highlighted by this study where the combination was approaching an inferior overall survival. Alternative design strategies such as a randomized Phase II/III design that can better balance benefit and risk for our patients and still achieve the goal should be considered. Criteria should be established to help investigators select the appropriate design. References 1. Spigel DR, Ervin TJ, Ramlau RA, Daniel DB, Goldschmidt JH Jr, Blumenschein GR Jr, Krzakowski MJ, Robinet G, Godbert B, Barlesi F, Govindan R, Patel T, Orlov SV, Wertheim MS, Yu W, Zha J, Yauch RL, Patel PH, Phan SC, Peterson AC. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2013, 31:4105-14. 2. 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MS 17 LESSONS LEARNED FROM NEGATIVE TRIALS
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MS 17.06 AVOIDING PHASE II-III ATTRITION: ENHANCED BIOMARKERS, BETTER DRUGS OR IMPROVED TRIAL DESIGN?

J. Crowley

Cancer Research and Biostatistics, Seattle/WA/US

In this talk I will cover reasons why phase III trials are "negative" and what can be done to increase the rate of true positive results. Reasons for failure in phase III include inactive agents, poor statistical design, and inadequate implementation. With targeted agents including immunotherapy, additional issues of statistical design arise, as well as

assay reliability. I will review the trials discussed in this section (PROCLAIM, MAGRIT, METLung, CheckMate026) with a view towards assessing the reasons these trials might have been negative, and make some suggestions for future trials.

Keywords: negative trials, statistical design, Targeted agents

MS 18 BIOMARKER FOR ANTI-PD-L1 THERAPY
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 18.04 PD-L1 EXPRESSION IN EARLY STAGE LUNG CANCER

J. Chung

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The significant activity of programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) checkpoint inhibitors in heavily pre-treated patients with advanced non–small-cell lung cancer (NSCLC) marked the beginning of a new era of immunotherapy. Recently published randomised clinical trials' data have led to the approval of 3 PD-1/PD-L1 inhibitors—nivolumab (Opdivo; Bristol-Myers Squibb Company), pembrolizumab (Keytruda; Merck Sharp & Dohme Corp), and atezolizumab (Tecentriq, Genentech/Roche)—for the treatment of advanced NSCLC after first-line therapy. Furthermore, pembrolizumab was recently approved by the FDA as a first-line therapy for patients with advanced NSCLC. However, the overall response rates to these agents in an unselected population are reportedly low, thus emphasising the need for predictive biomarkers that identify beneficial candidates. The recently approved tests for anti-PD-1/PD-L1 therapy in NSCLC include the assessment of PD-L1 expression using immunohistochemistry (IHC) as a companion diagnostic test (22C3 for pembrolizumab) and 2 complementary diagnostic tests (28-8 for nivolumab and SP142 for atezolizumab). Another PD-L1 assay is being currently tested in clinical trials (e.g. SP263). In addition to commercial assays, laboratories and research institutions may establish their own laboratory-developed tests (LDTs) using various antibodies available, most notably the E1L3N clone. Hence, the PD-L1 expression status, as well as its predictive and prognostic value, differ considerably based on the antibody clones, platforms, and interpretation criteria used. However, the current assays evaluating the predictive role of tumour PD-L1 expression remain without harmonization in terms of the staining analysis and scoring system. The intratumoural heterogeneity in PD-L1 expression is another important issue. At present, PD-L1 testing is mainly conducted on biopsy specimens, which may not represent the tumour as a whole, and it may lead to false results, particularly in cases where testing is conducted using small tissue specimens, such as bronchial or transthoracic biopsy specimens. The resulting false-negative results could lead to the under-treatment of patients.

In this presentation, I'd like to introduce 1) the results of comparison study between 4 different PD-L1 IHC and scoring systems in the surgically resected early stage lung cancer specimen 2) the correlation of PD-L1 expression between TMA specimens and the corresponding resected specimen to better understand the intratumoral heterogeneity.

Keywords: PD-L1, immunohistochemistry, lung cancer

MS 19 ELEVATING THE LUNG CANCER VOICE: RAISING AWARENESS AND CREATING COMMUNITY
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 19.01 TRANSFORMATIVE SCIENCE IN THE COMMUNITY

J. Baranski

Lung Cancer Foundation of America, Lung Cancer Foundation of America, Marina Del Rey/CA/US

This presentation will discuss 3 discoveries that radically changed our understanding of lung cancer. It will also address the challenges faced in communicating these life-saving "bench to bedside" discoveries to patients. In 2007, the National Science Foundation (NSF) released a report on the meaning of "transformative research" (TR) as follows: "Transformative research involves ideas, discoveries, or tools that radically change our understanding of an important existing scientific or engineering concept or educational practice or leads to the creation of a new paradigm or field of science, engineering, or education. Such research challenges current understanding or provides pathways to new frontiers." Discoveries that changed our understanding of lung cancer: 1. **PD-1/PD-L1**: The discovery of PD-1 leads to development of PD-1/PD-L1 inhibitors i.e. immunotherapy. 2. **Gene Defects**: The discovery of gene defects/mutations leads to understanding that lung cancer is in fact many lung cancer mutations and leads to development of targeted therapies and precision medicine. 3. **National Lung Cancer Screening Trial** (NLST): The NLST lead to the conclusion that low dose CT scans can detect lung cancer earlier and lead to better treatment options and increased survivorship for lung cancer. In the United States, according to a recent study by Northwestern University's Kellogg MBA program, the public is dangerously uninformed about our nation's second leading cause of death; only behind heart disease. Lung cancer accounts for more deaths than any other cancer. More than breast, prostate and colon cancer combined! An estimated 155,870 deaths are expected to occur in 2017 in the United States, accounting for about 26% of all cancer deaths. However, federal funding for lung cancer research per death was just $1,680 compared to $24,846 for breast, $12,644 for prostate and $6,344 for colon. Not surprisingly, lung cancer has the lowest 5-year survival rate of the other most common cancers: only 18%, versus prostate at 99%; breast at 89%; and colorectal at 65%. It is clear that lung cancer is the leading cause of cancer death, and yet, it is tragically underfunded in terms of research. We will explore communication tactics including multimedia public awareness campaigns, public service announcements and social media most effective in raising the voice of lung cancer and the impact of "transformative research" in the community.

MS 19 ELEVATING THE LUNG CANCER VOICE: RAISING AWARENESS AND CREATING COMMUNITY
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 19.02 LUNG CANCER AWARENESS MONTH: UNITY THROUGH IASLC – ORGANIZER PERSPECTIVE

K. Richeimer

Department of Membership, Iaslc, Aurora/US

A Harmonized Strategy for Lung Cancer Awareness Month – November 2016 In early 2016, IASLC proposed a common strategy for the benefit of all lung cancer organizations during Lung Cancer Awareness Month. It was agreed by advocates and advocacy groups that IASLC is in a unique position to lead this unified effort among advocacy organizations. This campaign was supported by independent educational grants from Merck & Co., Inc., Eli Lilly and Company and Helsinn. **Objectives for the common strategy for Awareness Month**: Inform the public that everyone can get lung cancer (e.g. break down stigma) and share stories. Raise money, increase resources for research. This was done via individual organizations, not a common donor campaign, so we do not necessarily have metrics on funds raised. Reduce mortality & suffering by communicating to the public the exciting scientific advancements, which provide HOPE and PROGRESS in lung cancer. **The joint public awareness campaign, supported by all the organizations, included the development of a c**ommon logo (seen above); common infographics featuring clear messages and vibrant photos showing people living their lives with lung cancer. The campaign shared stories that represented the demographics of spouses/caregivers/family and tried to show the diversity of all types who will get lung cancer. The common website (www.LCAM.org) was the focus and link shared during LCAM. We developed an advertising and public awareness campaign that included both print, digital and social media outlets. The advertising campaign included print advertising in New York Times and Wall Street Journal (Rocky Mountain Edition); a digital campaign featuring banner ads and video "pre-roll" ads; and a social media campaign utilizing both organic and paid campaigns. **Key Metrics: More than 60 Survivors & Caregivers shared their stories on. More than 20 partners participated in the campaign. More than 25,000 pins, t-shirts, bracelets and posters were distributed in November.**

Facebook	Twitter	LCAM Youtube Channel
9,500 Likes in November 2016	#LCAM Impressions - over 51M in November	15 Videos (:30 Seconds to 2 minutes long)
38,000 Likes as of January 31, 2017	Daily Tweets of Survivor Stories	Over 2,000 Views
28,000+ Post Likes/ Shares/Clicks	Over 100 Followers	
	Re-tweets by Alec Baldwin, US Actor	

Digital Analytics	Print Ads
Over 30,000 Website Visitors	1/2 page full color ad New York Times - Page A8
Video and Web Banner Impressions - More than 18M	NYT Circulation = 651,458
Video Views & Web Banner Clicks - 78,202	(2) 1/2 page full color ads WSJ Rocky Mountain Edition
Click-through-rate 8x industry benchmark	WSJ Rocky Mountain Edition Circulation = 45,000
View-through-rate of 80-84%	

Major Highlights/Activities:

- Organized Kickoff Event at the National Press Club in Washington, DC on November 1st
- 3 Travel Awards granted for LCAM 2016 Meeting in September 2016

2017 Objectives:

- Expand to include more global partners – Latin America, Asia, Rest of World
- Expand to include more Cancer Center/institutional partners
- Improve the diversity of the participants
- Improve website technology and social sharing
- Include more scientific advances linked with survivor stories
- Expand media kit and social sharing tools
- Increase sponsorship to support an expanded campaign

Thank you to our Partners!

Caring Ambassadors

Dusty Joy Foundation (LiveLung)

LUNGCAN

Free Me From Lung Cancer

Free To Breathe Lung Cancer

Foundation of America

Lungevity Lung Cancer Research Foundation

Chris Draft Family Foundation

Faces of Lung Cancer

Clifton Mountain Foundation

Bonnie J. Addario Foundation

American Lung Association

Lung Cancer Initiative of North Carolina

Lung Cancer Europe

Women Against Lung Cancer

Europe Patient Power Rexanna's Foundation

Upstage Lung Cancer

University of Colorado Cancer Center ...and many lung cancer survivors and researchers

Special thanks to the LCAM 2016 working group: Janet-Freeman Daily, Dusty Joy Donaldson, Cynamon Frierson and Mary Henningfield.

Participants: A consortium of individuals, including lung cancer survivors, and more than 20 different advocacy organizations in the USA and Europe, with IASLC coordinating the effort. There is potential for a worldwide campaign in the future.

MS 19 ELEVATING THE LUNG CANCER VOICE: RAISING AWARENESS AND CREATING COMMUNITY
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MS 19.03 THE ROS1DER STORY: HOW A GROUP OF PATIENTS, DOCTORS AND ADVOCATES LAUNCHED AN INTERNATIONAL RESEARCH EFFORT

L. Goldman

Patient Advocate/self, Mountain View/CA/US

In May 2015, I attended a conference for lung cancer patients in Washington DC. There were close to 200 patients in attendance, but only five with my specific diagnosis: ROS1+ Adenocarcinoma. We saw what a minority we were within the lung cancer community and knew it would be up to us to find and create our own "tribe." The five of us met up in the hotel bar to discuss how we might find other ROS1+ patients to share knowledge and improve our survival odds. Our first step was to create an online presence. Upon returning home from the conference, Tori Tomalia, Janet Freeman-Daily and I started a private Facebook group for people with ROS1+ cancer. We welcomed patients and caregivers and invited them to share their diagnosis stories, treatment paths and other experiences related to having ROS1+ cancer. We combed the internet searching for other ROS1+ patients, and we spoke to our doctors and friends in the lung cancer community to try to spread the word. In the first few months, membership ramped up fairly slowly, but we were a close knit group, sharing critical information, and making a difference in each other's lives. The more I learned, the more it became apparent that essentially no one was conducting research focusing on ROS1+ cancer. We had gotten lucky that the ROS1 fusion was similar enough to the ALK mutation (which occurs with more frequency and has a larger patient population), that ROS1 had been able to piggyback on the ALK research. But no one was specifically examining ROS1, and while the first generation ALK research generated Crizotinib, a therapy that proved exceptionally effective for ROS1, some of the most exciting second generation ALK research was not looking as promising for ROS1. Obviously, this was disconcerting. So, while attending WCLC in Denver in September of 2015, Janet and I pulled Dr. Ross Camidge (Univ. of Colorado) aside to ask him one very important question: How can we get ROS1-specific research going? His answer: Organize. Research cannot happen without a cohort of patients to study, and gathering enough ROS1+ patients is difficult for researchers. Dr. Camidge's words lit a fire under us. Janet, Tori and I decided to increase our efforts to recruit ROS1 patients to our Facebook group. All three of us published blogs, redoubled our efforts scouring the web and contacting doctors, and sought out other media opportunities. Within a couple of months, we'd doubled our membership, including many international patients, and we decided it was time to seek outside help. I contacted Bonnie Addario, a long-term lung cancer survivor and founder of the Addario Lung Cancer Foundation (ALCF). I knew Bonnie was a strong proponent of "patient centric" research, and I also knew the ALCF (and its sister organization, Addario Lung Cancer Medical Institute (ALCMI)) had successfully launched the "Young Lung Study" the previous year. Since both young lung cancer, and ROS1+ lung cancer, are minorities in the lung cancer space, requiring researchers to cast an international net to gather a critical mass, I felt that the ALCF and ALCMI had demonstrated both the interest and experience necessary to help shepherd a global ROS1 research effort. Luckily, Bonnie agreed, and soon the ALCF and ALCMI joined our team. As patients and caregivers, we began calling ourselves the "ROS1ders" (pronounced "ross-wonders"). A core group of about 5 ROS1ders did most of the work, but we would check in with the broader Facebook group for feedback periodically. By December 2015, the ROS1ders delivered a list of our research priorities to ALCF. Dr. Guneet Walia, ALCF's Senior Director of Research and Medical Affairs then began reaching out to researchers and industry--and the Global ROS1 Initiative (the "Initiative") was born. The first project of the Initiative was an epidemiological survey. ROS1ders worked together with Dr. Walia and a Stanford University researcher to develop a survey, designed to uncover commonalities which might indicate causes for the ROS1 oncogene, and help direct where to focus future research. Over 100 ROS1ders from around the world filled out the survey. Data analysis is underway, and a second generation follow-up survey is coming. Guneet discussed some of the initial findings of this study at WCLC 2016 in Vienna. Our second project is even more ambitious. Only a few models of ROS1 cancer exist. To encourage more research into ROS1 cancer, we are partnering with researchers and organizations to create new ROS1 cancer models (both cell lines and mouse models) using fresh biopsy and surgery specimens donated by ROS1ders. Models created by ROS1der donations will be made available (freely or at minimal cost) to academic researchers. Orchestrating the Initiative is a major undertaking. A group of the most involved ROS1ders and ALCF and ALCMI members have weekly conference calls. In between calls, each of us work on our individual pieces, such as meeting with researchers, negotiating contracts, writing content for websites, speaking at conferences, and fundraising. Since this project is the first of its kind, it's not surprising that sometimes we face hiccups and hurdles. Patients, caregivers, researchers, advocacy organizations and industry are learning how to work with each other as peers, and occasionally the learning curve is steep. The global nature of our project adds legal complexities, language barriers and time zone juggling to the mix. We are all evolving and changing the way research can be done. The Initiative is a groundbreaking example of international patient-driven research. Its success reflects the collaborative efforts of so many dedicated to achieving something truly special. From its inception at a hotel bar in Washington DC to today, ROS1der voices have been involved every step of the way. We hope the Initiative not only changes the lives of ROS1ders, but paves the way for other motivated patient groups to pursue their own goals. We are so proud and excited to see our vision manifest.

Keywords: ROS1+, Initiative, patient

MS 19 ELEVATING THE LUNG CANCER VOICE: RAISING AWARENESS AND CREATING COMMUNITY
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 19.04 SHINE A LIGHT ON LUNG CANCER: THE EVOLUTION

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Background/History: A lung cancer diagnosis can be devastating to both the patient and their loved ones. Often times, lung cancer patients and caregivers report feeling isolated and hopeless. In 2004, there were very few events across the United States which connected the lung cancer community. One advocate, whose husband was fighting lung cancer, sought to change that and held the very first Shine a Light event in November 2004 in Santa Rosa, CA. Little did they know, this local event would turn into a movement. In 2006, a few advocates in Boston held a similar Shine a Light on Lung Cancer Vigil—a "rally" for lung cancer on the steps of the Massachusetts state house, to honor and remember those who have been touched by the disease and to raise awareness during Lung Cancer Awareness Month (LCAM). In 2008, they were determined to grow this event and offer local communities an opportunity to connect with others impacted by this disease and Lung Cancer Alliance was there to help them achieve their vision. **Purpose**: Shine a Light on Lung Cancer's primary purpose was and continues to be raising awareness about lung cancer and connecting the community. The events are always free to attend and free to host as we want to eliminate any barriers to participation. Shine a Lights began as "vigils", and have always incorporated a moment of silence and the literal act of shining a light—whether that be a glow stick, flashlight, candle, or illumination of a room or building—to remember those we've lost to this disease. In 2014, Lung Cancer Alliance decided to drop the word "vigil" from the program title, as vigils often connote a feeling of sadness or mourning, and the purpose of Shine a Lights were to provide hope, support and inspiration to all those impacted. Each Shine a Light program still incorporates a moment of silence and shining of lights, however, we focus that moment to celebrate the survivors in attendance, while also remembering those who have passed away from this disease. This signature element of Shine a Lights can often be emotional and is typically the culminating activity of the event. Shine a Lights are also a great platform for local media attention. In an effort to leverage this attention, from 2008 through 2015, we encouraged organizers to host their event on the official Shine a Light date (voted on by past organizers and ultimately chosen by LCA). However, due to lack of national coverage and confusion from potential organizers on the official date, in 2016, we stopped choosing an official national date. **Impact**: The impact of our Shine a Light on Lung Cancer program has far exceeded our initial expectations. The initiative continues to grow and evolve year after year and we continually adapt and improve the program based on feedback from organizers and attendees. When Shine a Light began, events were typically organized by individuals in communities who wanted to do something during Lung Cancer Awareness Month. They incorporated survivors, caregivers, physicians and local notable members of their communities (i.e. news reporters, local politicians, and entertainers) into their programs, to educate attendees about lung cancer and inspire action with a unifying national call to action. In 2013, Lilly Oncology came on board as a national title sponsor and their sales force began to spread the word about these unique events to their customers—healthcare providers. Shine a Lights are a great way for nurse navigators to celebrate their patients during Lung Cancer Awareness

Month and highlight their programs and services—particularly on the heels of Breast Cancer Awareness Month—and especially with our "event in a box". Organizers complete a very simple online LOA which contains all of their event information, after which they receive access to our online resources (i.e. template flyers, programs, sponsor logos, media outreach instructions, and more). In October, each organizer will receive their Shine a Light "kit" in the mail, which contains bracelets, flashlights, a poster and educational materials for their attendees. Although we had had a handful of Shine a Lights taking place in healthcare facilities before 2013, with Lilly's involvement, the numbers grew. Simultaneously, we noticed Shine a Lights which were hosted by individuals were becoming more unique and personalized to their local community (i.e. paint and sip parties, yoga classes, and backyard barbecues). Because of this natural distinction, we evolved the program in 2016 to include Shine a Light, traditional events hosted by a healthcare facility during LCAM, and Shine a Light Your Way, unique awareness and fundraising events hosted by individuals in their local communities throughout the year. Due to this split, our traditional Shine a Light numbers saw a slight dip in 2016 as they no longer included events being hosted by individuals, but we anticipate continued growth in 2017 as the program evolves. **Future Goals** In 2016, 166 Shine a Light events were held in 38 states. Our goal for 2017 is to reach 200+ events in all 50 states and Washington, DC. We are also looking to make an even bigger global impact in 2018. The first international Shine a Light was held in partnership with the Australian Lung Foundation in 2011 and we have had seven unique countries host at least one Shine a Light since then. We hope to expand our national reach while bringing this unique program to many more worldwide, and continue connecting the lung cancer community—offering hope and inspiration, letting those who are impacted know they are not alone.

Keywords: Shine a Light, awareness, Event

MS 19 ELEVATING THE LUNG CANCER VOICE: RAISING AWARENESS AND CREATING COMMUNITY
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MS 19.05 "HOW TO BEAUTY YOUR DAY": LOOKING GOOD, FEELING BETTER - AN ITALIAN APPROACH

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Women Against Lung Cancer in Europe (Walce Onlus), Orbassano/IT

It is estimated that in 2015, approximately 3 million people in Italy have received a cancer diagnosis during their lifetime. While in men cancer has decreased of 2.5%, in women the cases have risen from 168,000 to 176,000. Epidemiological data of lung cancer reveal a dramatic increase of the incidence and mortality in women, mainly due to the tobacco consumption in the female population during the past 60 years and since the 1980s, the gap between the two genders has narrowed. Nowadays lung cancer represents a global Women's health issue and every year more women die due to lung cancer than for breast, ovarian and uterine cancer all together and receiving a cancer diagnosis together with the communication about treatment and care can lead to a series of extremely stressful and frightening events that cause both patients and their relatives to suffer emotionally. Psychological distress, depression and anxiety are related to poor quality of life in all its shapes and forms, including the physical-side. The disease and the treatments alter the patient body image and consequently change the personal identity; the body is no longer recognized and accepted in its new condition, and this may undercut the sense of femininity and diminish the confidence in the physical appearance and the self-esteem. It gets difficult for a woman to face the daily life because she is exposed to the external world with a body revealing visible signs of the illness and care. For addressing these issues, it is necessary to implement an holistic approach and this is one of the objectives behind the active commitment of WALCE (Women Against Lung Cancer in Europe) since 2006, when it was established. In 2009, it started the collaboration with "La forza e il sorriso – L.G.F.B. Italia", the Italian version of a well-known program called "Look Good .. Feel Better®", launched in US in 1989 and currently active in 26 countries worldwide. It is a free make-up workshop project for women diagnosed with cancer who are undergoing chemotherapy, radiotherapy or other cancer treatments. Beauty workshops are offered to help women to cope with treatment side effects and to regain the femininity and the self-confidence in their body with the aim to improve their quality of life by simple beauty techniques to enhance the appearance. Following this positive experience, WALCE designed a lung cancer awareness campaign, called: "How to beauty your day", a make-up session program for women of all ages affected by cancer with the aim to reach little and peripheral hospitals in Italy, where the initiative "La forza e il sorriso" has not been provided yet and hospitals, where no general support programs for women with cancer have been developed. This initiative was launched in November 2010, during the World Lung Cancer Awareness Month and in some way it recalls the other one, but with some new addition. Together with the beauty sessions, educational events are organized with the aim to improve and reinforce the knowledge of people about the disease, the current treatment options, the side effects and any other related issues. This program was firstly carried out just in Italy and later on, it was expanded in other European countries (Spain, Serbia and Greece). From November 2010 to November 2016, WALCE organized 76 make-up workshops in several Italian locations and in Europe, in collaboration both with cancer centres and no profit organizations working in these areas; about 750 ladies attended the make-up workshops, guided by 7 voluntary beauticians and with the support of a psycho-oncologist. At the end of the session, the women are invited to complete a survey to assess the event and benefits received. The general response received until now is positive; most of participants declare to have learnt useful advice and to be very enthusiastic, whereas very few are a little doubtful. The most common adjectives used to describe patient feelings at the end of the experience are: beautiful, happy, positive, pretty and attractive. From the survey results, it seems that most of the ladies don't think about the illness during the event and meeting other women in a similar situation is considered a positive experience. Cancer patients tend to better cope with the illness when self-confidence and self-esteem are regained. The sense of well-being shared in a relaxed atmosphere, acknowledging social, emotional and psychological needs and being amongst other ladies who feel the same fears or anxieties, has proven to be an incentive to fight against cancer.

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Keywords: lung cancer, body image, quality of life, femininity, self esteem

MS 20 VALUE-BASED MANAGEMENT FOR SPECIAL POPULATIONS
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 20.01 WHEN IS A TREATMENT CONSIDERED FUTILE?

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Introduction Futile care is defined as care that fails to provide a clinical benefit. This term can be controversial, especially when it's value of the caregivers, patient or his family are different. Discussion Poor communication between physicians, patients and their family members can lead to the misalignment of perceptions, ie. about life expectancy with or without treatments, about toxicities to be expected from a specific treatment, what quality of life (QOL) can be expected on certain treatments and what it means to receive as an alternative treatment a palliative care only.[1] [2] [3] [4] Sometimes the patient might refuse to know his prognosis and palliative care discussion.[5] [6]Doctor's perception is frequently influenced by patient's poor performance status (PS) of 3 or 4, very short estimated survival (sometimes in weeks only), difficulties with the management of the treatment toxicities which can cause a decline of QOL, different interventions and hospitalizations. The perceived patient's compliance with the treatments is an important factor, too. The interventions, ie. management of toxicities of the therapies, more frequent patients' visits, hospitalizations and the treatments without benefit further stress the futility with an increased cost for the society and institutions providing the health care. [7] The goals of patient care have to be discussed between oncologist, patient and his family. [8] [9] The final decision has to be shared and agreed on. The decisions have to include non-curative interventions, ie. other drugs, transfusions or even participation in Phase I trials,[10] which are conducted for safety of the drugs without an evidence of efficacy, but they are still not futile. It is very important to review if all the reasonable options of the interventions and the treatments were attempted, regardless of the timing of the situation at the time of the diagnosis or at the time of disease progression. The emotional needs of patients' caregivers, ie. family members, have to be considered and addressed, too. **Conclusion:** The discussion of disagreements with the patient, his family and health care providers regarding the treatment goals and interventions when considering the disease prognosis will lead to reasonable conclusions and avoid the futilities. As it was quoted, "In Oncology: clear and unequivocal situations of right and wrong are rare." The concerns and wishes of the patients, patients' families and oncologists have to be well balanced to avoid a futile treatment.

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Keywords: NSCLC, Futile treatment, mutual agreement

MS 20 VALUE-BASED MANAGEMENT FOR SPECIAL POPULATIONS
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 20.02 VALUE-BASED JUDGMENT IN ADVANCED NSCLC: THE EUROPEAN PERSPECTIVE

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Therapy of lung cancer depends on many factors including tumor-related factors, patient parameters and treatment-related factors. Tumor-related factors are histological subtype, molecular characteristics and stage as well as growth of tumors. Patient-related factors include age, life expectancy, gender, performance status, organ functions, co-morbidity, functional status, geriatric syndromes and patient preference. Drug-related parameters include convenience of administration, side effects of drugs, and polypharmacy. Costs, cost effectiveness and value-based judgements are also of major importance. Value-based judgements of anticancer therapies are based on the magnitude of the clinical benefit balanced against their costs (1). These judgements are gaining increasing importance because of the increasing costs of modern anticancer treatments including novel anticancer drugs. The benefit of treatments focus on living longer and living better. The evidence of the magnitude of the treatment benefit is derived from clinical trials such as phase 3 trials or from meta-analyses of randomized trials. Important outcome parameters focus on the impact of the treatments on overall survival, progression-free survival, response rates and symptom relief. Parameters for living longer are improved overall survival and/or improved surrogate of overall survival such as disease-free survival in the adjuvant setting or progression-free survival. With regard to living better, important parameters are improved quality of life, improved surrogate of quality of life, and reduced toxicity. The incremental cost-effectiveness ratio (ICER) is often used to evaluate the value of a new anticancer drug (2, 3). ICER refers to the costs per life year gained or costs per quality-adjusted life year gained. A drug is considered cost-effective if its ICER is below a certain threshold which depends on the country and may range from about 20.000 to 50.000 Euros or even higher. Several scientific and professional societies including ESMO have developed scales to determine the clinical benefit of systemic treatments in patients with cancer. The ESMO - Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a standardized, generic, validated tool to assess the magnitude of clinical benefit that can be expected form anticancer therapies (4, 5). This tool is dynamic and has been planned to be revised in regular intervals (4). Separate tools have been developed for the adjuvant and the palliative settings. For assessment of survival data, hazard ratios and median survival times are considered. Based on simulation data, the lower limit of the 95% confidence interval of the hazard ratios have been recommended for use (4). Form 1 of the ESMO-MCBS is used for adjuvant or neoadjuvant therapies and for localized or metastatic disease treated with curative intent (4). The grades are A, B and C, with grades A and B representing high levels of clinical benefit (4). Grade A refers to >5% improvement in survival or improvement in disease-free survival alone with a HR<0.65 in studies without mature survival data. Grade B refers to ≥3% but ≤5% improvement in survival or improvement in disease-free survival alone with hazard ratios <0.65-0.8 without mature survival data. In addition, non-inferior survival or disease-free survival with reduced treatment toxicity or improved quality of life, or non-inferior survival with reduced treatment costs are also graded as B. Grade C refers to <3% improvement of survival or improvement in disease-free survival alone with hazard ratios >0.8 in studies without mature survival data. Form 2 of the ESMO-MCBS is used for therapies without curative intent (4). The grades range from 1 to 5, with grades 4 and 5 representing high levels of proven clinical benefit (4). Form 2 is more complex and includes forms 2a, 2b and 2c. Form 2a is for therapies that are not likely to be curative and have overall survival as primary endpoint. Form 2b is for therapies that are not likely to be curative and have progression-free survival as primary endpoint. Form 2c is for therapies that are not likely to be curative and have primary endpoints other than overall survival or progression-free survival. The preliminary magnitude of clinical benefit is based on the efficacy of the treatment and is then adjusted according to quality of life and grade 3-4 toxicities. The preliminary score is upgraded by 1 if the treatment resulted in improved quality of life and/or less grade 3-4 toxicities. The ESMO-MCBS is planned for comparative analyses of different treatments (4, 5). The value of treatments of lung cancer measured according to the ESMO-MCBS in a single institution has recently been published (6). In summary, the evaluation of the clinical benefit of anticancer therapies in patients with lung cancer is a complex and rapidly moving area. It is based on the evidence from clinical trials, cost effectiveness analyses and, more recently, also valued-based judgements. The latter tools are dynamic and balance magnitudes of the benefits against the costs of specific treatments. Despite all these measures, clinically experienced doctors working in close co-operation with informed patients and their relatives are crucial for optimal treatment decisions in patients with lung cancer. References 1. Porter ME. NEJM 2010, 363, 2477 2. Dilla T et al. Patient Preference and Adherence 2016, 10, 1 3. Bae YHJ & Mullins CD. J Manag Care Pharm 2014, 20, 1086 4. Cherny NI et al, Ann Oncol 2015, 26, 1547 5. Cherny NI et al. ESMO Open 2016, 1, e000100 6. 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Keywords: Cost, cost effectiveness, value

MS 20 VALUE-BASED MANAGEMENT FOR SPECIAL POPULATIONS
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 20.03 WHAT DO PATIENTS WANT AT THE END OF LIFE? - EAST VS WEST

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Although advance care planning (ACP) may prevent non-beneficial care that is discordant with patient wishes at the end-of-life (EOL), nearly 40% of bereaved families in the US said their loved ones had not discussed their EOL care preferences with them (Narang et al, JAMA Oncol 2015). Fewer Japanese studies on EOL discussions (EOLd) with patients have been reported than studies in Western countries. Similarly, few studies investigating what patients want at the EOL have been reported in Japan. Most Japanese studies related to EOL have focused on medical staff, bereaved families, or healthy persons in the general population, rather than on patients themselves. In addition, the most common method of data collection for these studies in Japan has been through administration of questionnaire surveys by mail (J-HOPE3 study 2016, in Japanese). While the perspectives of care providers and family may indirectly reflect the preferences of patients, previous studies have not assessed cancer patients directly and therefore knowledge regarding EOL preferences for this population remains limited and unclear. Possible reasons for not directly investigating the EOL preferences of cancer patients may be related to Japanese cultural taboos regarding discussion of death with cancer patients and the positive cultural value of living without awareness of death, even in the terminal stage of disease. These factors lead to reluctance in discussing EOL care among patients, family members, and medical staff. In contrast, 70% of cancer patients in Sweden had discussions about death with family members within 3 months of their death (Jonasson et al, Eur J Cancer 2011).

In a previous study of 529 Japanese cancer patients, only half of the patients preferred to receive information regarding their life expectancy and 30% preferred not to receive such information. Furthermore, 90% of the patients preferred to have their physicians consider the feelings of their family as well (Fujimori et al, Psychooncology 2007). One Japanese research study on the hopes of terminally-ill patients found that symptom control was the most frequently expressed hope at the time of admission to a palliative care unit (PCU). However, patient hopes regarding symptom control and recovery decreased as death approached. In contrast, both existential hope and hope of good human relations increased by the time of death (Naka et al, Shi no rinsho 1998, in Japanese). EOLd should repeatedly occur among patients, families, and medical staff, before patients become incompetent, because patient preferences may change in unexpected ways, as was found in a study of advanced lung cancer patients (Pardon et al, Support Care Cancer 2012). Another Japanese study of advanced cancer patients found that patients strongly preferred that their physicians listen to their distress and concerns (96%), assure them that their painful symptoms would be controlled (97%), and explain the status of their illness and the physical symptoms that would likely occur in the future (95%) (Umezawa et al, Cancer 2015). Patient preferences or hopes near the EOL appear to be similar between Western and Japanese cultures. However, fewer Japanese studies on EOLd have been reported because of cultural taboo for talking about death. In our hospital, when patients with advanced lung cancer had an initial consultation with palliative care physicians to prepare for future PCU admission (N=46), the reasons expressed by patients or their families for considering PCU admission were "want to reduce pain (70%)", "want to reduce distress (59%)", "want to live without intensive life-sustaining care (52%)", and "recommendation by attending physicians or caregivers (39%)". However, only 9% of patients clearly understood their life expectancy when considering PCU admission. Interestingly, many terminally-ill Japanese cancer patients may wish to take a bath before death. For example, 40% of patients with advanced cancer were bathed while receiving home nursing services within 4 days of death (Tanabe et al, Hospice and Home Care 2015, in Japanese). The role of rehabilitation in PCUs remains unclear and one study found that only 20% of terminally ill cancer patients received rehabilitation in Japan. However, the rate of satisfaction for the rehabilitation reported by bereaved families was extremely high (80%) (J-HOPE3 study 2016, in Japanese). There is limited published information about how physicians obtain the skills necessary for managing their own discomfort with talking about death. Communicating in an honest manner, without taking away hope, is an essential skill for the physician treating terminally-ill cancer patients. Japanese physicians, however, are less likely to have educational opportunities to learn how to discuss bad news with patients. Japanese physicians, in particular, often feel discomfort with discussing prognosis, hospice, site of death, and do-not-resuscitate (DNR) status with patients. Improvement in the communication skills of physicians is key to facilitating more appropriate ACP with cancer patients. For communication with terminally-ill cancer patients, the classic strategy of "hope for the best and prepare for the worst" or "use more open questions rather than closed questions with patients" can be recommended as part of an ACP discussion. Using a palliative prognostic index may be helpful in predicting prognosis for terminally-ill cancer patients more accurately (Maltoni et al, Oncologist 2012). However, because accurate prognostic understanding has been found to be associated with lower quality of life (QOL) and worse anxiety, these patients should be offered psychosocial

support (El-Jawahri, Cancer 2014). Discordance between the care desired and the care received by patients is another important EOL issue. The use of structured communication tools, rather than an ad-hoc approach, is recommended to facilitate more appropriate EOLd, and to avoid care not desired by patients (Oczkowski et al, PLoS One 2016). Finally, a phase III study evaluating the role of early palliative care (EPC) suggested that EPC provided significantly better QOL and better survival than usual care in patients with advanced non-small cell lung cancer (Temel et al, N Engl J Med 2010). Similarly, our feasibility study demonstrated that EPC provided better QOL in patients with advanced lung cancer (Yokoyama et al. WCLC 2015). We recommend EPC referrals for lung cancer patients to support earlier EOLd and earlier understanding of the hopes and goals of patients with advanced lung cancer.

MS 21 BEING MORTAL: LEARNING FROM ZEN
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 21.01 SPIRITUALITY IN ASIA

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Human being is mortal. However, people don't want to think about death and prefer to live without considering it. Death has actually been hated in society. In general, death is thought as LOSS. Indeed, healthy body, time as a gift of life, society meaning, several experience, all achievements including money, house, family, friends, status and honor are LOST at death. In medicine which prolongation of life has been a primary purpose, death is considered as defeat. However, if we consider death as loss or defeat, theoretically goal of life itself would be futile definitely toward loss and defeat. "Human beings, who are all mortal and their own deaths are inevitable, seriously think, worry, are embarrassed and hate when they encounter death of other person. They think that death is not appropriate for them." Gautama Buddha who was born in India 5th century BC thought as above, tried to find the cause of death throes and search for how to deal with terror of death throes. Teaching of Buddha from India was introduced to China in where that was developed as ZEN. Teaching of ZEN has been growing calls in the world. ZEN stresses the importance of staring DEATH. In other words, that is to learn how to live responding enough to DEATH as inquiry. It is never to pursue a world after death, just to actively find meaning of life through staring death. We would like to learn how to live while reacting DEATH that tends to evade in modern society, through historical teaching of ZEN.

MS 21 BEING MORTAL: LEARNING FROM ZEN
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 21.02 MEDITATION: FROM THE TEMPLES TO THE CLINIC

A. Chaoul
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The Buddhist traditions are rich in meditation practices, utilizing them for their spiritual development as a tool towards enlightenment, and also for physical, emotional and mental wellbeing. For centuries, these practices were only for a select group of yogis in caves or nuns and monks in monasteries, but globalization and other movements of the Twentieth century helped bring these practices to a wider population, including people with illnesses such as cancer. This presentation will focus on how some of the philosophical Buddhist concepts, like the understanding of our own mortality or impermanence, and some of the meditation practices had been applied in a non-religious way as part of the offerings for cancer patients and their caregivers within contemporary western clinical settings in our Integrative Medicine Center at MD Anderson Cancer Center in Houston. George Engel's seminal 1977 paper in *Science* provides the background for a bio-psycho-social approach at our Integrative Medicine Center that is now part of the Department of Palliative, Rehabilitation and Integrative Medicine at MD Anderson. In other words, a healing focused not just on the physical (i.e., bio) but also on the psycho-social-spiritual aspects of the person, which sometimes seems to be forgotten in conventional allopathic medicine. The bio-psycho-social approach is very much in accordance to the Buddhist approach, and palliative care and integrative medicine are optimal settings. I will share how we bring these into our group classes as well as individual clinic sessions, where people with different kinds of cancers, including lung cancer, participate. In particular I will address cases of people with lung cancer, and issues of stigma, of facing one's own mortality, and how the concepts and practices that stem from a Buddhist perspective can have positive impact in their quality of life, overall survival, and better relationship to others, in particular their family members and caregivers. In addition I will share the results of a single arm clinical study of Tibetan Yoga (meditation and simple movements) for people with lung cancer and their caregivers that was held at MD Anderson Cancer Center in collaboration with the Ligmincha Texas Center for the Tibetan Meditative and Healing Arts. The purpose of this study was to establish feasibility and preliminary efficacy of a mind-body intervention in lung cancer patients and caregivers. Patients with stage I-III non-small cell lung cancer undergoing radiotherapy and their family caregiver participated in a 15-session Tibetan Yoga (TY) program that included breathing exercises, guided visualizations, and gentle movements. This single-arm trial assessed pre/post intervention levels of mental health (CESD; BSI), fatigue (BFI), sleep disturbances (PSQI), spiritual well-being (FACT-SP) and overall QOL (SF-36). Patients (mean age: 73 yrs., 62% male, 85% stage III) and caregivers (mean age: 65 yrs., 73% female, 85% spouses) completed a mean of 12 TY sessions (range: 6-15) and 95.5% of them rated the program as useful or very useful. Paired t-tests revealed a significant increase in spiritual well-being (P=.03; *d*=1.12) for patients and decrease in fatigue (P=.03; *d*=.87) and anxiety (P=.04; d=.91) for caregivers. This first couple-based Tibetan yoga program appears to be a safe, feasible, acceptable and subjectively useful supportive care strategy for patients and their caregivers. Based on these promising preliminary findings regarding treatment gains, the next step is to conduct a randomized controlled pilot trial. Furthermore, based on this and other Tibetan meditation and Tibetan yoga studies with other cancer populations (namely, lymphoma and women with breast cancer), we have incorporated this as a new class of Tibetan meditation and movement as part of our free offerings for people with cancer and their caregivers in our Integrative Medicine Center.

Keywords: Meditation, Tibetan Yoga, Integrative Medicine

MS 21 BEING MORTAL: LEARNING FROM ZEN
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 21.03 SELF-CARE: "PROVIDER, HEAL THYSELF"

M. Ftanou
Psychology, Peter MacCallum Cancer Insititue, Parkville/VIC/AU

This paper discusses the prevalence of burnout in oncology settings and strategies that can be implemented at both an individual and organizational level to maintain and create a healthy workforce. **Background** Lung cancer is the leading cause of death by cancer for both men and women worldwide. Most lung cancers are diagnosed at advanced stage and approximately 16% of lung cancer patients will be alive five years post-diagnosis [1]. Working in lung cancer can be gratifying and very rewarding; however it requires high levels of emotional engagement. Oncology professionals work intensively with patients, they provide sophisticated treatments, emotional support, and comfort to patients and their family across the cancer trajectory [2]. Burnout, which refers to feeling emotionally and physically exhausted is common in oncology settings. In a random sample of 1000 US oncologists, 56% experienced burnout at some point in their career [3]. In an Australian sample, 33% of staff with direct patient contact and 27% of staff with non-direct patient contact displayed high levels of emotional exhaustion [4]. Oncology staff who are younger, female, isolated and who work longer hours are more likely to experience burnout [5]. Predictors of stress and burnout include increased work demands, staff shortages, lack of communication training, lack of control or autonomy and dissatisfaction with leave arrangements [6]. Burnout has serious consequences for oncology professionals including elevated rates of mental and physical health concerns, suicidal ideation, difficulties sleeping, frequent bouts of illness, and addiction, intimacy and relationships problems. As a result, patient care is often compromised due to increased errors, turnover and absenteeism and reduced empathetic care. Assessment and strategies to combat burnout A number of tools can assist in better understanding levels of burnout in oncology staff. The most frequently used tool to determine rates of burnout is the Maslach Burnout Inventory (MBI-HSS). The MBI-HSS is a 22-item self-report questionnaire. It measures three distinct dimensions of burnout: (1) emotional exhaustion (EE) characterised by feeling emotionally overextended; (2) depersonalisation, which includes feeling disconnected, detached; and (3) personal accomplishment, the negative judgements one makes about their career and levels of success [7]. Assessing burnout can lead to early identification and interventions for stress management. To reduce burnout, both individual and organisational factors need to be implemented. Developing personal resilience is essential for combating stress and burnout. A number of individual strategies that can assist in developing and maintaining resilience, include creating a work-life balance and adopting self-care and relaxation routines [8]. At an organisational level, coping can be enhanced by the provision of supports such as supervision, professional development opportunities, and the development of work schedules that promote team engagement and address staff shortages and adequate leave arrangements. Furthermore, formal education on how to better manage stress, including mindfulness-based stress reduction, cognitive behaviour therapy and communication training interventions can improve stress management and staff wellbeing [8]. Conclusion Working in oncology can be very rewarding, but can also be emotionally and physically exhausting. The workforce is the most important resource in any organization and burnout needs to be addressed both at the individual and organisational level. At an individual level, oncology professionals need to acknowledge stress, create a work-life balance and adopt self-care and relaxation practices. To maintain a healthy workforce, organizations need to ensure adequate staffing, leave arrangements and provide access to appropriate training, professional and emotional supports. References 1. Cancer Australia. Lung cancer statistics: Australian Govenrment; 2017 2. Diggens J, Chesson T. Do factors of emotion-focussed patient care and communication impact job stress, satisfaction and burnout in radiation therapists? Journal of Radiotherapy in Practice 2014;13(1):4-17. doi: 10.1017/S146039691300006X 3. Whippen DA, Canellos GP. Burnout syndrome in the practice of oncology: results of a random survey of 1,000 oncologists. Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology 1991;9(10):1916-20. 4. Girgis A, Hansen V, Goldstein D. Are Australian oncology health professionals burning out? A view from the trenches. European Journal Of Cancer (Oxford, England: 1990) 2009;45(3):393-99. doi: 10.1016/j.ejca.2008.09.029 5. Kamal AH, Bull JH, Wolf SP, et al. 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Keywords: Burnout, stress management

MS 22 THE COST OF LUNG CANCER
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 22.02 THE COST-BENEFIT OF LUNG CANCER CARE FROM A PATIENT'S PERSPECTIVE

D. Hicks, G. Walia

Bonnie J. Addario Lung Cancer Foundation, San Carlos/US

Background: Several promising advances have been made in lung cancer treatment recently, specifically, targeted therapies and immunotherapies. However, these have been associated with high financial costs, bringing up discussions on 'value' of these new drugs. Currently there are 5 value-assessment models, however none of them incorporates the patient perspective. **Methods:** We conducted a qualitative survey of 26 lung cancer patients to evaluate perceptions of the cost-benefit/ value of care, and aid the development of a patient-centered value assessment model. The survey was conducted by an independent market research firm, in a blinded format, and the questions focused on patient preferences, goals and expectations, and how these influence healthcare decision-making. **Results:** The survey identified factors that matter most to patients during healthcare decision-making and their perception of value. 94% patients reported that the cost of care was a critical factor in healthcare decision-making, stating they are less likely to adhere to the treatment plan or forgo treatment completely as out-of-pocket costs rise. All patients agreed that a monetary value cannot be put on life; one patient stating "...if I could get one more day to spend with my family that should be value enough". Other factors included real-world evidence, complexity of treatment regimen, efficacy/effectiveness, side-effect profile, risk tolerance and benefit value, non-medical costs and burdens upon patient and caregivers. **Conclusion:** It is important to focus on the patient perspective and engage in shared-decision making as it has a significant impact on quality of life, clinical outcomes, cost of care and patient satisfaction.

MS 22 THE COST OF LUNG CANCER
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MS 22.04 THE ECONOMIC WORLD OF TOBACCO FREE INVESTMENTS

B. King

Ceo, Tobacco Free Portfolios, Melbourne/AU

Global tobacco control is like a gigantic cake, with innumerable slices dedicated to different tobacco control initiatives in different parts of the world. Each slice is vitally important, responsible for advancing our collective cause just that bit further. Each slice is in fact essential as the *magnitude* of the task simply demands a multitude of efforts and the *complexity* of the task – not knowing where or when the next breakthrough will occur (or where or when it will be halted due to tobacco industry interference) means that we need to simultaneously commit to a broad range of strategies. Up until a few years ago, there was, however, one slice missing - the slice that involved the finance sector. Never before had the global finance sector, and its almighty power, been leveraged in tobacco control efforts. In fact business as usual for the finance sector saw it working *against* every other slice of the cake. This situation was largely unintentional, simply a result of 'doing things the way they had always been done'. Most pension funds invest in tobacco companies. Most banks lend them money. It's been like that for about a hundred years. Professionally engaging with global finance leaders, asking them to learn about the tobacco epidemic and to reconsider commercial relationships with the tobacco industry, has seen significant changes implemented in the business models of banks, insurers, pension funds and fund managers. Since Tobacco Free Portfolios began in 2012, approximately USD $6 billion has been shifted from investment in the tobacco industry by financial institutions in ten different countries. Several banks have ceased lending money to tobacco companies and several insurers have ceased providing insurance. There is increasing acknowledgement of the significant reputational risk faced by financial organisations if they continue to maintain links with tobacco companies – companies that make products that kill two out of three of their best customers. To proceed with a tobacco-free investment decision, many conditions need to be in place. An open door to the CEOs office; willingness to consider the issue and to learn about something that sits outside the traditional paradigm of the finance sector; a country where public support of tobacco control is strong - where there is awareness of the cost-burden of tobacco, and understanding of the future financial risks associated with tobacco companies, spanning regulation, litigation and scrutiny of supply chains. Some individual finance leaders are more open to the tobacco-free conversation than others but interest is growing rapidly. Tobacco Free Portfolios is working towards a world where the global finance sector is aligned with the global health and governments sectors on tobacco. Our vision is for tobacco-free investment to be the baseline expected standard. With a forecast of one billion tobacco-related deaths this century, tobacco is a problem so profound that it cannot be adequately addressed unless *every sector* of society contributes to the solution. The changes witnessed in recent years are hopefully the start of a new frontier in truly comprehensive global tobacco control.

Keywords: tobacco, Tobacco Control, divestment

MS 23 MANAGEMENT OF N2 NSCLC: WHAT "OPERABLE" MEANS?
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 23.02 WHEN DO SURGEONS QUIT RESECTION DURING SURGERY?

J. Donington

Cardiothoracic Surgery, NYU Langone Medical Center, New York/NY/US

Reasons surgeons "quit" cancer operations are typically related to finding additional sites of disease, inability to perform necessary dissection, or disappearance of previously identified disease. In the setting of N2 positive non-small cell lung cancer (NSCLC) the disappearance of disease is not a consideration, so occult sites of disease or inability to perform safe hilar or mediastinal dissection are the most common reasons to back out of an operation once started. Incredibly precise pre-resection imaging has made this an uncommon scenario. Imaging techniques include functional and molecular correlates, and 3 and 4 dimensional reconstructions, which improve detection of very small lesions and appreciation of tumor interactions with adjacent structures. That being said, N2 involvement denotes locally advanced and often aggressive disease and use multimodality treatments and therefore the risk for unexpected findings in the operating room which alter resectability are more frequent than in early stage disease. Occult or unexpected disease encountered by thoracic surgeons in the operating room typically involves the parietal pleura, as occult carcinomatous pleuritis. Additional pulmonary nodules and unanticipated milliary spread are far less common. Pleural studding is defined as M1a disease in the 8th edition of AJCC staging. Chemotherapy is the recommended treatment for radiographically identified pleural involvement, but management recommendations are slightly less clear for disease found at the time of surgery. Pulmonary resections are generally contraindicated, but several investigators report favorable outcomes for those who can undergo macroscopic complete resection.[1,2] Carcinomatous pleuritis can escape radiographic detection, the incidence of occult disease at thoracotomy ranges from 1.5% to 4.5% for all lung cancer resections,[3] and is associated with large tumors, non-squamous histology, and lymph node involvement. [2] Carcinomatous pleuritis can escape radiographic detection, the incidence of occult disease at thoracotomy ranges from 1.5% to 4.5% for all lung cancer resections,[] and is associated with large tumors, non-squamous histology, and lymph node involvement. Intraoperative pleural lavage cytology (PLC) is a technique used for detecting subclinical dissemination of malignant cells in the pleural cavity. The boundary between malignant pleural effusion and positive PLC is not particularly well defined and most reports demonstrate a negative impact on prognosis in resected patients, but positive PLC does not upgrade tumors in the current TNM staging system. It also does not preclude resection in a patient with otherwise resectable disease. Similar to pleural studding positive cytology is consistently found to be more common in patients with higher stage and nodal involvement.[4] The presence of bulky N2 disease can greatly increase the complexity of hilar and mediastinal dissection. Modern techniques and intraoperative tools have increased surgeons ability to remove structures once considered unresectable including the spine, carina, and superior vena cava, but direct tumor extension or nodal involvement of the trachea, heart or great vessels can make safe resection impossible. Preoperative imaging typically allows for appropriate planning and decision making about these types of complex resections and controversy exists as to appropriateness of such resections in the setting of N2 disease. Induction therapy can make the pre-operative assessment of involved structures more complicated, differentiation between tumor and treatment effect is not always clear and therefore many surgeons make resection decisions on pre-treatment imaging. A more common scenario in thoracic oncology is that of the patient with marginal pulmonary reserve in whom the hilar resection is complicated by extensive nodal involvement or treatment effect; a pneumonectomy is technically feasible and would result in complete resection, but the patient would not tolerate that extensive a resection. Sleeve resections are used whenever possible, but widespread hilar and mediastinal scarring can sometimes exclude any safe surgery other than a pneumonectomy. The amount of fibrosis and scarring encountered at resection following induction therapy remains unpredictable. It is known to increase with time, which is why resection is recommended within 12 weeks induction therapy, but within that window, it can be quite variable. Review of recent large prospective trials for resectable IIIA NSCLC can help shed light on how frequently and why surgeons cannot complete the planned resection for N2 positive NSCLC. In the recent SAAK trial which compared induction chemotherapy to induction chemoradiotherapy in high volume operative centers in Europe, all patients who were taken to surgery, had a pulmonary resection, but R2 resections occurred in 3% of the trimodality group and 8% of the bimodality, reasons for incomplete resection were not delineated.[5] In the recent report of pooled data from RTOG 0229 and 0839, evaluating surgical outcomes after high dose induction chemo-radiotherapy, 7 of the 99 patients brought to surgery were not resected, 2 due to occult pleural metastasis, 2 because of persistent N2 involvement in patient with limited pulmonary reserve, and 3 were "unresectable", 2 because complete resection would require a pneumonectomy and they had poor pulmonary reserve and one due to extensive mediastinal fibrosis. [6] These trials were all limited to experienced thoracic surgeons, indicating that the inability to complete a planned resection for IIIA NSCLC remains a rare but real phenomenon even in skilled surgical hands.

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Keywords: lung cacner, surgery, stage IIIA

MS 23 MANAGEMENT OF N2 NSCLC: WHAT "OPERABLE" MEANS?
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 23.03 WHAT IS RESECTABLE N2 DISEASE, AND WHAT IS UNRESECTABLE N2 DISEASE: A MEDICAL ONCOLOGIST'S VIEWPOINT

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Various treatment strategies, including chemotherapy, radiotherapy and surgery have been developed for patient populations with N2 lymph node metastasis, especially clinical stage IIIA-N2 non-small cell lung cancer (cIIIA-N2 NSCLC). For potentially resectable patients, clinical trials including surgical treatment have been published. Among them, EORTC-08941, INT-0139, ESPATUE examined the efficacy of adding surgical treatment with chemotherapy and radiotherapy in randomized design. In the INT-0139 study, surgery after induction chemoradiotherapy (CRT) demonstrated a 7% gain on 5-year survival, however, it failed to show statistical significance mainly because of treatment-related death in patients received pneumonectomy after induction CRT. Although the contribution of surgery was recognized, the additional effect of surgery over CRT has not been confirmed consistently in other trials. On the other hand, trials investigating newer medical treatment and higher radiotherapy dose have been conducted for patients with unresectable stage III NSCLC. In this patient population, so-called third generation cytotoxic agents whose effects were confirmed in patients with advanced disease, including paclitaxel (WJTOG0105), docetaxel (OLCSG 0007), vinorelbine and pemetrexed (PROCLAIM) with platinum have been actively examined but failed to show improvement compared to older agents (etoposide, vindesine and mitomycin C). Furthermore, high-dose radiotherapy (74Gy) with platinum-doublet chemotherapy showed strikingly shorter survival than conventional radiation dose (60Gy) in RTOG-0617. After these continuous efforts, CRT stayed as standard for those patients with unresectable N2 disease. Besides CRT, induction therapy followed by surgery has also come to be recognized as a treatment option for potentially resectable N2 disease in major guideline including ACCP, NCCN and ESMO. However, no clear answer has been provided for the question: what is resectable N2 disease, and what is unresectable N2 disease? To refine the heterogeneity in cIIIA-N2 NSCLC patients and show clues to answer the question of resectable/unresectable, we analyzed the data of consecutive patients with cIIIA-N2 NSCLC diagnosed and treated by CRT in National Cancer Center Hospital, Tokyo, Japan. The appearance of the mediastinal lymph nodes (MLNs) was classified into discrete or infiltrative according to the criteria proposed by the ACCP. In addition, the extent of MLN involvement (MLNI) was classified as limited (close to the primary tumor) or extensive (including upper MLNI in the case of tumors in the lower lobes and vice versa). Those with a discrete appearance of the MLNIs and a limited extent of MLNIs at diagnosis could show favorable survival outcomes by CRT without surgery comparable to the data provided by induction CRT followed by surgery. Meanwhile, immune checkpoint inhibition by PD-1/PD-L1 antibody has been being actively examined as adjuvant for early stage resectable NSCLC patients and consolidation therapy for unresectable stage III NSCLC patients after CRT. The PACIFIC is a phase III randomized clinical trial investigating the efficacy of MEDI-4736 (PD-L1 antibody) as consolidative therapy in patients without progression after definitive CRT. Based on the press release by AstraZeneca, MEDI-4736 showed significant prolongation of progression-free survival, suggesting that there is a possibility of changing standard treatment. Under such circumstances that powerful medical treatment option will be introduced in unresectable N2 disease, there is increasing need for an appropriate guidance to select surgical candidates in potentially resectable population. Now is the time to respond to the question of resectable/unresectable that has not been answered for a long time.

Keywords: Chemoradiotherapy, N2 disease, Unresectable

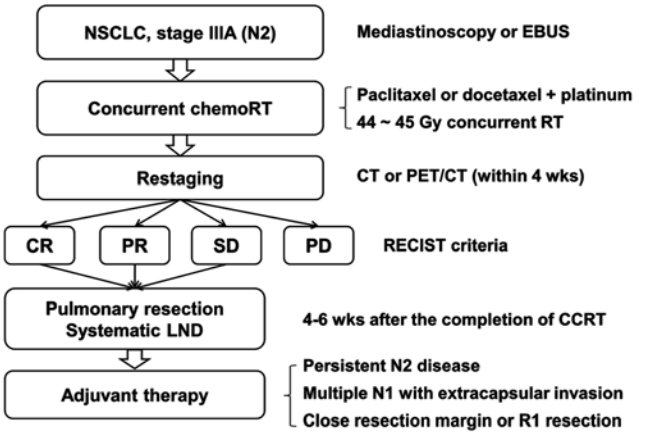
MS 23 MANAGEMENT OF N2 NSCLC: WHAT "OPERABLE" MEANS?
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 23.05 WHAT IS RESECTABLE N2 DISEASE, AND WHAT IS UNRESECTABLE N2 DISEASE: A SURGEON'S VIEWPOINT

J. Kim

Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/KR

What is Resectable N2 Disease, and What is Unresectable N2 Disease: A Surgeon's Viewpoint Jhingook Kim, MD (Samsung Medical Center, Sungkyunkwan University) The poor prognosis of N2 disease is related to the risk of occult systemic metastasis although N2 disease, by definition, is a localized disease. Therefore, multimodal treatment, including systemically chemotherapy and locally surgery or radiotherapy, is often required. However, the optimal multimodal approaches for N2 disease remain controversial. Although definitive concurrent chemoradiotherapy (CCRT) is considered the standard of care, its oncologic efficacy can be limited by the high rate of local failure. Adding surgical resection to this bimodal treatment as a neoadjuvant treatment setting or replacing the radiotherapy with surgery has been attempted and has achieved enhancement of local control and improved survival, but the main concern regarding this approach is the increased risk of postoperative mortality and morbidity. Since 1995, neoadjuvant CCRT followed by surgical resection has been the preferred treatment modality at our institution, and prospectively and consecutively performed for more than 800 medically fit patients with resectable NSCLC with N2 disease.



NSCLC, non-small cell lung cancer; EBUS, endobronchial ultrasound; RT, radiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LND, lymph node dissection

Fig. 1. Summary of treatment scheme Based on the previous analysis of 574 patients (From 1997 to 2013, 59 years of mean age, 444 men), complete resection was obtained in 543 patients (95%) by lobectomy (418 patients; 73%), pneumonectomy (73 patients; 13%) and sleeve resection (25 patients; 4.3%). Postoperative complications and in-hospital mortality occurred in 199 patients (35%) and 21 (3.7%), respectively. Pathologic complete response was achieved in 72 patients (13%) and 304 (53%) experienced mediastinal clearance. The 5-year overall and recurrence-free survival rates were 47 and 29%, respectively, and the median overall survival and recurrence-free survival were 56 months and 18 months, respectively. The 5-year OS rates were 61% in ypN0, 49% in ypN1, and 35% in ypN2 ($p = 0.001$). The 5-year RFS rates were 45% in ypN0, 23% in ypN1, and 17% in ypN2 ($p < 0.001$). Older age, advanced pTstage, persistent N2, large cell carcinoma, and pneumonectomy were independent prognostic factors associated with worse OS and poorer RFS. Evidence such as acceptable early postoperative outcomes, satisfactory local control and encouraging long-term survival has supported the need to expand the indication or situation. When investigating the timing and patterns of recurrence after treatment, of 290 patients with recurrence, 25 (8.4%) experienced loco-regional recurrence, whereas 238 (80.4%) had distant metastases. The hazard rate function for overall recurrence revealed a peak at approximately 8 months after surgery and a marked decline after 2 years (figure 2). The peak recurrence frequency of distant metastasis differed at each site, with isolated brain metastases exhibiting the earliest peak (6 months) and a narrow recurrence interval (15 months). Interestingly, the dynamics of recurrence after trimodality therapy varies according to pathologic factors and response to induction therapy (not specifically related with pre-induction presentation), which may mean personalized consideration of the treatment including surgery.

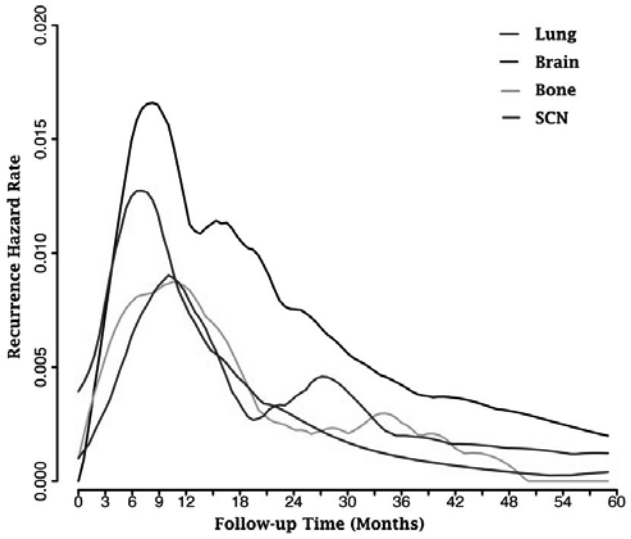


FIG 2. Comparison of the recurrence hazard rate according to the site of distant metastasis. Each organ has a different peak of recurrence, although the peaks and shapes of the hazard rate curves were similar between bone and supraclavicular lymph nodes. Therefore, in this session, we will discuss "resect or not to resect" in several specific situations such as 1) for the patients with invasive T3 or resectable T4 2) for the patients with multi-station, bulky lymph nodes (not every) 3) for the patients with central lung cancer with possible sleeve lobectomy 4) for the old patients (>75 year-old) with comorbidity By the rapid development of the medical sciences, especially in cancer medicine, there would be fundamental changes in the diagnosis and management of N2 disease. Especially, improvement in systemic treatment would have critical impact on the surgical role in locally-advanced lung cancer. Moreover, if systemic tumor burden or minimal residual disease could be assessed at the earliest, surgery would be applied with higher benefit, and thus, the survival outcome would be significantly improved. Therefore, there should be more studies of combined local control (surgery) and systemic control (chemo and/or immunotherapy); either as adjuvant, neoadjuvant or salvage purpose; either with or without radiotherapy; participated by thoracic surgeons, to maximize the survival of the patients from dreadful disease. References 1. Kim HK, Cho JH, Choi YS, et al. Outcomes of neoadjuvant concurrent chemotherapy followed by surgery for non-small cell lung cancer with N2 disease. *Lung Cancer* 2016; 96:56-92 2. Lee J, Kim HK, Park BJ, et al. Recurrence Dynamics after Trimodality Therapy (Neoadjuvant Concurrent Chemoradiotherapy and Surgery) in Patients with Stage IIIA (N2) Lung Cancer. *Lung Cancer* (submitted)

Keywords: N2 disease, neoadjuvant, resection

MS 24 MANAGEMENT OF GGO-CONTAINING NODULE
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 24.01 NATURAL HISTORY OF GGO-CONTAINING TUMORS

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The natural history of GGO-containing tumors, i.e., subsolid nodules (SSNs), is a major concern not only in CT lung cancer screening, but in daily clinical practice. SSNs are classified into pure ground-glass nodules (GGNs) and part-solid GGNs on the basis of their consistency. SSNs are classified according to their status as transient or persistent. Articles in the literature related to the natural history or long-term follow-up results of SSNs are summarized in Table. In the largest CT lung cancer screening cohort reported to date, nonsolid nodules (synonymous with pure GGNs) and part-solid nodules were detected in 4.2% (2392 of 57,496) and 5.0% (2892 of 57,496), respectively, of the participants at baseline (Table). The numbers of SSNs reported in the articles ranged from 19 to 3433 (median, 139). The median follow-up periods ranged from 1.1 years to 12 years (median, 2.9 years). The percentages of pure GGNs that grew ranged from 3% to 58% (median, 15%). The percentages of lung cancers among the SSNs ranged from 1% to 71% (median, 7%). An inherent limitation of studies of the natural history of SSNs is that not all of the SSNs are pathologically confirmed. The changes in persistent SSNs on sequential thin-section CT images in the Research Center for Cancer Prevention and Screening (RCCPS) examinations have tentatively been classified into six types; increasing type, stable type, decreasing type, fluctuating type, sudden onset type, and overtaking type. Some of the SSNs were evaluated on the basis of semiautomatic volumetry. Although the natural history of SSNs had gradually been clarified, the complete natural history of SSNs as a whole remains unknown. In the current era of ultralow-dose chest CT at a chest x-ray equivalent dose, a lifelong follow-up study should be considered.

			SSNs			Grew	Lung Cancer
Author	Journal	Year	Total	Consis-tency, n	Follow-up Period (yr.)	n (%)	n (%)
Kodama	Ann Thorac Surg	2002	19	PGGN*, 19	Median, 2.7	11 (58)	5 (26)
Hiramatsu	J Thorac Oncol	2008	125	PGGN, 95	Median, 2.9	14 (15)	8 (6)
				PSN**, 30		12 (40)	
Silva	J Thorac Oncol	2012	76	PGGN, 48	Mean, 4.2	8 (17)	4 (5)
				PSN, 28		12 (43)	
Takahashi	Jpn J Radiol	2012	150	PGGN, 150	Mean, 5.5	19 (13)	8 (5)
Chang	Chest	2013	122	PGGN, 122	Mean, 4.9	12 (10)	11 (9)
Kobayashi	J Thorac Oncol	2013	108	PGGN, 82	Median, 4.2	29†(27)	25 (23)
				PSN, 26			
Matsuguma	Chest	2013	174	PGGN, 98	Mean, 2.4	14 (14)	53 (30)
				PSN, 76		27 (36)	
Lee	Respir Med	2013	175	PGGN, 143	Median, 3.8	28 (20)	26 (15)
				PSN, 32		18 (56)	
Attina	Radiol Med	2013	146	PGGN, 140	Mean, 2.3	41 (29)	5 (3)
				PSN, 6		6 (100)	
Kim	Ann Thorac Surg	2013	139	PGGN, 69	Mean, 3.7	2 (3)	7 (5)
				PSN, 70		21 (30)	
Tamura	J Thorac Oncol	2014	63	PGGN, 63	Mean, 2.2	29 (46)	45 (71)
Eguchi	Lung Cancer	2014	124	PGGN, 124	Median, 4.8	64 (52)	32 (26)
Scholten	Eur Respir J	2015	117	PGGN, 69	Median, 7.9	33≠	28 (24)
				PSN, 48		46≠	
Kakinuma	Radiology	2015	439	PGGN, 439	Median, 6.0	45 (10)	4 (1)
Silva	Diagn Interv Radiol	2015	95	PGGN, 95	Median, 1.7ø	18 (19)	n/a
Yankelevitz	Radiology	2015	2877	Nonsolid$, 2392^	Median[1]	1764&	84 (3)
				Nonsolid, 485^^	Median[2]	163&	
Lee	Eur Radiol	2016	213	PGGN, 136	Median, 2.3	18 (13)	49 (23)
				PSN, 77		24 (31)	
Zhao	Br J Radiol	2016	70	PGGN, 62	Median, 2.1	6† (9)	5 (7)
				PSN, 8			
Kakinuma	J Thorac Oncol	2016	1231	PGGN, 1046	Mean, 4.3	116 (11)	85 (7)
				HGGN***, 81		23 (28)	
				PSN, 104		45 (43)	
Cho	J Thorac Oncol	2016	453	PGGN, 438	Median, 6.4	11 (3)	7 (2)
				PSN, 15		4 (27)	
Henschke	AJR	2016	3433	PSN, 2892^	Median[3]	2325&	107 (3)
				PSN, 541^^	Median[4]	164&	
Sawada	Chest	2017	226	PGGN, 166	§, #	39†(17)	124(55)
				PSN, 60			
Mets	Eur Radiol	2017	89	PGGN, 63	Median, 1.6	35†(39)	n/a
				PSN, 26			

Footnotes. ¶ SSN, subsolid nodule; * PGGN, pure ground-glass nodule; ** PSN, part-solid nodule; n/a, not available. † This study did not report the numbers of pure and part-solid GGNs separately. ≠ Growth was calculated by comparing actual mass to mass when first detected and is expressed as a percentage. $ A synonym of PGG.; ^ Baseline; ^^ Annual repeat screening. ø Follow-up period of the "grew" group. [1] Among the 1764 cases in which the nonsolid nodules were stable or growing, the median time to pathologic diagnosis was 1.7 years; the median follow-up time in the cases without a pathologic diagnosis was 1.4 years. [2] The median time from the initial identification of the nonsolid nodules to pathologic diagnosis was 1.2 years; the median follow-up time in the cases without a pathologic diagnosis was 1.7 years. [&] This study did not report the number of SSNs that grew and number of stable SSNs separately. ***HGGN, heterogeneous GGN. [3] Among the 2325 cases in which the PSNs were stable or growing, the median time to pathologic diagnosis was 0.5 years; the median follow-up time in the cases without a pathologic diagnosis was 1.1 years. [4] The median time from the initial identification of the PSN to pathologic diagnosis was 0.8 years; the median follow-up time of 0.7 years for cases without pathologic diagnosis. § Fifty-seven patients had stopped receiving follow-up examinations after a median of 5.6 years because of the presence of stable disease in 42 and reduced disease in 15. # Forty-five patients were continuing to undergo follow-up examinations, and their median follow-up period was 12 years; 40 were stable and 5 showed growth.

Keywords: Subsolid nodules, Natural history, lung adenocarcinoma

MS 24 MANAGEMENT OF GGO-CONTAINING NODULE
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 24.02 WHAT TYPE OF SURGERY SHOULD BE SELECTED FOR GGO-CONTAINING TUMORS?

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A ground glass opacity (GGO) is a radiographic finding defined as hazy, increased attenuation of the lung with preservation of bronchial vascular margin. A subsolid nodule (SSN) includes pure ground glass nodules and partsolid nodules in which both solid and ground glass components are present. These nodules are nowadays more commonly found with the introduction of CT screening programs. The optimal management of patients with SSN is of growing clinical concern. The newly (1) introduced adenocarcinoma classification makes a clear distinction between pre-invasive lesions (atypical adenomatous hyperplasia), adenocarcinoma in situ (AIS: ≤ 3cm pure lepidic growth without invasion), minimally invasive adenocarcinoma (MIA: ≤ 3cm lepidic growth with ≤ 5mm invasion) and invasive adenocarcinoma (IA) of different subtypes. Preinvasive lesions or MIA have an excellent survival and might be treated with sublobar resection. IA (especially certain subtypes) are more aggressive and should be treated with lobar resection combined with systematic nodal dissection. **Pure GGO lesions** can be non-specific inflammation, fibrosis or neoplasm. Recent guidelines (2) recommends for pure GGO nodules ≥6mm follow-up scan at 6 to 12 months and then every 2 years until 5 years. In a retrospective study (3) 83 patients with pure GGO lesion that had surgery and proved to be adenocarcinoma were described. 79,5 % were non IA and 20,5 % (IA). In a multivariate logistic regression analysis both preop GGO size on CT and pleural retraction were predictive factors for IA. Pure GGO lesions ≥ 10 mm should be resected if they persist or grow on follow-up CT. **Partsolid nodules**. When a nodule is partially solid or when in a GGO lesion a solid part appears, the risk of IA increases. In a prospective multicentric study Suzuki et al looked at radiologic criteria for predicting pathologic early (non-invasive) adenocarcinoma (4). In this study, the consolidation/tumor (C/T) ratio was measured in lung and mediastinal window settings. Radiologic non-invasive longadenocarcinoma could be defined as a subsolid nodule ≤2cm with a (C/T) ratio of 0.25 or less. Asamura et al (5) re-evaluated the radiology pathology correlation in this study in term of the prognosis. The radiologic criteria of a C/T ratio of 0.25 or less in tumor ≤3cm as well as 0.25 or less in tumors ≤2cm could be used to define a homogeneous group of patients with an excellent prognosis after surgery. These criteria can be used to select patients with early lung adenocarcinoma in which a sublobar resection (wedge or segmentectomy) would be safely indicated. For lesions with a tumor diameter of 2.0cm and a C/T ration >0.25 a prospective randomized fase III study comparing lobectomy and segmentectomy is ongoing (6). The incidence of N2 disease in clinical T1-T2N0 was evaluated (7). The incidence of unforeseen N2 disease was 1.5% in pure GGO lesions. N2 disease was found in 4.3% of semi solid tumors and 12.6% in pure solid tumors. In a multivariate analysis, tumors with any GGO components were less likely to have N2 disease (Odds ratio 0.14, 0.001). A recent study (8) used a nomogram for predicting the risk of IA in patients with solitary peripheral subsolid nodules. In a multivariate analysis the occurrence of IA was significantly correlated with lesion size, spiculation, vascular convergence and pleural tag. There are different subtypes of IA. The micropapillary and solid types are aggressive subtypes with a high rate of N2 (9). These types cannot be used for sublobar resection. Huang et al (10) analyzed histology obtained by CT guided needle biopsy or EBUS. Concordant subtyping of adenocarcinoma between the predominant pattern on resections and biopsy section was only observed in 58.6% of the cases. For high grade adenocarcinoma detection, preoperative biopsy had a low sensitivity (16.5%). So preoperative obtained histology cannot show us which type of resection we should perform. The degree of invasion is often overestimated in frozen section. However, frozen section has a high specificity for micropapillary and subsolid pattern (11). If this subtype is found during surgery by frozen section, lobectomy and lymph node dissection should be performed. **Conclusion** By modern imaging subsolid nodules containing GGO lesions are more often seen. When the C/T ratio is more than 50% there is a high risk of IA with certain subtypes which are very aggressive. These lesions should be managed by lobectomy and lymph node dissection until results from prospective studies are known. For lesions ≤2cm, with C/T ratio ≤25% wedge or segmentectomy can be the appropriate intervention. When a limited resection is performed, the margins and the lymph nodes should be examined by frozen section. 1.Travis WD, Brambilla E, Noguchi M et al. 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Keywords: GGO lesions - Prediction of invasive adenocarcinoma - Sublobar resection-

MS 24 MANAGEMENT OF GGO-CONTAINING NODULE
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MS 24.03 WHEN TO OPERATE GGO-CONTAINING TUMORS?

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With the advent of Chest CT screening, the identification of abnormalities has increased substantially. In addition to very small nodules of indeterminate significance, "ground glass opacities" (GGO) are often seen. Numerous series have been collected around the world attempting to define characteristics that predict the malignant potential of these GGOs. It is clear that a substantial fraction includes a component of invasive adenocarcinoma and warrant resection for cure prior to developing disseminated cancer. This presentation will review the literature for developing a rational algorithm for selection of those patients requiring which operation, as well as review outcomes. 1. Radiological determinants of malignancy using high-resolution CT and CT/PET 2. Criteria for patient section for resection or observation 3. Techniques for pre-resection localization for intraoperative identification of lesion 4. Appropriate selection lesions for extent of resection (lobe, segment or non-anatomic wedge) 5. Approach for resection 6. Outcomes after treatment **Selected References** Matsunaga T, Suziki K, Takamochi K, Oh S. What is the radiological definition of part-solid tumor in lung cancer? Eur J Cardiothorac Surg 2017; 51:242-247 Eguchi T, Kondo R, Kakkami S, Matsushita M, Yoshizawa A, Hara D, Matsuoka S, Tkeda T, et al. CT attenuation predicts the growth of pure GGO nodules Lung Can 2014;84:242-247 Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. Early peripheral lung cancer: prognostic significance of GGO on thin section CT scan Ann Thorac Surg 2002;74:1635-9 Lee S, Leem C, Kim T, Lee K, Chung J, Jheon WS, Lee C. The long term follow-up of GGO detected on thin-section CT Respir Med 2013;107:904-10 Suzuki K, Shimohira M, Hashizume T, Ozawa Y, Sobue R, Mimura M, Mori Y, Ijima H, Watanabe K, Yano M, Yoshioka H, Shibamoto Y. Usefulness of CT-guided hookwire marking before VATS for small pulmonary lesions J Med Imag Rad Oncol 2014; 58:657-662. Mong-Wei L, Yao-Hui T, Yee-Fan L, Min-Shu H, Wei-Chun K, Jo-Yu C, Hsao-Hsun H, Yeun-Chung C, Jin-Shing C. Comuted tomography-guided patent blue vital dye localization of pulmonary nodules in uniportal thoracoscopy J Cardiovasc Surg 2016; 152:535-44 Fukui M, Suziki K, Matsunaga T, Oh S, Takamochi K. Surgical intervention for GGO-dominant lesions: observation or outright resection? Pan J Clin Oncol 2017;18:1-6 Cao C, Gupta S, Chandrakumar D, Tian D, Black D, Yan T. Meta-analysis of intentional sublobar resections versus lobectomy for very early stage non-small cell lung cancer Ann Cardiothorac Surg 2014; 3:134-141 Kodama K, Higashiyayma M, Tkami K, Oda K, Okami J, Maeda J, Koyama M, Nakayama T. Treatment strategy for patients with small peripheral lung lesions: Prospective study Eur J Cardiothoracic Surg2008; 34:1068-74 Yoshioka M, Ichiguchi O. Selection of sublobar resection for c-stage1A non-small cell lung cancer based on a combination of structural imaging by CT and functional imaging by FDG-PET Ann Thorac Cardiovasc Surg 2009; 15:82-8. Kohno T, Fujimoro S, Kishi K, Fujii T. Safe and effective minimally invasive approaches for small GGOs Ann Thorac Surg 2010; 89; 1114-7 Tsutani Y, Miyata Y, Nakayama H, Okurmura S, Adachi S, Yoshimura M, Okada M. Appropriate sublobar resection choice for GGO-dominant clinical stage 1A lung Adenocarcinoma Chest 2014; 145:66-71 Sook Y, Sung S, Mankoong M, Park K. The effectiveness of mediastinal node evaluation in a patient with GGO tumor J Thorac Dis 2016; 8:2617-2623 Wei S, Khao K, Guo C, Mei J, Pu Q, Ma L, Che G, Chen G, Wu

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MS 24 MANAGEMENT OF GGO-CONTAINING NODULE
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MS 24.04 POSSIBILITY OF RADIOTHERAPY FOR GGO-CONTAINING TUMORS

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Purpose/Objective(s): The popularization of computed tomography (CT) in clinical practice have increased a frequency of discovering ground-glass opacity (GGO)-containing tumor in lung. Surgery has been regarded as the general treatment including a purpose of histological examination for such tumors and its prognosis is better than that of solid-type tumors. Stereotactic body radiation therapy (SBRT) is a rapidly prevailing treatment modality in the radical treatment of mainly inoperable or high risk operable cases with stage I non-small cell lung cancer (NSCLC), but the most tumors treated with SBRT were solid type because SBRT has been performed principally for the pathology-proven tumors and it is generally difficult to acquire histological specimen in the tumors composed of GGO. Therefore a prognosis of the stage I NSCLC cases treated with SBRT when their tumors contained GGO has not been clear. The purpose of this presentation is to review the treatment outcomes for SBRT for the patients with GGO-containing tumor in our multi-institutional SBRT study group of Japanese Radiological Society (JRS-SBRTSG), and to discuss how we consider the validity of SBRT for them. **Materials/Methods:** GGO was defined as hazy opacity that does not obscure underlying bronchial structures or pulmonary vessels at high-resolution computed tomography. We have reviewed 174 patients (89 men, 85 women; mean age, 74 years) treated with SBRT whose lung tumor showed appearance of GGO accompanying solid component ratio to the whole tumor (S/T ratio) less than 50 % in diameter of the tumor and no metastases. SBRT was done because of the pathological proof, positive accumulation on PET study or growth of the tumor. In histology, 69 tumors were adenocarcinoma, 8 were squamous cell carcinoma, 5 were unclassified carcinoma and 92 cases were histology-unproven. The median tumor size was 23 mm (range, 9-53 mm). SBRT was performed using non-coplanar multiple static ports or dynamic arcs. A total dose of 40 -70 Gy (6-15 Gy / fraction) was prescribed in 4-10 fractions. Median biological effective dose (BED) was 108 Gy (range, 72-150 Gy) based on alpha/beta = 10 Gy. Survival, recurrence, and metastases rates were calculated using Kaplan-Meier method. **Results:** Median follow-up was 32 months. The 3-year local recurrence, regional lymph-node metastases, and distant metastases rates were 3.8%, 4.1%, and 8.6%, respectively. Mean S/T ratios of the subgroup with any recurrences and the subgroup with no recurrence were 22% and 4%, respectively. The rates of cause-specific and overall survival (OS) at 3 years were 98.1% and 85.6%, respectively. The 3-year OS rates of medically operable and inoperable subgroups were 96.2% and 85.6%, respectively. The 3-year OS rate of medically operable and histology-proven subgroup was 88.1%. The 3-year OS of female subgroup was 95.0% and it was significantly better overall survival rate than male. The treatment-related pneumonitis of grade 3 or more was observed in 3.4% of the total patients. **Summary and Discussion:** Natural course of GGO-containing tumor is much better than that of solid-type tumors. Sublober limited resection would be acceptable in the subgroup of stage I NSCLC if the tumor appears GGO for the most part because they have mostly no invasion nor metastases. SBRT is a so localized treatment only for the tumor that a study comparing SBRT versus limited surgery without regional lymph node resection might have a rationale of randomization for such candidates, however, we have to demonstrate the prognosis and risk factors regarding recurrence, survival, and late toxicity after SBRT with longer follow-up (more than 10 years). In conclusion, the outcomes of SBRT for patients with GGO-containing tumor (solid component was less than 50 % in total diameter) were excellent but some cases had local recurrence or metastases. GGO-containing in most of the tumor seldom produced local progression, lymph node metastases, or distant metastases after SBRT. Although more cases and longer follow up are mandatory, SBRT may be one of the radical treatment options for stage I NSCLC patients with GGO-containing tumor. We hope to have a further discussion regarding the validity of SBRT for them.

Keywords: stage I non-small cell lung cancer, ground-glass opacity (GGO), stereotactic body radiation therapy (SBRT)

MS 24 MANAGEMENT OF GGO-CONTAINING NODULE
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MS 24.05 POSSIBILITY OF CHEMOTHERAPY FOR GGO-CONTAINING TUMORS

P.E. Postmus

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The radiological term GGO or ground-glass opacity was established when high-resolution CT (HRCT) became part of standard practice, and describes "a hazy attenuation of lung, with preservation of bronchial and vascular margins: caused by partial filling of air spaces, interstitial thickening, partial collapse of alveoli, normal expiration, or increased capillary blood volume..." (1). As such GGO is a nonspecific finding but depending on the clinical circumstances it may suggest a specific diagnosis and have consequences for the diagnostic and therapeutic approach. Most primary lung tumours present with masslike areas of consolidation, however there are other patterns. A specific subtype of adenocarcinoma may present as GGO, and this was described as bronchioloalveolar carcinoma (BAC) (2). It reflects the unique lepidic growth pattern along the alveolar septa with a relative lack of acinar filling. The classification BAC was used for a broad spectrum of tumours including small non-invasive peripheral lung tumours, invasive adenocarcinoma with minimal invasion, mixed subtype invasive adenocarcinoma, mucinous and nonmucinous subtypes, and widespread disease. As in this larger group GGO is present in only a minority, it is difficult to conclude from the chemotherapy trials done specifically in BAC (3) what the efficacy of chemotherapy in tumours with as feature GGO is, nor has the pathological feature of lepidic growth been reported in these studies. Overall the response rate in BAC of single agents seems not to be different from other types of NSCLC. At a later stage, it seemed that gefitinib was especially effective in the non-mucinous subtype (4), in retrospect this might be explained by the molecular characteristics of both. EGFR mutation was more related to lepidic growth, whereas KRAS was especially found in mucinous types (5). It became clear that the term BAC leads to confusion and is representing a very heterogeneous group of tumours. It was therefore recommended to discontinue the use of the term BAC (6), and use a more descriptive classification based on histological findings. Within this new grouping the radiological description of ground-glass opacity was related to the pathological pattern of adenocarcinoma: pure GGO would favour adenocarcinoma in situ (AIS) or possibly minimally invasive adenocarcinoma (MIA), and GGO with a solid component > 5 mm in diameter would favour lepidic adenocarcinoma (7). The natural course of pure GGO or GGO with a small solid component is rather benign. In a large Japanese cohort followed for 4.3±2.5 years (mean) the frequency of change from pure GGO towards a - still small - solid component was found in 6.6% (69 out of 1046), of the cases initially diagnosed with a very small solid component change into part-solid nodules was seen in almost 20% (16 of 81) (8). All these observations come from resected tumours and cannot be diagnosed in small biopsies, this makes it difficult to characterize more advanced adenocarcinoma in the same way. The likely most GGO containing advanced tumours will be those diagnosed with (dominant) lepidic growth (9). Reports of chemotherapy efficacy are infrequent but do not show a real difference in sensitivity if treated with one of the commonly used regimens carboplatin – paclitaxel (10). Although the LACE-Bio study contains only small numbers of cases with lepidic growth, combining these patients with the ones with the prognostically less unfavourable histology (papillary, acinar) failed to demonstrate benefit of adjuvant chemotherapy (11). The frequency of finding more than one GGO (with or without a solid component) is rather high and reported as almost 30% (12). If this is in a patient with stage IV NSCLC it is questionable whether these are separate primaries or metastases. The behaviour of these lesions has not been systematically reported, personal observations confirm the rather indolent role of these lesions, usually without any pathological proof of malignancy, and no change during systemic therapy for an other stage IV tumour. The question whether the presence of GGO as such, either as part of the stage IV tumour or as a different lesion, should affect the choice of systemic therapy can not be answered. References: 1. Austin JHM, Müller NL, Friedman PJ et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology 1996; 200: 327-331. 2. Jang HJ, Lee KS, Kwon OJ et al. Bronchioloalveolar carcinoma: focal area of ground-glass attenuationat thin-section CT as an early sign. Radiology 1996; 199: 485-488. 3. Miller VA, Hirsch FR, Johnson DH. Systemic Therapy of Advanced Bronchioloalveolar Cell Carcinoma: Challenges and Opportunities. J Clin Oncol 2005; 23:3288-3293 4. 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Keywords: GGO, chemotherapy

MS 25 NOVEL MOLECULAR TARGETS (KRAS/MET/NOVEL FUSIONS): DRUGGABLE OR NOT?
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 25.02 KRAS-TARGETED THERAPY OR ANGIOGENESIS: STILL A VIABLE TARGET?

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NSCLC is a heterogenous disease withvariable molecular mutations. Vi-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS) is one of the most common oncogenic drivers, especially in lung cancer, found in around 25-30% adenocarcinomas. The other molecular abnormalities related to RAS pathway are EGFR (10-23%), BRAF (2%), MET (2%), HER2 (1%) and NRAS (0.2%). Within KRAS, the most common mutations are G12C (40%), G12V (21%), G12D (17%), G12A (10%) and other (12%) G12 and G13 mutations [Dogan. Clinical Cancer Research 2012; 18: 6169-6177]. KRAS mutations are associated with poorer outcomes in NSCLC. Renaud et al, showed that KRAS mutant patients had worser outcomes compared to wild type cases[1]. KRAS may be a negative predictor of responsiveness to cytotoxic therapy based off of retrospective data. In addition, Renaud and colleagues have shown that KRAS mutations may be predictive of resistance to radiation therapy. Identifying ways to target these KRAS mutations may lead to benefit for patients in combination with other traditional means of treatment. Directly blocking RAS activity has remained difficult to attain, due to a variety of mechanisms and yet to demonstrate efficacy clinically. Therefore, much more focus has been spent on downstream targets of KRAS. Selumetinib an oral inhibitor of the mitogen-activated protein kinase kinase (MEK) 1/2 had promising phase II results in combination with docetaxel in comparison to docetaxel alone. Unfortunately, in the multicenter Phase III, SELECT-1 trial with 510 patients, PFS and OS were no different in the selumetinib and docetaxel arm versus docetaxel alone. This may be in part due to an increase in RAF-depedent MEK phosphorylation that may interfere with its efficacy. Combining inhibitors that target different components or parallel pathways have yielded success in other tumors like melanoma with combination MEK and BRAF inhibition. For KRAS mutant tumors, the PI3K-AKT- mTOR pathway has also been examined as it has been thought it can bypass resistance to MEK inhibition. The combination of MEK in addition to PI3K-aKT-mTOR has yet to yield any clinically impactful results. Inhibtion of the cysteine residue on KRAS G12C, which makes up more than 40% of KRAS mutants, has been shown to have some activity preclinically [2, 3] Our preliminary data shows that, KRAS is frequently associated with co-occuring mutations. The most common of these were TP53 (n=15, 25%), ATM (n=9, 15%), LRP1B (n=9, 15%), ARID1A (n=8, 13%), STK11 (n=8, 13%), ARID1B (n=7, 12%), TERT (n=7, 12%), EGFR (n=6, 10%), RBM10 (n=6, 10%), SPTA1 (n=6, 10%). We still are not clear on the role of co-mutations and their specific function as sensitizers or agents resistance. It was previously shown that KRAS plus TP-53 mutations had impaired response to docetaxel monotherapy. The addition of selumetinib provided substantial benefit in mice models [4]. Also, STK11 mutations in conjunction with KRAS mutant NSCLC has been shown to infer resistance to PD-1/PDL-1 blockade [5]. Lung cancer frequently exhibits upregulation of angiogenesis and has been reported to be associated with a negative prognostic factor. Over the past decade, novel insights into the role of angiogenesis in NSCLC tumor growth and progression have provided a rationale for the development of anti-angiogenic agents. The use of anti-angiogenic agents to treat NSCLC gained clinical interest in 2006, when the results of the Eastern Cooperative Oncology Group (ECOG) Trial 4599 were published in the New England Journal of Medicine and showed for the first-time improved overall survival(OS) and progression-free survival after the addition of bevacizumab (Avastin, Genentech), a humanized monoclonal antibody that inhibits the process of angiogenesis by binding to the vascular endothelial growth factor A (VEGF-A) protein, to treatment with carboplatin and paclitaxel in 878 patients who had recurrent or advanced NSCLC [6]. Since then, no other anti-angiogenic agent (such as sunitinib, sorafenib, etc.) has been able to demonstrate improved OS for patients with lung cancer. This may be in part because the mechanisms of actions for those drugs is completely different from bevacizumab; they work by inhibiting the internal tyrosine kinase domain of the VEGF receptor and are also not completely selective for the VEGF receptor and also hit other targets (such as PDGF, FGFR, etc.) [6]. This may play a role in the increased toxicity for these inhibitors and the subsequent lower OS. Since the recent positive data showing benefit of first-line carboplatin, pemetrexed, and pembrolizumab may lead to expedited FDA approval, the utility of anti-angiogenic drugs may enter a renaissance as a second-line therapeutic option. However, another consideration has to be made in the pursuit of improved anti-angiogenic drugs where the clinical and financial "value" for the patient are factored in clinical decision making. Though the VEGF/VEGFR pathway is seen as a crucial mediator of tumor survival and growth, the treatments currently available are overshadowed by excessive costs and several cost-effective analyses of bevacizumab have shown that the use of the drug can cost up to 350,000 per life-year gained [7].

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Keywords: lung cancer, KRAS, angiogenesis

MS 25 NOVEL MOLECULAR TARGETS (KRAS/MET/NOVEL FUSIONS): DRUGGABLE OR NOT?
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 25.03 MET-RELATED MOLECULAR TARGETS

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MET activation in non-small cell lung cancers (NSCLCs) can occur via mechanisms including mutation and amplification. *MET* exon 14 splicing alterations and *MET* amplification are clinically actionable genomic alterations. Response to MET-directed targeted therapy has been reported for both subsets. In a phase 1 study of crizotinib for patients with *MET* exon 14-altered NSCLCs, the overall response rate (ORR) was 39% and the median progression-free survival was 8 months (Drilon et al, ASCO 2016). In the same phase 1 study, the ORR for crizotinib in patients with *MET*-amplified NSCLC was 17% and 50% for tumors with a FISH *MET/CEP7* ratio of >2.2 to <5 and ≥5, respectively (Camidge et al, ASCO 2014). Furthermore, acquired *MET* amplification is associated with resistance to EGFR tyrosine kinase inhibition in *EGFR*-mutant lung cancers. Response to combined EGFR- and MET-directed therapy has been reported in patients with *EGFR*-mutant lung cancers with acquired resistance to prior EGFR tyrosine kinase inhibitor therapy. Prospective clinical trials of various MET inhibitors as single-agents or in combination with other therapies are ongoing. A number of different MET inhibitors have been tested in the clinic, including multikinase inhibitors with activity against MET such as crizotinib and cabozantinib, MET-selective inhibitors such as capmatinib, and MET antibodies such as onartuzumab and embituzumab. Newer agents such as MET antibody-drug conjugates are being explored. Data on acquired resistance to MET-directed targeted therapy has begun to emerge. The *MET* D1228N and D1228V kinase domain mutations have been identified as acquired mechanisms of resistance to MET tyrosine kinase inhibition (Heist et al, J Thoracic Oncol 2016; Bachall et al, Cancer Discov 2017)). The detection of *MET* mutation and amplification in the clinic is thus important, but is associated with specific challenges, and requires a comprehensive approach to testing. Notably, molecular profiling should not be restricted to the classic population of younger, never or former light cigarette smoker patients with advanced lung adenocarcinomas where other drivers such as sensitizing *EGFR* mutations and *ALK* or *ROS1* rearrangements are enriched; *MET* exon 14 alterations, for example, are found in older patients with a more substantial prior smoking history, and in sarcomatoid carcinomas of the lung. The role of MET immunohistochemistry in selecting patients for MET-directed targeted therapy in the absence of comprehensive molecular profiling remains controversial, although the experience with this approach in prior prospective clinical trials has been disappointing. Advances have clearly been made in the development of MET-directed targeted therapy for subsets of patients with advanced NSCLCs that are hopefully moving the field closer to the regulatory approval of one or more these agents in the future.

Keywords: MET exon 14, MET targeted therapy, MET amplification

MS 25 NOVEL MOLECULAR TARGETS (KRAS/MET/NOVEL FUSIONS): DRUGGABLE OR NOT?
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 25.05 NOVEL FUSIONS

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Chromosomal rearrangements or deletions can generate novel gene fusions that lead to the expression of chimeric proteins with oncogenic activity in lung and other cancers. The paradigm for gene fusions in lung cancer is the *EML4-ALK* gene fusion which is found in approximately 5% of lung adenocarcinomas.[1] Once identified, drug development for this target proceeded rapidly and crizotinib was the first approved tyrosine kinase inhibitor for patients with ALK+ non-small cell lung cancer based on its ability to generate substation objective response rates and prolonged progression free survival (NSCLC).[3,4] The development of CNS penetrant and/or

next generation ROS1 inhibitors including lorlatinib, entrectinib and TPX-0005 is ongoing. RET gene fusions are also found in 1-2% of NSCLC, but the use of multiple different RET inhibitors have failed to reproduce the success of targeting ALK or ROS1 fusions.[5] The development of more selective RET inhibitors such as LOXO-292, BLU-667, and RXDX-105 are currently in clinical trials for RET+ lung and other cancers. *NTRK1* fusions were recently identified in NSCLC and homologous NTRK2 and NTRK3 fusions are found in multiple tumor types.[6,7] Early clinical trials of larotrectinib showed an impressive objective response rate of 76% for 12 different tumor histologies harboring *NTRK1/2/3* fusions and the CNS-penetrant entrectinib is similarly being evaluated in a basket trial. Other rare, novel fusions have recently been identified in NSCLC including EGFR fusions or MET fusions.[7] Early evidence suggests that these fusions may also respond to cognate TKIs. *EGFR* fusions break the paradigm of *ALK* and *ROS1* fusions in which the 5' end of ALK or ROS1 is replaced with the 5' portion of another gene. *EGFR* fusions retain most of the EGFR gene, with the unrelated gene sequencing fusing at the 3' end of *EGFR*. A related oncogenic *EGFR* mutation in which the kinase domain of *EGFR* is duplicated in tandem has also been described and appears responsive to EGFR TKIs.[7] Additional fusions involving the receptor tyrosine kinase (RTK) encoding genes *AXL*, *PDGFRA, and ERBB4* fusions have been described, but little is known about the true incidence in lung cancer.[8,9] The fusions described thus far all involve genes that encode RTKs, but additional gene fusions have also been identified in lung cancer including *BRAF f*usions.[7,9] BRAF fusions replace the 5' region of BRAF, including the Ras-binding domain (RBD), with sequences from another gene. Anecdotal evidence suggests that these alterations may be responsive to MEK inhibition. Analogous splice alteration which remove a region including the RBD have also been described in cancer and are oncogenic. Finally, gene fusions involving NRG1, which encodes the HER3/4 ligand neuregulin-1, have been described, mostly in invasive mucinous adenocarcinomas of the lung.[9,10] Several challenges exist to the development of targeted therapies for these novel fusions. Even in the era of next-generation sequencing tests these alterations may go undetected due to limited testing of genes to those with approved therapies (*ALK*, *ROS1*, *EGFR*, and *BRAF*) and not all assays are designed to detect all of these alterations. Furthermore, the rarity of some of these alterations may make clinical trials for these novel fusions less appealing, although amalgamating some of these alterations with analogous mutations, e.g., *MET* gene fusions with *MET* exon 14 splice alterations or *MET* gene amplification, may allow for a more rapid path to approval. References 1. Chia PL, Mitchell P, Dobrovic A, et al: Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. Clin Epidemiol 6:423-32, 2014 2. Camidge DR, Bang YJ, Kwak EL, et al: Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. The lancet oncology 13:1011-9, 2012 3. Davies KD, Le AT, Theodoro MF, et al: Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 18:4570-9, 2012 4. Shaw AT, Ou SH, Bang YJ, et al: Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371:1963-71, 2014 5. Gautschi O, Milia J, Filleron T, et al: Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry. J Clin Oncol 35:1403-1410, 2017 6. Vaishnavi A, Capelletti M, Le AT, et al: Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nature medicine 19:1469-72, 2013 7. Stransky N, Cerami E, Schalm S, et al: The landscape of kinase fusions in cancer. Nat Commun 5:4846, 2014 8. Seo JS, Ju YS, Lee WC, et al: The transcriptional landscape and mutational profile of lung adenocarcinoma. Genome Res 22:2109-19, 2012 9. Nakaoku T, Tsuta K, Ichikawa H, et al: Druggable oncogene fusions in invasive mucinous lung adenocarcinoma. Clin Cancer Res 20:3087-93, 2014 10. Fernandez-Cuesta L, Plenker D, Osada H, et al: CD74-NRG1 fusions in lung adenocarcinoma. Cancer Discov 4:415-22, 2014

Keywords: gene fusions, Oncogenes, Tyrosine kinase inhibitors

MS 26 RE-MODELING MICROENVIRONMENT MIMICKING HUMAN CANCER
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 26.01 THERAPEUTIC STRATEGIES TARGETING CANCER STEM CELLS

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Cancer stem cells (CSCs) are a subset of tumor cells that are responsible for initiating and maintaining the disease. In the clinical point of view, the most important characteristics of CSCs include their resistance to various therapeutic interventions1). However, the underlying mechanisms of the resistance remain unclear. CD44 has been identified as a cell surface marker associated with cancer stem cells (CSCs) in several types of epithelial tumor. We have recently found that expression of CD44, in particular variant forms of CD44 (CD44v), contributes to the defense against reactive oxygen species (ROS) by promoting the synthesis of reduced gluathione (GSH), a primary intracellular antioxidant. CD44v interacts with and stabilizes xCT, a subunit of a glutamate-cystine transporter, and thereby promotes the uptake of cystine for GSH synthesis2). Therefore, ablation of CD44 reduced GSH levels and increased ROS levels, leading to suppression of tumor growth and metastasis in both transgenic and xenograft tumor models 3,4). Our findings reveal a novel function for CD44v in protection of CSCs from high levels of ROS in the tumor microenvironment 5). Expression of CD44v and xCT is associated with tumorigenesis and therapeutic resistance 6, 7). Based on these preclinical findings, we conducted clinical trials using an xCT inhibitor, sulfasalazine, for cancer patients having advanced gastric cancer and lung cancer. The clinical trials for gastric cancers revealed that sulfasalazine treatment reduceed the number of CD44v-positive cells in post-treatment tumor tissue 8,9). In terms of the clinical trial for lung cancer, chemotherapy-naive patients with advanced non-squamous nonsmall cell lung cancer were enrolled in a dose-escalation study (standard 3 + 3 design) of SASP in combination with cisplatin and pemetrexed10). Fifteen patients were enrolled in the study and dose-limiting toxicity was observed in one of six patients at a SASP dose of 1.5 g/day, two of five patients at 3 g/day, and two of three patients at 4.5 g/day. The maximum tolerated dose was thus 3 g/day, and the recommended dose was 1.5 g/day. The overall response rate was 26.7% and median progression-free survival (PFS) was 11.7 months, much longer than that for cisplatin–pemetrexed alone in previous studies. It is possible that the prolonged PFS was due to a sulfasalazine-induced reduction in the number of CD44v-positive CSCs that are the origin of disease recurrence. **References:**

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MS 26.02 INNATE IMMUNE MICROENVIRONMENT

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A better understanding of the interaction between tumors and the immune microenvironment has led to the successful development of immunotherapies for tumors traditionally considered poorly immunogenic, such as non-small cell lung cancer (NSCLC). Clinically approved immunotherapies for lung cancer are based on antibodies able to reactivate cytotoxic T cells by targeting the PD-1/PD-L1 immune checkpoint. However, the substantial proportion of tumors refractory to these treatments, together with the limited predictive value of PD-L1 expression, evidences the existence of additional immune suppressive regulatory systems. This calls for a more detailed understanding of the immune cell landscape related to lung tumors. Some studies have begun to dissect the details of immune cell distribution in lung cancer lesions using multiscale immune profiling strategies. Along with adaptive immune alterations in T cells, significant innate immune cell changes have been identified (1). We have recently reviewed the role played by the innate immune system in supporting tumor-promoting activities and an immunosuppressive

microenvironment (2). Innate immunity includes soluble components and immune cell populations, such as myeloid cells. Specific subpopulations of myeloid cells have been identified as specialized immunosuppressive cells. These myeloid-derived suppressor cells (MDSCs) are immature myeloid cells arrested in different stages of differentiation. The recognition of these cells as a defined cell lineage remains controversial, but their cancer-specific phenotypic and functional characteristics are manifest (3). Chronic inflammation factors released by tumors induce the accumulation of these immature cells in the bone marrow, which are released to the circulation and recruited to tumors. MDCSs are thought to be major contributors to T-cell exhaustion. They deplete the tumor microenvironment of amino acids essential for T cell proliferation (e.g. arginine) and produce immunosuppressive cytokines (e.g. IL10 and TGFβ). Increased levels of MDSCs have been described in patients with NSCLC, are associated with poor prognosis and can mediate resistance to chemotherapy (4). Interestingly, in tumor models, accumulation of MDSCs has been proposed as a contributor to the incapacity of the anti-PD-1/PD-L1 blockade to completely reverse the suppressive activity (5). Therefore, stimulation of effector T cells while blocking the immunosuppressive activity of MDSCs represents a rational immunotherapy combination potentially effective for lung cancer. Several agents used in conventional cancer chemotherapy (e.g. gemcitabine, 5-fluorouracil or cyclophosphamide) have been found to reduce MDSC numbers and can be used to deplete this cell subpopulation. However, the use of these drugs results in a profound and unpredictable remodeling of the myeloid cell compartment in the tumor stroma, and careful evaluation of the appropriate timing and dosing is required (6). An alternative strategy recently proposed by us to successfully reverse the tumor immunosuppressive microenvironment is based on the inhibition of the complement system, another essential element of innate immunity. The complement system has developed as a first defense against pathogens or unwanted host elements. The three major pathways of complement activation (the classical, alternative, and lectin pathways) converge in the cleavage of C3 into C3b. C3b deposition leads to the formation of C3 convertases that amplify both opsonization and the complement response, and eventually promote C5 convertase formation and assembly of the membrane attack complex. In addition, enzymatic cleavage of C3 and C5 releases C3a and C5a, two multifunctional immunomodulators. Traditionally, tumor-associated complement activation has been considered as part of the body's immunosurveillance against cancer. However significant work in recent years has identified new and surprising activities for complement within the tumor microenvironment. In the context of chronic inflammation, complement elements can promote an immunosuppressive response, induce angiogenesis, and activate cancer-related signaling pathways. In the seminal study that shifted the paradigm, Markiewski et al. reported that complement deficiencies were associated with impaired tumor growth in a syngeneic model of cervical carcinoma (7). This study demonstrated that the immunomodulator C5a, generated after complement activation within the tumors, is able to hamper antitumor CD8 T cell-mediated responses. Importantly, this activity was associated with the accumulation of MDSCs in the tumor stroma. In the case of lung cancer, reduction of tumor growth after blockade of the C5a receptor-1 (C5aR1) is accompanied by a decrease in the expression of immunosuppressive molecules and, again, a diminution in the percentage of MDSCs (8). These studies reveal the important role played by C5a/C5aR1 signaling in tumor immunity, and point to this pathway as a potential therapeutic target in the context of checkpoint inhibition. To support this hypothesis, we have recently evaluated the therapeutic efficacy of the combined administration of anti-PD-1 and anti-C5a drugs in a variety of syngeneic models of lung cancer. We demonstrated that the combination of C5a and PD-1 blockade synergistically impairs lung cancer growth and metastasis. This therapeutic effect is accompanied by a negative association between the frequency of CD8 T cells and MDSCs within the tumors, which may result in a more complete reversal of CD8 T-cell exhaustion (9). These studies suggest that inhibition of complement may overcome tumor resistance in cancer immunotherapy, providing support for the clinical evaluation of anti-PD-1 and anti-C5a drugs as a novel combination therapeutic strategy for lung cancer. In conclusion, immunotherapy strategies tailored to restore innate immune modifications might recondition the tumor immunosuppressed niche, strengthening anti-tumor T cell immunity after immune-checkpoint blockade. A more comprehensive knowledge of the dynamic spatiotemporal interactions between the tumors and the microenvironment would be required to predict response, facilitate further investigations in this field, and extend the benefit of immunotherapies to most patients. **References** 1. Lavin Y et at. *Cell* 2017;169:750-765. 2. Berraondo P et al. *Immunol Rev* 2016;274:290-306. 3. Escors T et al. *Oncoimmunology* 2013;2:e26148. 4. Huang A et al. *Cancer Immunol Immunother* 2013;62:1439-1451. 5. 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Keywords: Complement system, Immunotherapy, Innate immune microenvironment

MS 26 RE-MODELING MICROENVIRONMENT MIMICKING HUMAN CANCER
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MS 26.04 PDX MODEL

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The tumor microenvironment differs significantly from the controlled environment of in vitro cell culture. Whereas cell lines are typically grown in plastic vessels containing a pH buffered, nutrient rich liquid medium with 10% fetal bovine serum and incubated at 37 ºC and 5% CO_2, cancer cells in tumors experience different oxygen tension, growth substrate, nutrient, waste, and growth factor gradients, pH, and the presence of stromal support cells and infiltrating immune cells. The process of establishing a new cell line requires adaptation to this environment, which results in loss of genetic heterogeneity as well as irreversible epigenetic reprogramming that is maintained even when cultured cancer cells are re-introduced to an in vivo setting. Patient-derived xenografts (PDX) are direct human tumor xenografts established and maintained exclusively in mouse hosts. While these models can never perfectly recapitulate an autochthonous human tumor, they are increasingly used as tools in cancer research due to their utility in modeling therapeutic response with higher fidelity than either cell lines or cell line xenografts. A growing interest in defining the role of the tumor microenvironment and in testing the efficacy of immunotherapy in vivo has driven advances in PDX model development. The tumor microenvironment consists of stromal cell components including blood vessels, fibroblasts, and infiltrating immune cells as well as extracellular matrix, growth factors, and nutrients. In PDX, components of the tumor microenvironment are either provided by the mouse host or are excreted by the tumor cells themselves. However, paracrine effects between tumor and stroma may not be entirely replicated in a mouse host due to a lack of cross-species cytokine reactivity. The absence of compatible stroma may bias PDX engraftment toward tumors that are less dependent on paracrine factors or which are more adept at recruiting mouse stromal support cells through enhanced expression of mouse reactive factors. It remains a significant challenge to accurately assess the mechanistic activity of therapeutic approaches designed to inhibit these interactions in the absence of human tumor stroma. Anatomical context can also have significant impact on PDX tumor biology. PDX can be established as subcutaneous flank tumors or at any of a variety of orthotopic sites. Lung PDX are amenable to orthotopic growth in the lung, and can thus be used to model lung cancer growth and metastasis within its normal anatomical context. Orthotopic tumors can have vastly altered metastatic potential and organ preference as well as differential response to anti-cancer therapeutics in comparison to subcutaneous flank tumors. One of the primary limitations of PDX as a model for cancer is the need to use immunocompromised mouse hosts. The degree to which the immune system can be modeled with PDX is dependent on the mouse host chosen and the type of human immune cells used to reconstitute the human immune cell component. PDX can be established in a great variety of different strains of immunocompromised mice including athymic nude mice, severe combined immune deficiency (SCID) and non-obese-diabetic (NOD)-SCID strains, Rag null strains, and profoundly immunocompromised strains in which IL2-Rγc has been disrupted (NSG, NOG, BRG). Each of these strains differs with respect to the type and function of hematopoietic cells. For example, athymic nude mice have intact natural killer (NK) cells, whereas NSG mice do not; NSG mice therefore develop primary tumors and metastases at a much faster rate. Humanized mice are immunocompromised mice that have partially reconstituted human immune components for the purposes of modeling the behavior of the human immune system in a cancer context. NSG, NOG, and BRG mice have been engrafted with isolated peripheral blood mononuclear cells (PBMC) or tumor infiltrating lymphocytes (TIL) primarily to study mechanisms of lymphocyte recruitment; however, a major limitation of this approach is the rapid onset of graft versus host disease in the mouse host. Alternatively, different strains of mice can be engrafted with human CD34+ hematopoietic stem cells (HSC), which results in mouse hosts with fully human lymphocytes, monocytes, dendritic cells and in some cases NK cells. A variety of mouse strains engineered to express human cytokines such as IL-3 and GM-CSF have been developed to promote improved functional human immune system components. PDX models of lung cancer are growing in complexity, variety, and sophistication. These in vivo cancer models will be an integral component in a suite of tools for studying many aspects of lung cancer biology in a research environment. Recent advances in the humanization of mouse hosts promises texpand the possibilities of studying cancer immunology and immunotherapy of human tumors in an experimental setting in vivo.

Keywords: PDX, Xenograft

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MS 26.05 IN VITRO MODEL OF EARLY PROGRESSION IN SCLC

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The abundance of somatic alterations and their heterogeneity between SCLC patient tumors present the immense scientific and clinical challenges. Functional characterization of recurrent mutations in SCLC is an essential step towards understanding the pathogenesis. However, it remains extremely difficult due to the lack of systematic and informed ways of defining oncogenic drivers, especially those involved in early stage tumor development. While the inaccessibility of precancerous lesion in the patients has precluded characterization of lung cancer mutations, we have developed a precancerous cell-based model of SCLC development as a streamlined approach for characterizing novel mutations and determining mutation-driven oncogenic pathways [Kim et al. 2016, Genes and Development]. Using compound transgenic mice expressing neuroendocrine specific GFP in the GEMM of SCLC (*Chga-GFP/Rb/p53/Rbl2*), we isolated pulmonary neuroendocrine cells one month after adenoviral Cre-mediated tumor induction, at which time the lungs did not show macroscopic lesions (Figure 1). Notably, these cells from an early stage of tumor development grew as adherent monolayers in culture and did not form subcutaneous tumors in nude mice, whereas tumor cells formed floating aggregates and formed the subcutaneous tumors. These findings indicated that these neuroendocrine cells, lacking *Rb* and *p53*, were immortalized but not transformed. Therefore, we postulated that these cells were precancerous cells of SCLC (preSC). We then tested whether preSC could be transformed by an oncogene, using a retroviral vector carrying cDNA of L-Myc, one of the most frequently amplified genes in SCLC. The preSC transduced

with retroviral L-Myc (L-Myc-preSC) formed spheres characteristic of SCLC cells in culture and palpable tumors resemble primary SCLC in the flanks of nude mice, whereas GFP-preSCs (control) were morphologically identical to uninfected preSC and did not form aggregates and subcutaneous tumor (Figure 2A). Comparative expression profiling of preSCs and L-Myc-preSC or tumor cells permitted identification of the genes and pathways related to oncogene-driven tumor progression. Defining the MYC-driven oncogenic pathways led to a preclinical test of an existing drug that successfully targeted human and mouse SCLC tumors. Furthermore, using this preSC-based model in combination with CRISPR/Cas9 methods of gene targeting and *in vivo* models, we found that several loss-of-function mutations found in the SCLC tumors were sufficient to cause the tumorigenic progression of preSCs (Figure 2B). In conclusion, this engineered preSC-based model facilitates functional validation of the recurrent mutations in SCLC and discovery of biomarkers and molecular pathways that will be further explored for mechanistic elucidation and targeted therapies.

Figure 1. Isolation of precancerous cells (preSC) from the SCLC GEMM

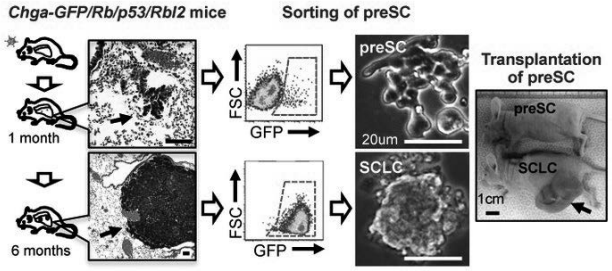
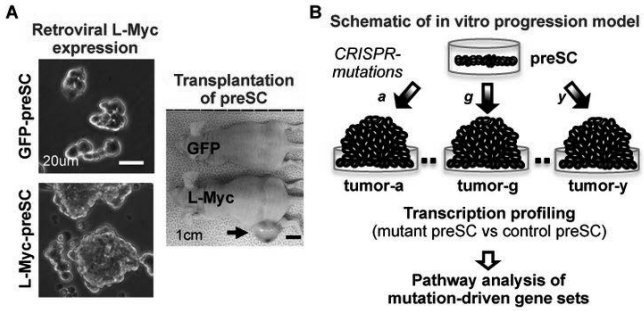


Figure 2. Genetic engineering of preSC for testing somatic alterations



MS 27 ENGAGING PATIENTS IN RESEARCH: BEST PRACTICES
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 27.02 LUNGMATCH: DEVELOPING A PATIENT-FRIENDLY, PERSONALIZED EDUCATION AND NAVIGATION PROGRAM TO INCREASE PARTICIPATION IN CLINICAL RESEARCH

J. King

Science & Research, Lung Cancer Alliance, Washington/DC/US

It is widely recognized that patient participation in clinical research is a significant challenge, with only less than 5% of adult patients with cancer entering on clinical trials. This issue is becoming exacerbated in the field of lung cancer. With the advent of new therapeutic options and strategies accompanied by endless potential combinations of these approaches, there are more important trials and research studies that need to be done than patients available to participate in them. To address this problem, Lung Cancer Alliance developed a unique, innovative program known as LungMATCH that combines direct patient services with increasing enrollment to clinical studies. LungMATCH provides patient education and navigation through the changing treatment landscape in lung cancer while informing and educating patients about research opportunities that they can discuss with their treatment team. There are multiple programs under the LungMATCH umbrella. These include a molecular testing service where patients can initiate the process of molecular testing themselves, a novel patient-friendly online clinical trial matching widget, and phone-based personalized treatment and trial specialists who are knowledgeable about the state of lung cancer today and the many clinical trials available. These specialists can empower a patient or caregiver to have an informed conversation with their treatment team. Notably, while providing the community with much-needed navigation services, the program also aims to accelerate research discoveries through patient enrollment on a registry protocol for the molecular testing component and increasing patient accrual to clinical trials. In the first six months since launch, there have been barriers to overcome and lessons learned but many successes. Over 50 patients have been referred to the molecular testing program. More than 10 times as many users are viewing clinical trial search results compared to a previous clinical trial matching tool. Patients who speak with the trial navigators report having conversations about clinical trials with their healthcare providers much more frequently than other callers. These initial data indicate that the program is filling a need in our community and can help provide support to patients and caregivers while accelerating lung cancer research.

Keywords: clinical trials, molecular testing, patient advocacy

MS 27 ENGAGING PATIENTS IN RESEARCH: BEST PRACTICES
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MS 27.03 LUNG CANCER REGISTRY: USING PATIENT DATA TO IMPROVE OUTCOMES AND QUALITY OF LIFE

D. LeDuc

Addario Lung Cancer Foundation, San Carlos/CA/US

Background: Decision makers in research, industry, policy and health-care settings are actively seeking robust sources of patient data to inform their practices. Patient registries are ideally positioned to capitalize on this growing interest by building high-impact source of patient information. Registries give patients a direct means to participate in the care continuum, leveraging their input and insights to focus priorities and improve outcomes. Definition: Patient registries are organized systems designed to directly involve patients in the collection of their disease data and engage the medical community in the analysis and use of this data to improve lung cancer patient care. By creating a centralized registry of robust, on-going data to which patients, health-care professionals, researchers, industry, and policy makers have open access, registries provide data-driven, longitudinal information to: • support and facilitate improved disease management and standard of care; • assess individual patients to help determine the best line(s) of treatment; • measure patient outcomes to assess the quality and efficacy of health care provided; • use aggregate data as a tool to find patterns (for example, by ethnicity, geographic location, sex, age, stage of diagnosis, treatment protocols, health care facility/clinic, etc.) that could better predict the medical future and lead to improved outcomes and quality of life for patients, both individually and as a group, over time. • eventually allow us to evaluate the clinical and cost effectiveness of different diagnostic tools, treatments, and services. Current Landscape: Launched in 2012, The Registry of Patient Registries run by the Agency for Healthcare Research and Quality[1] currently list over 3,100 registries on its site covering a wide variety of registry types, but with most being research or institution generated. According to the National Institutes of Health, "Registries can be used to recruit patients for clinical trials to learn about a particular disease or condition; to develop therapeutics or to learn about population behavior patterns and their association with disease development; developing research hypotheses; or for improving and monitoring the quality of health care."[2] In more recent times we have seen a rise in the development of Patient Powered Registries which "are somewhat indistinguishable from traditional registries, with one exception: In patient-powered patient registries, patients and family members "power" the registry by managing or controlling the collection of the data, the research agenda for the data, and/or the translation and dissemination of the research from the data.[3] Like researcher-generated patient registries, there is no single complete listing or documented number of PPRs in the United States however one study of 201 disease advocacy organizations found that forty-five percent had supported a research registry or biobank.[4] With the definition, purpose and current landscape being covered, we can now look at how registries continue to evolve both to meet the most common concerns and to greatly impact a patient's care and quality of life. **Multiple data sources**: By leveraging the power of digital technology many patient registries now supplement patient reported data with clinical data through integration with Electronic Heath Record (EHR) systems. This integration allows for the capture of additional data points and to verify patient reported data, specifically when the patient may be unsure of the answer. In addition, natural language processing now provides the capability to "pull" information from uploaded documents and reports such as CT scans, lab reports, x-rays, genomic tests. Having multiple data sources allows researchers to paint a more detailed picture of the patients within the registry and more accurately identify patterns and eventually interventions.**Clinical trial matching functionality**: As with the integration of EHR, digital technology is now facilitating clinical trial matching functionality directly into patient registries. This service now allows patients, based on the information provided to not only receive a list of potential matches, but even allows for direct communication to the investigators involved in the study. **Building patient communities**: Unlike research or institution generated studies, patient powered registries may serve as a tool for building connected patient communities particularly when matched with general social media platforms such as Facebook and LinkedIn or more specific patient communities such as Patients Like Me and Inspire. Because patient registries now ask participants to consent not only to sharing their data, but to be contacted by the provider, registries can quickly bring together patients from across the globe for a variety of purposes, including driving research into their specific disease. This is particularly important in lung cancer which we now know is not one disease, but a series of "rare diseases" based on genetic differentiation. **Educating patients**: Being able to communicate directly with patients not only helps facilitate the building of communities and clinical trial matching, it also allows the registry provider to disseminate customized, personalized education materials directly to the participant. Multiple studies have shown how access to such information improves not only quality of life, but satisfaction with care. **Conclusion:** Well-designed patient registries are based on the idea that to improve outcomes and quality of life, no silos within the care community should exist, collaboration is critical, and there must be open and shared access to all information. In addition, today's registries should leverage technology to allow for multiple data sources, longitudinal data collection, two-way communication and clinical trial matching to better serve its participants. By putting these tools to work and providing accurate, digestible information in the hands of industry, health IT companies, physicians and other health care practitioners, registries will organize and engage the entire lung cancer community around the common goal of better care for patients. 1. 4. Landy D, Brinich M, Colten M, et al. How disease advocacy organizations participate in clinical research: A survey of genetic organizations. Genetics in Medicine. 2012;14(2):223–8.

Keywords: Registry, lung, cancer

MS 27.04 APPROACHES TO PATIENT-CENTRIC CLINICAL TRIALS: SHARING CHALLENGES AND LESSONS LEARNED

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Introduction Patient-centricity means much more than episodic patient involvement in health care. A Patient-centric culture requires that patients play an active role in all health care subareas from identifying unmet needs, pre-clinical research, clinical research, drug authorization, drug reimbursement to drug prescription. This study focus on patient-centricity in clinical trials. While in former days a patient participating in a clinical trial very often felt like a "laboratory mouse" only being instructed what to do and often without any understandable information nowadays those responsible for research and drug development discover the advantages of patient involvement such as better recruitment, patient friendly protocols, a better retention rate etc. Till now the main focus was effectiveness and safety of drugs to be shown by cost-intensive clinical trials. Nowadays value of treatments and relevance of outcomes to patients are of special interest. Patient Advocacy organizations help with recruitment by informing their members about new clinical trials. Crowdsourcing techniques addressing different communities like medical experts, patients and researchers are used to provide responses to survey questions. Apart from the arising enthusiasm about the doubtlessly potential opportunities the necessary requirements and their costs such as patient education costs, efforts to establish long-term partnership with patient advocacy groups, implementing patient advisory boards, legal framework conditions which protect patients but do not hinder their active participation as stakeholders etc. should not be underestimated. Additionally, pharmaceutical companies need to implement patient-centricity as a strategy across their functional departments. Successful patient-centric clinical trials require the willingness of patients especially of those who experienced clinical trials to provide their input in order to support improvement. **Method:** An anonymous survey has been designed and submitted to patients who already participated in a clinical trial. As patient-centricity in clinical trials is not just a lung cancer but a general issue Patient Advocacy Groups for different diseases such as lung cancer, breast cancer, cancer in general, lung fibrosis, arthritis, HIV etc. have been involved in US and Europe and further countries aiming to learn more about patient experience in clinical trials. As there is an increasing number of industry-funded clinical trials[1] another online survey was submitted to pharmaceutical companies in order to to find out more about the daily practice. **Results:** 40 of 61 participants who already have been on a clinical trial completed the survey. Almost 50% recently (2016 or 2017) participated in a clinical trial. 16 patients live in US, followed by 8 patients from Austria and single patients from different European countries, one from Australia and one from Israel. Almost 40% of the surveyed have not been asked for feedback concerning the procedure during or after participation in the trial. 87% of patients would take part again in a clinical trial due to reasons like getting effective treatment, new treatment, helping others etc. Previous studies have found that trial participants do not receive the trial results.[2] This study replicated this finding. Almost 50% have not been informed about the final trial results although the WMA Declaration of Helsinki 2013 requested that *all medical research subjects should be given the option of being informed about the general outcome and results of the study.*[3] There is a high rate of willingness (82%) to provide input from patient perspective to improve the design of clinical trials. The analysis of the survey did not show any relevant differences concerning geographic area. 7 research-based pharmaceutical companies completed the second survey. Asking in which parts of the trial process (clinical question, clinical trial design, patient recruitment, trial management) patients are actively involved two companies indicated that patients are not involved in any of the mentioned parts. About 70% of the surveyed request feedback from patients about the procedure of clinical trials (30% do not). 3 of 7 companies do not see any hurdles for driving forward patient-centricity, 3 companies mentioned hurdles like e.g. substantial differences in the patients´ attitudes / concerns / current management across different countries/ regions, added complexity, clarity on compliance rules, contractual framework and often patient report disease impact is difficult to quantify (e.g. I'm feeling tired). The most important measures in the pharmaceutical companies are understanding of patient needs, inclusion of patient reported outcomes, patient satisfaction, safety of IMP (investigational medical product) and patient selection biomarkers. The 2 companies who do not actively involve patients in the different parts of the trial process mentioned patient selection biomarkers, safety of IMP, safeguarding of patient's rights, data quality and integrity as important measures. Both did not see any hurdles to drive forward patient-centricity in clinical trials. **Conclusion:** Although the number of participants in both surveys is quite low, the informational results gained by the patient survey can shed some light to the patient experience concerning clinical trials, the willingness as well as the reasons to participate more than once in a clinical trial. "Effective treatment" as most frequently mentioned reason to participate in a trial indicates a lack of information about clinical trials. There is a vast majority of patients with clinical trial experience being willed to provide their input in order to improve the design of new clinical trials. On the other hand there are researching companies who do not involve patients/patient advocates in the clinical trial process at all and the results of the survey provides an indication of the inconsistent proceedings within the pharmaceutical industry. In order to increase patient-centricity in clinical trials it is necessary that all relevant stakeholders (patients, patient advocates, regulators, medical experts, pharmaceutical companies etc.) compile consensual guidelines that ensure inclusion of relevant and adequately validated PRO, accurate patient information about clinical trials (in different languages), the option to be informed about the trial results for trial participants, information and education about clinical trials and collection and usage of patient feedback. [1]Ehrhardt S, Lawrence J. Trends in National Institutes of Health Funding for Clinical Trials Registered in ClinicalTrials. gov. JAMA. 2015;314(23):2566-2567 [2]Partridge AH, Winer EP. Informing clinical trial participants about study results. JAMA. 2002;288(3):363-365 [3]https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (August 2nd, 2017)

Keywords: clinical trials, Patient-centricity, Pharmaceutical industry

YOUNG INVESTIGATOR SESSION

YI 01 YOUNG INVESTIGATOR AND FIRST TIME ATTENDEE SESSION
SUNDAY, OCTOBER 15, 2017 - 08:00-11:30

YI 01.02 PLANNING AN ACADEMIC CAREER IN LUNG CANCER

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Decision making in life is not always easy. This is applicable not just for patient care but also for matters related to our own-self and is particularly true in the context of career options in medicine. Over the past few decades, the level of expertise provided by health-care providers has enhanced considerably from having comprehensive 'all-in-one' doctors to specialists to super-specialists and currently focused super-specialists. This has been associated with the practice of medicine having changed from 'evidence-based-medicine' to 'personalized medicine' and currently of 'precision medicine' and 'tailor-made' therapies. This has largely been based on an increase in the quantity and quality of research being conducted worldwide. A majority of this research occurs in academic medical centers/university hospitals wherein faculty/attending consultants are not just involved in patient care but have to devote a substantial percentage of their time in planning and conducting research as well as teaching undergraduate/postgraduate residents and fellows. So the natural questions that crop up for someone in training are: 1) 'How do I decide whether I am inclined to be working in an academic institute?' [Will I be able to 'gel-in' or be a complete misfit?] '2) What is the time-point during my training/post-training period when I need to take the decision of pursuing an academic career?' 3) 'What are the essential and desirable qualities/traits that are conducive to working in an academic set-up?' There are no straightforward answers to any of these. However, generally during the final year of fellowship, most individuals are able to decide whether they would like to continue working in an academic centre or not. This is often possible with guidance from course faculty. The chief-guide under whom the individual has been pursuing research (thesis/dissertation) may be able to identify if the latter has an 'academic bent of mind' and provide mentorship and help the transition from 'fellow' (in-training) to full-time faculty ['attending' consultant]. It is important for anyone intending to pursue an academic career to realize that conducting and participating in research is an integral part as opposed to working in non-academic centers where patient care is the primary focus. Inclination towards research may sometimes manifest as being able to identify 'grey' areas in practice of medicine (clinical situations for which there are no clear-cut answers). The best researchers are and often have been those who are able to identify these areas of uncertainty related to diagnosis and treatment of a particular condition or disease and carry out research directed to answer the queries that they had in their minds when picking up these uncertainties. Keeping abreast of the latest developments in one›s focus area (by regularly accessing and reading the latest publications in peer reviewed journals) as well as publishing one›s own experience/research in such journals is thus part and parcel of one›s job profile while working in an academic center. For lung cancer – a disease that carries the highest cancer-related mortality amongst both gender combined and the commonest cancer in males, there have been very encouraging developments in the last couple of decades and especially the last five years. We now have five pillars for treatment – targeted therapy and more lately immunotherapy coming in as very useful additions to traditional modalities (surgery, chemotherapy and radiotherapy). And these are truly exciting times for carrying out research in lung cancer in several ways: 1) Number of investigational molecules (targeted therapy and immunotherapy) being developed/tested in preclinical/clinical trials is increasing at an unparalleled rate 2) Conventional pathway followed for testing [preclinical, phase-1, phase-2, phase-3 clinical trials] is being modified to reduce time to clinical approval for successful drugs by having combined phase 1/2 or phase 2/3 trials. 3) Intense efforts are being made to expand indications for already approved/available drugs e.g. assessing utility of targeted agents in early stage/resectable NSCLC and of combination regimens (EGFR-TKIs/ALK inhibitors+ chemotherapy, PD-1/PD-L1 immune check-point inhibitors+ chemotherapy). Several unaddressed issues exist in lung cancer currently which require concerted efforts and inputs from researchers worldwide including: 1) Improving the screening algorithm for early detection such that false positive results and need for/number of invasive procedures required is reduced. Development of blood, sputum or exhaled-breath based screening tests could find greater acceptability and applicability worldwide. 2) Improving the genomic understanding of SCLC – a histological subtype without significant advances in the past leading treatment to be essentially with two modalities (chemotherapy and radiation). Identifying 'targetable' molecular aberrations can revolutionize management of this aggressive histological type while ongoing efforts to establish the role of immune check-point inhibitors continue. 3) Detection of EGFR sensitizing mutations and acquired T790M resistance-conferring mutation (for initiating 1st/2nd generation EGFR-TKIs and osimertinib respectively) in circulating tumor DNA (ctDNA; sometimes called circulating free tumor DNA - cfDNA) is already applicable in clinical practice and potentially can be used for monitoring treatment responses also. Next-generation-sequencing(NGS) platforms appear promising in detecting both somatic point-mutations and rearrangements/fusions with minimal tissue and/or ctDNA. Development and validation of methods for non-invasive biological monitoring of responses to chemotherapy, radiation, immunotherapy and non-EGFR targeted therapies in the complete spectrum of histological types (SCLC, squamous and non-squamous NSCLC) and disease stage distribution (neoadjuvant treatment preceding surgery, post surgery – adjuvant setting, locally advanced NSCLC following induction concurrent chemo-radiation and metastatic setting) will make it more convenient for patients and treating oncologists alike. The advantages of working in an academic setup in lung cancer are apparent both for the clinician and his/her colleagues in other clinical departments/basic sciences. Current research and clinical practice requires collaboration of different disciplines [pulmonology, diagnostic and interventional radiology (including nuclear imaging), pathology (histopathology, cytopathology, molecular pathology), thoracic surgery/surgical oncology, radiation oncology and medical oncology]. Based upon the academic institute's geographical location, the number/work profile of departments that exist for a given discipline may vary considerably. These variations notwithstanding, the bottom-line is that reaching out to and working together with colleagues from other departments and disciplines [multidisciplinary team approach] is mandatory for attempting conduct of high-quality research and delivery of high-quality patient care in thoracic oncology. This potential advantage and benefit also comes with several challenges. One is required to carefully balance and utilize working hours for patient care, research and training while attempting to do the best in all three fields. This invariably, if not mandatorily, leads to spill-over of work into 'off-work' hours and impinges on 'family-hours' or 'personal-time.' The support of one's spouse, parents and children in such settings cannot be undermined or understated. One needs to keep a balance between 'All-work-and-no-play makes Jack a frustrated man' versus 'Jack-of-all-trades and master-of-none'. Neither is desirable and the ultimate aim is to have a satisfying career in thoracic oncology while working in an academic setting wherein one is able to: 1) provide patients (often under-privileged and belonging to poor socio-economic strata) the best diagnostic and treatment facilities (despite presence of resource constraints) – Patient Care 2) be involved in clinically relevant basic and translational research that has the potential to improve patient care in one's own geographical location – Research 3) share one's experience with residents/fellows and colleagues within the institute and outside – Medical Education Navneet Singh MD DM Email: *[The author is a thoracic medical oncologist-cum-pulmonologist currently working as an Associate Professor of Pulmonary Medicine at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. He is a member of IASLC's Staging & Prognostic Factors Committee; Publications Committee and is IASLC's Regent for the Indian Subcontinent. Additionally, he is Chair-Elect of the American Society of Clinical Oncology's (ASCO) International Development and Education Award (IDEA) Working Group and a member of its Multidisciplinary Cancer Management Course Working Group and Thoracic Cancer Guideline Advisory Group. His detailed profile is accessible at* http://www.linkedin.com/in/navneet-singh-160012.]

Keywords: Academic Career, Lung Cancer Research, Challenges

YI 01 YOUNG INVESTIGATOR AND FIRST TIME ATTENDEE SESSION
SUNDAY, OCTOBER 15, 2017 - 08:00-11:30

YI 01.03 COMMUNITY VERSUS ACADEMIC ONCOLOGY

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Relatively little information is available for hematology oncology fellows to inform their choice for an academic oncology(AO) vs a community oncology(CO) career. In 2006, Desch and Blayney(1) described practical differences between AO and CO careers which are still pertinent today. A more recent report from Vanderbilt(2) describes factors which appear to influence oncology fellows' career decisions. Once a career path has been selected, does this choice affect career and work-life balance satisfaction? Shanafelt and his colleagues have described the impact of career choice and related factors on job satisfaction(3,4). This review will summarize the results of these reports and share a perspective regarding possible changes in oncology practices which could impact career choice. Desch and Blayney(1) describe mission, governance, patient care, financial considerations, referral bases, career flexibility, and determinants of success. The mission for community oncologists(COs) consists of delivering excellent patient care and running a successful business. In contrast, the mission for academic oncologists(AOs) encompasses patient care, research and teaching. CO governance offers more autonomy and usually consists of a doctor owned corporation with equal ownership. AOs work in a hierarchical system with multiple levels between the physician and senior leadership. There are significant differences in delivering patient care. Desch and Blayney point out that " COs are intern, resident, fellow, and attending all rolled into one. " COs have more weekend and night call. In addition, COs provide care for multiple types of cancer patients , while AOs' practice is usually limited to one or two types of malignancy. Patient referrals for COs depend upon building relationships with primary care physicians and surgeons in their community. AOs also get patient referrals from primary care physicians and surgeons, but they rely heavily on institutional reputation, the reputation of disease specific experts, and a robust clinical trial program. Publishing and giving presentations at local and national meetings establishes AOs as disease specific experts which results in physician referrals and in patient initiated consultations. Revenue for COs depends upon fees for physician services, for administration of intravenous treatment , for laboratory tests, for imaging, and revenue from chemotherapy/immunotherapy treatments. For AOs, revenue comes from fees for physician services, grants, clinical trial revenue, and philanthropy. In some academic institutions, revenue may also come from the ancillary sources, similar to private practice. Starting and subsequent compensation is higher for COs who receive significant salary increases when they become full partners in the corporation, 2-5 years after joining the practice. Salary for AOs increases with increasing academic rank and may be supplemented with bonuses and honorariums for lectures and participation in advisory boards. Desch and Blayney(1) suggest that there are critical success factors for COs and AOs. . Building a reputation as a local expert and being readily available to referring MD's and partners is essential for COs. . They also point out that it is essential for COs to invest time to understand bonuses and to show that they value and support the practice staff. AOs must focus on area of

expertise, choose a good mentor, publish results of research, and apply for grants. It is not realistic to expect AOs with a large clinical practice to be the principal investigator on a grant. However, these clinicians can learn the concepts of basic science and partner with laboratory investigators in translational research grant proposals. Horn and her collegues(2) studiedfactors associated with selecting an AO or CO career. They invited program directors at 56 NCI designated and National Comprehensive Cancer Network cancer centers. Fellows at these institutions were asked to complete a questionnaire regarding their interest in AO vs CO careers. . Fellows with a high interest in AO were more likely to be women, have an additional graduate degree, and to have participated in basic research. Also fellows who were more interested in AO gave more presentations at scientific meetings and had more publications. Having an influential mentor and a desire to teach were also related to pursuing a career in AO. . Fellows who were more interested in CO were motivated by work-life balance and autonomy. This study suggest that fellows who are primarily motivated by being involved in identifying new information and teaching are more likely to pursue AO , while fellows who are motivated by favorable work-life balance and having more autonomy are more likely to pursue a CO career. How do practicing oncologists feel about their careers? Shanafelt and colleagues(3,4) have published two reports describing results of a survey which evaluated burnout, career satisfaction, life – work balance satisfaction and retirement. They(3) found that COs spent more time in clinic and saw more patients. Younger age and more hours in clinic were associated with increased risk of burnout, which was defined as a combination of emotional exhaustion and depersonalization (loss of concern for patients),. There was a trend for higher rate of emotional exhaustion and a significantly higher rate of depersonalization in community oncologists. Although the majority of oncologists would choose a career in oncology, there was a higher number of COs who stated they would not choose an oncology career. In the second report(4), they did not compare AOs and COs. They saw that although most oncologists find meaning in their work, 52% were dissatisfied with work-life balance. "They like their work but want to do less of it." Work-life balance was affected by more night and weekend call, while method of compensation salary +/- bonuses (most AOs) versus incentive (most COs) was not related work-life balance. For oncologists who planned to reduce work hours, the most common reason was to spend more time with family. In summary, when making a career choice, oncology fellows should identify what motivates them. I suspect that the majority of oncologists will continue to be happy with their career choice and that the current differences between AO and CO careers may decrease because more COs will be employed by hospital systems. References 1.Desch CE, Blayney DW. Making the Choice Between Academic Oncology and Community Practice: The Big Picture and Details About Each Career. Oncol Pract 2:132-138, 2006 2.Horn L, Koehler E, Gilbert J, et al. Factors Associated with the Career Choices of Hematology and Medical Oncology Fellow Trained ar Academic Insitutions in the United States. J Clin Oncol 29: 3932 - 3938, 2011 3.Shanafelt TD, Gradishar WJ, Kosty M, et al.Burnout and Career Satisfaction Among US Oncologists. J Clin Oncol 32: 678-686, 2016 4.Shanafelt TD, Raymond M, Kosty M, et al.Satisfaction with Work-Life Balance and the Career and Retirement Plans of US Oncologists.J Clin Oncol 32:1127-1135, 2014

Keywords: academic community careers

YI 01 YOUNG INVESTIGATOR AND FIRST TIME ATTENDEE SESSION
SUNDAY, OCTOBER 15, 2017 - 08:00-11:30

YI 01.11 THE YOUNG INVESTIGATOR TRAVEL AWARD EXPERIENCE - A REPORT FROM A PREVIOUS AWARD WINNERS

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I received the WCLC 2016 Young Investigator Travel Award for my presentation entitled "Immunogram for cancer-immunity cycle towards personalized immunotherapy of lung cancer". It was my great honor to receive the award, and I want to thank the conference committee and all the conference attendees. This was my first time to attend the WCLC, and I enjoyed the conference and my stay in Vienna. I was given the opportunity to join the Faculty Dinner held in Vienna City Hall. It was a fabulous experience, and I thoroughly enjoyed sitting at the same table as world-renowned surgeons and oncologists. During the conference, I mainly attended immunotherapy sessions where I learned about the results of the most recent clinical studies. Furthermore, while attending the biomarker session, I realized that biomarkers in this field are still inadequate and the development of useful biomarkers in immunotherapy is an urgent need. Receiving the young investigator scholarship has encouraged me to continue our efforts to unveil the tumor microenvironment in each patient using individual next-generation sequencing data in order to develop "next-generation biomarkers" and achieve optimal personalized immunotherapy. Last year, in a Perspectives article in *Science*, Blank et al. proposed the concept of the cancer immunogram, a framework to illustrate multiple parameters that influence the cancer-immunity interaction (1). In their article, the concept was applied theoretically to patients but not tested in practice. To accomplish this, we developed an immunogram reflecting the cancer immunity cycle using next-generation sequencing data, and applied it to real patients with lung cancer. An immunogram for the cancer immunity cycle is a radar chart that consists of eight molecular profiles relevant to the development of T-cell immunity to tumor cells. We sought to translate cumbersome omics data into easily comprehensible "report cards" for clinicians. Immunograms can be used as integrated biomarkers, and may become a valuable resource for optimal personalized immunotherapy. After the presentation at the WCLC 2016, our findings were published in the *Journal of Thoracic Oncology* in May (2). It was an honor that our article was chosen by the Editor to be a featured article and was introduced by an elegant review (3). We recently updated our method by normalizing the immunogram score using TCGA data. We are pleased to share the details of this improvement during the present conference. Although we are working in a challenging field and there is still a long way to go, we are encouraged by the award and will continue to struggle toward further breakthroughs.^(References (1) Blank CU, Haanen JB, Ribas A, Schumacher TN. Cancer immunology. The "cancer immunogram" Science. 2016;352:658-60. (2) Karasaki T, Nagayama K, Kuwano H, et al. An Immunogram for the Cancer-Immunity Cycle: Towards Personalized Immunotherapy of Lung Cancer. J Thorac Oncol.2017;12(5):791-803. (3) Botling J, Sandelin M. Immune Biomarkers on the Radar-Comprehensive "Immunograms" for Multimodal Treatment Prediction. J Thorac Oncol.2017;12(5):770-2.

YI 01 YOUNG INVESTIGATOR AND FIRST TIME ATTENDEE SESSION
SUNDAY, OCTOBER 15, 2017 - 08:00-11:30

YI 01.13 MAKING THE MOST OF THE WCLC: A GUIDE FOR FIRST TIME ATTENDEE - FROM A SECOND TIME ATTENDEE

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The IASLC (International association for the study of lung cancer) WCLC (World Conference on Lung Cancer) is world's largest academic platform dedicated for the study of lung cancer and other thoracic malignancies which not only caters to physicians but also includes active participation from each discipline of medicine involves in patient care. In addition health advocacy groups and patients will also join WCLC to obtain and exchange the information. The focus of the meeting is on the biology, diagnosis, pathogenesis, treatment and management of lung cancer so to begin from active prevention and accurate diagnosis to advanced care. Because of advancing science of lung cancer, IASLC decided to hold WCLC every year so people will be kept abreast with the current knowledge and updates in this field. There are many academic opportunities for the young investigators or first-time attendee to pursue their career in the field of thoracic oncology. They can meet the experts during the conference, attend various educational sessions and take guidance in the field of basic, translational and clinical research. There are many awards which help in not only enhancement of academic career but also in attending conference from resource poor countries. Travel awards given to developing nation investigators so that they can attend the conference and present their latest research in addition to make collaborations and academic networking. International mentorship program of IASLC is very useful professional development and education program for early-career doctors from economically-developing countries in which you get an opportunity to spend a week time in a well established hospital or laboratory under the mentorship of an international expert in that field. This year, the Core Program Committee has organized a scientific program that includes more than 450 presentations. The conference motto is **"Synergy to Conquer Lung Cancer"** which will be very overwhelming at both scientific and educational fronts. The education sessions include state-of-the-art talks by experts on academically challenging and evolving topics. The scientific program includes research presentations in the form of posters and platform formats. There are many events and platforms where first time attendees can interact and do networking for future collaborations. It is certain that the 18th WCLC will help young investigators and first time attendees to build and shape-up their career in thoracic oncology.

Keywords: lung cancer, IASLC, WCLC

JOINT IASLC – CSCO – CAALC SESSION

JCSE 01 JOINT SESSION IASLC/CSCO/CAALC: IMMUNOTHERAPY FOR MANAGEMENT OF LUNG CANCER: ONGOING RESEARCH FROM EAST AND WEST
SUNDAY, OCTOBER 15, 2017 - 07:30-11:30

JCES 01.07 ONGOING TRIALS IN CHINA ON CHECKPOINT INHIBITORS AND OTHER IMMUNOTHERAPIES

Q. Zhou

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Immunotherapy gets the breakthrough after almost 100 years of silence. PD1/PD-L1 inhibitors as the representative has been extensively studied in various human malignant tumors and get promising long term response with relatively fewer adverse event. The first PD1 inhibitor indication was approved for melanoma in Japan on July 2014. By the end of December 2016, the US Food and Drug Administration had approved several PD-1 pathway blockade treatments including nivolumab, pembrolizumab and atezolizumab using in first line and second line of NSCLC. But In China, no PD-1 or PD-L1 inhibitors have received marketing approval from the Chinese Food and Drug Administration (CFDA) until July 2017. One sides, IO arena faces intense in-class competition from both MNC (Multi-National Corporation) and domestic pharmaceutical company in China. Now there are 20 IO antibodies from 7 MNCs and 10 pharmaceutical companies in China. But all the antibodies only confined to PD1/PD-L1 and CTLA4, no other hot IO drugs such as IDO or Lag3 et al. In the field of innovation, China is several years behind research in other areas of the world. The other sides various clinical trials are actively investigating MNC and domestic drugs in China. Between January 1, 2013 and April 6, 2017, Clinical Trials.-gov registered 270 international clinical trials using PD-1/PD-L1 therapies for NSCLC (e.g.nivolumab,pembrolizumab,atezolizumab,and durvalumab). These 270 trials included 61 studies that involved East Asian sites and 14studies that involved Chinese sites (12 multinational trials and 2 trials that only evaluated Chinese patients). These trials cover from second line and first line to adjuvant therapy in NSCLC. Most of the ongoing MNC NSCLC clinical trials joined in global study design that may accelerate the patient access to PD1/PD-L1. But Chinese population has relatively high rates of hepatitis B virus infection and much higher proportion of EGFR mutation. The delightful changing recently is some studies emerging to consider the characteristics of the Chinese or Asian populations. Domestic company clinical trials focus on GI (Gastrointestinal) and only 1 NSCLC study in China. Chinese clinical trials using IO remain in their early stages, and further efforts are needed to improve the design of future clinical trials. Meanwhile, the other hot IO drug phase I study need speed up in China.

Keywords: ongoing clinical trials, Immunotherapy, China

JCSE 01 JOINT SESSION IASLC/CSCO/CAALC: IMMUNOTHERAPY FOR MANAGEMENT OF LUNG CANCER: ONGOING RESEARCH FROM EAST AND WEST
SUNDAY, OCTOBER 15, 2017 - 07:30-11:30

JCES 01.10 THE MAIN TREATMENT FAILURE PATTERN FOR COMPLETELY RESECTED STAGE II–IIIA (N1–N2) EGFR-MUTATION POSITIVE LUNG CANCER

S. Xu[1], W. Zhong[2], Y. Zhang[1], W. Mao[3], L. Wu[4], Y. Shen[5], Y. Liu[6], C. Chen[7], Y. Cheng[8], L. Xu[9], J. Wang[10], K. Fei[11], X. Li[12], J. Li[13], C. Huang[14], Z. Liu[15], S. Xu[16], K. Chen[17], S. Xu[18], L. Liu[19], P. Yu[20], B. Wang[21], H. Ma[22], H. Yan[2], X. Yang[2], Y. Wu[23], Q. Wang[1]

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Background: ADJUVANT (CTONG 1104) is the first randomized trial shows significantly prolonged disease-free survival (DFS) in completely resected stage II-IIIA (N1-N2) epidermal growth factor receptor (EGFR)-mutation positive non-small-cell lung cancer (NSCLC) through adjuvant gefitinib compare with vinorelbine plus cisplatin (VP). Further we aim to analyze the treatment failure pattern in ADJUVANT study. **Method:** In the ADJUVANT trial, a total of 222 patients with completely resected stage N1–N2 EGFR-mutation positive NSCLC were randomized 1:1 into gefitinib group (250mg, QD, 24 months) or vinorelbine (25mg/m^2 Day 1/Day 8) plus cisplatin (75mg/m^2 Day 1) group (every 3 weeks for 4 cycles) respectively. Any recurrence or metastases occurred during the follow-up period was defined as treatment failure. Recurrent pattern in both group were analyzed with follow-up data (until Mar 9th 2017) integrated. **Result:** At the Data cut-off date for the primary analysis of DFS, 124 progression events (55.9% maturity overall) had occurred; 114 patients had disease recurrence, 10 patients died before disease recurrence. Analysed recurrent pattern include lung, brain, liver, bone adrenal gland, pleura, pericardium, spleen and regional lymph nodes metastasis. Even no significant differences were found, highest proportion of patients in both group(18.9% for VP and 26.1% for gefitinib, p=0.199) surfer brain metastasis with lung metastases being the second common recurrent site. Time to brain metastases showed no significantly difference between the two groups (not reach vs 40.8m, p>0.05). Among the 29 brain metastases patients with gefitinib, the brain metastases occurred in 17 patients during the gefitinib treament, and 12 patients relapse after the gefitnib termination. **Conclusion:** Compared with other site metastases, lung, brain and regional lymph nodes metastases account for major proportion of recurrence in ADJUVANT study. (NCT01405079)

Keywords: non-small-cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) mutation

JCSE 01 JOINT SESSION IASLC/CSCO/CAALC: IMMUNOTHERAPY FOR MANAGEMENT OF LUNG CANCER: ONGOING RESEARCH FROM EAST AND WEST
SUNDAY, OCTOBER 15, 2017 - 07:30-11:30

JCES 01.11 A MULTICENTER, NON-INTERVENTIONAL STUDY ON REAL WORLD EGFR TESTING AND IN PATIENTS WITH IIIB/IV NSCLC IN NORTHERN CHINA

Y. Cheng[1], Y. Wang[2], J. Zhao[3], Y. Liu[4], H. Gao[5], K. Ma[6], S. Zhang[7], H. Xin[8], J. Liu[9], H. Chengbo[10], Z. Zhu[11], Y. Wang[12], J. Chen[13], F. Wen[14], J. Li[12], Z. Jie[15], Z. Zheng[16], Z. Dai[13], H. Piao[17], X. Li[18], Y. Li[19], M. Zhong[20], R. Ma[18], Y. Zhuang[21], Y. Xu[22], Z. Qu[23], H. Yang[24], C. Pan[25], F. Yang[26], D. Zhang[27], B. Li[28]

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Background: EGFR mutation plays a dominant role in the precise treatment of non-small cell lung cancer (NSCLC), and EGFR-TKIs has been recommended for patients with positive EGFR-sensitive mutation as a standard regimen in clinical practice. In China, application of EGFR-TKIs without knowing EGFR mutation status has been a common phenomenon due to various reasons including the vast territory, uneven distribution of medical resources, differences level of testing technology and others. Therefore, we prospectively conducted a real-world investigation to understand the actual situation of EGFR testing in Northern China, and identify the underlying causes affecting EGFR detection, in order to provide references to improve the standardized treatment. (NCT02620657) **Method:** The patients with IIIB/IV NSCLC who were firstly diagnosed or postoperative recurrence between 2014-1-1 and 2014-12-31 in 28 research centers of Northern China were analyzed. The primary endpoint was testing rate,the secondary endpoints were factors affecting EGFR testing, EGFR mutation status, detection methods and the survival outcomes of patients. **Result:** Among 2809 patients, 2250 (90.78%) were adenocarcinoma, 208 (7.40%) were squamous carcinoma, 51 (1.82%) were other pathologic types. Testing rate was 42.54% (1195/2809) and was significantly related to city level (first-tier cities vs. new first-tier cities vs. second-tier cities vs. third-tier and above cities: 69.04% vs. 38.08% vs. 34.05% vs. 14.11%, P < 0.001), smoking status (never smoking vs. ever smoking vs. smoking: 45.42% vs. 51.10% vs. 33.37%, P<0.001), ECOG PS (0 vs.1vs.2vs.≥3:47.93%vs. 44.48vs.34.89%vs.20.37%, P=0.011), pathological type (adenocarcinoma vs. squamous carcinoma: 44.94% vs.19.23%, P=0.003) and medical insurance situation (social basic medical insurance vs. new rural cooperative medical insurance vs. own expense: 44.98% vs. 36.49% vs. 29.55%, P=0.001). EGFR sensitive mutation rate was 46.44%, the most common subtype was 19Del (42.16%), followed by L858R (40.00%), Exon 20 insertions (1.62%) and other subtypes (16.20%). The most common methodology is ARMS (63.77%), the second common one is DNA sequencing (5.36%). The 1-year and 2-year survival rate in patients receiving EGFR testing was 73.6% and 51.9%, compared with 64.3% and 43.7% respectively in patients without EGFR testing. **Conclusion:** There were regional differences in EGFR testing rates among IIIB/IV NSCLC patients in Northern China. The intention of doctors and patients, medical insurance coverage and differences technical level are major factors affecting the testing rate of EGFR. Approaches should be taken to improve the situation, such as strengthening the training, expanding the coverage of medical insurance, and relying on commercial gene detection companies, and further standardize the molecularly pathological diagnosis and treatment of NSCLC.

Keywords: Epidermal growth factor receptor, testing frequency, non-small cell lung cancer

JCES 01.12 A PHASE II STUDY OF FRUQUINTINIB IN COMBINATION WITH GEFITINIB IN STAGE IIIB/IV NSCLC PATIENTS HARBORING EGFR ACTIVATING MUTATIONS

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Background: Seveal studies have demonstrated targeting EGFR mutations and tumor angiogenesis simultaneously has synergistic effect in the 1st line setting in EGFR mutant NSCLC. However, in JO25567 trial, the ≥grade 3 hypertension incidence with combination therapy was much higher (60%) when compared to historic incidence of hypertension with bevacizumab (10-15%). Considering relatively shorter half-lives for small molecule tyrosine kinase inhibitors, it might be a better choice to combine EGFR TKI and VEGFR TKI when it comes to hypertension management. Fruquintinib is a potent and highly selective oral kinase inhibitor targeting VEGFR and it has demonstrated favorable benefit-to-risk profile in third line treatment in NSCLC patients.Thus it is important to assess safety, tolerability and efficacy of this new combination in the 1st line setting in EGFR mutant NSCLC patients. NCT02976116 **Method:** This is a single arm, open-label, multi-center study. All patients will receive gefitinib continuously at 250 mg qd. Fruquintinib will be given at 4 mg as starting dose for 3 weeks followed by 1 week off in the first 4-week cycle. Fruquintinib dose can be escalated to 5 mg with the same 4-week cycle if no ≥grade 3 adverse event (AE) or ≥grades 2 liver dysfunction occurs in the first cycle. Treatment continues until disease progression, unacceptable toxicity, or patient withdrawal. The primary objective is to assess the safety and tolerability of this combination. Key eligibility criteria include: histologically or cytologically confirmed NSCLC, ECOG PS 0-1, no prior systematic treatment, no brain metastasis. Key exclusion criteria include: known T790M mutation and bleeding history within 1 month before enrollment. **Result:** As of Jun 20, 2017, 9 patients have been enrolled and received at least one dose of fruquintinib and gefitinib. Six patients had L858R mutations, and three patients had exon 19 deletions. All patients reported AEs, but only one patient (11.1%) had grade 3 proteinuria. No SAE was reported. The most common AEs were increased ALT (3 [33.3%] patients), increased AST (3 [33.3%] patients), increased TBIL (3 [33.3%] patients), proteinuria (3 [33.3%] patients) and rash (3 [33.3%] patients). Fruquintinib dose reduction occurred in 3 patients due to grade 3 proteinuria, grade 2 increased ALT and grade 2 hemoptysis, respectively. **Conclusion:** The study is ongoing. As of the cut-off date, no unexpected toxicities were identified. The combination of fruquintinib and gefitinib showed an expected and manageable preliminary safety profile. Additional patients and follow-up data are required to further confirm the full potential of this combination treatment.

Keywords: Fruquintinib, non-small cell lung cancer, gefitinib

JCES 01.15 NEXT GENERATION SEQUENCING OF LARGE-CELL NEUROENDOCRINE CARCINOMA REVEALS AN ASSOCIATION OF PIK3CA MUTATIONS WITH BRAIN METASTASES

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Background: Large-scale genomic characterization of large-cell neuroendocrine carcinoma (LCNEC) has revealed several putative oncogenic drivers. There are, however, little data to suggest that these alterations have clinical relevance. **Method:** We performed comprehensive genomic profiling of 68 stage IV LCNECs of the lung (including next-generation sequencing) and analyzed differences in the clinical characteristics of two major LCNECs subtypes: KRAS mutation and PIK3CA mutation. In order to better understand the divergence that might exist between brain metastases and their lung primaries, we performed whole-exome sequencing of paired lung primaries and brain metastases from four lung LCNEC patients. **Result:** Patients with PIK3CA mutation tumors had aggressive disease marked by worse survival (median OS 7.9 vs. 18.6 mo, $P = 0.002$), higher metastatic burden (> 3 organs 15.2% vs. 4.7%, $P = 0.029$), and greater incidence of brain metastases (19.0% vs.2.3% in others, $P = 0.001$). Whole-exome and RNA sequencing on paired brain metastases and primary LCNECs of the lung revealed that LCNEC primaries that gave rise to brain metastases harbored PIK3CA mutation. Significant tumor growth inhibition with GDC0941 was observed exclusively in the LCNEC patient-derived xenograft model that harbored PIK3CA mutation. **Conclusion:** PIK3CA mutation defines a distinct disease phenotype characterized by brain metastasis in LCNEC of the lung. The result may be relevant for targeted therapy and prophylaxis of NSCLC brain metastases.

Keywords: large-cell neuroendocrine carcinoma, lung cancer, Brain metastasis

JCES 01.16 ALTERED EXPRESSION OF PROGRAMMED DEATH-1 RECEPTOR (PD-1)AND ITS LIGAND PD-L1, PD-L2 AFTER NEO-ADJUVANT CHEMOTHERAPY IN LUNG CANCER

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Background: Immunotherapy is a new research direction in the treatment of lung cancer. PD1/PD-L1, PD-L2 pathway as representative of the immune checkpoint, play critical roles in the development and progression of cancer. And the expression of PD-1, PD-L1, PD-L2 were associated with therapeutic effect. Many studys have shown that many factors may effect the expression of PD1, PD-L1, PD-L2, such as chemotherapy. The present study aims to examine the impact of neo-adjuvant chemotherapy (NAC) on PD-1, PD-L1, PD-L2 expression in lung cancer. **Method:** In this study, tumor samples were obtained from 26 patients who confirmed primary lung cancer prior to and after NAC (platinum-based)from June, 2009 to May, 2016 in the First Hospital of Jilin University. Expression of PD-1, PD-L1, PD-L2 in lung cancer tumor specimens were assessed by immunohistochemistry (IHC). Using 5%, 10%, 20%, 30%, 50% expression threshold to define PD-1, PD-L1, PD-L2 positive status, respectively. The variation of PD-1, PD-L1, PD-L2 in prior to and after NAC were evaluated by Matching chi-square test. Besides that, Spearman's rank correlation and non-parametric test were used to calculate the relationship between the changes of PD-1, PD-L1, PD-L2 and tumor shrinkage rate, interval from the end of NAC to operation, pathological type, gender, smoking or not. P value < 0.05 was considered statistically significant. **Result:** Using 5%, 10%, 20% expression threshold to define PD-L1 positive status, 65.4%(17/26), 53.8%(14/26), 42.3%(11/26) were found to be PD-L1 positive prior to NAC, and 92.3% (24/26), 80.8%(21/26), 69.2%(18/26) expressed positively after NAC, PD-L1 was up-regulated after NAC (p=0.003, p=0.016, p=0.016), however, there were no obviously statistical significance about the expression of PD-L1 (p>0.05)when using 30%, 50% expression threshold. The expression of PD1, PD-L2 were not show any statistical significance before and after NAC (p>0.05). Furthermore, there were no relationship between the changes of PD-1, PD-L1, PD-L2 and pathological type, interval from the end of NAC to operation, gender, smoking or not (p>0.05). **Conclusion:** The expression of PD-L1 was up-regulated after NAC when using 5%, 10%, 20% expression threshold, there were obviously statistical significance. No correlations existed between the variation of PD-1, PD-L1, PD-L2 and tumor shrinkage rate, interval from the end of NAC to operation, pathological type, gender, smoking or not.

Keywords: lung cancer, Programmed death-ligand 1, neo-adjuvant chemotherapy

JCES 01.17 THE CORRELATION OF DLL3 EXPRESSION WITH HIGH-GRADE PULMONARY NEUROENDOCRINE CARCINOMA CLINICOPATHOLOGIC FEATURES AND PROGNOSE

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Background: Rovalpituzumab tesirine is a promising first-in-class DLL3-targeted antibody-drug conjugate for the treatment of HGNECs. In clinical practice, biopsies are often rendered for diagnoses of HGNECs before treatment. We tested DLL3 in paired biopsy and surgical specimens, aiming to assess the reliability of the scoring system in biopsy specimens and the correlation with HGNEC clinical characteristics and prognoses. **Method:** A total of 378 patients with *de novo* HGNECs, including 43 LCNECs and 335 SCLCs, were recruited between 2006 and 2015. All 43 LCNECs and 42 of 335 SCLCs had paired biopsy and surgical excision specimens, and the remaining 293 SCLCs had only biopsies. Immunohistochemical evaluation of DLL3 expression was performed using anti-DLL3 antibody (Abcam, ab103102) and was determined using immunohistochemical H score (HS). **Result:** No significant differences of DLL3 expression levels were observed in paired biopsy and excision specimens of LCNECs and SCLCs (Figure B-C). Discordant DLL3 results (high, HS > 150 vs low, HS ≤ 150) in paired specimens were observed in none of LCNECs and 2 of 42 SCLCs. DLL3 levels were significantly higher ($p = 0.015$) in all SCLCs (n = 335, median HS 200, IQR 100-300) than in LCNECs (n = 43, HS 160, IQR 100-200; Figure D). SCLCs with high DLL3 levels were more frequently male ($p = 0.037$), smokers ($p = 0.019$), and TTF-1 positive ($p = 0.005$) than SCLCs with low DLL3. SCLCs with low DLL3 experienced a superior overall survival compared with SCLCs with high DLL3, with the difference, however, not reaching statistical significance ($p = 0.077$; Figure F). **Conclusion:** Biopsy specimen is a reliable material for evaluating DLL3 expression, which is equivalent to surgical specimen in a large percentage of HGNECs. High DLL3 level in SCLCs demonstrate a correlation with smoking history, TTF1 (neuroendocrine differentiation) and a trend of poor survival.

Keywords: Delta-like ligand 3 (DLL3), clinicopathologic features, High-grade pulmonary neuroendocrine carcinomas

JCES 01.18 UNCOMMON MUTATION TYPES OF EGFR AND RESPONSE TO EGFR TYROSINE KINASE INHIBITORS IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is the standard therapy for advanced lung adenocarcinomas with common EGFR mutations. However, the efficacy of EGFR-TKIs in patients with these uncommon EGFR mutations (other than exon 19 deletions or exon 21 L858R mutation) remains undetermined. **Method:** Seven hundred and fifty-five non-small cell lung cancer (NSCLC) patients with EGFR mutation analyses for TKI therapy were identified between October 2010 and December 2015 in East of China. And 66 patients bearing uncommon EGFR mutations were included to collect data from TKI response and prognosis. **Result:** Rare sensitive mutations (G719X, L861Q, S768I), primary resistant mutation (Ex20 ins), and complex mutations (G719X + L861Q, G719X+S768I, 19 del+T790M, 19 del+L858R, L858R+S768I, and L858R+T790M) of EGFR were identified in 37 (56.1%), 9 (13.6%), and 20 (33.3%) patients, respectively. TKI treatment in patients harboring uncommon EGFR mutations exhibited a tumor response rate of 28.8% and a median progression-free survival (PFS) of 4.8 months. Importantly, patients with complex EGFR mutations had significantly longer PFS when compared with the remaining sensitizing rare mutations or Ex20 ins (8.6 versus 4.1 versus 3.1 months; p=0.041). Furthermore, complex EGFR mutations were independent predictors of increased overall survival in NSCLC patients (Hazard Ratios=0.31; 95% confidence intervals: 0.11-0.90; p=0.031). Among them, patients harboring Del-19 compound L858R mutations showed a tendency to have higher response rate and improved median PFS than those regarding patients with other complex mutations patterns (66.7% verse14.3%, p=0.021; 10.1 verse 8.6 months, p=0.232). **Conclusion:** Personalized treatment should be evolving in different types of uncommon EGFR mutations. And complex mutations of EGFR may benefit more from EGFR-TKIs than other uncommon mutations in Chinese NSCLC patients.

Keywords: Tyrosine kinase inhibitors, Epidermal growth factor receptor, uncommon mutation

JCES 01.19 EGFR MUTATION CORRELATES WITH UNINFLAMED PHENOTYPE AND WEAK IMMUNOGENICITY, CAUSING IMPAIRED RESPONSE TO PD-1 BLOCKADE IN NSCLC

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Background: Patients with EGFR mutations showed unfavorable response to programmed cell death-1 (PD-1) blockade immunotherapy in non-small cell lung cancer (NSCLC). Yet the underlying association between *EGFR* mutation and immune resistance remains largely unclear. **Method:** We performed an integrated analysis of PD-ligand 1(PD-L1)/CD8 expression and mutation profile based on the repository database and resected early-stage NSCLC in Guangdong Lung Cancer Institute (GLCI). Meanwhile, two pool-analyses were set to clarify the correlation between *EGFR* mutation and PD-L1 expression, and the association of *EGFR* status with response to anti-PD-1/L1 therapy. **Result:** Pool-analysis of 15 public studies suggested that patients with *EGFR* mutations had decreased PD-L1 expression (odds ratio: 1.79, 95% CI: 1.10-2.93; P = 0.02). Analysis of The Cancer Genome Atlas (TCGA) and the GCLI cohort confirmed the inverse correlation between *EGFR* mutation and PD-L1 expression. Furthermore, patients with *EGFR* mutation showed a lack of T-cell infiltration (P = 0.003) and shrinking proportion of PD-L1$^+$/CD8$^+$TIL (P = 0.005). Importantly, patients with *EGFR* mutations, especially the sensitive subtype (exon 19Del, L858R, L861Q, G719X, S768I), showed a significantly decreased mutation burden, based on analysis of the discovery and validation sets. Finally, a pool-analysis of 4 randomized control trials confirmed that patients with *EGFR* mutation did not benefit from PD-1/L1 inhibitors (Hazard ratio [HR] = 1.09, P = 0.51) while patients with EGFR wild-type did (HR = 0.73, P < 0.00001). Three cases treated with PD-1 inhibitor in our center also supported that EGFR mutation was unfavorable to PD-1 blockade even when those with strong positive of PD-L1 and CD8$^+$TIL. **Conclusion:** This study provided evidence of a correlation between *EGFR* mutations and an uninflamed tumor microenvironment with immunological tolerance and weak immunogenicity, which caused an inferior response to PD-1 blockade in NSCLCs.

Keywords: EGFR, programmed cell death protein-1, Mutation burden

JCES 01.20 PRIMARY TUMOR RESECTION VERSUS MAINTENANCE THERAPY FOR PATIENTS WITH OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER

X. Kang, H. Zhou, W. Yan, L. Dai, Y. Yang, H. Yang, H. Fu, M. Fan, Y. Lin, Z. Liang, H. Xiong, K. Chen
Peking University Cancer Hospital, Beijing/CN

Background: To evaluate (1) the potential effect of primary tumor resection, an aggressive local consolidative therapy, for patients with oligometastatic NSCLC on 3 year overall survival; (2) the surgical outcomes in the treatment of patients with oligometastatic NSCLC; (3) the potential clinical factors predicting survival in order to better select patients for surgery. **Method:** According to the extent of pulmonary resection, the patients were divided into two subgroups. A. intent to cure (ITC: removal of total or primary pulmonary lesions); B. intent to biopsy (ITB: preservation of major lesions, only diagnostic biopsy via minimally invasive approach). M stage classified based on 8th UICC/AJCC TNM M categories. **Result:** From Jan 2002 through Dec 2015, a total of 115 consecutive metastatic NSCLC patients were enrolled from Peking University Cancer Hospital. The 3-year overall survival (OS) of ITC and ITB were 64.3% and 34.9% (log-rank p = 0.0009), respectively. Multivariate cox proportional regression analysis identified multiple station lymph nodes (LN) and bone involvement may be prognostic indicators. **Conclusion:** The current findings suggest that aggressive surgical therapy can extend the survival in selected stage IV NSCLC patients, and should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.

Keywords: lung cancer, Surgery, oligomestasis

JCES 01.21 COMBINATION OF BIOMARKER AND CLINICOPATHOLOGIC CHARACTERS MAY CIRCLE OUT BENEFICIARIES THROUGH SECOND-LINE IMMUNOTHERAPY: A META ANALYSE

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Background: Programmed cell death ligand 1 (PD-L1) expression had been proposed as predictive biomarker to immune-checkpoint inhibitors. Yet treatment responses are not always consistent with this single agent in the second-line therapy of NSCLC. Whether combination of PD-L1 and clinicopathologic characters could circle out optimal beneficiaries are still unknown. **Method:** We performed a meta-analysis of randomized control trials that compared immune-checkpoint inhibitors against chemotherapy in second-line therapy. Data including smoking status, EGFR status, KRAS status and histology were extracted as subgroup analyse to estimate the potential predictor of efficacy for anti PD-1/L1. **Result:** Five clinical trials that compared immune-checkpoint inhibitors against chemotherapy for second-line therapy were included. Both PD-L1 positive (HR=0.64, 95%CI=0.56-0.73, P<0.00001) and PD-L1 negative (HR=0.88, 95%CI=0.78-1.00, P=0.05) favored anti PD-1/L1. Subgroup analyse indicated that adenocarcinoma (ADC) as well as squamous cell carcinoma (SCC) preferred anti PD-1/L1. Never smokers may not benefit from anti PD-1/L1 but current/ever smokers did (HR=0.70, 95%CI=0.63-0.79, P<0.00001). Patients with EGFR mutation could not gain benefit from anti PD-1/L1 while the EGFR wild type could (HR=0.67, 95%CI=0.60-0.76, P<0.00001). Both KRAS mutation (HR=0.60, 95%CI=0.39-0.92, P=0.02) and wild type/unknown (HR=0.81, 95%CI=0.67-0.97, P=0.02) were apt to anti PD-1/L1. **Conclusion:** Regardless of PD-L1 status, immune-checkpoint inhibitors could achieve better efficacy than chemotherapy in second-line therapy. Current/ever smokers without EGFR mutations may benefit more from anti PD-1/L1. Combination of PD-L1 and strongly relevant clinicopathologic characters should be considered to tailor optimal patients for anti PD-1/L1.

Keywords: non-small cell lung cancer, Immunotherapy, biomarker and clinicopathologic characters

JCES 01.22 IS PREOPERATIVE EGFR-TKI COMPARABLE WITH CHEMOTHERAPY FOR STAGE II-IIIA LUNG ADENOCARCINOMA?

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Background: Although it has been proved that preoperative chemotherapy could improve disease-free survival (DFS) and overall survival in stage IB-IIIA resectable NSCLC, the role of neoadjuvant targeted therapy has not been established. Our purpose is to investigate the efficacy and safety of induction EGFR-TKI compared

with neoadjuvant chemotherapy, in order to explore optimal strategy for the treatment. **Method:** From 2013 to 2016, we retrospectively reviewed clinical records of stage I-IIIA lung adenocarcinoma patients, who had received at least two cycles of neoadjuvant chemotherapy or at least 4 weeks of induction targeted therapy followed by surgery. Gathered data were tested for significance between chemo and targeted therapy group. Tumor samples were collected and analyzed by sequencing to explore EGFR-TKI resistance mechanisms. **Result:** 60 patients were enrolled in this study, of whom 80% were stage II-IIIA. Of all the cases, 17 harboring EGFR mutation received induction EGFR-TKI, whereas 39 received chemotherapy. Another 4 received TKI following chemo before surgery. Among EGFR mutant patients, objective response rate (ORR) was 47.6% for neoadjuvant EGFR-TKI, and 32.6% for chemotherapy (p=0.300). In subset analysis, for stage II to IIIA EGFR mutant patients, neoadjuvant targeted therapy had significant tumor response compared with chemotherapy (ORR: 66.7% vs. 34.8%, p=0.020). Of 21 preoperative EGFR-TKI cases, 10 patients received continued administration (47.6%): a further tumor size reduction was noted by the second month of TKI administration if clinical response was achieved initially, whereas no apparent shrinkage was observed by the third month's TKI. No further shrinkage was achieved by continued administration if initial tumor size reduction was little. No difference in postoperative complication, drainage volume and hospital days was seen between chemo and targeted therapy. A series of molecular mechanisms of EGFR-TKI resistance including BIM deletion polymorphisms, T790M mutation, loss of PTEN, AKT and PIK3CA mutation were detected. **Conclusion:** Compared with chemotherapy, neoadjuvant EGFR-TKI is an efficacious approach for stage II-IIIA EGFR mutant NSCLC patients. A second month's extended TKI administration could be recommended if initial clinical response was achieved. These results, together with molecular detection, might provide evidence for further investigation of the treatment by randomized controlled trials.

Keywords: lung adenocarcinoma, EGFR mutation, neoadjuvant targeted therapy

JCSE 01 JOINT SESSION IASLC/CSCO/CAALC: IMMUNOTHERAPY FOR MANAGEMENT OF LUNG CANCER: ONGOING RESEARCH FROM EAST AND WEST
SUNDAY, OCTOBER 15, 2017 - 07:30-11:30

JCES 01.23 THE FEASIBILITY OF OSIMERTINIB TREATMENT ON BRAIN METASTASES IN NSCLC PATIENTS AFTER 1ST GENERATION EGFR-TKI RESISTANCE: A PRELIMINARY STUDY

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Background: NSCLC patients with activating EGFR mutations benefit from 1st generation EGFR-TKIs. It eventually develops acquire resistance after 10-12 months during of response. Of note, approximately one-third of those patients develop brain metastases, which deteriorate their quality of life and survival. Few effective therapeutic options are currently available for BM patients. Several case studies have showed the well response with osimertinib in BM patients. BM model also found the high penetration rate of Osimertinib into blood-brain barrier. This study evaluated the feasibility of osimertinib treatment on BM patients after 1st generation EGFR-TKI resistance. **Method:** Patients with advanced or recurrent NSCLC who had progressed during EGFR-TKIs treatment were collected from our previous clinical trial (NCT02418234) from March 2015 to March 2016. Blood samples were drawn within two weeks from PD occurred. T790M mutations were evaluated by droplet digital PCR. We undertook follow-up every 3 months by phone until April 2017. The median follow-up time was 11 months (range, 2 to 22 months). **Result:** Fifty NSCLC patients with BM after EGFR-TKI resistance were collected from our previous trials. After TKI resistance, ten patients received subsequent osimertinib treatment. Finally, ten patients included three males and seven females were included in the study. The median age was 66.5 (56 to 73). Seven were detected acquired T790M mutation. The median survival was 15.3 months (95% CI, 10.1 to 20.6 mo), 15.3 mo for T790M negative and 12.9 mo for T790M positive patients. **Conclusion:** Our preliminary study showed the well efficacy of osimertinib on NSCLC patients with BM. It provides well survival benefit. Randomized control trials should be required before it is widely used.

Keywords: Brain metastasis, lung cancer, osimertinib

JCSE 01 JOINT SESSION IASLC/CSCO/CAALC: IMMUNOTHERAPY FOR MANAGEMENT OF LUNG CANCER: ONGOING RESEARCH FROM EAST AND WEST
SUNDAY, OCTOBER 15, 2017 - 07:30-11:30

JCES 01.24 DETECTION OF EGFR, ALK AND OTHER DRIVER ONCOGENES FROM PLASMA CFDNA BY SINGLE MOLECULE AMPLIFICATION AND RE-SEQUENCING TECHNOLOGY (CSMART)

T. Mok[1], S. Lu[2], Y. Cheng[3], J. Wang[4], Y. Wang[5], T. Wang[5], T. Yung[6], X. Su[5], F. Sun[5], F. Sun[5], L.T. Wang[5], Y. Wu[7]

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Background: All patients with advanced stage NSCLC should have their EGFR and ALK mutation status known prior to initiation of first line therapy. Multiple plasma-based technologies such as ARMS and ddPCR are available for rapid detection of EGFR mutation, while only the more laborious Next Generation Sequencing (NGS) may cover EGFR, ALK and other uncommon mutations in a single blood test. cSMART is a novel NGS-based technology with rapid turnaround time that can detect EGFR, ALK and KRAS mutations plus others less common lung cancer specific driver oncogenes (BRAF, ROS-1, HER-2, PIK3CA, RET, MET14skipping). **Method:** Objectives of this study is to investigate the clinical application of cSMART on patients with advanced NSCLC. In cSMART assay, each cfDNA single allelic molecule is uniquely barcoded and universally amplified to make duplications. The amplified products are circularized and re-amplified with target-specific back-to-back primers. These DNA are then ligated with sequencing adapters and pair-end sequenced (>40,000x) with illumine sequencers. The original cfDNA molecules are reconstituted by multi-step bioinformatics pipeline for censor and correction. The final products are quantified for calculation of allele frequencies **Result:** Out of the 1664 samples tested, total of 1469 were of advanced stage NSCLC. We detected EGFR mutations in 758 (51.6%), ALK translocation in 34 (2.3%) and KRAS mutation in 78 (5.8%) patients. Among the patients with activating EGFR mutations, 301(39.7%) have exon 19 deletion and 279 (36.8%) have exon 21 point-mutation. Total of 6 (0.8%) patients with EGFR mutation have concurrent presence of ALK translocation. Incidence and mean allele frequency of the less common target mutation is summarized in Table. Median sample turnaround time is 7 days.

	Incidence (%)	Median Mutation Allele frequency (%)
BRAF	29 (1.97%)	0.08%
ROS1	2 (0.14%)	0.77%
HER-2	19 (1.29%)	0.20%
PIK3CA	70 (4.77%)	0.17%
RET	14 (0.95%)	0.57%
MET14skipping	63 (4.29%)	0.08%

Conclusion: cSMART is a novel plasma cfDNA-based technology that can detect the actionable target oncogenes for patients with advanced NSCLC. This is a sensitive method with capacity of detecting the uncommon targets at relatively low allele frequency.

Keywords: cSMART, Genome profiling, EGFR mutation

JCSE 01 JOINT SESSION IASLC/CSCO/CAALC: IMMUNOTHERAPY FOR MANAGEMENT OF LUNG CANCER: ONGOING RESEARCH FROM EAST AND WEST
SUNDAY, OCTOBER 15, 2017 - 07:30-11:30

JCES 01.25 DETECTION OF EGFR T790M MUTATIONS BY FOUR TESTING PLATFORMS IN CTDNA FROM CHINESE PATIENTS WITH ADVANCED NSCLC

X. Zhang[1], Z. Liang[2], Y. Chen[3], H. Zhang[4], W. Gang[5], Y. Lu[6], Z. Liang[6], Y. Cheng[7], Y. Hu[8], J. Wang[9], J. Ying[9], W. Liu[6], Y. Wu[1]

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Background: Osimertinib is used to treat patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). Detection of the T790M mutation in tissue samples may not be possible in some patients due to unfeasible or unsuccessful rebiopsies; detection in circulating cell-free tumor DNA (ctDNA) may represent a promising alternative. Here we evaluated four platforms to detect T790M using ctDNA in plasma from Chinese patients as part of the ADELOS study. **Method:** ADELOS is being conducted in China in 256 patients with advanced NSCLC, sensitizing mutations and progression on previous tyrosine kinase inhibitor. T790M was detected in plasma ctDNA by cobas® real-time polymerase chain reaction (PCR), super amplification refractory mutation system (Super-ARMS) PCR, QuantStudio3D digital PCR, and next-generation sequencing (NGS). T790M positive patients by any of the four platforms received osimertinib 80 mg/day orally. The relationship between T790M detection by each platform and objective response rate (ORR) was investigated. Concordance, sensitivity and specificity, and positive/negative predictive value between platforms were assessed. T790M mutation level in ctDNA was dynamically monitored every 6 weeks using digital PCR and NGS during osimertinib treatment, and its correlation with clinical outcome was evaluated. NGS also provided information about the heterogeneity of other genetic alterations in patients before osimertinib treatment. **Result:** Section will be completed in late-breaking abstract submission **Conclusion:** Section will be completed in late-breaking abstract submission

Keywords: osimertinib, T790M, Circulating Tumor DNA

JCES 01.26 CIRCULATING CELL-FREE DNA OF CEREBROSPINAL FLUID MAY FUNCTION AS LIQUID BIOPSY FOR LEPTOMENINGEAL METASTASES OF ALK REARRANGEMENT NSCLC

Y. Li[1], B. Jiang[1], J.-. Yang[1], X. Zhang[1], Z. Zhang[2], Q. Zhou[1], H. Tu[1], Z. Wang[1], H. Chen[1], C. Xu[1], B. Wang[1], Y. Wu[3]

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Background: Leptomeningeal metastases (LM) are more frequent in non-small cell lung cancer (NSCLC) patients with oncogenic drivers. Resistance mechanisms of LM with *ALK* rearrangement remained unclear due to limited access to leptomeningeal lesions. **Method:** Primary tumor, cerebrospinal fluid (CSF) and plasma in patients with suspected LM of NSCLC were tested by Next-Generation Sequencing. **Result:** In patents with ALKrearrangement, driver genes were detected in 66.7%, 50.0% and 28.6% patients of CSF cfDNA, CSF precipitates and plasma, respectively; and all of them had much higher allele fractions in CSF cfDNA than the other two media. The diagnosis criteria of LM were positive in brain MRI or CSF cytology, and driver genes were identified in CSF cfDNA of all patients with positive CSF cytology while in those CSF cytology negative all genes were negative. Resistance mutations including gatekeeper genes ALK G1202R and ALK G1269A were identified in CSF cfDNA but they were absent in their plasma. Moreover, tailor therapy based on CSF cfDNA obtained surprising outcomes, and genetic profiles of CSF cfDNA showed dynamic changes, suggesting the potential role of CSF for follow-up studies. **Conclusion:** CSF cfDNA could reveal the driver and resistant genes of LM, and it may function as the media of liquid biopsy for LM in NSCLC with *ALK* rearrangement.

Keywords: ALK rearrangement, cell-free DNA, Leptomeningeal metastases

JCES 01.27 PATIENTS WITH ALK IHC-POSITIVE/FISH-NEGATIVE NSCLC BENEFIT FROM ALK TKI TREATMENT: RESPONSE DATA FROM THE GLOBAL ALEX TRIAL

T. Mok[1], S. Peters[2], D. Ross Camidge[3], S. Gadgeel[4], S.I. Ou[5], D. Kim[6], R. Dziadziuszko[7], F. De Marinis[8], R. Sangha[9], A. Zeaiter[10], J. Noe[10], E. Nueesch[10], T. Liu[10], I. Loftin[11], C. Williams[11], A. Shaw[12]

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Background: Patients with *ALK*-positive NSCLC have seen significant advances and increased options in *ALK* targeted therapies recently, and therefore rely on high quality, robust *ALK* status testing. Fluorescence in-situ hybridization (FISH) and immunohistochemistry (IHC) are the most common methods to determine *ALK* status for ALK tyrosine kinase inhibitor (TKI) treatment. However, availability of clinical outcome data from randomized trials linked directly to specific methods is limited. The ALEX trial (BO28984, NCT02075840) provides a unique dataset to assess *ALK* IHC- and FISH-based assays regarding clinical outcome for alectinib and crizotinib, particularly for the subset of patients with IHC-positive/FISH-negative NSCLC. **Method:** The VENTANA ALK (D5F3) CDx Assay (ALK IHC) performed in central laboratories was used as an enrollment assay for the selection of patients with *ALK*-positive NSCLC for inclusion in the ALEX trial. Additional samples from these patients were retrospectively tested in central laboratories with the Vysis ALK Break Apart FISH Probe Kit (ALK FISH). **Result:** Overall, 303 patients all with *ALK* IHC-positive NSCLC were randomized in the ALEX trial, of those 242 patients also had a valid *ALK* FISH result, with 203 patients having *ALK* FISH-positive disease and 39 patients having *ALK* FISH-negative disease (alectinib, n=21; crizotinib, n=18). For 61 of 303 (20.1%) patients with an *ALK* IHC-positive result, a valid *ALK* FISH result could not be obtained due to the test leading to an uninformative FISH result (10.9%), or not having adequate/no tissue available (9.2%). Ventana IHC staining success rates were higher than for Vysis FISH testing for the ALEX samples. Exploratory analysis of investigator-assessed progression-free survival (PFS) in patients with a FISH-positive result (HR 0.40, 95% CI 0.27–0.61; p<0.0001; median not reached [alectinib] versus 12.7 months [crizotinib]) was consistent with the primary endpoint analysis in the Ventana *ALK* IHC-positive population. Patient outcome data show that 28% of central *ALK* IHC-positive/*ALK* FISH-negative samples were from patients who responded to ALK TKI treatment (complete response or partial response) and 33% had stable disease according to investigator assessment. **Conclusion:** This analysis shows that *ALK* IHC is a robust testing approach, which may identify more patients with a valid *ALK* testing result who benefit from ALK TKI treatment than *ALK* FISH testing. While PFS of patients with *ALK* FISH-positive NSCLC was similar to that of patients with *ALK* IHC-positive NSCLC, the analysis also revealed that the majority of patients with *ALK* IHC-positive/*ALK* FISH-negative NSCLC may derive clinical benefit from ALK TKI treatment.

Keywords: Alectinib, NSCLC, FISH

JCES 01.28 NGS SEQUENCING BASED LIQUID / TISSUE BIOPSY IDENTIFIED COEXISTENCE OF HER2 AMPLIFICATION AND MUTATION IN ADVANCED NSCLC PATIENTS

R. Chen[1], J. Zhao[2], G. Lin[3], L. Liu[4], L. Chen[5], X. Hu[6], X. Ai[7], Z. Fan[8], C. Xu[9], W. Wang[10], W. Zhuang[3], M. Fang[11], Y. Zhu[12], G. Chen[3], Y. Guan[1], L. Yang[1], X. Xia[1], X. Yi[1]

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Background: Human epidermal growth factor 2 (*HER2, ERBB2*) mutations / amplifications have been identified as oncogenic drivers in 2-5% of lung cancers. It has been reported that hybridization capture-based next-generation sequencing (NGS) could reliably detect *HER2* amplification in qualified breast and gastroesophageal tumor tissue samples. However, there is little data in lung cancer, especially for advance NSCLC with only ctDNA samples available. **Method:** We reviewed 2000 consecutive samples from advanced NSCLC patients sequenced in our institute between 2015 and 2016. Tumor biopsy and/or ctDNA samples were analyzed using hybridization capture-based NGS ER-Seq method, which enables simultaneously assess single-nucleotide variants, insertions/deletions, rearrangements, and somatic copy-number alterations at least 59 genes (range 59 – 1021 genes). **Result:** We identified 54 samples from 48 patients with *HER2*-mutation or amplification in the cohort (54/2000=2.7%). The 54 samples included 14 tissue biopsy samples, 37 ctDNA samples, and 3 pleural effusion samples. Thirty-six samples carried *HER2* mutations, and 23 samples carried *HER2* amplification with 5 samples have concurrent *HER2* mutation and amplification. A 9-base pair (bp) in-frame insertion in exon 20 (Y772_A775dup) was detected in 18 samples (18/36=50%). In addition, there were 5 other insertions in exon 20; eight single bp substitutions (S310F) in exon 8; three exon 17 V659E mutations (from the sample patient with 3 ctDNA samples submitted at different time); one exon 19 D769H mutation; and one exon 21 V842I mutation. Amplification were identified in 23 samples, with copy number range from 3.8 to 19.6 in tissue samples (n=7, medium 11.6); from 4.3 to 51.8 in ctDNA samples (n=16, medium 7.3); 3.2 and 6 in the 2 pleural effusion samples. Interestingly, the allele frequency (AF) of *HER2* mutation was the maximal in 4 of the 5 patients with concurrent *HER2* mutation and amplification. Two patients were EGFR-TKI resistant with *EGFR* L858R mutation remaining and *HER2* mutation and amplification might be the major reason for the resistance. **Conclusion:** *HER2* mutations might coexist with *HER2* amplification in advanced NSCLC patients, and it could be detected simultaneously with hybridization capture-based NGS sequencing both in tissue and liquid biopsy samples. Further quantative analysis of *HER2* amplification / mutation and anti-HER2 therapeutic effects are underway.

Keywords: next generation sequencing (NGS), ctDNA, HER2 amplification and mutation

WS 02 IASLC SYMPOSIUM ON THE ADVANCES IN LUNG CANCER CT SCREENING (TICKETED SESSION)
SATURDAY, OCTOBER 14, 2017 - 09:00-18:15

WS 02.03 LUNG CANCER SCREENING – IELCAP CONTRIBUTION TO CT SCREENING IMPLEMENTATION

C. Henschke[1], A. Reeves[2], D. Yankelevitz[1]

[1]Radiology, Icahn School of Medicine at Mount Sinai, New York/US, [2]School of Electrical and Computer Engineering, Cornell University, Ithaca/NY/US

1. Introduction of CT screening and showing its value. First to introduce CT screening in a novel cohort design comparing CT with chest radiography, providing a workup strategy for screen-detected nodules. Predicted outcome of well-designed and correctly powered RCT studies Henschke C, McCauley D, Yankelevitz D, Naidich D, McGuinness G, Miettinen O, Libby D, Pasmantier M, Koizumi J, Altorki N, and Smith J. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354:99-105. **2. Long-term survival rates of patients diagnosed with lung cancer in a program of CT screening.** First to provide estimated cure rates under screening by measuring long-term survivial. The International Early Lung Cancer Action Program Investigators. Survival of Patients with Stage I lung cancer detected on CT screening. NEJM 2006; 355:1763-71 **3. 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Keywords: baseline, annual rounds, positive results, growth rates, other thoracic and abdominal findings

WS 02 IASLC SYMPOSIUM ON THE ADVANCES IN LUNG CANCER CT SCREENING (TICKETED SESSION)
SATURDAY, OCTOBER 14, 2017 - 09:00-18:15

WS02.05 THE EUROPEAN COMMISSION RECOMMENDATIONS ON LUNG CANCER SCREENING

D. Horgan

European Alliance for Personalised Medicine (EUAPM)/BE

Around one billion people on the planet are regular smokers. And lung cancer is one of the biggest killers. We all now know that there is a direct connection in many cases. Non-smokers do get lung cancer, but the risks if you are a smoker are significantly. Undoubtedly, tobacco smoking is the major risk factor for lung cancer, although passive smoking, and a family history of lung, head and neck cancer are, among other factors, also important. Figures show that lung cancer causes almost 1.4 million deaths each year worldwide, representing almost one-fifth of all cancer deaths. Within the EU, meanwhile, lung cancer is also the biggest killer of all cancers, responsible for almost 270,000 annual deaths (some 21%). It is at the very least surprising that the biggest cancer killer of all does not have a solid set of screening guidelines across Europe, Doctors need to quickly identify high quality, trustworthy clinical practice guidelines, in order to improve decision making for the benefit of their patients. The Alliance has turned its attention to need for more guidelines across the arena of healthcare, especially in screening for lung cancer. There is a need for agreement and coordination across the European Union's 28 Member States. In the US, the American Cancer Society has stated that it had "thoroughly reviewed the subject of lung cancer screening" and issued guidelines that are aimed at doctors and other health care providers. Europe, among other things, is looking at risk prediction models to identify patients for screening, plus determination of how many annual screening rounds is enough. Of course, cost-effectiveness questions arise whenever population-wide screening is considered, especially in relation to frequency and duration. Yet, the potential benefit of low-dose CT lung cancer screening would almost certainly see an improvement in the lung cancer mortality rate in Europe. Stakeholders are aware that screening for lung cancer also has potential harms. These include radiation risks (increased risk of other cancers), identification of often harmless nodules, which could lead to further evaluation (including biopsy or surgery), unnecessary fear in the patient and those close to him or her, and over-diagnosis and possibly subsequent treatment of cancerous cells that would cause no ill effects over a lifetime. Often, malignant small lesions are found that would not grow, spread, or cause death. This could lead to over-diagnosis or over-treatment, bringing about extra cost, anxiety and ill-effect (even death) caused by the treatment itself. On the other hand screening can help to ensure that surgery in lung cancer's early stages can continue to be the most effective treatment for the disease. As it stands, most patients are diagnosed at an advanced stage - usually non-curable. EAPM, along with other aforementioned stakeholders, believes that there is a strong case for lung cancer screening programmes across the 28 EU Member States to reduce the cases of advanced-stage lung cancer. Among recommendations currently being discussed in European forums are the setting of minimum requirements, which should include standardised operating procedures for low-dose imaging, criteria for inclusion (or exclusion) for screening and, of course, smoking cessation programmes. Also important are improving the quality, outcome and cost-effectiveness of screening,

reducing radiation risks, and making thorough assessments of other risks, such as co-morbidities. ERS and ESR have stated that "the establishment of a central registry, including biobank and image bank, and preferably on a European level, is strongly encouraged", and EAPM is in full support of this. **Current situation** In the US, lung cancer screening has been the subject of major policy decisions and investigations. One finding showed that a screening trial brought about a 20% drop in lung cancer mortality. On the back of this, several mainstream clinical and professional organisation recommended the implementation of screening. In Europe, the Dutch and Belgian NELSON lower-dose computed tomography (CT) trial is producing data on mortality rates (and, of course, cost effectiveness). The NELSON study was designed to investigate whether screening for lung cancer by low-dose CT in high-risk subjects would lead to a decrease in 10-year lung cancer mortality of at least 25%. This to be looked at in comparison to a control group which was not undergoing screening. The NELSON study began in 2003, using men aged 50–75 years from seven districts in the Netherlands and subjects from both sexes from 14 close geographical areas in Belgium. Initially, these subjects were sent a questionnaire about general health, how much they smoked, their cancer history, and several other lifestyle and health factors. Based on the smoking history, the estimated lung cancer mortality risk of the respondents was determined. Next, the required sample size including required participation rate was determined. Thirteen years on and the results from the final, fourth round of what is EU's largest trial have found that leaving a two-and-a-half-year interval reduced the effect of screening. In essence this means that the cancer rate showed higher levels than found with one-year and two-year screening intervals. Crucially, in the final round, occurrences of the advanced-stage disease were higher than previous rounds and, as discussed above, that invariably means more deaths. Further EU pooled trial results are expected to come along soon, in the wake of NELSON. **Conclusions** Findings in both Europe and the US strongly suggest that lung cancer screening works. Current evidence is, as yet, limited and the discussion continues. But there is hard evidence, although debate continues about the best way to implement screening of this kind, and even how to properly evaluate 'cost effectiveness' - who should decide? Of course, guidelines could help to tether costs, by bringing in improvements to the efficiency of screening methodologies and, thus, programmes themselves. Key to such a situation would be making the best use of efficient risk-assessment methods,

top-of-the-range imaging technology, and guidelines that encourage the minimisation of invasive procedures and risk to the patient.

WS 02 IASLC SYMPOSIUM ON THE ADVANCES IN LUNG CANCER CT SCREENING (TICKETED SESSION)
SATURDAY, OCTOBER 14, 2017 - 09:00-18:15

WS 02.12 LUNG CANCER BIOMARKERS - DO WE HAVE GOOD CANDIDATES FOR EARLY DETECTION?

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Are we screening the at risk population? How can we bring imaging and molecular tools to improve the early detection/treatment rates of lung cancer and decrease the false positive rates? The National Lung Screening Trial (NLST) demonstrated that low dose CT screening among high risk individuals reduces the relative risk for lung cancer mortality by 20%. Yet the poor specificity of chest CT, which forces us to deal with large proportions of false positive results, morbidity and cost, pushes us to improve the risk assessment and diagnostic accuracy of the tests offered. A large proportion of individuals will be diagnosed with lung cancer and still do not meet the population criteria studied in NLST trial. So the scientific community is charged to improving early detection of invasive lung cancers to a definitive treatment. An estimated 43% of individuals diagnosed with lung cancer meet the NLST criteria, thus missing an opportunity to screen another large at-risk population. There are currently no accepted strategies for screening patients who fall outside of these criteria. Therefore tools of risk assessment and early detection could profoundly reduce lung cancer mortality. Considerations for familial history with or without germline DNA mutation carriers, exposure to carcinogens, chronic pulmonary obstructive lung disease, are being proposed for integration in risk prediction strategies. The reporting tools for findings at the time of CT screening have been replaced by the American Radiology Association's LungRADS score which reduces the false positives rate among the most highly suspicious lesions from 27% to 13%. On the imaging diagnostic side, the emerging field of radiomics involves computational analysis of extracted quantitative data from clinical radiology images. Rapid progress in this field offers the promise of diagnostic accuracies that will surpass the one of expert radiologists. On the molecular diagnostic side, diagnostic tools for risk adjustment and to augment current lung cancer detection strategies are urgently needed. Circulating tumor cells are shed from primary tumors into the blood stream, so is circulating tumor DNA naked or in microvesicles. Proteins, RNA moieties and epigenetic changes can be captured in the circulation and also have the promise of changing the landscape of non-invasive diagnosis of early lung cancer. Some of these strategies will be discussed to illustrate the impressive and rapid progress soon coming to the clinic to address the primary goals of early detection.

Keywords: Interception, validation, Utility

WS 02 IASLC SYMPOSIUM ON THE ADVANCES IN LUNG CANCER CT SCREENING (TICKETED SESSION)
SATURDAY, OCTOBER 14, 2017 - 09:00-18:15

WS 02.15 QUALITY CONTROL FOR LUNG IMAGING BIOMARKERS

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Computed Tomography (CT) imaging of the lung has been routinely used over the last few decades to detect and treat early lung cancer and other related diseases. As CT image acquisition technology has improved, the use of CT for quantitative and precise lung imaging clinical applications has greatly expanded. High resolution CT studies, which now easily obtain sub-millimeter resolution of the entire chest within a breath-hold, are now widely used to detect and measure changes in early lung cancer lesions and COPD. Traditionally, several concurrent methods have been used to ensure that the quality of acquired CT images is adequate for general clinical use. This includes regular scanning and analysis of CT quality control phantoms from ACR (as well as from individual CT scanner manufacturers) and visual inspection of acquired images by radiologists for significant image artifacts. While these methods have served the field of radiology well for identifying and correcting major image quality issues, there has not been standard image quality assessment methods available for specific clinical applications that require precise image-based measurements. To improve global quality control of lung imaging studies, several clinical societies and organizations have provided image acquisition and measurement guidance documents intended to be followed by clinical sites [1, 2, 3]. We are entering a new era of quantitative imaging where easy to use tools are available that ensure that precise quantitative image measurements can be routinely and reliably obtained. To achieve this goal, a new set of task-based image quality control measures is being developed by research groups and radiology societies such as the RSNA's Quantitative Imaging Biomarkers Alliance [4]. Each major quantitative imaging-based clinical task is being extensively studied to determine the fundamental image quality properties needed (e.g. resolution, sampling rate, noise, intensity linearity, spatial warping) to achieve a minimum level of measurement performance. In addition, new low-cost phantoms are being developed that can be quickly scanned and automatically analyzed to estimate these fundamental properties throughout the full three-dimensional CT scanner field of view. Deploying these low-cost phantoms and automated phantom analysis software on the cloud further enables global clinical sites to quickly and easily verify the quality of a CT scanner and acquisition protocol for a specific quantitative clinical task. In addition to providing a fast method for verifying conformance with minimum quantitative imaging performance standards, the reports generated can provide guidance as to the best protocols observed for a particular CT scanner model, thereby allowing a clinical site to optimize image acquisition protocols with the best evidence obtained through crowd-sourcing task-specific image quality information. The QIBA CT lung nodule task force is now preparing to launch a pilot project to evaluate the utility of these new image quality control measures for the quantitative measurement of the change in volume of solid lung nodules (6mm to 10mm diameter) [5]. Over the coming months this new "active" and cloud-based analysis approach will be deployed at international lung cancer screening institutions and use statistics will be assembled. The data collected has the potential not only to inform the lung cancer screening community on the global quality of lung cancer screening imaging, but also to establish early data on whether these new methods can one day serve as a more effective approach to providing quality control for quantitative imaging methods. **References** 1. Kauczor HU, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, Remy-Jardin M, von Stackelberg O, Sculier JP; European Society of Radiology (ESR); European Respiratory Society (ERS), ESR/ERS white paper on lung cancer screening, ESR/ERS white paper on lung cancer screening. 2. IELCAP, IELCAP Protocol Document, http://www.ielcap.org/sites/default/files/I-ELCAP-protocol.pdf Accessed May 31, 2017. 3. Fintelmann FJ, Bernheim A, Digumarthy SR, Lennes IT, Kalra MK, Gilman MD, Sharma A, Flores EJ, Muse VV, Shepard JA, The 10 Pillars of Lung Cancer Screening: Rationale and Logistics of a Lung Cancer Screening Program, Radiographics. 2015 Nov-Dec;35(7):1893-908. 4. https://www.rsna.org/QIBA/ 5. RSNA QIBA, Draft QIBA Profile: Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening, http://qibawiki.rsna.org/images/e/e6/QIBA_CT_Vol_LungNoduleAssessmentInCTScreening_2017.05.15.docx, May 15, 2017.

Keywords: computed tomography, lung cancer screening, Image Quality

WS 02 IASLC SYMPOSIUM ON THE ADVANCES IN LUNG CANCER CT SCREENING (TICKETED SESSION)
SATURDAY, OCTOBER 14, 2017 - 09:00-18:15

WS 02.20 COMMUNICATING COMPLEX ISSUES SIMPLY: PIVOTAL ROLE OF NURSING IN LUNG CANCER SCREENING

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Lung cancer screening offers a unique opportunity for medicine to closely partner with nursing in detecting lung cancers at earlier, treatable stages, address other tobacco related diseases, and assist patients in smoking cessation efforts. Foundational nursing principles are universal around the world with an emphasis on clinical care, research and implementation science, patient education and health coaching, performance improvement and quality outcomes processes, and patient-centered care. Given this preparation, nursing professionals can be potent if positioned predominantly at the helm of lung cancer screening programs with the most touch-points and direct interaction with screening recipients, over the screening

continuum. Lung cancer screening encounters present an opportunity for early rather than late detection of preventable and treatable diseases through low dose CT scan. Additionally, lung cancer screening can be utilized as a transformational health tool by positioning nursing at the center of the integrative care delivery model and drive beneficial health outcomes through direct counseling, and health coaching. This includes facilitating preventive measures that directly impact the natural history of tobacco related diseases through smoking cessation counseling and treatment services and health coaching as it relates to the individual patient, their current health state, and low dose CT scan results. The professional services that nursing is keenly positioned to offer within the multidisciplinary lung cancer screening setting hold great potential for an international sustainable screening model. This presentation will discuss pragmatic, approaches to evidence based screening programs, led by nursing, in which high-risk patients receive the care they need and deserve, encourages active engagement in the critical continuum of screening and opens opportunity for improvements in individual and population health.

Keywords: lung cancer screening, nursing, tobacco related disease

OA 01 THE NEW ASPECT OF RADIATION THERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

OA 01.02 STEREOTACTIC RADIOTHERAPY AS SALVAGE TREATMENT AFTER SURGERY AND CURATIVE INTENDED RADIOTHERAPY FOR PATIENTS WITH NSCLC

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Background: Stereotactic radiotherapy (SBRT) is an efficient treatment for early stages of inoperable NSCLC. SBRT may, however, also be used as salvage treatment for recurrent disease. This retrospective study reports and compares the outcome of patients initially treated with surgery and patients initially treated with curative radiotherapy (RT). **Method:** All cases of NSCLC treated with RT with curative intent at our institution are prospectively recorded. We here report the results of 114 cases treated at our institution July 2009 to June 2016 with SBRT as salvage therapy. The doses used for peripheral located tumors have been 45-66 Gy (central doses) in 3 fractions (F) while centrally located tumors have been treated with 50-78.4 Gy/ 5-8 F. The patients have been treated with IMRT or VMAT. A group of 80 patients had surgery initially (Surg-Grp): Resection 19 (24%), lobectomy 56 (70%), bi-lobectomy 1 (1%), and pneumonectomy 4 (5%). Another group of 34 patients was initially treated with RT (RT-Grp): SBRT 30 (88%) and conformal chemo-RT 4 (12%). All patients had more than 1 year of potential follow-up. **Result:**

The patient characteristics			
	Surg-Grp	RT-Grp	p-value
Age (yr.)	72.6 (55.1; 89.3)	71.7 (53.5; 87.1)	0.56
Female /Male	45 / 35	18 /16	0.91
PS 0-1	55 (69%)	15 (44%)	
PS 2	21 (26%)	15 (44%)	
PS 3	4 (5%)	4 (12%)	
Median FEV1 (L/sec)	1.54 (.39-2.72)	1.37 (.42-2.75)	0.59
Time from initial treatment to salvage treatment (mo)	22.4 (0.6; 272)	20.7 (4.4; 100)	
Salvage RT			
45 Gy/3 F	10 (13%)	9 (26%)	
66 Gy/3 F	54 (68%)	18 (53%)	
50 Gy /5 F	3 (4%)	0	
78.4 Gy /8 F	13 (16%)	7 (21%)	

The median, 1, 2, 3, and 4 year overall survival was 50.5 mo, 85%, 72%, 59%, and 59 % in the Surg-Grp and 31.3 mo., 71%, 55%, 46%, and 46% in the RT-Grp, (p=.13). **Conclusion:** SBRT gives excellent survival used as salvage therapy after surgery and curative intended radiotherapy.

Keywords: SBRT, Salvage treatment, Radiotherapy

OA 01 THE NEW ASPECT OF RADIATION THERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

OA 01.03 PATTERNS OF CHANGE IN HIGH-RISK RADIOLOGICAL FEATURES IN PATIENTS WITHOUT LOCAL RECURRENCE AFTER SABR FOR EARLY-STAGE NSCLC

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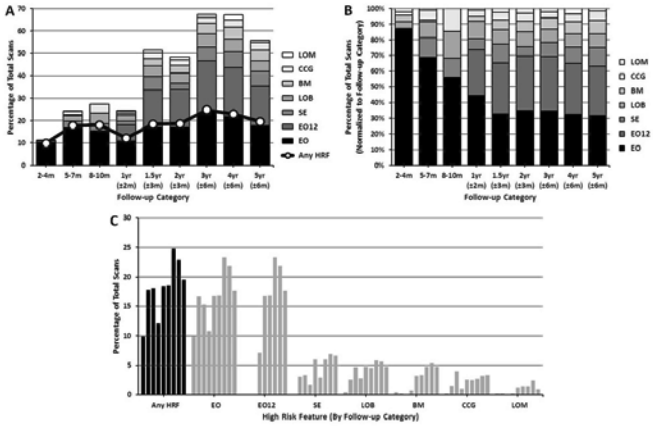
Background: Five-year local control rates in early-stage NSCLC following stereotactic ablative radiotherapy (SABR) are approximately 90%. However, the resulting focal fibrosis can be difficult to distinguish from tumor recurrences. We investigated the incidence, and patterns of change in previously reported high-risk radiological features (HRF's), in patients who were known to have no local recurrence. **Method:** Patients treated using volumetric modulated arc therapy SABR were eligible if follow-up CT-scans were available for at least 2 years. Five clinicians who were unaware of clinical outcomes scored the following HRF's on CT-scans: enlarging opacity(EO), sequential enlarging opacity(SE), enlarging opacity after 12 months(EO12), bulging margin(BM), loss of linear margins(LOM), cranio-caudal growth(CCG) and loss of air bronchogram(LOB). CT-scans were reviewed at a workstation using in-house plugin customized for ClearCanvas (Synaptive Medical, Toronto, Canada). After each review, clinicians recommended follow-up procedures based on previously published recommendations. **Result:** In 88 patients (747 CT-scans) evaluated, the HRF's most frequently recorded by ≥3 observers on at least one follow-up CT-scan were EO (64.8%), EO12 (50.0%) and SE (13.6%). Cumulative mean incidence rates of each HRF per category are displayed (figure). Fifty-six patients developed EO in the first year, and 46 of these patients developed subsequent EO12. In 76 patients who developed EO12, 30 had no EO previously. The presence of ≥3 HRF's have been associated with recurrences, and this was observed in 20 patients. When HRF's were identified, clinicians indicated that they were either very certain (mean: 37.2%, range: 11.9-70.4%) or moderately certain (mean: 51.2%, range: 26.5-87.1%) about the presence of this feature. In routine care, only 6 patients underwent PET-scans because of a suspected local recurrence, an attempt at biopsy.

Cumulative mean incidence rates of each HRF per follow-up category based on a total of 88 patients and 747 CT - scans for (a) percentage of total scans with overlaid incidence rates of any HRF, (b) percentage of total scans nor - malized to follow-up category cumulative totals and (c) percentage of total scans grouped by HRF showing inter - and intra-HRF incidence rate fluctuation.



Conclusion: Although HRF's on CT-scan develop in more than 50% of patients without local recurrence after SABR, only 23% had ≥3 HRF's.

Keywords: Stereotactic ablative radiotherapy, non-small cell lung cancer, high-risk radiological features

OA 01 THE NEW ASPECT OF RADIATION THERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

OA 01.05 ANALYSIS OF RADIOTHERAPY QUALITY ASSURANCE DATA FOR THE CONVERT TRIAL - DOES NON-COMPLIANCE TO PROTOCOL AFFECT SURVIVAL?

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Background: The CONVERT Trial is a multicentre phase III study which recruited 547 patients with limited-stage SCLC from April 2008 to November 2013. Patients were randomised to receive once daily (66Gy in 33 fractions) or twice daily (45Gy in 30 fractions) radiotherapy concurrently with chemotherapy. The primary endpoint was overall survival. This study investigates the effect of non-compliance to radiotherapy protocol on survival for the CONVERT Trial. **Method:** 489/557 received chemo-radiotherapy according to protocol. As part of the CONVERT trial quality assurance (QA) programme, 94 patient datasets (19.2%) treated with concurrent chemoradiotherapy (n=489) were reviewed and deviations from protocol were categorised as acceptable, acceptable variation and unacceptable variation using the Global Harmonisation Group (GHG) variation definitions. Organ at risk outlining (heart, spinal canal and lung minus planning target volume (PTV)), target delineation and margins applied, PTV coverage, treatment planning technique and radiotherapy treatment time were reviewed and classified according to the GHG definitions. A multiplicative factor (F) was calculated for each treatment plan, based on the GHG definitions. A low factor indicates a low number of protocol deviations. Protocol deviations were correlated with survival and number of patients recruited per centre. **Result:** 94/489 patients were included in this analysis (19.2% of the randomised patients). The median number of patients recruited per centre was 6 (range 1-109). Protocol deviations were categorised as acceptable (57.6%), acceptable variation (23.3%) or unacceptable variation (19.1%). Amongst the unacceptable variations the PTV coverage was the most common deviation to protocol. In these 71 patients (75.5%) the dose distribution within the PTV was greater than 7% of the prescribed dose. Patients with increasing number of organ at risk outlining protocol deviations and with an increase in the multiplicative factor (F) had a lower survival. Further details will be presented at the meeting including survival in the 3 GHG categories. Centres recruiting >25 patients were found to have a lower number of protocol deviations (median 2, range 2-3) compared with centres recruiting fewer than 25 patients (median 3, range 0-4.5), and were most likely to delineate organs at risk correctly. **Conclusion:** High recruiting centres are most likely to comply with a trial protocol. Overall survival was affected by the number and type of protocol deviations, highlighting the importance of a robust trial QA programme in prospective radiotherapy trials.

Keywords: protocol compliance, survival, quality assurance

OA 01.06 RADIATION THERAPY IS ASSOCIATED WITH AN INCREASED INCIDENCE OF CARDIAC EVENTS IN SMALL CELL LUNG CANCER PATIENTS

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Background: Radiation (RT) dose to the heart was a predictor of inferior overall survival (OS) in the non-small cell lung cancer trial RTOG 0617, but little data quantifies cardiac morbidity for small cell lung cancer (SCLC) patients treated with RT. **Method:** The Surveillance, Epidemiology, and End Results (SEER) Program database and Medicare claims data were queried to establish rates of cardiac events (CE) among SCLC patients treated with chemotherapy (CTX) +/- RT. CE were defined as any new cardiac diagnosis including ischemic disease, cardiomyopathy, dysrhythmia, heart failure, and pericarditis. Chronic/pre-existing diagnoses were not counted as events. CTX-only patients were matched to CTX + RT patients to account for start date of RT. Second phase of propensity score matching (PSM) balanced demographical and clinical differences. Multivariate analysis (MVA) determined effect of tumor and RT covariates on CE and OS. Kaplan-Meier and cumulative incidence (CI) function curves were generated. **Result:** From 2000 – 2011, 7,060 patients were available: 2,892 (40.9%) limited-stage and 4,168 (59.0%) extensive-stage. As expected, CTX + RT patients had better OS ($p < 0.001$). OS for the CTX + RT and CTX-only groups: 35.0 vs. 21.4% at 12 months, and 6.6 vs 2.3% at 60 months, respectively. RT was associated with CE ($p = 0.008$), with CI as follows for the CTX + RT and CTX-only groups: 36.4 vs. 35.4% at 12 months, and 44.1 vs 39.0% at 60 months, respectively. MVA demonstrated higher hazard ratio of CE for extensive-stage patients ($p < 0.001$), black race ($p < 0.001$), and increased Charlson-Deyo score ($p = 0.001$). After PSM, 5,286 patients were included. Again, CTX + RT patients had better OS ($p < 0.0001$). OS for the CTX + RT and CTX-only groups: 30.6 vs. 22.5% at 12 months, and 5.3 vs 2.7% at 60 months, respectively. RT was still associated with CE ($p = 0.033$) after PSM, with CI of CE for the CTX + RT and CTX-only groups: 36.3 vs. 34.8% at 12 months, and 43.0 vs 38.6% at 60 months, respectively. Tumor laterality ($p = 0.84$) and RT modality ($p = 0.62$) were not associated with CE, though low numbers were treated with intensity-modulated versus 3D conformal RT (1:15 ratio). **Conclusion:** In this large database study we demonstrated RT is associated with an absolute increase in the rate of CE at 5-years of approximately 5%. Further evaluation of cardiac sparing radiation techniques should be evaluated for patients with SCLC.

Keywords: Radiotherapy, small cell lung cancer, Cardiac Events

OA 01.07 TRACKING MAJOR SYMPTOM BURDEN FROM CHEMOTHERAPY CONCURRENT WITH 3D VS. IMRT VS. PROTON BEAM RADIOTHERAPY FOR NSCLC

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Background: During standard concurrent chemoradiotherapy (CRT), patients with NSCLC often report severe symptoms that should be routinely assessed and managed. According to the United States FDA specified standards, patient-reported outcome (PRO) instruments used in clinical trials should have good measurement properties of reliability, validity, and the ability to detect change. This quantitative study used a validated PRO symptom-assessment tool, the MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC), to compare a cluster of CRT-related symptoms in NSCLC patients receiving CRT, and to investigate the sensitivity of a composite score of these symptoms. **Method:** We enrolled patients with locally advanced NSCLC (n=118) who underwent intensity-modulated radiation therapy (IMRT, n=33), 3-dimensional conformal radiation therapy (3DCRT, n=22), or proton-beam therapy (PBT, n=63). Patients completed the MDASI-LC weekly for up to 12 weeks. Two criteria used for item selection to form a subscale for CRT-related symptoms: MDASI-LC items rated 4-10 in >25% of observations, and that increased significantly during therapy (by mixed-effect models). A CRT-symptom score (MDASI-LC-CRT) was generated by averaging scores from those symptoms. The MDASI-LC-CRT's responsiveness to treatment was examined by within-person change over time and effect size (ES) statistics. **Result:** Six symptoms—pain, fatigue, drowsiness, lack of appetite, sore throat, coughing—were identified as the most-severe CRT-related symptoms during and after therapy. Before CRT, MDASI-LC-CRT scores did not differ by treatment (3DCRT 2.2±1.8, IMRT 1.6±1.5, PBT 1.8±1.7, p=0.329). At the end of CRT, MDASI-LC-CRT was highest for 3DCRT (4.85±2.40), followed by IMRT (3.18±1.85) and PBT (2.29±1.65). A large ES (1.24) was found for 3DCRT vs. PBT; medium ES were found for 3DCRT vs. IMRT (0.78) and IMRT vs. PBT (0.51). The ES for pre-CRT vs. post-CRT difference (1.8±1.7 vs. 3.0±2.1) was medium (0.63) for all patients, large for 3DCRT (1.25) and IMRT (0.93), and small for PBT (0.28). The MDASI-LC-CRT score increased significantly over treatment (estimated weekly increase=0.21, p<0.0001), peaking at week 7 (95%CL=6.2-7.8, p<.0001) and then decreasing to week 12 (est=0.18, p=0.001). Significantly larger weekly increase was reported by 3DCRT and IMRT patients, compared with PBT patients (all p<0.0001). **Conclusion:** The MDASI-LC-CRT is a sensitive indicator of dynamic change in major symptom burden during CRT. This subscale could be routinely used for symptom monitoring while patients are going through CRT and appropriate supportive measures could be instituted early. PBT was the best tolerated of the radiation modalities when given concurrently with chemotherapy with the least worsening of symptoms over the CRT period.

Keywords: Patient-reported outcomes, chemoradiation, MD Anderson Symptom Inventory

OA 02.01 RANDOMIZED PHASE II STUDY OF ANETUMAB RAVTANSINE OR VINORELBINE IN PATIENTS WITH METASTATIC PLEURAL MESOTHELIOMA

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Background: Anetumab ravtansine (BAY 94-9343) is a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4. We report the results of a randomized phase II trial of anetumab ravtansine compared to vinorelbine in patients with advanced malignant pleural mesothelioma (MPM) who have high mesothelin expression and have progressed on platinum/pemetrexed-based first-line chemotherapy (NCT02610140). **Method:** Patients (≥18 years) with locally advanced or metastatic MPM with progressive disease following first-line treatment with pemetrexed-based chemotherapy, with or without bevacizumab, were eligible. Patients were pre-screened based on obligatory tumor staining for mesothelin as determined by the Ventana MSLN (SP74) immunohistochemistry assay. The primary efficacy endpoint was progression-free survival (PFS) per central radiologic review using modified RECIST criteria for MPM. Secondary objectives included overall survival, tumor response, and safety. Patients were randomized in a 2:1 ratio to anetumab ravtansine 6.5 mg/kg Q3W IV or vinorelbine 30 mg/m^2 QW IV. **Result:** A total of 166 patients were randomized to anetumab ravtansine and 82 to vinorelbine; 3 and 10 patients, respectively, not receiving treatment were included for efficacy but not safety assessments. The treatment arms were evenly balanced, with 73% male, 64% ECOG performance status 1, 96% epithelioid histology, and a mean 2.5 (±2.4) months since last progression. The median duration of treatment (anetumab vs vinorelbine) was 12.6 weeks (range 3-61) vs 13.0 weeks (range 1-43). Treatment-emergent grade (G) ≥3 adverse events (AEs) were seen in 85 (52.1%) and 53 (73.6%) of patients, respectively. G3/G4 neutropenia (22.2%/16.7%) occurred in the vinorelbine arm whereas corneal epitheliopathy (39.3% all grade, 1.8% G3) was distinct for the anetumab ravtansine arm. Serious AEs (any grade) were similar; 52 (31.9%) vs 25 (34.7%). Treatment-emergent AEs leading to dose modification were 42.9% in the anetumab ravtansine arm and 80.6% in the vinorelbine arm. There was one treatment-related G5 event in each arm. Median PFS was 4.3 months (95% CI:4.1, 5.2) for anetumab ravtansine vs 4.5 months (4.1, 5.8) for vinorelbine; hazard ratio 1.22 (0.85, 1.74), p=0.859. Fourteen (8.4%) patients in the anetumab ravtansine arm had an objective response vs 5 (6.1%) in the vinorelbine arm, with no complete responses. Interim median overall survival was 10.1 mo (7.6, -) vs 11.6 mo (7.7, 12.5), respectively, p-value 0.721. **Conclusion:** In relapsed MPM, anetumab ravtansine was not superior to vinorelbine with respect to PFS.

Keywords: Mesothelioma, mesothelin

OA 02.02 IPILIMUMAB AND NIVOLUMAB IN THE TREATMENT OF RECURRENT MALIGNANT PLEURAL MESOTHELIOMA: A PHASE II STUDY

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Background: There is an increasing interest in the use of IO therapy in Mesothelioma (MPM). We previously reported on the effect of nivolumab (s.a) in patients with recurrent MPM with a disease control rate of 50% at 12 weeks. We therefore decided to test the effect of the combination of nivolumab and ipilimumab in recurrent MPM. **Method:** Patients with previously treated MPM and a PS of 0-1 are consented in this single arm prospective study. Pleural lesions must be available for biopsy

before and after 6 weeks of treatment.Nivolumab is administered at a fixed dose of 240 mg (q2w) until progression and combined with ipilimumab (1mg/kg) on week 1, 7, 13 and 19. CT scans are performed every 6 weeks for analysis and duration of response. The primary endpoint is disease controle rate at 12 weeks. Translational research is performed on paired biopsies. A Simon's minimax two-stage design is used to identify a DCR of >50%. Therefore 33 patients will be included. **Result:** From October 2016 until August 2017 38 patients gave informed consent. Three patients did not start due to progression or impossibility to biopsy. Two stopped after 1 cycle (due to progression or withdrawn consent). At time of analysis (August 29) 25 patients could be evaluated for response. At 12 weeks a DCR of 72% (18/25) and ORR of 28% (7/25) is observed. Two patients continued treatment after progression at 6 weeks; 1 achieved a PR after 4 months , and the other one is stable. Of the first 11 patients that have been in study for **6** months, 5 have PR, 1 SD and 4 PD. Toxicity is mild. SAE's reported in the 38 patients occurred in 11 patients with grade 3 or 4 toxicity. No grade 5 toxicity was observed. **Conclusion:** In this interim analysis nivolumab plus ipilimumab meets the primary endpoint for patients with recurrent malignant mesothelioma. Toxicity is mild. The full data set will be presented at the WCLC.

Keywords: Mesothelioma, Nivolumab, Ipilimumab

OA 02 MESOTHELIOMA: CHALLENGES FOR NEW TREATMENT
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

OA 02.03 PROPHYLACTIC IRRADIATION OF TRACTS (PIT) IN PATIENTS WITH PLEURAL MESOTHELIOMA: RESULTS OF A MULTICENTRE PHASE III TRIAL

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Background: It has been widespread practice across Europe to irradiate diagnostic or therapeutic chest wall (CW) intervention sites in patients with malignant pleural mesothelioma (MPM) post-procedure - a practice known as prophylactic irradiation of tracts (PIT). This study aims to determine the efficacy of PIT in reducing the incidence of CW metastases following a chest wall procedure in MPM. **Method:** In this multicentre phase III randomised controlled trial, MPM patients following a chest wall procedure were randomised 1: 1 to receive PIT (within 42-days of procedure) or no PIT. Large thoracotomies, needle biopsy sites and indwelling pleural catheters were excluded. PIT was delivered at a dose of 21Gy in 3 fractions over 3 consecutive weekdays using a single electron field adapted to maximise coverage of the tract from skin surface to pleura. The primary outcome was the incidence of CW metastases within 6 months from randomisation, assessed in the intention-to-treat population. Stratification factors included epitheloid histology and intention to give chemotherapy. Trial registration number NCT01604005. **Result:** 375 patients (186 PIT and 189 no PIT) were randomised between 06/2012-12/2015 from 54 UK centres. Comparing PIT vs no PIT, %male patients was 89.8/88.4%, median age 72.8/74.6 years, %ECOG PS (0,1,2) 32.2,56.5,11.3/23.8,56.1,20.1%, %confirmed epithelioid histology 79.6/74.1%, and %with intention to give chemotherapy 71.5/71.4%. The chest wall procedures were VATS (58.1/51.3%), open surgical biopsy (2.7/5.3%), local-anaesthetic-thoracoscopy (26.9/27.0%), chest drain (5.9/8.5%) and others (6.5/7.9%) for the PIT vs no PIT arm respectively. Radiotherapy was received as intended by 181/186 patients in the PIT arm. The proportion of CW metastases by 6 months was 6/186 (3.2%) vs 10/189 (5.3%) for the PIT vs no PIT arm respectively (odds ratio 0.60 [95% CI 0.17-1.86]; p=0.44) and by 12 months 15/186 (8.1%) versus 19/189 (10.1%) respectively (OR=0.79 [95% CI 0.36-1.69];p=0.59). Cumulative incidence of CW metastases at 6months/12 months/24 months was 3.3/8.5/10.0% in the PIT arm vs 5.6/10.9/18.7% in the no PIT arm. Evaluable patients who developed CW metastases reported a mean increase in visual analogue scale pain score of 13.3 (p<0.01) compared to baseline. Skin toxicity was the most common radiotherapy-related adverse event in the PIT arm with 96(51.6%) grade 1, 19(10.2%) grade 2, and 1(0.5%) grade 3 radiation dermatitis (CTCAE V4.0). There were no other grade 3 or higher radiotherapy-related adverse events. **Conclusion:** There is no role for the routine use of PIT following diagnostic or therapeutic CW procedures in patients with MPM.

Keywords: prophylactic, Radiotherapy, Mesothelioma

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OA 02.05 RESPECT-MESO: AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL TO ASSESS EARLY SPECIALIST PALLIATIVE CARE IN MALIGNANT PLEURAL MESOTHELIOMA

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This abstract is under embargo until October 16 @ 08:00.

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OA 02.06 RADIOIMMUNOTHERAPY COMBINING CTLA-4 BLOCKADE OR LOW-DOSE CYCLOPHOSPHAMIDE WITH LOCAL RADIATION IN MURINE MALIGNANT MESOTHELIOMA

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Background: Our group has developed a new approach focusing on Surgery for Mesothelioma After Radiation Therapy (SMART), with encouraging results in a phase I/II clinical trial. The impact on the immune system of high-dose hypofractionated radiation therapy is expected to open the door for new combination therapy of immunotherapy and radiation to optimize their synergism on the immune system. The aim of this study is to investigate the antitumor effect of non-ablative hypofractionated radiation combined with anti-CTLA-4 antibody (a-CTLA-4) or low-dose cyclophosphamide (LD-CTX) in murine malignant mesothelioma model. **Method:** Balb/c mice were subcutaneously injected with murine mesothelioma AB12 cells into the left flank on day 0 (primary tumor) and into the right flank on day 7 (secondary tumor). Local radiotherapy (LRT) 5 Gy was delivered to primary tumor once daily for 3 consecutive days (total dose: 15 Gy). Mice were randomized into six groups: (1) No treatment, (2) LRT, (3) a-CTLA-4, (4) LRT+a-CTLA-4, (5) LD-CTX, (6) LRT+LD-CTX. We assessed local and abscopal effects by measuring primary and secondary tumor growth. Furthermore, CD4+ and CD8+ T cell proportion in tumor, spleen and peripheral blood were determined by flow cytometry. **Result:** Mice treated with LRT+a-CTLA-4 and LRT+LD-CTX showed the most significant deceleration in primary tumor growth compared to the other 4 groups. Both combination groups showed similar antitumor effects on the primary tumor. The secondary tumor growth tested the abscopal effect tended to be decreased in mice treated with LRT and LRT+a-CTLA-4 or LRT+LD-CTX compared to untreated mice, but the difference was not significant. Quantification of tumor-infiltrating T cells by flow cytometry showed that the percentages of total T cells, and CD4+ and CD8+ T cells in the primary tumor were increased in the combination groups. **Conclusion:** Combination of LRT and immunotherapy showed synergistic antitumor effects in controlling irradiated-tumor growth. CTLA-4 blockade and LD-CTX might be good candidates in combination with radiotherapy.

Keywords: Mesothelioma, Radiotherapy, Immunotherapy

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OA 02.07 SURGICAL SELECTION IN PLEURECTOMY DECORTICATION FOR MESOTHELIOMA – AN OVERVIEW FROM SCREENING AND SELECTION FROM MARS 2 PILOT

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Background: Encouraging survival has been reported with pleurectomy decortication (PD) for malignant pleural mesothelioma (MPM) in several surgical case series. However, doubts remain over the degree of selection bias that constitutes the final composition of these series which therefore lead to questions surrounding the validity of the reported outcomes. We have reviewed our initial experience in the MARS 2 study to analyse this surgical selection process in more detail. **Method:** The MARS 2 pilot is randomised trial of RCT of 14 UK centres recruiting into a cisplatin/pemetrexed with or without the addition of PD for meseothelioma in those who remain suitable after an induction two cycle regime. We completed the pilot to analyse screening, eligibility, consent and randomisation data to estimate the eventual pool of patients considered suitable for surgery. **Result:** From 19 Jun 2015 to 5 Dec 2016, 331 patients were screened from the participating centres. In total, 254 patients were excluded, 176 for failed screening and 78 who declined participation. Of the 176, who failed screening the reasons were non resectable disease (74), poor performance status (24), not fit for surgery (4), not mesothelioma (6), death (5) and other (63). From the 331 screened participants, 77 were enrolled to and received the initial two cycles of chemotherapy and a further 21 withdrew. The reasons for withdrawal were declining randomisation (5), progressive disease (10) and other reasons (6), leaving 56 participants randomised into the trial. **Conclusion:** Screening data of a prospective randomised trial (MARS 2) has provided a unique insight into the detailed selection process for PD for MPM. Exclusions occurred at multiple points in the pathway but these have identified potential points for intervention in patient education, staging and fitness assessment and the proportion of tumour progression which will inform the forthcoming phase III study. The clear extent of possible selection bias underscores the importance of evaluating the efficacy of surgery within the context of this randomised trial to be able derive robust estimates of treatment effect.

Keywords: surgery mesothelioma clinical trial

OA 03 MEDIASTINAL AND ESOPHAGEAL TUMOR: INSIGHT AND NEW TREATMENT
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

OA 03.01 PREVALENCE OF AUTOIMMUNE DISEASES IN THYMIC EPITHELIAL TUMORS (TET) INSIGHTS FROM RYTHMIC

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Background: TET have been associated with autoimmune disorders (AID) in up to 30 % of patients. However, there have been wide variations in the reported prevalence of TET associated disorders based mostly on small single center series. RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a French network mandated to systematically discuss every case of TET. Using our database, we aimed to describe the prevalence of AID in a large French population with TET. **Method:** RYTHMIC database prospectively includes all consecutive patients with a diagnosis of TET discussed in our national tumor board. We calculated the prevalence and described epidemiologic, clinical and pathological characteristics of patients with TET's related autoimmune diseases. **Result:** From January 2012 to May 2017, 1693 patients were included in the registry. Of these, 200 patients (11.8%) had autoimmune disorder. The mean age at diagnosis of TET was 54 years old and 52% were male. 149 had myasthenia gravis (75.3%), 15 Good syndrome (7.6%), 14 pure red cell aplasia (7.1%), 12 systemic erythematous lupus (6.1%) and 12 thyroiditis (6.1%). Some patients (14.5%) eventually developed more than 1 AID. Diagnosis of AID was mostly done at the same time of TET diagnosis (54.6%) but some patient had their AID diagnosed before (19.8%) or during follow up (13.4%). Masaoka Koga stages were overall well balanced with 16.5% stage III, 16% stage IIb, 13.5% stage I, 13% stage IIa and IV. Histologic subtype distribution was in order of frequency; B2 (37%), AB (14.5%), B3 (14%), B1 (10.5%), thymic carcinoma (4.5 %) and A (4%). **Conclusion:** In our registry of TET, the prevalence of autoimmune diseases was 11.8% and most diagnosis were established at the same time as TET. The extent of disease, measured by Masaoka Koga staging, does not seem correlated.

OA 03 MEDIASTINAL AND ESOPHAGEAL TUMOR: INSIGHT AND NEW TREATMENT
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OA 03.02 COMPREHENSIVE CHARACTERIZATION OF THYMIC EPITHELIAL TUMOUR SUBTYPES THROUGH AN ANALYSIS OF SOMATIC MUTATIONS AND COPY NUMBER ALTERATIONS

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Background: Thymic epithelial tumours (TETs) are rare and under-researched intrathoracic cancers. So far the only significant finding is a recurrent (43%) missense mutation in *GTF2I*. In addition to validating this finding, we set out to expand our understanding of the molecular changes underlying TETs through whole exome sequencing (WES) and detection of copy number alterations (CNAs) following SNP genotyping. **Method:** WES was performed on 17 TETs (2AB, 1B1, 3B2, 2B3, 6CA and 3NETT) and matched normal tissue. Somatic single nucleotide variants (SNVs) were identified with the GATK HaplotypeCaller and annotated for impact prediction (SnpEff 3.6b and SnpSift 1.3.4b) and population frequency (SnpSift 1.3.4b). The frequency of the *GTF2I* mutation was assessed with Sanger sequencing with semi-nested primers on DNA from 144 TETs of all subtypes. SNP genotyping was performed on 100 TETs of all subtypes with matched normal tissue in most cases, to identify somatic CNAs. Analysis was performed with ASCAT (v2.4.4) and copy number segments were annotated with Bedtools (v2.26.0). **Result:** WES confirmed a low mutation burden for TETs. No highly recurrent mutations were found. Hotspot mutations in NRAS and KRAS were seen, as was a hotspot mutation in TP53 in a NETT. A high impact frameshift MSH6 somatic mutation was noted in one of the squamous cell carcinomas (SCCs). Another SCC had a germline BAP1 mutation and a family history of other cancers, suggesting a BAP1 familial cancer predisposition syndrome in this individual. The *GTF2I* mutation was seen in 48 of 141 evaluable TETs (34%) and was present more commonly in type A (90%) and AB (69%) thymomas. The frequency decreased to 16%, 6% and 13% in B1, B2 and B3 thymomas respectively and was not seen in any squamous (0/12) or neuroendocrine carcinomas (0/6). Overall, the most frequent copy number gains in TETs involved chromosomes 7q (22%), 1q (17%) and 11q (17%). The commonest gain was in a gene not previously found to be amplified in solid tumours. The most frequent copy number losses were in chromosomes 6p (40%), 2q (37%) and 7q (32%). Gains and losses demonstrated distinct patterns between aggressive versus indolent subtypes. **Conclusion:** The mutation in GTF2I remains the single most frequently recurrent mutation in TETs. We are in the process of establishing a clinical use for this finding. Results from WES and CNA through SNP genotyping have provided important insight into other potential key players in the aetiology of this intriguing malignancy.

Keywords: thymic, copy number alterations, Whole exome sequencing

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OA 03.03 PHASE II TRIAL OF CETUXIMAB AND CHEMOTHERAPY FOLLOWED BY SURGICAL RESECTION FOR LOCALLY ADVANCED THYMOMA

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Background: The mainstay of treatment for thymoma is surgery with neoadjuvant chemotherapy recommended to patients with locally advanced disease. EGFR is overexpressed in thymoma. Clinical responses to single-agent cetuximab have been reported in patients with advanced cetuximab. We conducted this two-site prospective phase II trial of cetuximab combined with a standard induction chemotherapy regimen of cisplatin, doxorubicin and cyclophosphamide (PAC) in patients with locally advanced thymoma prior to surgical resection. **Method:** Patients with clinical Masaoka stage III-IVA thymoma were treated with cetuximab (250mg/m^2 weekly x 4 weeks) followed by cetuximab (250 mg/m^2 weekly) combined with cisplatin (50mg/m^2), doxorubicin (50 mg/m^2) and cyclophosphamide (500mg/m^2) 3 weeks x 4 cycles). Radiographic response was assessed by CT using RECIST 1.1 and FDG-PET using PERCIST. All patients went on to surgery after completion of induction therapy. The primary endpoint was major pathologic response (MPR, >90% treatment effect). Planned enrollment was 18 patients in first stage of a two stage design. If 1 MPR was observed, then enrollment would expand to 28 patients. **Result:** Eighteen patients were enrolled: 8 women, median age 53 (range 32-73). WHO Histologic subtype A: 2, AB: 3, B1: 3, B2: 7, B3: 3. Final Masaoka stage I: 2, II: 2, III: 5, IVA: 9. There were no responses to cetuximab alone by RECIST criteria, although 1 patient had a 25% reduction in indicator lesions. Response rate (CR+PR), in evaluable patients after complete treatment course was 50% (8/16, 95% CI 28-72%). Partial responses by PERCIST criteria were seen on PET in 11/18 (61%) evaluable patients. There were no MPRs. R0 resection was obtained in 7 patients; 5 had R1 and 6 had R2 resections. **Conclusion:** The addition of cetuximab to PAC chemotherapy did not lead to pathologic complete responses in the neoadjuvant setting. Cetuximab alone appears to have little effect during 4 weeks of treatment. There was no apparent increase in radiographic response rate with the addition of cetuximab to PAC chemotherapy compared to historical series.

Keywords: Thymoma, neoadjuvant, Cetuximab

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OA 03.04 A PHASE II STUDY OF PEMBROLIZUMAB FOR PATIENTS WITH REFRACTORY OR RELAPSED THYMIC EPITHELIAL TUMOR

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Background: No standard treatment exists for patients with thymic epithelial tumor (TET) who progress after platinum-containing chemotherapy. We conducted a phase II study of pembrolizumab in patients with refractory or relapsed TET to evaluate the efficacy and safety. **Method:** Between March 2016 and June 2017, patients with histologically confirmed TET who progressed after at least one platinum-containing chemotherapy were eligible. Patients were excluded if they had an active autoimmune disease requiring systemic treatment within the past one year or documented history of clinically severe autoimmune disease. Patients received 200mg of pembrolizumab intravenously every 3 weeks until tumor progression or unacceptable toxicity. Response was assessed every 9 weeks by investigator. The trial was registered with ClinicalTrials.gov, number NCT02607631. **Result:** Thirty-three patients were enrolled, 26 with thymic carcinoma and 7 with thymoma. 19 (57.3%) patients received two or more prior lines of systemic chemotherapy. Median number of cycles was 8 (ranges, 1-22) and median follow-up was 11.8 months (ranges, 1.6-14.9 months). Of 33 patients, eight (24.2%) achieved partial responses, 17 (51.5%) stable disease, and 8 (24.2%) progressive disease as best response, resulting in overall response rate of 24.2% (7 confirmed PR). The median progression-free survival was 6.1 months for both of thymoma and thymic carcinoma. The most common adverse events of any grade include dyspnea (11 [33.3%] of 33 patients), chest wall pain (10 [30.3%]), anorexia (7 [21.2%]) and fatigue (7 [21.2%]). Treatment-related adverse events ≥ grade 3 associated with immune related adverse events (irAE) include hepatitis (4 [12.1%]), myocarditis (3 [9.1%]), myasthenia gravis (2 [6.1%]), thyroiditis (1 [3.0%]), ANCA-associated rapidly progressive glomerulonephritis (1 [3.0%]), colitis (1 [3.0%]), and subacute myoclonus (1 [3.0%]) except anemia (1 [3.0%]). Eight (24.2%) patients (5 thymoma, 3 thymic carcinoma) discontinued study treatment due to irAE, whereas irAEs were manageable with immediate administration of high dose corticosteroid and other immunosuppressive agents in most of patients (7 of 8 [87.5%]). In 18 (54.5%)

patients who had tumor specimens available for correlative biomarker analysis, all of four patients achieved partial response had 50% or more proportion score of PD-L1 immunostaining and higher PD-L1 RNA expression compared with non-responders (p=0.0471). **Conclusion:** Pembrolizumab showed promising antitumor activity in patients with refractory or relapsed TET. Given the relatively high incidence of irAEs especially in thymoma, early detection and management of autoimmune toxicity is essential to ensure feasibility of pembrolizumab treatment in patients with TET.

Keywords: thymoma, thymic carcinoma, pembrolizumab

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OA 03.06 CLINICOPATHOLOGIC, IMMUNOPHENOTYPIC AND GENETIC STUDIES OF MEDIASTINAL PARAGANGLIOMAS

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Background: Paragangliomas (PGLs) are rare neuroendocrine neoplasms arising from paraganglia of the autonomic nervous system. Only about 2% of all PGLs are found in the mediastinum; therefore they are not thoroughly investigated. Our study aims to characterize the clinicopathologic, immunophenotypic and genetic features of mediastinal PGLs. **Method:** Surgical files of Mayo Clinic Rochester and an institutional database (1973-2015) were searched for mediastinal PGLs. Thirteen patients were previously reported (Brown ML et al, *Ann Thorac Surg* 2008). All cases were reviewed by a thoracic pathologist to confirm the diagnosis. Immunohistochemistry was performed using antibodies to SDHB, Ki-67, ATRX, p53, PD-L1 (clone SP263) and ASCL1. Ki-67 labelling index (LI) was calculated as the mean percent Ki-67-positive cells per 3 HPF. Next generation sequencing (NGS) used a 50-gene neuro-oncology panel. Clinical data were retrieved from medical records. Statistical analysis was performed. **Result:** Twenty-four patients with mediastinal PGLs (7 men, 29.2%) had a median age at time of surgery of 44.6 years (19.8-72.2). Twenty-one (87.5%) paragangliomas were completely resected, 3 had an incomplete resection. The median tumor size was 5.1 cm (1.6-14). The median Ki-67 LI was 4.1% (0.5-29.7). PD-L1 was expressed in 10% (n=2), 1% (n=4) or 0% (n=17) of tumor cells. ASCL1 was focally expressed in 2 of 23 (8.7%) cases. Diffuse loss of SDHB expression was seen in 17 of 22 (77.3%) cases. ATRX was expressed in all 22 cases tested, but its expression was patchy in 1 case that showed ATRX duplication by NGS. NGS, performed in 19 cases, revealed a single pathogenic mutation in 10 cases including SDHB (n=3), SDHD (n=6) and ATRX (n=1); and two or more mutations in 2 cases including SDHC+TERT (n=1) and SDHB+ATRX+TP53 (n=1). Two additional patients were found to have an SDHB mutation. Ten of 21 patients with available SDHx mutation status (47.6%) had no SDHx mutation. Median follow up, available in 21 patients, was 4.7 years (0.8-11.5). Five patients (2 of which with SDHx mutation) developed metastases and/or recurrence; 4 patients (2 without SDHx mutation, 2 with unknown SDHx mutation status) died (1 perisurgically, 3 of unknown cause at 2.3, 5.8, and 10.6 years after surgery each). Statistical analysis of clinicopathologic features based upon SDHx mutation could not be performed due to the small number of cases. **Conclusion:** Our study demonstrates that the majority of mediastinal PGLs harbors an SDHx gene mutation. Alterations in ATRX gene might represent another genetic event in mediastinal PGLs.

Keywords: ATRX, paraganglioma, SDH mutation

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OA 03.07 DEVELOPING PROGNOSTIC NOMOGRAM AND EVALUATING ITS ROLE IN PERSONALIZED ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH ESCC

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Background: Nomogram has demonstrated its capability in individualized survival estimates. Some nomogram studies on esophageal squamous cell carcinoma (ESCC) have been reported, but accuracy of those nomograms is not high enough. Also, the role of ESCC nomogram in adjuvant chemotherapy remains unclear. Therefore, clinicopathological prognostic nomogram was developed and validated for patients with ESCC in this study. Its role in personalized adjuvant chemotherapy was investigated as well. **Method:** Data were retrieved about 1042 ESCC patients undergoing right transthoracic radical esophageactomy at Sun Yat-sen University Cancer Centre from January 1997 to December 2013. Of 1042 patients, 886 without adjuvant chemotherapy were divided into training set (Group A, n=590) and validation set (Group B, n=296) in a 2:1 ratio. Group C (the remaining 156 patients with adjuvant chemotherapy plus Group B, n=452) was used to evaluate the role of nomogram in personalized adjuvant chemotherapy. Cut-off points of continuous variables were established by X-tile. Survival and univariate analyses were calculated by Kaplan–Meier method. R software and "rms" package were used to perform Cox proportional hazard (CPH) regression model, plot nomogram, compute C-index, compare models, validate model, and plot calibration curve. The "survivalROC" package was used to plot time-dependent receiver operating curve (ROC). **Result:** The 1-, 3- and 5-year overall survival (OS) for the entire cohort was 88.3%, 64.5% and 54.8%, respectively. Univariate analyses were performed for 13 potential clinicopathological factors. Significant variables were analyzed for CPH regression model using R software and "rms" package. A prognostic nomogram including 8 factors (grade, location, T, N, resected negative nodes, length, gender, drinking history) was developed. C-index of the model was 0.739 (95% CI 0.719-0.759), higher than that of the 7th TNM staging system (0.696, 95% CI 0.676-0.716), $p < 0.001$. The calibration curve and time-dependent ROC showed this nomogram was superior to the 7th TNM staging system. The cut-off of prognostic score was 160, by which we grouped patients into low and high prognostic risk subgroup. In Group C, 209 patients belonged to high prognostic risk subgroup. Among them, patients receiving adjuvant chemotherapy had longer OS ($p = 0.035$). The remaining 243 patients belonged to low prognostic risk subgroup. Adjuvant chemotherapy didn't improve OS ($p = 0.799$) in this subgroup. **Conclusion:** An accuracy clinicopathological prognostic nomogram was developed and validated for ESCC patients undergoing right transthoracic radical esophagectomy. The nomogram provided individual prediction of survival. Risk group stratification based on nomogram prognostic score successfully guided personalized adjuvant chemotherapy for ESCC patients.

Keywords: Prognostic nomogram, personalized adjuvant chemotherapy, Esophageal squamous cell carcinoma

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OA 04.01 RANDOMISED TRIAL OF SYSTEMATIC LYMPH NODE DISSECTION VERSUS BILATERAL MEDIASTINAL LYMPHADENECTOMY IN PATIENTS WITH NON-SMALL CELL CARCINOMA

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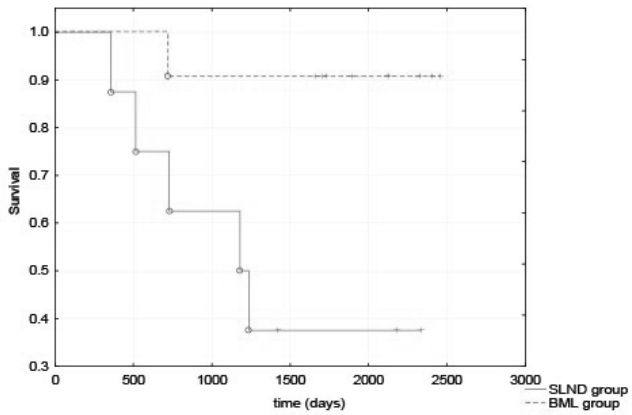
Background: Experimental studies have shown different pathways of lymphatic drainage from particular pulmonary lobes. Especially important is lymphatic drainage from the left lower lobe to the contralateral mediastinal nodes. The aim of this study was to analyse the impact of bilateral mediastinal lymphadenectomy (BML) on survival in non small-cell lung cancer (NSCLC) patients. **Method:** Prospective, randomised trial including patients with proven or suspected NSCLC, stage cI-IIIA. Randomisation was performed in ratio 1:1. In the BML group, systematic lymph node dissection (SLND) was supplemented with contralateral mediastinal lymphadenectomy via additional cervical incision. In the SLND group, standard lung resection with SLND was performed. **Result:** 102 patients were enrolled. 13 of them met the exclusion criteria, and data of 89 patients were analysed: 40 in the BML group and 49 in the SLND group. There were no significant differences between groups regarding age, sex, Thoracoscore, Revised Cardiac Risk Index, dyspnoea, lobar location of the tumour, histology and cTNM. Mean follow-up time was 66.5 months. In the whole group, the 4-year survival rate was significantly higher in the BML group than in the SLND group (72.5% vs 51%, p=0.039). Separate comparisons were performed for different lobar locations of the tumour. There was no significant difference in 4-year survival rates and mean survival time between both groups for tumours located in the right lung and those located in the left upper lobe. For the left lower lobe, the 4-year survival rate, and mean survival time was significantly higher in the BML group (90.9% vs 25%, p=0.003, and 1923 vs 1244 days, p=0.027, respectively). Also, analysis of the survival curves (Figure) has shown significant difference (p=0.018.)



Conclusion: For NSCLC located in the left lower lobe, removal of the contralateral mediastinal lymph nodes is associated with survival benefit. These results should be confirmed in larger studies.

Keywords: lung cancer, mediastinum, Lymphadenectomy

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OA 04.02 FEASIBILITY OF PULMONARY RESECTION FOLLOWING DEFINITIVE CHEMORADIOTHERAPY FOR PRIMARY LUNG CARCINOMA

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Background: Induction chemoradiation (ICR) for advanced non-small cell lung caner is often limited to 50Gy or less to avoid perioperative complications. Pulmonary resection following definitive chemoradiotherapy (DCR) has been an alternative approach for locally advanced lung cancer. **Method:** In this study, we compared pulmonary resection following ICR and DCR. From 1997 to 2016, we had 31 pulmonary resections following CR. There were 13 ICR and 18 DCR. Intercostal muscle flaps were used in 7 ICR and 2 DCR. Omental flaps were used in 12 DCR. Pericardial fat pad was used in 1 DCR. There was no mortality in any groups. **Result:** In comparison with ICR and HCR, operation time (min, interquartile range) were 344 (283-513) and 418 (563-572) (p = 0.057), estimated blood loss (ml) were 440 (225-575) and 525 (323-1313) (p =0,262), morbidity (%), 69 and 28 (p = 0.021). Bronchopleural fistula developed in one case of DCR who used intercostal muscle flap. Post operation hospital stay (days) was 21 (13.5-26.5) in ICR, 14.5 (13-20) in DCR (P = 0.221). Although operation time was longer and there were more blood loss in DCR, there was no significant increase of peri- and post-operative complications. 2- and 5-year over all survival rates (%) were 50 and 42 in ICR, and 68 and 51 in DCR (p=0.73, log-rank test). **Conclusion:** As a conclusion, high dose ICR may contribute to better local control and longer survival. Pulmonary resection after DCR is as safe as that following ICR.

Keywords: locally advanced lung cancer, salvage surgery, chemoradiation

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OA 04.03 PRIMARY TUMOR RESECTION VERSUS MAINTENANCE THERAPY FOR PATIENTS WITH OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER

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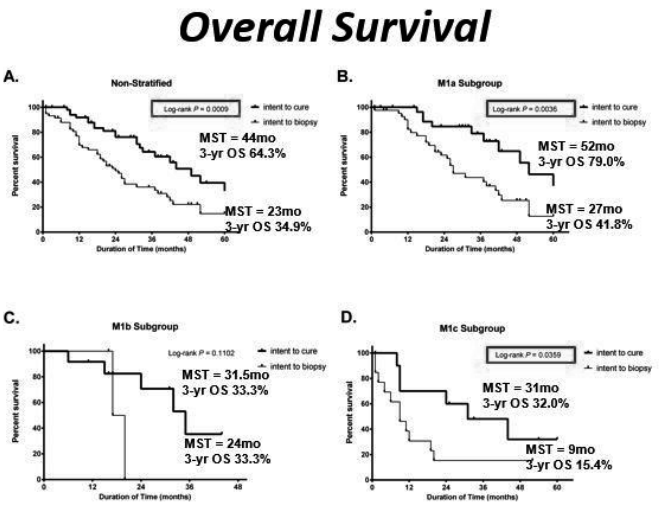
Background: To evaluate (1) the potential effect of primary tumor resection, an aggressive local consolidative therapy, for patients with oligometastatic NSCLC on 3 year overall survival; (2) the surgical outcomes in the treatment of patients with oligometastatic NSCLC; (3) the potential clinical factors predicting survival in order to better select patients for surgery. **Method:** According to the extent of pulmonary resection, the patients were divided into two subgroups. A. intent to cure (ITC: removal of total or primary pulmonary lesions); B. intent to biopsy (ITB: preservation of major lesions, only diagnostic biopsy via minimally invasive approach). M stage classified based on 8th UICC/AJCC TNM M categories. **Result:** From Jan 2002 through Dec 2015, a total of 115 consecutive metastatic NSCLC patients were enrolled from Peking University Cancer Hospital. The 3-year overall survival (OS) of ITC and ITB were 64.3% and 34.9% (log-rank p = 0.0009), respectively. Multivariate cox proportional regression analysis identified multiple station lymph nodes (LN) and bone involvement may be prognostic indicators.



Multivariate Analysis of Patient Characteristics (Cox Proportional Hazards Model)

	Hazard ratio	95% CI	P
Age			
< 60 yo	*1.014*	*0.489 - 2.548*	*0.623*
Gender			
Female	*1.115*	*0.426 - 2.733*	*0.760*
p-stage N			
Positive	*1.723*	*0.864 - 3.624*	*0.127*
Multiple Stations	***2.867***	*0.996 - 8.410*	***0.051***
Site of metastasis			
Ipsilateral pleural + lung	*0.689*	*0.334 - 2.182*	*0.192*
Contralateral lung	*0.424*	*0.301 - 1.156*	*0.336*
Brain	*1.095*	*0.688 - 2.947*	*0.724*
Bone	***2.446***	*0.979 - 5.118*	***0.072***
Histology			
Adenocarcinoma	*0.782*	*0.452 - 1.694*	*0.347*
Squamous cell carcinoma	*0.890*	*0.667 - 2.351*	*0.214*
Surgical procedure			
Partial resection	*1.267*	*0.569 - 2.442*	*0.245*

Conclusion: The current findings suggest that aggressive surgical therapy can extend the survival in selected stage IV NSCLC patients, and should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.

Keywords: lung cancer, Surgery, oligomestasis

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OA 04.05 INTERMEDIATE RESULTS OF ICG ANATOMICAL SEGMENTECTOMY BASED ON THE VIRTUAL SEGMENTECTOMY SIMULATION

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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 lung segmentectomy for pulmonary malignancies. And the precise anatomical segmentectomy is also important for preserving pulmonary function. We evaluated intermediate results of tumor recurrence after anatomical ICG segmentectomy based on the virtual segmentectomy simulation. **Method:** From August 2014 to May 2017, forty-five patients underwent pulmonary segmentectomy under the guidance of ICG fluorescence. Before operation, several types of virtual segmentectomy were created by using Volume Analyzer Synapse VINCENT (Fujifilm co., Tokyo, Japan). We measured the shortest distance from the tumor to the resection margin in each simulated segmentectomy and selected the most appropriate area of sublobar resection based on the adequate resection margin of approximately 2 cm from the tumor. After this virtual segmentectomy, we performed segmentectomy 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. Segmentectomy was performed under ICG visualization. We evaluated tumor recurrence and survival after the operation. **Result:** Thirty-seven patients were primary lung cancer and eight patients were metastatic lung tumor. Active limited resection was done in 28 patients, passive limited resection was in nine and metastatic lung tumor resection was in eight. Subsegmental resection was done in five, segmental resection in 22 and extended segmentectomy, which indicates resection of several segments with adjacent subsegment(s), was 18. The average shortest distance from the tumor to the resection margin in simulation and resected specimen were 22.5+/-11.7 mm and 24.1+/-7.3 mm, respectively (p=0.405). Postoperative complications were prolonged air leak longer than seven days in two cases and atrial fibrillation in one. In terms of the recurrence and survival after ICG segmentectomy, although the mean duration of follow-up was still short (530+/-349 days), no cancer recurrence in the ipsilateral lung was identified in lung cancer patients. In particular, no recurrence was found in the lung as well as lymph node in active segmentectomy patients. **Conclusion:** The combination of lung volume analyzer and ICG segmentectomy was an excellent tool for precise anatomical segmentectomy with an appropriate resection margin and excellent control of tumor recurrence.

Keywords: fluorescence imaging, lung cancer, limited resection

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OA 04.06 SURGEON PRACTICES FOR POST RESECTION LUNG CANCER SURVEILLANCE: COMPARISONS OF STS AND ESTS MEMBERS

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Background: A 1995 survey of Society of Thoracic Surgeons (STS) members revealed widespread variation in post resection lung cancer surveillance practices as well as pessimism regarding any survival benefit. We sought to compare contemporary practice patterns and attitudes toward post-resection surveillance among members of STS and of European Society of Thoracic Surgeons (ESTS). **Method:** A survey identical to one conducted in 1995 was administered via mail or electronically to surgeon members of the STS and ESTS requesting response from those treating NSCLC. Demographic information, type, frequency and duration of post-resection testing were collected. Goodness of fit tests were used to compare profiles of respondents and attitudes toward testing between groups. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). **Result:** Between 8/2016-10/2016, 2978 STS members (response rate 7.8%, n=234) and 1450 ESTS members (response rate 8.4%, n=122) were surveyed. ESTS and STS respondents were similar in their frequent use of history and physical examination (75% vs 78%, p=0.26) and CT chest (71% vs 73%, p=0.61) although the timing of testing was widely variable. Compared to STS members, ESTS members reported more frequent use of testing not recommended by guidelines (for asymptomatic patients) including CXR (46% vs 34%, p=0.02) bronchoscopy (10% vs 1% p<0.01), bone scan (5% vs 0, p<0.01), brain CT (6% vs 0, p<0.01), and brain MRI (3% vs 0%, p=0.01). Compared to STS members, ESTS surgeons were more likely to "agree" or "strongly agree" that routine testing for NSCLC recurrence results in potentially curative treatment (86% vs 70%, p<0.01). Similarly, ESTS respondents were more likely to believe surveillance would identify a curable second primary NSCLC (94% vs 84%, p<0.01). More ESTS than STS respondents believed that current literature documents definitive survival benefits from routine follow-up testing (57% vs 30%, p<0.01), a misconception reported by only 26% STS respondents in the identical 1995 survey. **Conclusion:** Our survey suggests significant differences between ESTS and STS members regarding the method, frequency and attitudes regarding post-resection surveillance for NSCLC. European surgeons report a more optimistic belief in significant survival benefit from early detection of both recurrent and second primary NSCLC thus adopting more aggressive surveillance practices. This is in spite of a lack of definitive evidence-based literature underscoring the need for both better prospective studies and joint recommendations to standardize practice.

Keywords: Surveillance, guidelines, resection

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OA 04.07 INITIAL RESULTS OF TUBELESS SINGLE-PORT THORACOSCOPIC SURGERY FOR PULMONARY TUMOR

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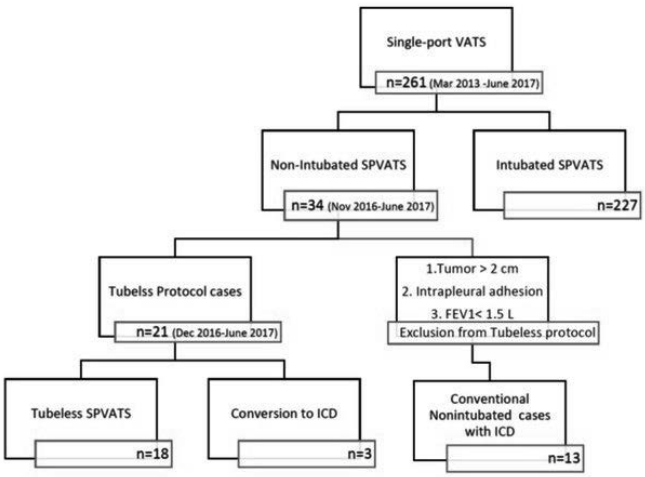
Background: Tubeless technique, defined as non-intubated anesthesia and omitting chest tube after lung resection surgery, is a new concept to further minimize surgical trauma of thoracoscopic surgery. However, the feasibility and safety have been less investigated. Here we set up a protocol to prevent postoperative pneumothorax after tubeless single-port thoracoscopic surgery with the aid of digital chest drainage system (DCS). **Method:** From Nov. 2016 to Jun. 2017, 34 consecutive non-intubated single-port thoracoscopic surgery were performed in patients with pulmonary nodules. After excluding patients with nodule≧2 cm, intrapleural adhesion, and FEV1< 1.5 L/sec., 21 patients were selected to enter the tubeless protocol. At the end of the procedure, a single 16-Fr. catheter was placed into the pleural cavity and connected to a DCS which pressure was set at –15 cmH2O. Then the single incision was closed continuously. If the air flow reached zero after completion of wound closure, the catheter will be removed immediately; otherwise the catheter will be kept for drainage. The clinical characteristics and perioperative outcomes of patients were presented.

Figure 1. Flowchart for Tubeless Protocol Cases (VATS, Video-assisted thoracic surgery; SPVATS, Single-port video-assisted thoracic surgery; ICD, Intercostal drainage.



Result: Among tubeless protocol cases, 3 patients were detected to have minor air leak by DCS and were converted to have intrapleural drainage remained after closure of surgical wound. Among the remaining 18 patients, in whom the DCS showed no air leak, the intrapleural drainage catheter was not placed. Immediate postoperative chest roentgenogram showed full expansion in all protocol patients without pneumothorax. Only 5 (23.8%) patients developed minor subclinical pneumothorax on the first postoperative day. All patients were discharged uneventful without the need of intervention. **Conclusion:** Our tubeless protocol utilizes DCS to select patients for omitting intrapleural drainage after non-intubated single-port thoracoscopic surgery. With objective parameters by DCS, we believe that this is an effective way to reduce the rate of pneumothorax after tubeless single-port thoracoscopic surgery in selected patients after lung resection.

Keywords: Pneumothorax, tubeless, single-port

OA 04 SURGERY FROM MINIMAL TO RADICAL
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 04.08 IS LOBE-SPECIFIC LYMPH NODE DISSECTION IN CLINICAL N0-1 NON-SMALL CELL LUNG CANCER ADEQUATE FOR PATHOLOGICAL NODAL STAGING

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Background: Lobe-specific lymph node dissection (L-SND) was proposed for clinical T1a-2b N0-1 non-small cell lung cancer (NSCLC), however, the benefit of this approach is still uncertain, especially for pathological nodal staging. In this study, we evaluated the percent detection of pN2 disease in L-SND and in systematic lymph node dissection (SLND). **Method:** From 2010 to 2016, 166 patients with cT1a-T2b N0-1 NSCLC underwent a lobectomy with SLND at Chiang Mai University Hospital. The pathologic results of the lymph nodes dissected in each station were extracted form medical records. Patients who underwent a SLND when then reclassified as L-SLN according to the site of the primary tumor; right upper lobe (station 2R-4R), left upper lobe (station 4L-6), and both lower lobes (station 7-9). Percent detection of pN2 disease was compared between L-SLN and SLND. **Result:** The rate of detection of pN2 in the SLND was higher than in the L-SLD, but the difference was not statistically significant (27.0 %versus 23.6%, p=0.474). The overall percent of cases upstaged to pN2 was only 4.4% after SLND; it was 4.4% in right upper lobe, 3.4 % in left lower lobe, 3.2 % in right lower lobe, and 1.9 % in left upper lobe (p=0.904). The pN2 disease detection agreement between L-SND and SLND was high (kappa=0.911 (95% CI; 0.784 - 0.957). Table 1 pathological N2 status in lobe-specific dissection and systematic lymph node dissection

Location of primary tumor	Clinical N0-1 status		Pathologic N2 status (lobe-specific dissection)		Pathologic N2 status (Systematic dissection)		% upstaged to N2 disease
	Negative	Positive	Negative	Positive	Negative	Positive	
RUL (n=67)	57 (85.1)	10 (14.9)	52 (77.6)	15 (22.4)	49 (73.1)	18 (26.9)	4.5
RLL (n=31)	29 (93.65)	2 (6.5)	24 (77.4)	7 (22.6)	23 (74.2)	8 (25.8)	3.2
LUL (n=51)	43(84.3)	8 (15.7)	37 (72.5)	14 (27.5)	36 (70.6)	15 (29.4)	1.9
LLL (n=29)	24 (82.8)	5 (17.2)	23 (79.3)	6 (20.7)	22 (75.9)	7 (24.1)	3.4

Conclusion: These results suggest that lobe-specific lymph node dissection is as adequate as SLND for pathological N2 staging in clinically early stage NSCLC surgery. However, systematic lymph node dissection achieved a higher detection of pN2 disease. Further studies with a larger sample size are warranted to confirm these results.

Keywords: lobe-specific lymph node dissection, NSCLC, pN2 upstaging

OA 05 NEXT GENERATION TKI
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 05.01 FIRST-LINE DACOMITINIB VERSUS GEFITINIB IN ADVANCED NON-SMALL-CELL LUNG CANCER WITH EGFR MUTATION SUBGROUPS

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Background: The ARCHER 1050 study (NCT01774721) demonstrated benefits of dacomitinib compared with gefitinib as first-line therapy for patients with advanced non-small-cell lung cancer (NSCLC) and *EGFR*-activating mutation. Here, we present the results of a prospective subgroup analysis by *EGFR* mutation subtype. **Method:** In this ongoing phase 3, open-label study, eligible patients with newly diagnosed stage IIIb/IV or recurrent NSCLC and *EGFR*-activating mutation (exon 19 deletion or L858R mutation ± T790M mutation) with an Eastern Cooperative Oncology Group performance status of 0–1 were randomized (1:1) to receive dacomitinib or gefitinib, stratified by race and *EGFR* mutation subtype. The primary endpoint was progression-free survival (PFS) by blinded independent radiologic central (IRC) review. Secondary endpoints included overall survival and objective response rate (ORR), as determined by IRC and investigators' assessments. **Result:** A total of 452 patients were randomized (dacomitinib, n=227; gefitinib, n=225). Among the dacomitinib and gefitinib arms, respectively, 134 (59%) and 133 (59%) had exon 19 deletions and 93 (41%) and 92 (41%) had L858R mutations. The Table shows PFS, ORR, and duration of response by *EGFR* mutation per IRC. Results based on investigators' assessments were consistent with those based on IRC review. Overall survival data are immature.

	Exon 19 Deletion		L858R Mutation	
	Dacomitinib (n=134)	**Gefitinib (n=133)**	**Dacomitinib (n=93)**	**Gefitinib (n=92)**
PFS per IRC				
Median, months (95% CI)	16.5 (11.3–18.4)	9.2 (9.1–11.0)	12.3 (9.2–16.0)	9.8 (7.6–11.1)
Hazard ratio (95% CI) 1-sided P value	0.551 (0.408–0.745) <0.0001		0.626 (0.444–0.883) 0.0034	
ORR per IRC				
CR, n (%)	7 (5.2)	3 (2.3)	5 (5.4)	1 (1.1)
PR, n (%)	95 (70.9)	90 (67.7)	63 (67.7)	67 (72.8)
ORR (CR + PR), n (%) (95% CI)	102 (76.1) (68.0–83.1)	93 (69.9) (61.4–77.6)	68 (73.1) (62.9–81.8)	68 (73.9) (63.7–82.5)
1-sided P value	0.1143		0.5395	
DoR in responders per IRC				
Median, months (95% CI)	15.6 (13.1–19.6)	8.3 (7.9–10.1)	13.7 (9.2–17.4)	7.5 (6.5–10.2)
Hazard ratio (95% CI) 1-sided P value	0.454 (0.319–0.645) <0.0001		0.403 (0.267–0.607) <0.0001	

CI, confidence interval; CR, complete response; DoR, duration of response; PR, partial response.

Conclusion: By IRC and investigators' assessments, PFS with dacomitinib was superior to that with gefitinib in patients with either *EGFR* mutation. Despite a similar ORR among the treatment and *EGFR* mutation subgroups, duration of response was longer with dacomitinib for both mutations.

Keywords: EGFR mutations, Dacomitinib, advanced non-small-cell lung cancer

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MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 05.02 OSIMERTINIB VS SOC EGFR-TKI AS FIRST-LINE TREATMENT IN PATIENTS WITH EGFRM ADVANCED NSCLC (FLAURA): PLASMA CTDNA ANALYSIS

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Background: FLAURA (NCT02296125) is a Phase III, double-blind, randomized study assessing efficacy and safety of osimertinib vs standard of care (SoC) EGFR-TKI as first-line treatment for patients with EGFRm advanced NSCLC. Concordance between tissue and plasma testing for EGFRm (Ex19del/L858R), and progression-free survival (PFS) by baseline plasma EGFRm status were evaluated. **Method:** Eligible patients: ≥18 years (Japan ≥20 years); Ex19del/L858R mutation-positive lung adenocarcinoma; no prior systemic anti-cancer/EGFR-TKI therapy for advanced NSCLC. Randomization: 1:1 to osimertinib 80 mg once daily (qd) orally (po) or SoC (gefitinib 250 mg or erlotinib 150 mg, qd po). At baseline, patients provided tumor tissue samples for central analysis of EGFRm status (cobas EGFR Mutation Test) and blood samples for retrospective analysis of EGFRm status by plasma ctDNA (cobas EGFR Mutation Test v2). PFS by baseline plasma EGFRm status was assessed. Comparison of EGFRm status between baseline tumor tissue and evaluable ctDNA samples was an exploratory endpoint. **Result:** Globally, 556 patients were randomized: osimertinib, n=279; SoC, n=277. Good concordance was observed between central laboratory tissue and plasma testing for EGFRm in the screened population (see table). In plasma EGFRm-positive patients (n=359), osimertinib (n=183) reduced the risk of progression or death by 56% vs SoC (n=176), hazard ratio (HR) 0.44 (95% CI 0.34, 0.57). This was consistent with the overall PFS result observed with osimertinib vs SoC in the full analysis set (FAS; tumor tissue EGFRm-positive by local/central testing), HR 0.46 (95% CI 0.37, 0.57); p<0.0001 and in plasma EGFRm-negative patients (n=124: osimertinib, n=60; SoC, n=64), HR 0.48 (95% CI 0.28, 0.80).

Concordance for EGFRm
Agreement of the cobas plasma test with the cobas tissue test, % (95% CI)*

Exon 19 deletion (N=348)	
Concordance	87 (84, 90)
Positive percent agreement	79 (74, 84)
Negative percent agreement	99 (96, 100)
L858R (N=214)	
Concordance	88 (85, 91)
Positive percent agreement	68 (61, 75)
Negative percent agreement	99 (97, 100)

Positive and negative percent agreements are measures of test sensitivity and specificity, respectively, and calculated excluding invalid results. *Patients with tissue mutation-positive status.

Conclusion: In the subgroup of plasma EGFRm-positive patients, clinical benefit of osimertinib was superior to SoC, consistent with the overall FLAURA FAS. These results, and good concordance between tissue and plasma testing for EGFRm, support the utility of plasma EGFRm testing for selecting patients eligible for first-line osimertinib treatment.

Keywords: first-line treatment, EGFR-TKI, ctDNA

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OA 05.03 CLINICAL ACTIVITY OF ASP8273 IN ASIAN NON-SMALL CELL LUNG CANCER PATIENTS WITH EGFR ACTIVATING AND T790M MUTATIONS

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Background: Epidermal growth factor receptor (EGFR) activating mutations confer sensitivity to tyrosine kinase inhibitor (TKI) treatment for non-small cell lung cancer (NSCLC) and occur in ~50% of East Asian patients with NSCLC. While initial TKI treatment can be effective, acquired resistance inevitably develops with a secondary mutation (T790M). ASP8273 is a highly specific, irreversible, once-daily, oral, EGFR TKI which inhibits both activating (eg, exon 19 deletions, L858R) and resistance (eg T790M) mutations. **Method:** This dose-escalation/dose-expansion study (NCT02192697) was conducted in two phases. In Phase 1, adult Japanese patients (≥20 yr) with NSCLC previously treated with ≥1 EGFR TKI were enrolled and received escalating ASP8273 doses (25–600mg) to assess safety/tolerability as well as to determine maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D). In phase 2, adult T790M-positive NSCLC patients in Japan, Korea, and Taiwan were enrolled to further define the ASP8273 safety/tolerability profile at RP2D and determine antitumor activity (assessed using RECIST v1.1). Antitumor activity in phase 2 was evaluated according to Simon's 2-stage design (uninteresting response=0.3, desired response=0.5, α=0.05, β=0.1). If ≥9 of 24 ASP8273-treated patients achieved a desired response in the first stage, then 39 additional patients would be enrolled. If ≥ 25 of the 63 total patients achieved response, ASP8273 would be considered to have antitumor effects. **Result:** A total of 123 patients (n=47 phase 1; n=76 phase 2) were enrolled. In both phases, more women were enrolled. The median age was 65 years in phase 1 and 63 years in phase 2. Based on phase 1 findings, MTD and RP2D were 400mg and 300mg, respectively. As 27 of the 63 patients treated with ASP8273 300mg in the first and second stages combined achieved a clinical response (based on independent central review), ASP8273 was determined to have antitumor activity (ORR=42.9%; 95% CI: 30.5–56.0). The ORR at week 24 in all patients in the full analysis set was 42.1% (n=32/76; 95% CI: 30.9, 54.0). The median duration of PFS (central review) was 8.1 months (95%CI: 5.6,--). The most commonly reported treatment-emergent AEs (TEAE) in phase 2 were diarrhea (n=50/76), nausea (n=31/76), increased alanine

aminotransferase (n=27/76), decreased appetite and vomiting (n=26/76 each), and hyponatremia (n=25/76). Drug-related TEAEs were reported in 93.4% (n=71/76) of patients, the most common of which was diarrhea (n=43/76). **Conclusion:** ASP8273 was generally well tolerated and demonstrated antitumor activity in Asian patients with both EGFR activating and T790M mutations.

Keywords: NSCLC, EGFR, T790M

OA 05 NEXT GENERATION TKI
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OA 05.05 BRIGATINIB IN CRIZOTINIB-REFRACTORY ALK+ NSCLC: UPDATED EFFICACY AND SAFETY RESULTS FROM ALTA, A RANDOMIZED PHASE 2 TRIAL

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Background: Brigatinib, a next-generation ALK inhibitor, recently received accelerated approval in the United States for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant to crizotinib. We report updated data from the randomized phase 2 trial (ALTA; NCT02094573), which was designed to investigate the efficacy and safety of 2 brigatinib regimens in patients with crizotinib-refractory, advanced ALK+ NSCLC. **Method:** Patients were stratified by presence of brain metastases at baseline and best response to prior crizotinib and randomized 1:1 to receive brigatinib at 90 mg qd (arm A) or 180 mg qd with a 7-day lead-in at 90 mg (arm B). Investigator-assessed confirmed objective response rate (ORR) per RECIST v1.1 was the primary endpoint. **Result:** Among 222 patients (n=112/n=110, arm A/B), median age was 51/57 years; 71%/67% had brain metastases. As of February 21, 2017, 17 full months since the last patient enrolled, median follow-up was 16.8/18.6 months and 32%/41% of patients continued to receive brigatinib in A/B. The table shows brigatinib efficacy. Per independent review committee, confirmed ORR was 51%/55% and median PFS was 9.2/16.7 months in A/B. Among patients with measurable baseline brain metastases (n=26/n=18, A/B), confirmed intracranial ORR was 50%/67% as of January 24, 2017; median intracranial DoR was not reached/16.6 months. The most common treatment-emergent adverse events (TEAEs) were: nausea (38%/47%, A/B), diarrhea (28%/44%), cough (28%/40%), headache (30%/35%), and vomiting (36%/30%); the most common grade ≥3 TEAEs were: increased creatine phosphokinase (5%/13%), hypertension (6%/8%), pneumonia (4%/5%), and increased lipase (5%/4%). Dose reduction (9%/30%, A/B) or discontinuation (4%/11%) due to TEAEs was reported. **Conclusion:** In ALTA, brigatinib continues to show substantial efficacy and acceptable safety at both dose levels, with numerically longer PFS and higher intracranial ORR at the recommended dosing regimen of 180 mg qd (with lead-in) vs 90 mg qd.

	Investigator Assessment		**Independent Reviewa**	
	Arm A (n=112)	**Arm B (n=110)**	**Arm A (n=112)**	**Arm B (n=110)**
Confirmed ORR, %	46 (35–57[b])	55 (44–66[b])	51 (41–61[c])	55 (45–64[c])
Median DoR in responders,[d] months	12.0 (9.2–17.7[c])	13.8 (10.2–17.5[c])	13.8 (7.4–NR[c])	14.8 (12.6–NR[c])
Median PFS,[d] months [% of events]	9.2 (7.4–11.1[c]) [65]	15.6 (11.1–19.4[c]) [50]	9.2 (7.4–12.8[c]) [54]	16.7 (11.6–NR[c]) [41]
Median OS,[d] months [% of events]	NR (20.2–NR[c]) [38]	27.6 (27.6–NR[c]) [29]	—	—
1-year OS probability,[d]%	70 (61–78[c])	80 (71–87[c])	—	—
DoR, duration of response NR, not reached OS, overall survival PFS, progression-free survival [a]Last scan date: February 28, 2017 [b]97.5% CI for primary endpoint [c]95% CI [d]Kaplan-Meier estimate				

Keywords: ALK, brigatinib, NSCLC

OA 05 NEXT GENERATION TKI
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 05.06 PHASE 2 STUDY OF LORLATINIB IN PATIENTS WITH ADVANCED ALK+/ROS1+ NON-SMALL-CELL LUNG CANCER

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Background: Lorlatinib, a selective, potent, brain-penetrant ALK/ROS1 TKI, is active against most known ALK kinase domain mutations. In phase 1 of this ongoing study (NCT01970865), lorlatinib displayed robust clinical activity among patients with *ALK+/ROS1+* non-small-cell lung cancer (NSCLC), most of whom were heavily pretreated and had CNS metastases. Phase 2 evaluated efficacy (overall and intracranial), according to prior treatment, and safety at the recommended phase 2 dose (100 mg QD). **Method:** Patients with NSCLC ± asymptomatic CNS metastases enrolled in 6 cohorts (EXP1–5, ALK+; EXP6, *ROS1+*). The primary endpoint was objective response rate (ORR) and intracranial ORR by independent central review. Safety, patient-reported outcomes and molecular profiling were also assessed. **Result:** As of 15-March-2017, 227 *ALK+* patients were evaluated for ORR (Table), including 140 with CNS involvement who were evaluated for intracranial ORR.

	Confirmed ORR		Confirmed IC-ORR	
	N	n (%)	N	n (%)
ALK+ cohorts				
EXP1 (treatment-naïve, no prior ALK-TKIs or CT)	30	27 (90)	8	6 (75)
EXP2 (prior crizotinib only)	27	20 (74)	17	10 (59)
EXP3 (1 prior ALK TKI ± CT)	59	30 (51)	32	20 (63)
EXP3A (prior crizotinib + CT)	32	21 (66)	20	15 (75)
EXP3B (any 1 other ALK TKI ± CT)	27	9 (33)	12	5 (42)
EXP4 (2 prior ALK TKIs ± CT)	65	27 (42)	45	25 (56)
EXP5 (3 prior ALK TKIs ± CT)	46	16 (35)	38	(15 (39)
CT, chemotherapy; IC, intracranial.				

Of 219 ALK+ patients analyzed for ALK kinase domain mutations at baseline, 46/219 (21%) had ≥1 mutation detected in circulating free DNA; most derived treatment benefit with an ORR of (27/46) 59%. Across all cohorts (N=275), the most common treatment-related adverse events (AEs) and grade 3/4 treatment-related AEs were hypercholesterolemia (81%/16%) and hypertriglyceridemia (60%/16%); 30% and 22% of patients had treatment-related AEs associated with dose interruptions and reductions, respectively. No treatment-related deaths occurred; 7 patients (3%) had treatment-related AEs leading to treatment discontinuation. 157/275 (57%) patients remained on treatment at data cutoff. Most patients reported stable/improved global quality of life (40%/43%). **Conclusion:** Lorlatinib showed clinically meaningful activity, including substantial intracranial efficacy, among *ALK+/ROS1+* patients who were either treatment-naïve or failed ≥1 prior ALK TKI. Overall lorlatinib was well tolerated and when needed, AEs were managed by dose delay/reduction or standard medical therapy.

Keywords: lorlatinib, ALK-positive NSCLC, intracranial

OA 05 NEXT GENERATION TKI
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OA 05.07 EFFICACY AND UPDATED SAFETY OF CERITINIB (450 MG OR 600 MG) WITH LOW-FAT MEAL VS 750 MG FASTED IN ALK+ METASTATIC NSCLC

B.C. Cho[1], R. Obermannová[2], A. Bearz[3], D. Kim[4], S. Orlov[5], G. Borra[6], S. Kim[7], P.E. Postmus[8], S. Laurie[9], K. Park[10], S. Geater[11], A.C. Bettini[12], K. Osborne[13], V.Q. Passos[14], Z. Chen[14], R. Dziadziuszko[15]

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Background: Ceritinib is a next-generation anaplastic lymphoma kinase (ALK) inhibitor approved for the treatment of patients with *ALK+* non-small cell lung cancer (NSCLC) who are treatment-naive or have progressed on crizotinib at the recommended dose of 750 mg/day under fasted state. Gastrointestinal (GI) adverse events (AEs), eg, diarrhea, nausea, vomiting, are common with ceritinib 750 mg/day under fasting conditions. ASCEND8 study, (NCT02299505) evaluated alternative methods of ceritinib administration, utilizing potential benefit of dosing ceritinib with food to reduce GI toxicity, while maintaining the pharmacokinetic exposure at lower doses. Based on the primary pharmacokinetics analysis previously presented (n=137;

WCLC 2016), ceritinib 450 mg with food had similar exposure and a more favorable GI safety profile vs ceritinib 750 mg fasted in patients with *ALK*+ NSCLC. **Method:** This is a multicenter, randomized, 3-arm (450 mg or 600 mg ceritinib taken with low-fat meal vs 750 mg ceritinib taken in fasted state), open-label, phase 1 study (ASCEND-8). Patients were eligible if they had stage IIIB or IV *ALK*+ advanced NSCLC, were aged 18 years or older, who were either previously treated with chemotherapy and/or crizotinib or treatment naive. We plan to report the updated safety (n=228) and preliminary efficacy for treatment-naïve patients (ALK+ by immunohistochemistry [IHC]) who were randomized at least 18 weeks before the cutoff date (March 28, 2017; n=79). Updated analysis is planned to be made available by August 2017 and the following data will be included at the time of final abstract submission: patient disposition; patient demographics; disease characteristics and prior therapies; overall response rate and duration of response by blinded independent review committee (BIRC; key secondary endpoints) in treatment-naïve patients (ALK+ by IHC) randomized at least 18 weeks prior to the cut-off date; progression-free survival per BIRC in treatment-naïve patients (ALK+ by IHC) randomized at least 18 weeks prior to the cut-off date; updated safety results with detailed information on GI (diarrhea, nausea, vomiting) and liver (alanine transaminase/aspartate transaminase) toxicities. **Result:** LBA shell - not applicable **Conclusion:** LBA shell - not applicable

Keywords: Ceritinib, ALK, NSCLC

OA 05 NEXT GENERATION TKI
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OA 05.08 FINAL RESULT OF PHASE I/II STUDY (AF-001JP) OF ALECTINIB, A SELECTIVE CNS-ACTIVE ALK INHIBITOR, IN ALK+ NSCLC PATIENTS (PTS)

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Background: Alectinib (ALC) is a selective, CNS-active ALK tyrosine kinase inhibitor. In two Phase 3 studies (J-ALEX and ALEX), ALC proved superior efficacy and tolerability compared to crizotinib (CRZ). Here we report the final efficacy and safety results of the 46 pts enrolled in the phase II part of study AF-001JP with a longer follow-up period than that observed in J-ALEX and ALEX studies. **Method:** ALC 300 mg b.i.d was given to *ALK*+ NSCLC pts who were ALK inhibitor-naive and had disease progression after at least one line of chemotherapy to investigate the efficacy and safety until the investigator confirmed no further clinical benefits. **Result:** This study was completed in December 2016. The median treatment duration was 46.1 months (range: 1-62). 20 of 46 pts were on treatment with alectinib at the study termination. Progressive disease (PD) was confirmed in 20 pts (43%). Median PFS was not reached and 4-year PFS rate was 52% (95% CI: 36-66). 14 of 46 pts had CNS metastasis at baseline. Median PFS was 38 months (95% CI: 9-NE) in pts with CNS metastases and was not reached in pts without CNS metastases. Four pts had CNS progression and the 4-year cumulative incidence rate of CNS progression was 9.5%. Median OS was not reached and the 4-year OS rate was 70% (95% CI: 54-81). Safety profile was similar to that reported previously and there were no treatment-related Grade 4 or 5 adverse events for this long administration period. **Conclusion:** Regardless of CNS metastases at baseline, ALC have demonstrated excellent efficacy in *ALK*+ NSCLC pts without prior ALK inhibitor treatment. ALC was well tolerated over a prolonged administration period.

Keywords: CNS metastases, Alectinib, NSCLC

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 06.01 COSTS AND COST-EFFECTIVENESS OF SMOKING CESSATION WITHIN AN ORGANIZED CT LUNG CANCER (LC) SCREENING PROGRAM

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This abstract is under embargo until October 16 @ 08:00.

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 06.02 FINAL REPORT OF THE INHERIT EGFR STUDY - 33 UNRELATED KINDREDS CARRYING GERMLINE EGFR MUTATIONS

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Background: Anecdotal reports of families carrying germline *EGFR* mutations force us to reconsider our understanding of inherited lung cancer risk in non-smokers. We launched this prospective trial (NCT01754025; ALCMI-002) to remotely enroll and characterize these rare families. **Method:** Eligible subjects were recruited at participating cancer centers or through an online referral system. Following consent (in person or by phone), subjects received genetic counseling and sequencing of saliva or blood for germline *EGFR* mutations. Cancer specimens and CT scans were additionally analyzed when available. **Result:** Between 12/2012-6/2017, 105 participants were enrolled from 30 US states. Germline *EGFR* mutations were found in 63% of patients (31 of 49) with *EGFR* T790M in their lung cancer at diagnosis, and in 62% (16 of 27) and 44% (4 of 9) of first- and second-degree relatives of germline carriers. Pedigrees were available for 32 unrelated kindreds (31 germline T790M, 1 germline R776H): 4 with no family history of lung cancer, 8 with a family history of lung cancer in non-smokers, 18 with multiple relatives with lung cancer. Characteristics of 31 lung cancer probands: median age of lung cancer diagnosis was 57 (range 28-82); 81% white, 19% black; 52% never-smokers; 65% stage IV at diagnosis; 65% were from states in or bordering the US Southeast. Tumor genotyping revealed somatic *EGFR* co-mutations in 29 (94%) of probands: 6 exon 19 del, 12 L858R, 6 G719X, 1 exon 19 del & G719R, 1 L861Q, 2 H773R, 1 V774M. Imaging analysis suggests a unique pattern of cancer evolution including an indolent multi-focal nodular phase which then progresses to lymph nodes and then remote metastatic disease. Of 8 probands with sensitizing *EGFR* co-mutations treated with osimertinib, no unexpected toxicities were seen, and 4 have had durable benefit exceeding 12 months. Of 9 relatives with germline *EGFR* mutations and CT imaging available, 2 have a lung cancer diagnosis and 6 others have lung nodules. **Conclusion:** This study confirms the high likelihood of a germline mutation in lung cancer patients with *EGFR* T790M detected at diagnosis, and suggests a risk of lung nodules and lung cancer in germline carriers. The regional enrichment in the US Southeast suggests a possible founder effect; haplotyping is planned. A registry is under development to continue follow-up of these rare individuals. Further investigation of germline risk alleles associated with lung cancer risk in non-smokers is needed. Funding: Bonnie J. Addario Lung Cancer Foundation, Conquer Cancer Foundation of ASCO.

Keywords: Germline EGFR mutations, EGFR T790M, familial lung cancer

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
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OA 06.03 COMORBIDITY AND COMPETING CAUSES OF DEATH ATTENUATE OUTCOMES IN THE NLST.

R. Young[1], R. Hopkins[2], G. Gamble[2]

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Background: In the National Lung Screening Trial (NLST), annual CT screening reduced lung cancer-specific mortality by 20% and all-cause mortality by 7% relative to chest x-ray (CXR) screening. However, in contrast to other screening approaches, recommendations for CT screening for lung cancer is limited to older heavy smokers, where the risk of death from all smoking-related complications is high, relative to the unscreened population. In the NLST, airflow limitation affects 35% of screening participants and is associated with a 2-4 fold increase risk of lung cancer. We have recently shown that for screening participants with COPD, the reduction in lung cancer-specific mortality with CT screening is only half that seen in those with no COPD (15% vs 28%). We hypothesise that this reduction is due in part to a "competing cause of death" effect. **Method:** Using 10,054 subjects from the ACRIN-NLST sub-study, the current study aimed to compare disease-specific mortality according to the severity of airflow limitation at baseline to better understand it's relationship with dying of lung cancer and dying of other smoking-related diseases. We also examined this relationship according to baseline risk of lung cancer, using the Brock (Lung cancer risk) Model, and outcomes from screening. **Result:** After 6.4 years of follow-up, there were 699 deaths; 189 (27%) attributed to lung cancer, 166 (24%) to cardiovascular disease, 61 (9%) to respiratory disease and 150 (21%) to other cancers. After stratifying the 10,054 subjects according to severity of airflow limitation (baseline FEV1%predicted and GOLD grade), we found that the risk of dying of lung cancer and risk of dying of other diseases diverged favouring a stronger relationship with non-lung cancer causes. After stratifying the 10,054 subjects according to their risk of lung cancer (tertiles), we found that CT screening in those at highest risk (highest tertile) had only a 12% reduction in lung cancer-specific deaths compared to 23-24% in other lower risk tertiles. This was associated with higher deaths from cardiovascular disease, respiratory disease and other cancers. **Conclusion:** In a CT screening study, where smokers were followed for a mean of 6.4 years, we found worsening lung function and higher underlying risk for lung cancer was associated with a greater tendency to die of causes other than

lung cancer. We suggest smokers at the greatest risk for lung cancer, and those with worse lung function, benefit less from CT screening due to a "competing cause of death" effect.

Keywords: lung cancer, Comorbidities, Airflow Limitation

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 06.05 SOCIOECONOMIC FACTORS AFFECTING OUTCOMES IN NON-SMALL CELL LUNG CANCER (NSCLC): A LARGE POPULATION-BASED ANALYSIS

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This abstract is under embargo until October 16 @ 08:00.

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 06.06 CHR15Q25 LOCUS CONFERS RISK OF LUNG CANCER, COPD AND SMOKING: TRIPLE WHAMMY EFFECT IN THE ACRIN NLST SUB-STUDY (N=9,270)

R. Hopkins[1], F. Duan[2], E. Greco[2], C. Chiles[3], G. Gamble[1], D. Aberle[4], R. Young[5]

[1]University of Auckland, Auckland/NZ, [2]Brown University, Providence/US, [3]Wake Forest University Baptist Medical Center, Winston-Salem/US, [4]Department of Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles/CA/US, [5]Faculty of Medical Health Sciences, University of Auckland, Auckland/NZ

Background: Several large genetic studies have consistently linked the cholinergic nicotinic receptor polymorphism (CHRNA3/5, rs 16969968) to lung cancer and smoking addiction. However, we have shown that this genetic variant was also independently associated with susceptibility to chronic obstructive pulmonary disease (COPD). To date this observation, independently linking CHRNA3/5 polymorphism to both COPD and lung cancer, has not been tested prospectively in a cohort study. Using 10,054 subjects from the ACRIN-NLST cohort, a sub-study of the NLST that recruited high risk smokers and followed them for an average of 6.4 years, we examined the association between the CHRNA3/5 variant in the development of lung cancer relative to its role in COPD and lifelong smoking exposure. **Method:** We compared the frequency of the high risk AA genotype in our cohort of 10,054 high risk smokers according to their smoking status, lung function and COPD status. We also compared the lung cancer incidence rate according to the CHRNA3/5 genotype. Lastly we used stepwise logistic regression and mediation analysis to examine the role of the AA genotype of the CHRNA3/5 variant in smoking exposure, COPD and lung cancer. **Result:** Relative to healthy smoking controls, the AA genotype was associated with the presence of COPD (OR=1.3, P<0.001) and the development of lung cancer overall (OR=1.5, P<0.01), lung cancer with pre-existing COPD (OR=1.5, P=0.04), lung cancer with no COPD (OR=1.5, P=0.04). Compared to the GG and AG genotypes, the AA genotype was associated with (a) lower FEV1%pred, lower FEV1/FVC and a 19% increase in risk of COPD; and (b) greater cigs/day, pack years exposure and a 47% increased risk of lung cancer. No differences were found for age, gender, smoking duration, years since quitting and current smoking status. In stepwise logistic regression, we found that age, BMI, AA genotype, smoking exposure and lung function were independently associated with getting lung cancer. In the mediation analyses we found that the AA genotype was independently associated with smoking (OR=1.42,P<0.05), COPD (OR=1.25,P<0.05) and getting lung cancer (OR=1.37, P<0.05). **Conclusion:** This is the first prospective study to confirm that while the CHRNA3/5 variant is associated with lung cancer, more importantly this variant is also independently associated with airflow limitation (COPD). It is also the first cohort study to show that while this genetic variant is also associated with smoking exposure (triple whammy effect), this is independent of its effects on predisposition to both COPD and lung cancer.

Keywords: Cholinergic Nicotinic Receptor, triple whammy, lung cancer

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
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OA 06.07 SURVIVAL TRENDS AMONG NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS OVER A DECADE: IMPACT OF INITIAL THERAPY AT ACADEMIC CENTERS

B. Dholaria[1], S. Ailawadhi[1], A. Soyano[2], D. Hodge[3], R. Manochakian[1], M. Menefee[4], E. Johnson[1], M. Thomas[5], S. Ko[6], R. Miller[6], M. Johnson[7], N. Patel[7], K. Mody[1], R. Joseph[1], Y. Lou[1]

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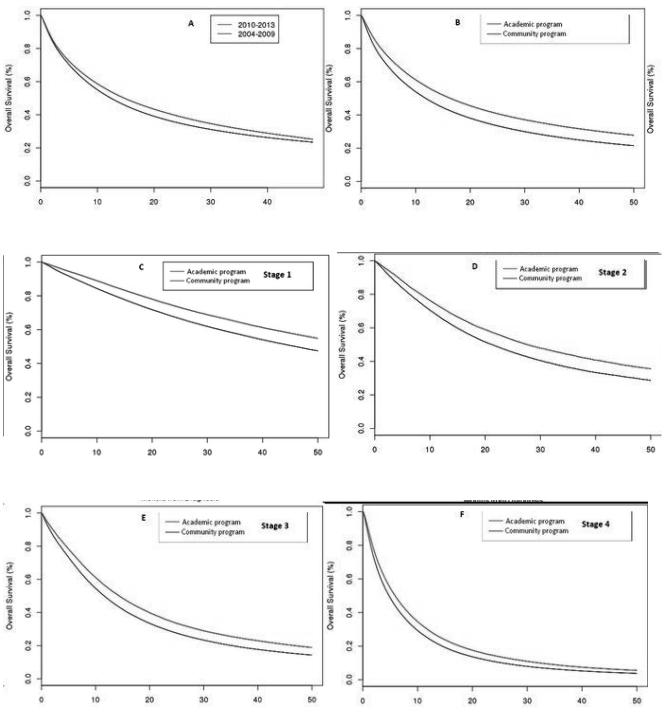
Background: Treatment of NSCLC is rapidly advancing and academic centers are considered equipped with better expertise. NSCLC outcome trends in novel therapeutic era and impact of initial treatment at academic centers have not been reported. **Method:** The National Cancer Database (NCDB) with NSCLC incident cases between 2004-2013 was used. Overall survival (OS) was plotted by year of diagnosis and type of treatment facility, accounting for several available factors in NCDB. **Result:** A total of 1,150,722 NSCLC patients were included and separated by initial treatment facility type (academic: 31.5%, non-academic: 68.5%). Several characteristics were significantly different between the two cohorts (Table 1). Median OS for all patients was 13.1 months and improved significantly for those diagnosed in 2010-2013 (14.8 months) as compared to 2004-2009 (12.4 months) (p<0.001). Treatment at academic centers was associated with reduced risk of death [Multivariate HR=0.91 (95% CI 0.906-0.919), P<0.001]. Four-year OS for academic and non-academic cohorts was 25% and 19%, respectively (p<0.001), the difference more pronounced in stage 1-3. (Figure 1)

Parameters	Academic (N=362247)	Non-Academic (N=788475)	p value
Median Age at Diagnosis (years)	68 (40.0-90.0)	70 (40.0-90.0)	<0.0001
Race-Ethnicity			<0.0001
NH White	289097 (80.8%)	696610 (88.9%)	
NH Black	55564 (15.5%)	69055 (8.8%)	
NH Asian/PI	10227 (2.9%)	13313 (1.7%)	
NH NA/AN	543 (0.2%)	2147 (0.3%)	
Hispanic	2153 (0.6%)	2457 (0.3%)	
Charlson-Deyo Comorbidity Score			<0.0001
0	228517 (63.1%)	453021 (57.5%)	
1	93742 (25.9%)	232322 (29.5%)	
≥2	39988 (11.0%)	103132 (13.1%)	
Median Income Quartiles 2008-2012			<0.0001
<$38,000	77385 (21.8%)	155164 (20.2%)	
$38,000-$47,999	78906 (22.2%)	209503 (27.2%)	
$48,000-$62,999	87802 (24.7%)	211346 (27.4%)	
$63,000+	110998 (31.3%)	194024 (25.2%)	
Insurance status			<0.0001
Not insured	13429 (3.8%)	23342 (3.0%)	
Insured	335764 (96.2%)	753375 (97.0%)	
Median Great Circle Distance (miles)	11.2	8.1	<0.0001
TNM stage			<0.0001
Stage 1	83398 (27.8%)	157977 (24.1%)	
Stage 2	19881 (6.6%)	45890 (7.0%)	
Stage 3	68832 (23.0%)	160407 (24.5%)	
Stage 4	127558 (42.6%)	290783 (44.4%)	
Year of Diagnosis			<0.0001
2004-2009	204897 (30.6%)	465401 (69.4%)	
2010-2013	157350 (32.8%)	323074 (67.3%)	
Radiation as Part of Initial Therapy	141842 (39.6%)	316214 (40.5%)	<0.0001
Surgery of Primary Site	126128 (34.9%)	213605 (27.2%)	<0.0001
Chemotherapy as Part of Initial Therapy	151604 (43.4%)	341973 (44.7%)	<0.0001
Mean Regional Lymph Nodes Examined	11.2	7.9	<0.0001
High Volume Center	193244 (53.3%)	155050 (19.7%)	<0.0001
Median OS (months)	16.4	11.9	<0.0001



Conclusion: In this largest analysis thus far, NSCLC survival has improved over time and type of treatment facility significantly influences survival. Factors influencing

treatment facility choice should be addressed for easier access to academic centers.

Keywords: non-small cell lung cancer, survival outcome, Initial Therapy at Academic Centers

OA 06 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY I
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OA 06.08 IS LUNG CANCER SCREENING ASSOCIATED WITH A NEGATIVE PSYCHOLOGICAL IMPACT?

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Background: Lung cancer screening can reduce lung cancer mortality by 20%. It is currently recommended in the USA, but not in the UK and ensuring any potential psychological harm is minimised is important. Current evidence is limited to the psychological impact of CT lung cancer screening. This study assesses psychological responses in the Early Cancer Detection Test - Lung Cancer Scotland Study (ECLS Study), whose participants have a tumour antibody blood test (Early CDT®-Lung test) and CT scans only for those with positive blood tests. **Method:** ECLS study participants were randomised to an Early CDT®-Lung test group or a control group. A sample (n=1032) participated in a nested psychological outcomes study. Questionnaires measured psychological responses (positive and negative affect scale (PANAS), lung cancer worry scale (LCWS) and impact of events scale (IES)) at baseline and 1, 3, 6 and 12 months post-trial recruitment. Psychological responses over time were assessed using multilevel modelling and compared between those in the control group, the test-positive group and the testnegative group. **Result:** In total, 350, 361 and 321 participants were in the control, test-negative and test-positive groups respectively. Follow-up questionnaire completion rates were ≥90% at all time-points. Baseline psychological measures did not differ significantly between groups. Significant differences were found between PANAS scores, but absolute differences between the groups were very small and unlikely to be clinically significant. The IES avoidance and intrusion scores were significantly higher in the positive than the negative group at all time-points and at 1, 3 and 6 months respectively. However, median scores for both subscales at all the time-points were in the subclinical range. Anxiety about future tests and treatment at 1 month was significantly higher in the test-positive group than the control (OR (95%CI) 3.55 (1.70, 7.41)), or the negative group (OR (95%CI) 5.74 (2.69, 12.2)). Worry about getting lung cancer in the future was significantly higher in the test-positive than the test-negative group at 1 month (OR (95%CI) 2.61 (1.35, 5.02)), 3 months (OR (95%CI) 2.52 (1.30, 4.87)) and 6 months ((OR (95%CI) 2.98 (1.53, 5.82)). **Conclusion:** Lung cancer screening using a blood test followed by CT scanning for test-positive individuals does not appear to impact on affect, intrusive thoughts or avoidant behaviour to a clinically important degree. However, anxiety about future tests and treatment and future worry about lung cancer needs to be addressed if lung cancer screening is implemented in the UK.

Keywords: lung cancer worry, lung cancer screening, psychological harm

OA 07 BIOMARKER FOR LUNG CANCER
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

OA 07.01 A PROSPECTIVE STUDY OF PERIOPERATIVE RAPID CLEARANCE OF CIRCULATING TUMOR DNA IN R0 RESECTED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Our previous study has shown the feasibility and clinical application of circulating tumor DNA(ctDNA) detection in stage I-IIIA surgical non-small cell lung cancer (NSCLC) patients(NCT02645318). The aim of this prospective study is to investigate the perioerative changes of ct DNA in surgical NSCLC patients. **Method:** From 11/2016, suspected lung cancer patients who proposed radical tumor resection were enrolled prospectively. Six precise time points plasma samples were obtained before surgery(time A) and after tumor resection (time B to F, 5min-3days) before discharge. A series driver mutations were quantitatively evaluated by multiplex assay based on circulating single-molecule amplification and resequencing technology (cSMART). Positive plasma mutations were validated in tumor tissue by targeted sequencing. Normal tissue and white blood cell DNA were used as controls. Study protocol (NCT02965391) was approved by Medical Ethics Committee (2016PHB156-01). **Result:** The consort diagram was shown in Fig 1. Thirteen R0 resected patients met the inclusion criteria. Fifteen genetic alterations were identified including four EGFR, seven TP53, two PIK3CA, one KRAS mutation and one ALK rearrangement. Ten (76.9%) cases had a gradually decrease of mutation ratio as time went on, and the average mutation ratio was 3.32%, 2.68%, 1.38%, 0.07%, 0.04% and 0 at the time-points A to F, respectively. Eight patients' and three patients' mutation ratio in time point D and time point E were not decease to zero, respectively. Advanced stage patients were more likely to have a positive ctDNA in time D and E, although there was no significant difference. All the mutations' ratio dropped to zero in time F. No patients' had positive ctDNA one month after surgery.

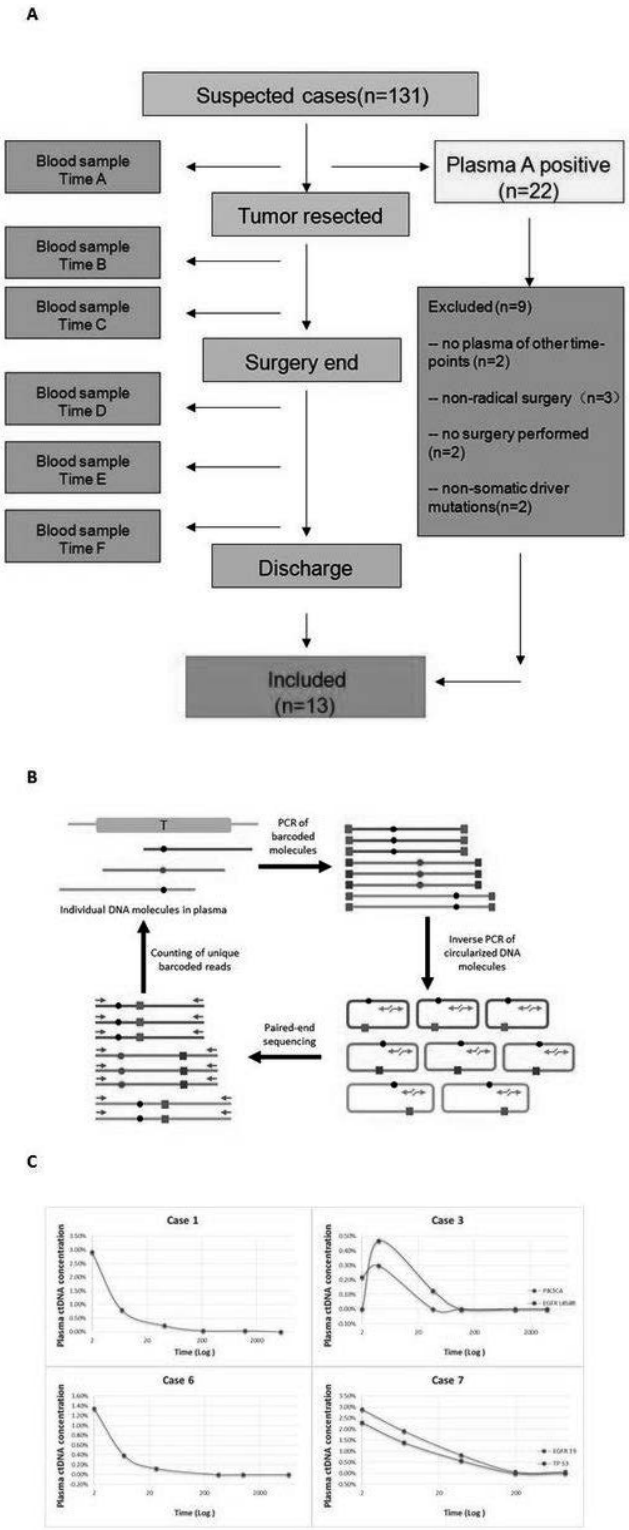

Figure 1（A）Consort diagram（B）Concept of cSMART for quantification of allelic variants in plasma（C）Dynamic changes in plasma ctDNA concentration in lung cancer patients during tumor resection and in the postoperative period（4 cases）

Conclusion: This is the first prospective study to evaluate the dynamic changes of ctDNA in surgical lung cancer patients. ctDNA has a rapid clearance in R0 resected lung cancer patients, but is not completely regression until 72h after surgery.

Keywords: lung cancer, Circulating Tumor DNA, Surgery

OA 07.02 CHARACTERISTICS OF LUNG CANCER CELL-FREE TUMOR DNA (CFDNA) SHEDDING AND CORRELATION WITH TUMOR BURDEN AS MEASURED BY RECIST

V. Lam[1], L. Li[2], J. Wang[2], H. Tran[1], W. Rinsurongkawong[3], R. Lanman[4], J. Lewis[3], J. Roth[5], S. Swisher[5], V. Papadimitrakopoulou[1], J. Lee[3], J. Zhang[1], J. Heymach[1]

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Background: cfDNA is a promising biomarker for early recurrence detection and disease monitoring in the NSCLC curative setting. However, less is known about cfDNA shedding characteristics and correlation with tumor burden in advanced NSCLC. **Method:** We reviewed cfDNA results of NSCLC patients tested at our institution between November 2015 and December 2016 with Guardant 360, a comprehensive cfDNA assay that detects genomic alterations in 70-73 cancer genes. 141 cases with evaluable imaging were selected for this analysis, enriching for *EGFR* and *KRAS* mutated cases to facilitate comparisons of major genomic subtypes (Table 1). Tumor burden was approximated using the sum of longest diameters (SLD), per RECIST v1.1. **Result:** There was a statistically significant correlation of moderate strength between cfDNA maximum variant allele frequency (VAF) detected and SLD (Spearman's rho = 0.35, p < 0.001). This correlation was strongest in *KRAS* mutant cases (rho = 0.52, p = 0.001) and weakest in *EGFR* mutated tumors (rho = 0.21, p < 0.24). Multi-variate regression that included stage, histology, and mutation status confirmed the predictive value of cfDNA VAF for SLD (p = 0.03). *TP53* mutants had higher cfDNA VAF (Wilcox p < 0.001), even after accounting for SLD. Increased cfDNA VAF was also seen with *EGFR* mutants and patients with visceral metastasis, though possibly confounded by concomitant *EGFR* amplification and increased tumor burden, respectively. CNS metastasis was not associated with differential cfDNA shedding.

Table 1: Baseline characteristics

Characteristic	Number (%)
Stage	
II	3 (2.1)
III	7 (5.0)
IV	131 (92.9)
Histology	
Adenocarcinoma	103 (73.0)
Squamous cell	36 (25.5)
NSCLC NOS	2 (1.4)
Alteration	
TP53 mutation	64 (45.4)
EGFR mutation	34 (24.1)
KRAS mutation	34 (24.1)
ALK fusion	4 (2.8)

Conclusion: In this primarily metastatic cohort, cfDNA VAF correlated with radiographic assessment of tumor burden by RECIST. This correlation was partially mediated by the presence of key driver mutations. *TP53* and *EGFR* mutant tumors and the presence of visceral metastasis are associated with higher cfDNA VAF. These findings have potential implications for the use of cfDNA in advanced-stage NSCLC disease monitoring, where RECIST is more clinically applicable than formal volumetrics.

Keywords: cfDNA, biomarker, RECIST

OA 07.03 CIRCULATING TUMOR DNA MUTANT ALLELE FREQUENCY AND TUMOR BURDEN AS BIOMARKERS FOR RESPONSE TO IMMUNE CHECKPOINT BLOCKADE

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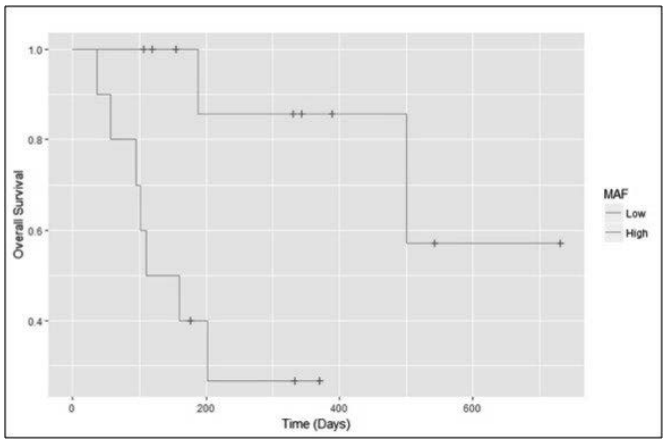
Background: Identifying biomarkers to select patients who respond to immune checkpoint blockade in non-small cell lung cancer (NSCLC) remains a challenge. Cell-free circulating tumor DNA (ctDNA) has emerged as a non-invasive, quantitative method of monitoring genomic alterations in the peripheral blood. We evaluated the clinical utility of ctDNA mutant allele frequency (MAF) and tumor burden based on imaging as biomarkers for response to immune checkpoint blockade in NSCLC. **Method:** From a cohort of 136 patients with ctDNA samples, 20 patients were retrospectively identified with ctDNA testing before initiation of anti-PD-1/PD-L1 treatment or within 90 days of therapy initiation. ctDNA testing was performed by Guardant360 (Guardant Health, Redwood City, CA). MAF of the dominant clone was identified quantitatively for each patient. In addition, baseline tumor burden was estimated using RECIST version 1.1. MAF and tumor burden were correlated with progression free survival (PFS) and overall survival (OS). Logistic regression of response rate (RR) and clinical benefit rate (CBR) was also performed. **Result:** Higher median ctDNA MAF was correlated with significantly shorter PFS and OS (hazard ratio (HR) 3.4, p=0.03 and HR 10.4, p=0.03, respectively) (Figure 1). There was no significant association between tumor burden estimation and PFS and OS. However, tumor burden was significantly correlated with MAF (r=0.58, p=0.007). MAF and tumor burden estimation did not correlate with RR or CBR in this small sample.



Conclusion: ctDNA MAF appears to be a promising, non-invasive, prognostic biomarker for response to immune checkpoint blockade in NSCLC with higher MAF associated with shorter PFS and OS. ctDNA MAF may also serve as a surrogate for tumor burden. Prospective studies with serial ctDNA sampling are necessary to further validate these findings.

Keywords: non-small cell lung cancer, Biomarkers, Circulating Tumor DNA

OA 07.05 SERIAL BIOPSIES IN PATIENTS WITH EGFR-MUTANT NSCLC HIGHLIGHT THE SPATIAL AND TEMPORAL HETEROGENEITY OF RESISTANCE MECHANISMS

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Background: Resistance to EGFR tyrosine kinase inhibitors (TKIs) limits treatment outcomes among patients with EGFR-mutant NSCLC. Resistance mechanisms have previously been conceptualized as binary "positive/negative" variables, but emerging evidence suggests resistant cancers are heterogeneous, and subclones may be appreciated through multiple biopsies. **Method:** We retrospectively analyzed 221 EGFR mutant pts at MGH who had ≥1 biopsy after progression on their initial EGFR inhibitor. Data on acquired resistance (AR) mechanisms observed at each biopsy, adverse events, and treatment were collected. **Result:** Among 221 pts with a total of 355 post-AR tissue biopsies, median age was 59 (range, 28-88), 69% were female, 64% had EGFR del19, 33% L858R and 3% other activating mutations. Median number of biopsies per patient was 1 (range, 1-4). Biopsies at first resistance to EGFR TKI showed 61% T790M, 5% MET amplification (amp), 3% SCLC transformation, 2% acquired PIK3CA and 1% acquired BRAF mutations. 83 pts had two biopsies during their post-resistance course; 43/83 (52%) had heterogeneity between biopsy 1 and 2. In particular, 20% "lost" T790M, while 11% "gained" T790M. Among 17 pts who lost T790M, 3 gained a separate resistance mechanism, including MET amp and BRAF V600E. In some cases, synchronous biopsies identified spatial heterogeneity. For example, an osimertinib-resistant patient had a T790M/C797S lung nodule, while a concurrent mediastinal lymph node was wild-type at both loci (both sites retained the activating EGFR mutation). Similarly, another osimertinib-resistant patient with MET amp in a pleural effusion cell block had a lung nodule biopsy which lacked MET amp; the patient was treated with combination EGFR and MET inhibitors with a partial response. Additional details regarding concurrent liquid biopsies, treatment histories and clinical outcomes will be presented. **Conclusion:** In this large cohort of EGFR mutant NSCLC patients, we frequently observed variations in resistance mechanisms in patients with > 1 post-AR biopsy. Our data highlights the heterogeneity of resistant cancers and the limitations of a single biopsy in fully capturing the spectrum of resistance mechanisms in each patient. Serial biopsies or non-invasive methods may be required to characterize resistance and identify potential therapeutic targets.

Keywords: Resistance, EGFR, Heterogeneity

OA 07.06 INNATE GENETIC EVOLUTION OF LUNG CANCERS AND SPATIAL HETEROGENEITY: ANALYSIS OF TREATMENT-NAÏVE LESIONS

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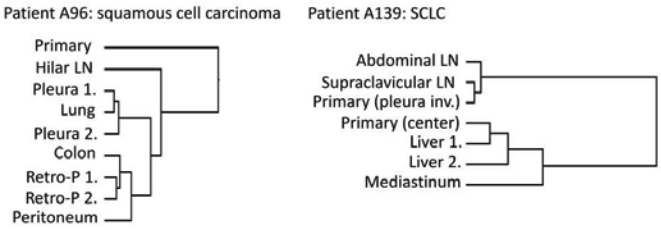
Background: Cancers are composed of heterogeneous cell populations in terms of somatic mutations and dysregulated signaling pathways. We hypothesized that such heterogeneity, together with selection advantages conferred by distinct microenvironments, may contribute to tumor evolution and metastatic patterns. **Method:** We collected tumor specimens and non-cancer tissues from treatment-naïve autopsied patients to study the innate genetic evolution and spatial heterogeneity by RNA-sequencing. Our cohort consists of four NSCLC patients and one SCLC patient. Each patient had 5 – 9 primary and metastatic lesions, including metastases to lung, liver, colon (distant metastases), visceral or parietal pleura (pleural metastases), and intra- or extra-thoracic lymph nodes (lymph nodes metastases). Comprehensive data analyses were performed, including gene expression / pathway analyses and fusions / somatic variants detection. **Result:** Global unsupervised clustering analysis of expression data reveals that lesions from each patient clustered together, indicating that tumor cells themselves have greater effects on the gene expression signature than the microenvironment. Pathway analyses in individual patients revealed that the primary lesion is distinct from metastatic lesions in NSCLCs (Figure-left). For the SCLC patient, distant metastases and lymph node metastases clustered according to different parts of the primary tumor (Figure-right). Pathway analyses also revealed that cell-cycle, DNA replication, RNA polymerase, and spliceosome-related pathways are upregulated, while immune-related pathways are downregulated in all metastatic patterns compared with primary lesions. In particular, we observed that multiple immune-related pathways, related to NK cells and T-cells, were downregulated in pleural metastases. Detection of fusions / somatic variants identified the KIF5B-RET fusion as a founder mutation in a never-smoking adenocarcinoma patient. Notch signaling was upregulated, in this patient, in all metastatic lesions but not the primary site.



Conclusion: These data demonstrate the similarity and the heterogeneity between primary and metastatic lesions in lung cancer patients. In addition, we identified the correlation between tumor heterogeneity and metastatic patterns.

Keywords: RNA-sequencing, Pathway analysis, Inter-tumor heterogeneity

OA 07.07 INHIBITION OF THE NOVEL ONCOGENE ELF3 ABOLISHES LUNG ADENOCARCINOMA GROWTH

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Background: Oncogenic reactivation of transcription factors involved in fetal lung development is integral to lung adenocarcinoma (LUAD) biology, as observed with TITF1/NKX2-1 and the ETS transcription factors ETV4 and ETV5. ELF3 is an uncharacterized ETS family member implicated in fetal lung development encoded at 1q32.1. Interestingly, chromosome 1q is a region of frequent gain in LUAD that lacks a bona fide oncogene. We hypothesize that ELF3 is a novel oncogene and putative therapeutic target in LUAD. **Method:** Multiple independent datasets encompassing 1,685 clinical samples of LUAD, lung squamous cell carcinoma (LUSC), small cell lung cancer, and non-malignant lung tissues were analyzed to establish the frequency of *ELF3* overexpression and underlying genetic mechanisms of selection. Protein-protein interaction (PPI) networks were constructed around ELF3, and integrated pathway analysis was performed to decipher the signaling network disruptions resulting from ELF3 overexpression. Isogenic cell lines were established to assess the ability of ELF3 to regulate oncogenic phenotypes. The effect of ELF3 loss on tumour growth was assessed in xenograft mouse models. **Result:** Strong *ELF3* overexpression was frequently observed in LUAD (>2-fold: TCGA 40% p=1.5E-07; BCCA 73% p=1.6E-21), but was not observed in other lung cancer subtypes. Similarly, high *ELF3* expression was significantly associated with poor overall survival of LUAD patients (all Stages $p<0.0001$, Stage I $p<0.0001$), but not LUSC patients ($p>0.05$). These clinical associations prompted further examination of ELF3 in the LUAD subtype of lung cancer. While mutations in *ELF3* were rare, up to 80% of LUAD patients harboured focal amplification, DNA gain, and/or promoter hypomethylation at the *ELF3* locus, which resulted in transcript overexpression. ELF3 overexpression induces remodeling of 23 direct PPI networks, resulting in loss of interaction with proteins such as MYC and GLI2, while forming new interactions with NKX2-1, HOXA5 and CDK8, among others. This reprogramming of PPI networks affects multiple oncogenic pathways including MAPK, TGF-beta and WNT. ELF3 knockdown in LUAD cell lines resulted in significantly reduced proliferation, viability, and anchorage-independent growth, demonstrating ELF3 has oncogenic properties. Loss of ELF3 abolished the ability of LUAD cells to establish tumours in xenograft mouse models, demonstrating the requirement of ELF3 expression for tumour growth. **Conclusion:** ELF3 is a novel LUAD oncogene encoded on chromosome 1q, activated in up to 73% of patients, and strongly associated with poor overall survival. As ELF3 inhibition abolished tumour growth, therapeutic targeting of ELF3 could benefit LUAD patient outcome.

Keywords: Genomics, transcription factor, oncogene

OA 07.08 CLINICAL POTENTIAL OF SPUTUM IN DETECTING DRIVER MUTATIONS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER: A PRELIMINARY STUDY

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Background: The incidence of lung cancer has significantly increased over the last century and remains the most common cause of cancer deaths worldwide. Our better understanding of the tumor microenvironment and the systemic actions of tumors, combined with the recent advent of the liquid biopsy, may allow molecular diagnostics to be done with non-invasive method for detection and monitoring of patient tumors. Sputum has been the target for the discovery of non-invasive biomarkers for lung cancer because it contains airway epithelial cells, and molecular alterations identified in sputum are most likely to reflect tumor-associated changes. Since January of 2017, sputum samples have been prospectively collected at the time of diagnosis for future evaluation of actionable mutations in *EGFR*, *KRAS*, *BRAF* and *NRAS* in patients with non-small cell lung cancer in our center. Currently, from 20 sputum samples already collected, 5 are confirmed for driver mutations (one in *KRAS* and 4 in *EGFR*) in tissue biopsy, with 2 of the samples being positive for T790M in circulating tumor DNA (ctDNA) isolated from plasma. Our aim is to evaluate whether sputum may be representative in the detection of these mutations. **Method:** DNA was extracted from sputum using QIAamp DNA midi kit (Qiagen). Tumor somatic mutations were investigated by target-sequencing using a custom Ion Ampliseq™ Panel (ThermoFisher Scientific), containing hotspot regions of 14 genes frequently mutated in solid tumors (including *EGFR*). Multiplex amplification was performed with 10 ng of DNA using Multiplex PCR Master Mix (Qiagen) and high-throughput sequencing was performed using Ion Proton platform. Somatic mutations were considered if the variant allele was present in more than 0.5% of the reads, considering a minimum coverage depth of 20,000X. A medium coverage of 172,524X was obtained in the five samples. **Result:** We detected mutations in 3 out of 5 sputum samples of patients with previously known driver mutations (two exon 19 deletions and one exon 18 G719A in EGFR). The highest frequency was detected in the only patient with spontaneous sputum collection (23%).The other two mutations were detected in low frequencies (0.5 and 0.6%) in samples derived from sputum induction. We found T790M in one patient positive for T790M in ctDNA isolated from plasma. **Conclusion:** These preliminary findings indicate that driver mutations can be identified in sputum routinely obtained from sputum samples. Thus, the ability to examine sputum might provide a convenient source of sampling and may be adapted for future large-scale screening.

Keywords: sputum, circulating tumor DNA (ctDNA), actionable mutations, Lung Cancer, liquid biopsy

OA 08 NEUROENDOCRINE CARCINOMA: TRANSLATIONAL
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

OA 08.01 NEXT GENERATION SEQUENCING OF LARGE-CELL NEUROENDOCRINE CARCINOMA REVEALS AN ASSOCIATION OF PIK3CA MUTATIONS WITH BRAIN METASTASES

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Background: Large-scale genomic characterization of large-cell neuroendocrine carcinoma (LCNEC) has revealed several putative oncogenic drivers. There are, however, little data to suggest that these alterations have clinical relevance. **Method:** We performed comprehensive genomic profiling of 68 stage IV LCNECs of the lung (including next-generation sequencing) and analyzed differences in the clinical characteristics of two major LCNECs subtypes: KRAS mutation and PIK3CA mutation. In order to better understand the divergence that might exist between brain metastases and their lung primaries, we performed whole-exome sequencing of paired lung primaries and brain metastases from four lung LCNEC patients. **Result:** Patients with PIK3CA mutation tumors had aggressive disease marked by worse survival (median OS 7.9 vs. 18.6 mo, $P = 0.002$), higher metastatic burden (> 3 organs 15.2% vs. 4.7%, $P = 0.029$), and greater incidence of brain metastases (19.0% vs.2.3% in others, $P = 0.001$). Whole-exome and RNA sequencing on paired brain metastases and primary LCNECs of the lung revealed that LCNEC primaries that gave rise to brain metastases harbored PIK3CA mutation. Significant tumor growth inhibition with GDC0941 was observed exclusively in the LCNEC patient-derived xenograft model that harbored PIK3CA mutation. **Conclusion:** PIK3CA mutation defines a distinct disease phenotype characterized by brain metastasis in LCNEC of the lung. The result may be relevant for targeted therapy and prophylaxis of NSCLC brain metastases.

Keywords: large-cell neuroendocrine carcinoma, lung cancer, Brain metastasis

OA 08 NEUROENDOCRINE CARCINOMA: TRANSLATIONAL
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OA 08.02 THE CORRELATION OF DLL3 EXPRESSION WITH HIGH-GRADE PULMONARY NEUROENDOCRINE CARCINOMA CLINICOPATHOLOGIC FEATURES AND PROGNOSES

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This abstract is under embargo until October 17 @ 08:00.

OA 08 NEUROENDOCRINE CARCINOMA: TRANSLATIONAL
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OA 08.03 EFFECT OF TOP2A AND ERCC1 GENES POLYMORPHISM ON THE EFFICACY AND TOXICITY OF CISPLATIN AND ETOPOSIDE THERAPY IN SCLC PATIENTS

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Background: Small cell lung cancer (SCLC) shows an aggressive course with early metastases to distant organs. The main treatment regimen for SCLC patients involves platinum based chemotherapy (cisplatin or carboplatin) and etoposide. Genetic alternations, as single-nucleotide polymorphisms (SNPs) in *TOP2A* (topoisomerase II alpha) and in *ERCC1* (endonuclease non-catalytic subunit) genes, were tested as a prognostic and predictive factors in patients with non-small cell lung cancer (NSCLC) treated with chemotherapy. However, there is limited data about clinical relevance of these genetic alternations in SCLC. Therefore, we undertook the present retrospective study to determine the influence of SNPs in *TOP2A* (rs34300454; rs13695; rs11540720) and ERCC1 (rs11615; rs3212986) genes on efficiency and toxicity of chemotherapy with platinum and etoposide in patients with SCLC. **Method:** The studied group included 103 Caucasian SCLC patients (65 male, 38 female, median age 65 ± 7,5 years). We collected detailed clinical-demographical data including: smoking history, environmental/occupational exposure to carcinogens, performance status, disease stage, and the presence of distant metastases. The response to the treatment was carefully monitored according to RECIST criteria, as well as side effects as anemia, neutropenia or weight loss were noted. For SNPs genotyping, we used DNA isolated from peripheral blood leukocytes using Qiamp DNA Mini Kit (Qiagen, *Germany*) and TaqMan hydrolyzing probes (Applied Biosystem, *USA*) in real-time PCR technique on Eco Illumina (Illumina, *USA*) device. **Result:** Patients with C/C genotype in rs13695 of *TOP2A* gene had significantly lower risk of neutropenia during chemotherapy than C/T heterozygous patients (p=0,01894; χ^2=5.51; OR=2,676; 95% CI=1,165-6,143). Patients harbouring homozygous C/C genotype in rs3212986 of *ERCC1* gene had significantly higher risk of anaemia during chemotherapy than heterozygous C/A patients (p=0,04531; χ^2=4,01; OR=0,417; 95% CI=0,175-0,991). Furthermore, homozygous A/A genotype in rs11615 of *ERCC1* gene was associated with significant prolongation of overall survival (12 vs. 9 months) compared to heterozygous G/A genotype of this gene (p=0,0120; χ^2=6,3063; HR=1,657; 95% CI=1,0710-2,5633). **Conclusion:** SNPs in *ERCC1* and *TOP2* genes are associated with the toxicities and overall survival of SCLC patients treated with platinum and etoposide based chemotherapy.

Keywords: SCLC, chemotherapy, SNPs

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OA 08.05 MAJOR DRIVERS OF CHEMOTHERAPY AND RADIATION UTILIZATION FOR LIMITED-STAGE SMALL CELL LUNG CANCER IN THE UNITED STATES

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Background: Small cell lung cancer (SCLC) accounts for 15-30% of newly diagnosed lung cancers. Although chemotherapy and radiation play a vital role in the initial management of limited-stage SCLC, rates of combined modality utilization in the United States have not been comprehensively studied. As such, the National Cancer Database (NCDB) is a valuable resource to understand patterns of care for limited-stage SCLC, as it captures the majority of newly diagnosed thoracic malignancies in the United States. **Method:** All cases of IASLC defined limited-stage SCLC in the United States National Cancer Database (NCDB) were identified from 2004 to 2013. Rates of chemotherapy and radiation utilization were determined along with key factors associated with their use. Kaplan-Meier analysis and multivariable analysis were used to determine factors independently associated with overall survival. **Result:** From 2004 to 2013, there were 70,247 cases with analyzable data in the NCDB that met IASLC criteria for limited-stage SCLC. Of these cases, 40% did not receive radiation and 20% received neither chemotherapy nor radiation. For the irradiated group, the mean radiation dose was 52.8 Gy with a 16.2 Gy interquartile range. On multivariable analysis, being uninsured (OR 0.75, 95% CI 0.67-0.85, $p < 0.001$), Medicaid (OR 0.79, 95% CI 0.72-0.87, $p < 0.001$), and Medicare (OR 0.86, 95% CI 0.82-0.91, $p < 0.001$) were independently associated with a lower likelihood of radiation delivery in comparison to private/managed care insurance (after adjusting for age, tumor stage, and co-morbidity score). The irradiated group had significantly better median survival than the non-radiated group (33 vs. 17 months, $p < 0.001$). Radiation (HR 0.62, 95% CI 0.6-0.63, $p < 0.001$) and chemotherapy (HR 0.55, 95% CI 0.54-0.57, $p < 0.001$) delivery were both independently associated with better survival on multivariable analysis. Adjusted analysis showed that non-academic programs (HR > 1, $p < 0.001$) and non-private/managed care insurance (HR > 1, $p < 0.001$) was independently associated with a survival detriment. **Conclusion:** This is the most comprehensive study currently available describing the utilization of combined modality therapy in the initial management of limited-stage SCLC in the United States. A remarkable number of patients received neither radiation nor chemotherapy as part of their initial oncologic treatment. Insurance status was a key determinant of radiation and chemotherapy delivery even after adjusting for potentially confounding factors. Our findings highlight substantial barriers to quality care delivery and challenges in accrual seen for cooperative group clinical trials for limited-stage SCLC.

Keywords: chemoradiation, limited-stage small cell, insurance status

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OA 08.06 EXPLORATORY ANALYSIS FOR PREDICTORS OF BENEFIT OF PARP INHIBITOR THERAPY IN EXTENSIVE STAGE SMALL CELL LUNG CANCER: ECOG-ACRIN 2511 STUDY

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Background: Veliparib, a potent inhibitor of Poly (ADP) ribose polymerase (PARP) enzyme potentiates standard chemotherapy against small cell lung cancer (SCLC) in preclinical studies. The combination of veliparib (V) with cisplatin/etoposide (CE) doublet as first-line therapy of extensive stage SCLC (ES-SCLC) showed significant signal of efficacy with adjusted PFS HR: 0.63 1-sided p=0.01. There was strata by treatment interaction indicating different efficacy benefit in patient subsets (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). We explored clinical and tissue-based biomarkers as predictors of benefit from this treatment strategy. **Method:** Post-hoc

analysis of clinical data was conducted to identify clinical differences in patients who derived significant benefit from the experimental therapy. Clinical differences were compared between patients in the control and experimental arms within the patient stratum with significant clinical benefit. Similarly, comparison was performed between the strata. Archival tissue samples collected from patients with ES-SCLC enrolled and treated on E2511 study was employed for biomarker analysis using immunohistochemistry to assessSLFN11 and DNA-PK expression. The study has 88% power to detect a PFS hazard ratio of 0.5 comparing biomarker positive to negative 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. Mutivariable analysis controlling for these imbalances still showed a benefit of veliparib (HR=0.26, p=0.001). Comparison of "in strata" group (N=46) to the "not in strata" group (N=82) showed significant imbalance in pleural effusion (p=0.058); elevated AST (p=0.0099) and bilirubin (p=0.0447). Median PFS was identical at 5.9 mos for both groups while median OS was 10.7 mos (95% CI 8.9-13.2) for "not in strata" subsests vs. 8.8 mos (95% CI 7.8-10.8) for "in strata" with a HR of 1.57 (p=0.027) comparing "in strata" to "not in strata". Outcome differences based on SLFN11 and DNA-PK expression will be presented at the meeting. **Conclusion:** PFS benefit of PARP inhibitor therapy in extensive stage SCLC patients with elevated LDH and male gender was not associated with any other clinical characteristics.

Keywords: biomarker, PARP INHIBITOR, SCLC

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OA 08.07 PAZOPANIB MAINTENANCE FOR EXTENSIVE DISEASE SMALL CELL LUNG CANCER: A RANDOMIZED, PLACEBO-CONTROLLED PHASE II STUDY (KCSG-LU12-07)

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Background: We investigated whether pazopanib maintenance following first-line chemotherapy would improve survival in patients with extensive disease small-cell lung cancer (ED-SCLD). **Method:** This study is a randomized, placebo-controlled, phase II study that enrolled ED-SCLC patients who had not progressed after four cycles of etoposide plus platinum combination therapy. Eligible patients were randomly assigned (1:1 ratio) to either placebo or pazopanib 800 mg per day until progression or unacceptable toxicity. The primary end point was progression-free survival (PFS). **Result:** *Ninety-seven patients were enrolled and randomly assigned; 2 patients did not receive study drugs. In total, 95 patients received maintenance therapy (pazopanib, n = 48; placebo, n = 47) and were included into the analyses. Grade 3 toxicities for pazopanib maintenance included thrombocytopenia (10.4%, including 1 case with grade 4 toxicity), liver enzyme elevation (10.4%), fatigue (6.3%), and hypertension (6.3%). Median PFS was 3.7 months for pazopanib maintenance and 1.8 months for placebo (Hazard ratio [HR] 0.44, 95% CI: 0.29 – 0.69, p < 0.0001). Median PFS longer than 6 months were achieved by 9 patients (18.8%) in pazopanib arm and 2 (4.3%) in placebo. Median overall survival for the pazopanib and placebo arms were 10.6 months and 12.9 months, respectively (HR 1.14, 95% CI: 0.74 – 1.76, p = 0.54).* **Conclusion:** Though this study met the primary endpoint of PFS, it failed to translate into improvement of overall survival with pazopanib maintenance. Given the unneglectable toxicity profiles, relevant biomarkers to select patients for benefit from pazopanib should be further investigated.

Keywords: maintenance therapy, small cell lung cancer, pazopanib

OA 09 EGFR TKI RESISTANCE
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

OA 09.01 CHARACTERIZING THE GENOMIC LANDSCAPE OF EGFR C797S IN LUNG CANCER USING CTDNA NEXT-GENERATION SEQUENCING

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Background: Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) active in T790M-positive lung cancer. Acquired resistance to osimertinib is driven by *EGFR* C797S in ~20-30% of cases. Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) can be used to identify resistance mechanisms. The allelic configuration (*cis* vs. *trans*) of C797S with respect to T790M has therapeutic implications, but the relative frequency of each and other co-occurring genomic alterations are not well defined in clinical samples. **Method:** We queried the Guardant Health database for lung adenocarcinoma patients and an *EGFR* C797S mutation. All patients had comprehensive ctDNA testing using the Guardant360 NGS assay between June 2015 and June 2017. *Cis/trans* configuration for T790M and C797S was determined using Integrated Genomics Viewer software. **Result:** We identified 50 unique patients with a total of 66 samples which were C797S positive. All had a co-existent *EGFR* activating mutation (del19 74%, L858R 24%, other 2%). 60/66 (91%) C797S+ samples were also T790M+. In the 6 samples with C797S but *without* T790M in ctDNA, 4 were from patients who were T790M+ on a prior Guardant360 assay, 1 never had T790M in blood or tissue and developed C797S while on 1st-line afatinib, and 1 had no further clinical details available. T790M and C797S were on the same allele (*cis* configuration) in 44/46 evaluable patients (98%); 1 (2%) was in *trans*. One sample had two different C797S mutations, one *cis* and one *trans* to T790M. 13 C797S+/T790M+ samples (22%) had multiple C797X mutations detected and 12 samples carried other mutations in or adjacent to the *EGFR* ATP-binding pocket (e.g. L792, F795, G796, etc). The most common non-*EGFR* mutations co-occurring with C797S were *BRAF* amplification/mutation (20%), *MET* amplification (17%), *PIK3CA* mutation/amplification (15%), *CCNE1* amplification 14% and *MYC* amplification (14%). **Conclusion:** Understanding *EGFR* TKI resistance mechanisms is critical to developing more effective therapies. ctDNA offers a non-invasive method to characterize the resistance landscape. Our data suggests C797S most commonly occurs with T790M in *cis* (98%), a state associated with resistance to all currently available EGFR TKIs. The trans configuration, which may respond to combined 1st/3rd-gen EGFR TKIs, is rare (2%). Moreover, C797S is frequently detected along with other resistance mechanisms in ctDNA, underscoring the heterogeneity of resistant cancers. New treatments targeting C797S/T790M are needed, as is a deeper understanding of therapeutic targeting of heterogeneity in resistant cancers.

Keywords: Circulating Tumor DNA, C797S, EGFR lung cancer

OA 09 EGFR TKI RESISTANCE
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

OA 09.02 OSIMERTINIB RESISTANCE MEDIATED BY LOSS OF EGFR T790M IS ASSOCIATED WITH EARLY RESISTANCE AND COMPETING RESISTANCE MECHANISMS

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Background: Osimertinib is a third-generation *EGFR* tyrosine kinase inhibitor (TKI) active in *EGFR*-mutant NSCLC with resistance to prior TKI. Improved understanding of the clinical and molecular characteristics of acquired resistance to osimertinib is needed. **Method:** We initially studied resistance biopsies and plasma specimens from an institutional cohort of 119 patients treated with osimertinib for T790M-positive NSCLC with resistance to prior TKI. For validation, we studied plasma from 157 patients treated with osimertinib on the AURA trial (NCT01802632). **Result:** 45 of 119 patients underwent a resistance biopsy and 33 had resistance tumor genotyping available. 11 patients maintained T790M at resistance: 7 acquired *EGFR* C797S, 1 had a PIK3CA mutation. 22 patients had loss of T790M at resistance: 14 harbored a competing resistance mechanism, including histologic transformation to SCLC, *MET* amplification, mutations in *BRAF, PIK3CA*, or KRAS, or fusions in RET or FGFR. Median time to treatment failure (TTF) on osimertinib was 3 months in patients with loss of T790M and 15 months in patients with maintained T790M. In the validation cohort, 110 of 157 patients had detectable tumor DNA in plasma and were eligible for analysis. 58 patients (53%) maintained T790M at resistance; 24 (22%) also acquired a C797S mutation. 52 patients (47%) had loss of T790M at resistance and no C797S. Median TTF was shorter in patients with loss of T790M than in those with maintained T790M at resistance (5.7 vs 12.5 months). 50 patients had both pre- and post-osimertinib plasma genotyping. Studying the relative allelic fraction (AF) of T790M compared to driver *EGFR* mutation, patients with T790M loss had only slightly lower relative T790M AF pretreatment (29% vs. 38% median, p = 0.06). The ability of plasma response to predict subsequent resistance was studied in 19 patients from the initial cohort with baseline and follow-up plasma genotyping after 1-3 weeks on osimertinib. Studying the difference between the relative change in plasma levels of T790M and the *EGFR* driver, patients with T790M loss at time of resistance consistently had a greater T790M response than driver response (median difference 16%), suggesting incomplete suppression of the driver due to competing resistance mechanisms. **Conclusion:** In patients with acquired resistance to osimertinib, repeat testing for T790M could offer key insights into disease biology. Patients with early resistance on osimertinib are at risk of T790M loss with emergence of a complex variety of competing resistance mechanisms, and represent intuitive candidates for combination approaches such as combined EGFR & MET inhibition.

Keywords: NSCLC, drug resistance, osimertinib

OA 09.03 TATTON PH IB EXPANSION COHORT: OSIMERTINIB PLUS SAVOLITINIB FOR PTS WITH EGFR-MUTANT MET-AMPLIFIED NSCLC AFTER PROGRESSION ON PRIOR EGFR-TKI

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Background: *MET* amplification is a well described mechanism of acquired resistance to EGFR inhibition in *EGFR*-mutant NSCLC, making combined MET/EGFR inhibition a compelling therapeutic approach. We previously reported tolerability of the oral, CNS active, third-generation EGFR-TKI osimertinib, which is selective for both EGFR-TKI sensitizing and *EGFR* T790M resistance mutations, combined with the highly selective MET-TKI savolitinib (volitinib, HMPL-504, AZD6094). Here we assess safety and preliminary activity of this combination in a cohort of patients (pts) with *EGFR*-mutant NSCLC and MET-positive acquired resistance in the multi-arm, Phase Ib TATTON study (NCT02143466). **Method:** Eligible pts were aged ≥18 years (WHO performance status 0/1) with locally advanced or metastatic *EGFR*-mutant NSCLC who progressed on at least one prior EGFR-TKI with centrally confirmed *MET*-amplification (fluorescence in-situ hybridisation, *MET* gene copy ≥5 or *MET/CEP7* ratio ≥2). Pts received osimertinib 80 mg QD plus savolitinib 600 mg QD. Primary objective was safety and tolerability; secondary objectives included preliminary assessment of anti-tumour activity and pharmacokinetics. **Result:** As of data-cut off (15 April 2017), 45 pts with centrally confirmed *MET*-amplification (FISH) were enrolled and received treatment, including 25 pts previously treated with a third-generation EGFR-TKI and 20 without prior third-generation EGFR-TKI treatment (T790M negative n=13; T790M positive n=7). At baseline, median age was 58 years (range 38–76), 24 (53%) were female, 36 (80%) were Asian. The most frequent adverse events (AEs) were nausea (n=21, 47%), decreased appetite (n=15, 33%), fatigue (n=13, 29%) vomiting (n=13, 29%), rash (n=11, 24%), myalgia (n=8, 18%), pyrexia (n=7, 16%), ALT/AST increased (n=6, 13%), and WBC decreased (n=6, 13%), consistent with the known safety profiles. Serious AEs were reported in 15 (33%) pts; events reported in >1 patient were pneumonia, dyspnoea, acute kidney injury and pyrexia (all n=2). Four pts died due to AEs, none were considered related to study drugs. At data cut-off, confirmed partial responses were reported in 5/25 (20%) pts previously treated with a third-generation EGFR-TKI; 5/12 (42%) T790M negative pts without prior third-generation EGFR-TKI and 3/7 (43%) T790M positive pts without prior third-generation EGFRTKI. Twenty-eight (62%) pts are ongoing treatment. Preliminary steady-state exposures and pharmacokinetic parameters of savolitinib and osimertinib were consistent with historical data. **Conclusion:** These findings demonstrate promising safety, tolerability, and preliminary activity of osimertinib plus savolitinib and support further investigation of this combination for the treatment of pts with locally advanced or metastatic *EGFR*-mutant NSCLC and *MET*-amplification. Updated data will be presented.

Keywords: non-small cell lung cancer, EGFR-Mutant, MET-amplification

OA 09.05 IDENTIFICATION OF NOVEL POTENTIALLY TARGETABLE GENOMIC ALTERATIONS IN PAIRED TUMORS WITH ACQUIRED EGFR TKI RESISTANCE BY NGS

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Background: While previous reports have established MET and HER2 amplification as two mechanisms of non-T790M driven EGFR TKI resistance in EGFR mutant NSCLC, resistance occurs in the absence of these modifications in a significant number of patients. Therefore, there exists an unmet need to define additional mechanisms of resistance to EGFR TKIs. We hypothesized that targeted next-generation sequencing could detect additional targetable activating mutations in paired tumor samples from patients with acquired resistance to first or second generation EGFR TKIs. **Method:** We conducted an analysis of clinical and molecular data prospectively collected from 285 EGFR-mutant NSCLC patients enrolled into the MD Anderson Lung Cancer GEMINI database. Of 157 patients treated with first-line therapy (erlotinib, gefitinib, or afatinib), we identified 75 patients with TKI-acquired resistance with matched pre/post-TKI tumor samples. Matched tumor samples were analyzed with targeted gene sequencing. Recurrent alterations were defined as an alteration occurring more than 2 times. Recurrent acquired mutations were expressed in Ba/F3 and EGFR mutant (T790M+/-) NSCLC cells. Mutation expressing Ba/F3 cell lines were assayed for IL-3 independence, and mutation expressing NSCLC cell were screened against combination targeted TKIs. **Result:** EGFR mutant NSCLC patients treated with first-line therapy had a median PFS of 14 months; and, of the patients with pre/post-TKI tumor molecular data, 47% of patients were T790M negative. There were 30 recurrent acquired alterations identified in 13 different genes. Genes included ARAF, BRAF, EGFR, FGFR, GNAS, JAK2, MCL1, PDGFRα, PIK3CA, RAF1, RB1, SMAD4, and TP53. Of the alterations identified, most occurred in 1 of 4 targetable genes: BRAF (N=3), FGFR (N=5), PDGFRα (N=3), or PIK3CA (N=2). Both previously reported and novel mutations were identified, and preliminary screening of mutant expressing Ba/F3 cell lines found that of the mutations tested (BRAF WT & G469H, FGFR2 A371G, PDGFRα WT & L682F, and PIK3Ca E545K) all grew independent of IL-3. HCC827 and H1975 cell lines expressing acquired mutations in BRAF, FGFR, PDGFRα, or PIK3CA were more sensitive to combination targeted therapy compared to EGFR TKIs or mutation specific TKIs alone unlike control cell lines, supporting the possibility that targeting these mutations would be of therapeutic benefit. **Conclusion:** Analysis of patient data identified 30 recurrent genomic alterations in 13 different genes including novel alterations in BRAF, EGFR, FGFR, PDGFRα, RB1, and SMAD4, many of which were found to be activating mutations. Our analysis identified potentially targetable mutations of BRAF, FGFR, PDGFRα, and PIK3CA which merits further pre-clinical and clinical investigation.

Keywords: EGFR acquired resistance

OA 09.06 A PHASE IB TRIAL OF SAVOLITINIB PLUS GEFITINIB FOR CHINESE PATIENTS WITH EGFR-MUTANT MET-AMPLIFIED ADVANCED NSCLC

J.-. Yang[1], J. Fang[2], Y. Shu[3], J. Chang[4], G. Chen[5], J. He[6], W. Li[7], X. Liu[8], N. Yang[9], C. Zhou[10], J. Huang[11], L. Yang[12], A. Handzel[13], M. Frigault[13], G. Ahmed[14], C. Egile[14], S. Morgan[14], Y. Wu[15]

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Background: EGFR-tyrosine kinase inhibitor (TKI) treatment failure has been attributed to innate and/or acquired *MET*-amplification in patients with advanced *EGFR*-mutant NSCLC. Savolitinib (volitinib, HMPL-504, AZD6094), a highly selective small molecule MET-TKI, demonstrated greater efficacy combined with gefitinib than either compound alone in preclinical *EGFR*-mutant NSCLC models (D'Cruz et al. AACR, 2015). **Method:** This open-label, multi-centre, Phase Ib study (NCT02374645) assessed savolitinib plus gefitinib in patients enrolled in China with *EGFR*-mutant advanced NSCLC who progressed on prior EGFR-TKI. Primary objective was safety, tolerability, and identification of recommended Phase II dose (RP2D). Secondary objectives included preliminary anti-tumour activity (RECIST 1.1), pharmacokinetics, and ctDNA analysis for *EGFR* T790M mutation status. Eligible patients (≥18 years) had measurable disease, radiological disease progression on treatment, ECOG performance status 0/1, and adequate organ function. Patients had central evaluation of *EGFR* mutation (plasma based BEAMing digital PCR) and central screening for *MET*-amplification (*MET/CEP7* ratio ≥2 or *MET* gene number ≥5, defined by tumour tissue FISH). Patients received gefitinib 250 mg once daily (QD) plus savolitinib 600 mg QD. **Result:** As of data-cut off (March 2017), 44 patients received study treatment. Median age was 61 years, 64% of patients were female; 6 patients were *EGFR* T790M positive and 5 were T790M negative (interim readout). The most common (≥20% patients) all causality adverse events (AEs), were vomiting (n=18, 41%), nausea (n=17, 39%), rash (n=16, 36%), increased ALT (n=14, 32%), increased AST (n=13, 30%), hypoalbuminaemia and gammaglutamyl transpeptidase increase (both n=11, 25%), and increased blood alkaline phosphatase (n=9, 21%). Grade ≥3 all causality AEs were reported in 14 (32%) patients; increased AST and increased ALT (both n=3, 7%) were most frequent. Three (7%) patients died due to an AE (respiratory failure [n=1], lung neoplasm [n=2]); none were considered treatment related. Anti-tumour activity was observed; confirmed partial responses were reported in 11/44 (25%) patients and a further 4 patients are awaiting confirmation of response (confirmed and unconfirmed response rate 15/44 [34%]). At the time of the scheduled 12 week study assessment, 20 (46%) patients remained on study treatment. Preliminary steady-state exposures and pharmacokinetic parameters of savolitinib and gefitinib were consistent with historical data. **Conclusion:** These encouraging findings warrant further assessment of savolitinib plus gefitinib for patients with *EGFR*-mutant, *MET*-amplified NSCLC who progressed on prior EGFR-TKI. The RP2D was confirmed as savolitinib 600 mg QD plus gefitinib 250 mg QD. This study is ongoing; updated safety and efficacy including anti-tumour activity by T790M status will be presented.

OA 09 EGFR TKI RESISTANCE
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

OA 09.07 CLONALITY OF C-MET COPY NUMBER GAIN AS A DETERMINANT OF PRIMARY TKI RESISTANCE IN EGFR-MUTANT NSCLC

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Background: cMET activation is a valid mechanism of secondary TKI resistance in EGFR mutation-positive (EGFR-M+) NSCLC. However, its role in the treatment-naïve setting remains unclear. We sought to ascertain the prevalence and clinical impact of co-existing cMET copy number gain(CNG) in TKI-naïve early-stage and metastatic EGFR-M+ NSCLC. **Method:** Multi-region SNP array analysis (n=59 sectors) was performed on 13 early-stage resected EGFR-M+ NSCLC. cMET FISH was performed in a separate cohort of 206 metastatic treatment-naïve EGFR-M+ patients, all of whom were treated with first-line EGFR TKIs. We defined cMET-high as CNG≥5 copies, with an additional criteria of MET:CEP7 ratio >2.0 for amplification. Time-to-treatment failure(TTF) in patients cMET-high/low was estimated by Kaplan-Meier method and compared using log-rank test. A cell line from a cMET-high patient exhibiting primary TKI resistance was established. **Result:** Relative to median ploidy across sectors, 7/13(53.8%) early-stage EGFR-M+ tumors showed cMET CNG in at least one sector, with majority displaying(n=6/7) copy number intra-tumor heterogeneity. In the metastatic cohort, 55/206 patients (26.7%) were found to be cMET-high at diagnosis: 6(10.9%) had MET amplification, 49(89.1%) MET polysomy, with the following distribution: 5-6 copies(n=11), 6-8 copies(n=32), and >8 copies(n=12). We next evaluated clinical outcomes stratified by MET-high v low: median TTF was 14.7m(12.2–NE) vs 14.6m(12.7–16.5), p=0.985 respectively, with no significant difference in response rates(RR) to EGFR TKI (66.7%v73.7%; p=0.940). Further stratification by level of CNG did not reveal any differences in RR (5-6 copies:75.0%, 6-8 copies:63.0%, >8 copies:71.4%; p=0.868). In MET-high amplified group, only 2/6 (33.3%) had a partial response to EGFR TKI. In the cohort with suboptimal TKI response (PFS<6m, n=22), we did not observe significant enrichment for MET-high, relative to rest of the cohort (36.4%v25.5%, p=0.278). Finally, in 6 patients with progressive disease within 4 weeks of initiating EGFR TKI, 2/6(33.3%) were MET-high. In a cell line model derived from a MET-high patient (L858R, cMET:7.3 copies) genomic profiling of cell colonies revealed clonal cMET CNG and subclonal EGFR, with the patient demonstrating clinical response to crizotinib. **Conclusion:** Although up to 26% of TKI-naïve EGFR-M+ NSCLC harbor high cMET CNG by FISH, this occurs on the background of a highly variegated copy number landscape. cMET CNG alone does not significantly impact clinical outcomes to EGFR TKI, with the exception of one patient with a clonal cMET-driven tumor. Our data challenges the utility of arbitrary copy number thresholds to define clinically relevant MET pathway dysregulation and underscores the importance of targeting dominant truncal drivers.

Keywords: Primary EGFR TKI resistance, CMET dysregulation, Truncal drivers

ORAL ABSTRACT SESSIONS | WEDNESDAY, OCTOBER 18, 2017

OA 10 LIQUID BIOPSY FOR GENOMIC ALTERATIONS
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 10.01 DETECTION OF EGFR MUTATIONS FROM PLASMA CTDNA IN THE OSIMERTINIB PHASE III TRIAL (AURA3): COMPARISON OF THREE PLASMA ASSAYS

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Background: AURA3 (NCT02151981) showed osimertinib, a third-generation EGFR-TKI, significantly prolongs progressionfree survival and improves response rate vs platinumpemetrexed in patients with T790M-positive advanced NSCLC, whose tumors had progressed on first-line EGFR-TKI therapy. Using patient baseline samples, we report concordance between plasma circulating tumor DNA (ctDNA) and tissue for the detection of *EGFR* mutations (T790M, exon 19 deletions [Ex19Del], L858R) using three distinct plasma detection technologies. **Method:** Tumor tissue biopsy samples were taken following progression on first-line EGFRTKI treatment. Baseline central confirmation of *EGFR* mutation status was by **cobas**® EGFR Mutation Test (Roche Molecular Systems). Where possible, baseline blood samples for plasma ctDNA screening were collected from patients in the osimertinib treatment group and analyzed using allele specific (AS)PCR (**cobas**® EGFR Mutation Test v2), ddPCR (Biodesix) and next generation sequencing (NGS, Guardant Health). **Result:**

Concordance data from a subset of osimertinib-dosed patients with a valid cobas tissue T790M-positive result and matched plasma samples.

	EGFR T790M		*EGFR* Ex19Del		*EGFR* L858R	
Test	PPA	NPA*	PPA	NPA	PPA	NPA
AS-PCR (n=226)	51% (115/226)	NA	85% (132/155)	99% (70/71)	59% (40/68)	100% (158/158)
ddPCR (n=208)	57% (118/208)	NA	72% (102/142)	100% (66/66)	69% (44/64)	99% (141/143)
NGS (n=227)	65% (148/227)	NA	81% (126/156)	99% (70/71)	62% (42/68)	98% (156/159)

*Specificity for the detection of T790M was not evaluable as only T790M-positive tissue samples were available.
NA, not applicable; NPA, negative percent agreement (specificity); PPA, positive percent agreement (sensitivity).

ctDNA was undetectable (negative for all three *EGFR* mutations [T790M, Ex19Del, L858R]) in 51/228 (22%) patients by AS-PCR, 58/211 (27%) by ddPCR, and 54/230 (23%) by NGS. Robust correlations (Spearman's Rank) were observed for *EGFR* mutant allelic fractions (AFs) between ddPCR and NGS assays: T790M R^2 0.9129 (n=201), Ex19Del R^2 0.9384 (n=201), L858R R^2 0.8090 (n=200). Discordant results between ddPCR and NGS were observed in 24/201 (12%) samples for T790M, 17/201 (8%) Ex19Del and 11/200 (6%) L858R. All discordant samples had AFs ≤1% by both assays. **Conclusion:** Using cobas tissue test as a reference, sensitivity for the detection of plasma T790M appeared higher for ddPCR and NGS assays compared with AS-PCR. Robust correlations were observed between quantitative ddPCR and NGS assays for determination of AFs across all three mutations. About 25% of AURA3 patients did not appear to shed ctDNA, as evidenced by absence of all three *EGFR* mutations across the three platforms.

Keywords: T790M, plasma, osimertinib

OA 10 LIQUID BIOPSY FOR GENOMIC ALTERATIONS
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 10.02 UNIQUE GENETIC PROFILES FROM CIRCULATING CELL-FREE DNA OF CEREBROSPINAL FLUID IN LEPTOMENINGEAL METASTASES OF EGFR MUTANT NSCLC

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Background: Leptomeningeal metastases (LM) are more frequent in non-small cell lung cancer (NSCLC) with EGFR mutations. Resistance mechanisms of LM remained unclear due to limited access to leptomeningeal lesions. **Method:** Primary tumor, cerebrospinal fluid (CSF) and plasma in patients with suspected LM of NSCLC were tested by Next-Generation Sequencing with 168 genes panel. Thirty patients diagnosed as LM and harboring EGFR mutation were enrolled in this cohort, and CSF cfDNA and plasma of two patients and CSF precipitates of another two patients were not available **Result:** Driver genes were detected in 100% (28/28) , 85.7% (24/28) and 75% (21/28) patients of CSF cfDNA, CSF precipitates and plasma, respectively; and 92.9% (26/28) patients had much higher allele fractions in CSF cfDNA than the other two media. Unique genetic profiles were captured in CSF cfDNA when compared with those in plasma and primary tissue. Multiple copy number variations (CNVs) were privately detected in CSF cfDNA, and CNVs in patients after TKI failure were more complicated when compared to those TKI naïve before LM. MET copy number gain identified in 44.0% (11/25) patients was the most frequent one, other CNVs included ERBB2, KRAS, ALK, MYC and FGFR1. Moreover, loss of heterozygosity (LOH) of TP53 was identified in 67.9% (19/28) CSF cfDNA, which was much higher than that in plasma (2/28, 7.1%; p<0.001), and there was a trend towards higher rate of concomitant resistance mutations in patients with TP53 LOH than those without one (70.6% vs. 25%; p=0.036). EGFR T790M was identified in 28% (7/25) patients with progression to TKIs in CSF cfDNA. **Conclusion:** CSF cfDNA could reveal the unique genetic profiles of LM, and it should be the most representative medium of liquid biopsy for LM in NSCLC harboring EGFR mutations.

OA 10.03 LIQUID BIOPSY IN THE LUNG CANCER CLINIC: A PROSPECTIVE STUDY OF PLASMA DNA NEXT GENERATION SEQUENCING TO GUIDE MATCHED THERAPY

J. Sabari[1], D. Stephens[1], A. Ni[1], A. Lee[2], N. Pavlakis[2], S. Clarke[2], C. Diakos[2], M. Offin[1], S. Datta[1], N. Tandon[1], M. Duboff[1], J. Simpronio[1], A. Martinez[1], J. Isbell[1], V. Rusch[1], D. Jones[1], A. Rimner[1], S. Henderson[3], C. Raymond[3], L. Lim[3], M. Li[3], G. Riely[1], C. Rudin[1], B. Li[1]

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Background: Liquid biopsy for plasma circulating tumor DNA (ctDNA) next generation sequencing (NGS) is now commercially available and increasingly adopted in clinical practice with a paucity of evidence based guidance. We set out to prospectively determine the utility of plasma ctDNA NGS in the lung cancer clinic. **Method:** Patients (pts) with advanced NSCLC who were driver unknown or resistance mechanism unknown were eligible. Pts were enrolled prospectively at Memorial Sloan Kettering (NY, USA) and Northern Cancer Institute (Sydney, Australia). Peripheral blood was collected in Streck tubes (10-20mL) and sent to Resolution Bioscience (*Bellevue, WA*) for targeted NGS of extracted DNA using a bias corrected hybrid capture 21 gene assay in a CLIA laboratory with unique reads at 3000x and sensitive detection at variant allele frequency above 0.1%. Clinical endpoints included detection of oncogenic drivers, turnaround time, comparison to tissue NGS when available, and ability to match pts to targeted therapy along with their treatment outcomes. **Result:** Seventy-six pts were prospectively accrued. Plasma NGS detected an oncogenic driver in 36% (27/76) of pts, of whom 14% (11/76) were matched to targeted therapy; including pts matched to clinical trials for *HER2* exon 20 insYVMA, *BRAF* L597Q and *MET* exon14. Of the 10 evaluable pts, 10 partial responses were observed. Mean turnaround time for plasma was 6 days (3-12) vs 21 days (16-30) for tissue ($P<0.0001$). Plasma ctDNA was detected in 60% (46/76) of pts; detection rate was 46% (16/35) if blood was drawn on active therapy and 73% (30/41) if drawn off therapy, either at diagnosis or progression (Odds ratio 0.31, 95% CI 0.12 – 0.81; $P=0.02$). Of the 25 concurrent tissue NGS performed to date, there was a 96% plasma concordance with tissue and a 60% tissue concordance with plasma for driver mutations. **Conclusion:** In pts who were driver or resistance mechanism unknown, plasma NGS identified a variety of oncogenic drivers with significantly shorter turnaround time compared to tissue NGS, and matched patients onto targeted therapy with clinical benefit. Plasma ctDNA is best detected at diagnosis of metastatic disease or at progression. A positive finding of an oncogenic driver in plasma is highly specific and can immediately guide treatment, but a negative finding may still require tissue biopsy. Our findings provide evidence to support the incorporation of plasma NGS into practice guidelines.

Keywords: liquid biopsy, Targeted therapy, next generation sequencing

OA 10.05 NON-INVASIVE MOLECULAR PROFILING IN NSCLC BY TARGETED AND WHOLE EXOME ANALYSIS OF PLASMA CFDNA

M. Cheng[1], J. Yang[1], M. Shady[2], P. Ulz[3], E. Heitzer[3], N. Socci[1], V. Seshan[4], M. Offin[5], D. Stephens[5], A. Makhnin[5], N. Tandon[5], S. Datta[5], D. Selcuklu[1], K. Huberman[1], K. Vanness[1], E. Gedvilaite[1], A. Viale[1], M. Arcila[6], M. Ladanyi[6], J. Chaft[7], C. Rudin[8], M. Berger[1], D. Solit[1], B. Li[9], D. Tsui[1]

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Background: Molecular characterization of tumor can guide the choice of therapy for NSCLC patients. However, tumors are complicated by spatial heterogeneity and sometimes may not be of sufficient quality and quantity for analysis. NGS using plasma cell-free DNA (cfDNA) input may capture temporal and spatial heterogeneity, and enable genomic profiling in patients without adequate available tumor tissue. Targeted gene panels allow for robust detection of known oncogenic drivers, but may not be comprehensive enough to screen for novel biomarkers or mechanisms of acquired resistance. Whole exome sequencing (WES) allows for hypothesis-free biomarker discovery, but may be technically challenging in the setting of limited tumor-derived DNA content in plasma cfDNA. In this study, we aim to develop a workflow to guide the selection of samples for targeted and whole exome sequencing for noninvasive molecular profiling. **Method:** Plasma samples were collected from 20 NSCLC patients receiving a variety of treatment (chemotherapy, targeted therapy, or immunotherapy). Most patients (>70%) had stage III or IV disease at the time of plasma collection. CfDNA was extracted from 3 mL of plasma, and analyzed using low-pass shallow whole genome sequencing (sWGS) and MSK-IMPACT, a hybridization capture-based assay targeting over 400 cancer-related genes. Analysis of matched normal was performed for somatic variant calling. **Result:** Median cfDNA yield per plasma sample was 28ng (range 7 - 236ng). We applied z-score statistics to estimate the levels of tumor-derived mutant allele fractions in cfDNA based on sWGS data. We trained the algorithm using a separate cohort of cfDNA data from >100 patients with metastatic solid tumors to classify samples by mutant allele fraction (MAF) as either low (<5% MAF) or high (>5% MAF) tumor-derived DNA. In the subset of 10 patients with unknown drivers, two were estimated to have MAF >5% in cfDNA, and WES recapture was performed. MSK-IMPACT targeted sequencing identified actionable alterations in a subset of patients who did not have sufficient materials for tissue profiling. WES in cases with high tumor-derived DNA content by sWGS identified alterations in genes outside of the MSK-IMPACT panel. **Conclusion:** Molecular profiling using cfDNA is feasible in lung cancer and may identify actionable alterations to inform treatment decisions in patients without sufficient tissue for molecular characterization. The application of sWGS to estimate the levels of tumor-derived mutant allele fractions in plasma cfDNA samples may help guide selection of the optimal downstream sequencing strategy.

Keywords: cell-free DNA, NSCLC, molecular profiling

OA 10.06 LONGITUDINAL MUTATION MONITORING IN PLASMA BY DEEP SEQUENCING AS A POTENTIAL PREDICTOR OF DISEASE PROGRESSION IN NSCLC

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Background: Circulating tumor DNA (ctDNA) sequencing and analysis has the potential to transform clinical management of patients with advanced NSCLC. Non-invasive sampling of blood draws at different time points during treatment could potentially be used for routine monitoring of disease progression and detection of therapy resistant mutations by using next generation sequencing (NGS). **Method:** 448 longitudinal plasma samples (mean 6.3 per subject) collected from 71 subjects with advanced NSCLC during 1st line treatment were analyzed by NGS. Of these 71 subjects, 47 also had matched baseline tumor tissue samples. The AVENIO ctDNA Surveillance kit and AVENIO FFPET Analysis kit (RUO, Roche, Pleasanton, CA, USA) were used for sequencing analysis. The Surveillance kit contains 17 cancer driver genes and additional 180 frequently mutated genes mainly selected for NSCLC and colorectal cancer. This kit is capable of detecting four mutation classes: SNVs, fusions, CNVs and InDels. CT images were reviewed centrally using RECIST v1.1. **Result:** Somatic, disease-associated mutations were detected with allele frequency (AF) of >5% in 94% of baseline tumor samples (44/47), and in 100% of plasma samples with AF in ctDNA ranging from ≥0.5% to ≤30%. The most commonly mutated genes in tumors were TP53 (22/47 subjects), KRAS (14/47), BRAF (7/47), STK11 (5/47), and ERBB2 (5/47). Tracking the AF's of key tumor mutations by the Surveillance panel in the paired longitudinal plasma samples allowed the monitoring of treatment response at the molecular level. We identified a number of subjects in which the AF of cfDNA mutations increased three to four months before clinical evidence of progression of disease detected by CT scans that were centrally reviewed according to RECIST v1.1. Cases were also observed where the AF's of key mutations decreased in 1st line chemotherapy to nearly zero which correlated with clinical partial response and stable disease. . Additionally, first post treatment plasma samples collected during first line treatment showed a difference of 96 days in median survival times of ctDNA- vs ctDNA+ groups (logrank p value =0.0371). **Conclusion:** ctDNA testing with molecular bar coded duplex sequencing and digital background error suppression of a large 197 gene panel offers high sensitivity for tumor variant detection. The study demonstrated that the presence of tumor variants detected in blood at the beginning and end of 1st line treatment is a risk factor for early disease progression. Longitudinal mutation monitoring has the potential to predict disease progression earlier than regular CT imaging.

Keywords: NSCLC, Longitudinal mutation monitoring, Deep sequencing

OA 10.07 GENOMIC PROFILE OF CELL-FREE DNA FROM SPUTUM, PLASMA, URINE AND TUMOR TISSUE AND CORRELATION WITH CLINICAL EFFECT IN ADVANCED NSCLC

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Background: The detection of driver gene mutation based on tumor tissue can instruct target therapy and conduct molecular monitoring after drug-resistance in advanced NSCLC, but many patients have no access to this kind of test because of inadequate tumor tissue or inability to tolerate the invasive test. Some studies have explored the value of EGFR mutation test in body fluids such as plasma, urine and sputum from NSCLC patients. But the sensitivity based on individual liquid specimen is poor compared with gold standard---tissue. We detect multi-genes in multi-liquid samples in parallel to investigate the Consistency and complementarity of genetic profile in different liquid samples and it's correlation with efficacy of the real world therapy in advanced NSCLC. **Method:** The patients newly diagnosed with NSCLC and first-generation EGFR-TKI acquired drug-resistance were enrolled into our research (NCT:02778854) prospectively, the pre-treatment samples including tumor tissue, plasma, urine and sputum were collected. We conducted capture-based NGS (next generation sequencing) on all of these samples from 50 patients

with a ctDNA panel covering significant exons and introns from 400 human genes including EGFR, KRAS, ALK, ROS1, c-MET and other important genes in the tumor related singling pathways such as PI3K-AKT-mTOR, JAK-STAT, Notch, Wnt and so on. Patients recruited in our experiment have been given unique treatment such as targeted treatment or chemotherapy according to the clinical examination. The final molecular diagnostic results of all clinical liquid or tissue specimen are supposed to be correlated with clinical response data. **Result:** (Applied for Late-Breaking Abstract) This section is not applicable now because the sequencing and complex data analysis is in progress. Therefore, we will submit the final results as late-breaking abstract. **Conclusion:** Section not applicable. We expect to figure out the molecular diagnostic value of different body fluid compared with tumor tissue. we are able to analyze for correlation of the genomic profile derived from liquid samples and respective tissue results and clinical response of each patient.

Keywords: liquid biopsy, cell-free DNA, Advanced Non-Small Cell Lung Cancer

OA 11 REDUCING BURDEN: PATIENT-CENTERED CARE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 11.01 IMPACT OF TOBACCO SMOKING ON THE HUMANISTIC AND FINANCIAL BURDEN OF ADVANCED NON-SMALL CELL LUNG CANCER (A-NSCLC)

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Background: Tobacco smoking has a negative impact on the prognosis of A-NSCLC. It is less well known how smoking impacts the burden of disease. As such, an analysis was conducted to evaluate the impact of a current tobacco smoking habit and/or history of smoking on the burden of A-NSCLC. **Method:** Data were collected between May 2015 and June 2016 from adult patients with Stage IIIB or IV NSCLC via medical chart reviews and patient self-completion forms as part of a multicentre, cross-sectional study conducted in France, Germany and Italy. Health status was measured using the EQ-5D-3L (including the visual analogue scale, EQ-VAS), quality of life (QoL) using the EORTC QLQ-C30 and work/activity impairment using the WPAI:GH questionnaire. Costs of NSCLC-related productivity losses and out-of-pocket expenses were also collected. Outcomes were stratified by smoking status (current/former smoker vs never smoked); no adjustments were made for possible confounding factors. Statistical significance was assessed using Mann–Whitney U tests. **Result:** 1030 patients were recruited: mean patient age, 64.5 years; male, 65.9%; Stage IV NSCLC, 88.4%; non-squamous histology, 70.3%; receiving first-line therapy, 70.5%. Patients were largely receiving chemotherapy, regardless of line of therapy. In total, 1010 patients had smoking status recorded; 787 (77.9%) were current/former smokers and 223 (22.1%) had never smoked. Significant differences were observed between current/former smokers and patients who had never smoked for health status, QoL, work- and activity-related impairments, and NSCLC-related costs (TABLE).

Table: Humanistic and financial burden of A-NSCLC stratified by smoking status

	Measure (means)	Never smoked	Current/ former smoker	*P*-value
Health status and QoL*	EQ-5D-3L utility index	0.71	0.65	0.0142
	EQ-VAS	61.9	56.0	<0.0001
	EORTC QLQ-C30 global health status	52.2	46.8	0.0002
Work and productivity	WPAI:GH % overall work impairment†	32.0%	40.3%	0.0349
	WPAI:GH % activity impairment	44.6%	55.5%	<0.0001
Costs (due to NSCLC)	Annual productivity losses†	€7503.16	€9637.53	0.0170
	Annual out-of-pocket costs	€2654.58	€4235.76	0.0289

EQ-5D-3L, EuroQoL-5D 3-level questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer QLQ-C30 QoL questionnaire; WPAI:GH, Work Productivity and Activity Impairment: General Health questionnaire. *Lower scores represent worse health status or QoL; †Analysis performed using data only from patients in employment (never smoked, n = 57; current/former smoker, n = 104).

Conclusion: A significant deterioration in health status and QoL, along with greater work- and activity-related impairments, was observed in current/former smokers with A-NSCLC. Moreover, costs of NSCLC-related productivity losses and out-of-pocket expenses were also higher versus those who had never smoked. These findings suggest an association between tobacco smoking and the humanistic and financial burden incurred by patients with A-NSCLC.

Keywords: Health Economics, tobacco smoking, Advanced Non-Small Cell Lung Cancer

OA 11 REDUCING BURDEN: PATIENT-CENTERED CARE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 11.02 EXERCISE IMPROVES FUNCTIONAL CAPACITY IN PATIENTS WITH ADVANCE STAGE LUNG CANCER

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This abstract is under embargo until October 18 @ 08:00.

OA 11 REDUCING BURDEN: PATIENT-CENTERED CARE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 11.03 REDUCING LUNG CANCER MORTALITY IN DISPARATE POPULATIONS THROUGH CANCER-COMMUNITY AWARENESS ACCESS RESEARCH AND EDUCATION (C-CARE)

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This abstract is under embargo until October 17 @ 08:00.

OA 11 REDUCING BURDEN: PATIENT-CENTERED CARE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 11.04 EFFECT OF EARLY PALLIATIVE CARE ON AGGRESSIVENESS OF CANCER CARE NEAR END OF LIFE IN LUNG CANCER PATIENT

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Background: Aggressive care and chemotherapy worsens quality of life (QoL) of dying cancer patients. Early palliative care (EPC) in patients with metastatic non small cell lung cancer (NSCLC) is associated with improvements in QoL. Thus, we aimed to explore an impact of EPC on the aggressiveness of care at the end of life (EOL). **Method:** An observational cohort enrolled newly diagnosed metastasis NSCLC at Ramathibodi hospital from 31st August 2015 to 1st September 2016. In EPC group, the consultation of specialized palliative team was performed ≤ 4 weeks of diagnosis and before start chemotherapy treatment, then monthly visits until death and the last visit for bereavement. The palliative consultation in standard of care (SOC) patients performed as their routine practices. The cutoff date for survival analysis was on 31st December 2016. The aggressiveness of care in EOL was defined as the composite outcome as any of the followings: last dose of chemotherapy received < 14 days of death, a new chemotherapy regimen starting < 30 days before death, ≥ 1 hospital admissions or emergency room visits or hospitalizations > 14 days in 30 days of death, or an ICU admission in 30 days of death. **Result:** 105 patients were enrolled, 38 out of 70 patients (54%) in SOC group and 17 out of 35 patients (48%) in EPC group died. More aggressiveness of care at the EOL (97.3% vs 64.7%, p=0.003), more in-patient death (89.5% vs 58.8%; p=0.009) and longer hospitalization before death were observed in the SOC group (12 days vs 4 days, p=0.028). The cost analysis of patients who died at the hospital showed higher hospitalized cost in the SOC group (p=0.005). The EPC group received less aggressive treatments such as using less than 3 regimens of chemotherapy (77.1% vs 94.3%; p=0.028), but the survival rate was not different (11.3 months vs 6.6 months; p=0.08). **Conclusion:** Early palliative care reduced the aggressiveness of care at the end of life, shortened hospitalization and covered less cost of treatment.

Keywords: Aggressiveness of cancer care, early palliative care, end of life

OA 11 REDUCING BURDEN: PATIENT-CENTERED CARE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 11.06 LUNG CANCER DIAGNOSIS AND ASSESSMENT AS A SYSTEM DESIGN PROBLEM: CREATING AN AWARD WINNING PROGRAM WITH PATIENT ADVOCATES AS CO-DESIGNERS

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Background: Lung cancer continues to have a high mortality in Canada, with many patients presenting with advanced stage disease. The Ottawa Hospital (TOH) used a learning health systems (LHS) approach to redesign regional diagnostic processes to reduce the overall time from presentation with a suspicious lung mass to diagnosis and treatment. As previously published by our group, an LHS approach is driven by feedback utilizing operational and clinical information to drive system optimization and innovation. TOH is the only provider of cancer services for a population of 1.3 million people in eastern Ontario and hence the need for an integrated patient journey from regional health facility to tertiary care centre was identified. Patient advocates have been incorporated as key members of the LHS from inception to implementation to post-implementation review. **Method:** The Ottawa Health Transformation model (OHTM) was developed as a means of operationalizing a LHS. A kick off meeting brought together cancer patients and their families to map out existing processes and document the patient experience. A regional lung cancer Community of Practice (CoP) of clinical and non-clinical stakeholders was then established to guide and

approve the work of a core transformation team. The team had patient and family advocates as key members and they were tasked with identifying appropriate wait time targets and vetting proposed processes. A consensus approach was used to address process barriers, resistance to change and conflicting priorities in regular meetings spanning over two years. Commercially available software was used to track patient progress through the diagnostic process and to report real time metrics to the transformation team. **Result:** The project operationalized lung cancer diagnostic pathway guidance and optimized patient flow from referral to initiation of treatment. Twelve major processes in referral, review, diagnostics, assessment, triage and consult were redesigned. TOH now provides a diagnosis to 80% of referrals within the provincial target of 28 days and leads all other jurisdictions in Ontario in this metric by a wide margin. The median patient journey from referral to initial treatment decreased 48% from 92 to 47 days. In 2016 this work was recognized by a provincial cancer agency with a quality award. **Conclusion:** A learning health system has significantly reduced the time from referral with suspicion of lung cancer to diagnosis to treatment. Achievements require a multi-disciplinary approach with a regional perspective. Patient and family advocates have an important voice in re-designing health care systems.

Keywords: diagnosis, advocacy, wait time

OA 11 REDUCING BURDEN: PATIENT-CENTERED CARE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 11.07 ENHANCING LUNG CANCER (LC) CARE IN THE COMMUNITY SETTING THROUGH A PATIENT ADVOCACY 'CENTERS OF EXCELLENCE' (COE) PROGRAM

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Background: The Addario Lung Cancer Foundation's community hospital COE Program seeks to improve LC outcomes by catalyzing the dissemination of coordinated, evidence-based multidisciplinary care incorporating institutional performance benchmarks across the LC care continuum. The COE program is a network of community-level institutions committed to objectively-measured quality improvement through annual cycles of data collection, comparative analysis and feedback. We analyzed 2016 benchmarks, comparing COE and non-COE programs. **Method:** The annual COE Impact Survey instrument includes an 81-item questionnaire administered by ZoomRx, an independent survey company. Respondents were key institutional representatives of COE- and community-level non-COE institutions. The survey measured the care continuum from screening to end-of-life care. Patient- and institutional-level data for 2016 were analyzed. **Result:** Cohort- 15 COE v 15 non-COE, mean number of annual patients per site 264 v 279; % stage III/IV patients 62 v 74; Medicare-enrolled patients, 54% v 40%; patients 61-80 years 61% v 46%; % patients who encountered financial difficulty in 2016, 42% v 34%. Institutional screening/nodule management programs: 71% of COE v 60% of non-COE programs had a low-dose CT (LDCT) screening program; 86% v 80% used a standard protocol to follow patients with suspicious nodules; 35% v 28% LDCT patients were requested to follow up on suspicious findings; 76% v 67% patients actually followed up. Diagnostic biopsy of LC was by minimally invasive endobronchial approaches in 47% v 15%. Programmatic management of patients with stage III/IV disease: 75% v 49% of patients with stage III/IV disease were reviewed at a Tumor Board and 74% v 62% had a palliative care discussion. Molecular testing was used in 51% v 81%. In patients undergoing molecular testing, institutional use of blood-based 'liquid biopsies' was 86% v 18% and next generation sequencing of tissue 67% v 58%. Clinical trials enrollment rates were 20% v 13%, but 18% v 31% of patients were not screened for clinical trials. In weighting factors driving treatment selection on a 100-point relative scale, COE programs weighted 'quality of life' (39% v 26%) and 'patient expense' (22% v 11%) more than non-COE programs. Non-COE programs weighted 'product attributes' (efficacy and safety) 48% (v 14% in COE) more. **Conclusion:** Differences exist in the approach to LC care between COE and non-COE programs. Future iterations of the COE Impact Survey will enable a data-driven approach to disseminating high quality LC care at community-level institutions, where the majority of patients seek care for lung cancer.

Keywords: community, quality, comparative

OA 12 EMERGING GENOMIC TARGETS
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

OA 12.01 THE PRECLINICAL AND CLINICAL ACTIVITY OF POZIOTINIB, A POTENT, SELECTIVE INHIBITOR OF EGFR EXON 20 MUTANT NSCLC

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Background: Approximately 10% of EGFR mutant NSCLCs have an insertion/mutation in exon 20 of EGFR resulting in primary resistance to currently available tyrosine kinase inhibitors (TKIs). We previously reported that the structural features of poziotinib could potentially enable it to circumvent the steric hindrance induced by exon 20 mutations. Here we further characterize the preclinical activity of poziotinib and report on initial clinical activity of poziotinib in patients with EGFR exon 20 mutations from an ongoing phase II study. **Method:** We evaluated poziotinib activity in vitro using human NSCLC cell lines and the BAF3 model as well as several patient-derived xenograft (PDX) models and genetically engineered mouse models (GEMMs) of exon 20 insertion. We launched a phase 2 investigator-initiated trial of poziotinib in patients with metastatic NSCLC with EGFR exon 20 insertions (NCT03066206). **Result:** In vitro poziotinib was approximately 100x more potent than osimertinib and 40x more potent than afatinib against a common panel of EGFR exon 20 insertions. Furthermore, it had ~65-fold greater potency against common exon 20 insertions compared with EGFR T790M mutations; 3rd generation inhibitors osimertinib, EGF816, and rociletinib were all significantly less potent for exon 20 mutations/insertions compared with T790M. *in vivo* poziotinib led to >85% reduction in tumor burden in GEM models of EGFR exon 20 insertion (D770insNPG) NSCLC and the PDX model LU0387 (H773insNPH). To date, 8 platinum-refractory patients with EGFR exon 20 insertion mutation metastatic NSCLC have been enrolled in the clinical trial and treated with poziotinib at a dose of 16 mg PO daily. Two patients have reached the first interval-imaging time point (at 8 weeks of therapy per protocol). Both patients exhibited dramatic partial response, with one patient reporting improvement in dyspnea and cough at one week of therapy. In this early stage of the study, one case of grade 3 paronchycia was observed. One additional platinum- and erlotinib-refractory patient with EGFR exon 20 insertion was treated with poziotinib on compassionate basis. The patient achieved partial response after three weeks of treatment. **Conclusion:** Poziotinib has selective activity against EGFR exon 20 mutations and potent activity in cell lines, PDX, and GEM models. Three platinum-refractory patients with EGFR exon 20 mutations have been treated thus far and are evaluable for response; all three had partial responses at the time of the initial scan. Updated data from the ongoing phase 2 clinical trial of poziotinib will be presented at the meeting.

Keywords: EGFR Exon 20 Insertion mutation, Novel targeted therapy

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OA 12.02 FINAL RESULTS OF A PHASE 2 STUDY OF THE HSP90 INHIBITOR LUMINESPIB (AUY922) IN NSCLC PATIENTS HARBORING EGFR EXON 20 INSERTIONS

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Background: *EGFR* exon 20 insertions (ins20) comprise 4-10% of EGFR mutations in NSCLC and are refractory to 1st/2nd generation EGFR TKIs. No effective targeted therapies exist for patients with *EGFR* ins20. EGFR is a client protein of the molecular chaperone Heat Shock Protein 90 (hsp90). Here, we present the final results of a phase II investigator-initiated trial to assess the activity of the Hsp90 inhibitor luminespib (AUY922) in NSCLC patients with EGFR ins20 (NCT01854034). **Method:** Between 8/2013 and 10/2016, the study enrolled 29 patients with stage IV NSCLC, *EGFR* ins20 identified on local testing, ECOG PS 0-2, at least one prior line of therapy and no untreated brain metastases. The study was closed on 2/28/17 when the available drug supply was exhausted. Luminespib was given at 70mg/m2 IV weekly. Response was assessed by RECIST 1.1 every 6 weeks; treatment beyond progression was allowed. Dose interruptions and dose reductions were allowed as needed for toxicity management. Primary endpoint was ORR with a target disease control rate (DCR; PR/CR plus SD lasting > 3 mos) of ≥ 20%. Secondary endpoints were PFS, OS, safety and response by EGFR ins20 subtype. **Result:** 29 patients (18 female/11 male, median age 60 (range, 31-79)) were enrolled. Median number of prior therapies = 1 (range, 1-5.) 4/29 achieved PR and 1 CR (ORR 5/29; 17%). 15 patients had SD and 9 had PD as their best response. mPFS was 2.9 mos (95% CI, 1.4-5.6,) mOS was 13 mos (95% CI, 4.9-19.5.) DCR was 11/29 (38%). Among 19 patients with baseline PS 0-1 and ≤ 2 prior therapies, ORR = 21% and mPFS = 5.1 mos (95% CI, 2.1-11.8.) The most common luminespib-related toxicities were visual changes (22/29; 76%) diarrhea (21/29; 72%) and fatigue (13/29; 45%). Treatment-related grade 3 toxicities included ocular toxicity (1/29; 3%), hypertension (3/29; 10%) and hypophosphatemia (1/29; 3%). All study treatment was stopped on 2/28/17 due to lack of drug availability; 3 patients were on treatment without progression at study termination. **Conclusion:** The study met its primary endpoint and suggests that luminespib may be an active therapy for advanced NSCLC patients with *EGFR* ins20. Luminespib is generally well-tolerated, though reversible low-grade ocular toxicity is common. Further study of luminespib and other Hsp90 inhibitors in this population is warranted, as are novel systems to continue drug supply for benefitting patients when availability of experimental compounds is limited.

Keywords: EGFR, AUY922, Luminespib

OA 12.03 CLINICAL FEATURES OF ADVANCED LUNG CANCER HARBORING HER2 ABERRATIONS: A LARGE PROSPECTIVE COHORT STUDY (HER2-CS STUDY)

S. Hosokawa[1], A. Bessho[1], K. Ninomiya[2], T. Tanaka[3], N. Ishikawa[4], M. Yamasaki[5], T. Shibayama[6], K. Aoe[7], T. Kozuki[8], N. Fujimoto[9], K. Gemba[10], Y. Ueda[11], M. Inoue[12], T. Murakami[13], S. Kuyama[14], H. Kawai[15], K. Fujitaka[16], K. Inoue[17], M. Takata[18], H. Yanai[19], K. Hotta[19], K. Kiura[19]

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Background: HER2 is a potential driver oncogene. HER2-targeted precision therapy has been tested in NSCLC. However, the demographics of HER2-positive NSCLC have not been defined systematically. **Method:** Pts with advanced NSCLC were registered. HER2-IHC and FISH assays were performed with commercial kits. HER2 mutations were identified by the direct sequencing. The aim of this study was to clarify the frequency, characteristics and outcome of HER2-positive NSCLC. **Result:** Of 1,126 tumors screened (Table A), 34 (3.0%) were IHC3+, and 34 (3.0%) were IHC2+/FISH+. Among the 724 EGFR wild-type tumors, 21 (2.9%) were HER2-mutant tumors, including A775_G776insYVMA (n = 15). Interestingly, the IHC3+ tumors and mutant tumors were entirely exclusive. Female pts had HER2 mutant tumors more frequently, while IHC/FISH+ tumors were detected more often in males (Table B). HER2-positive tumors had similar survival outcome to triple negative tumors, but significantly worse prognoses than EGFR-mutant and ALK-positive tumors ($p < 0.05$ each). The treament info will be presented at the meeting.

A. The Genotype-Specific Subsets*					
	HER2 (n = 88)	EGFR (n = 358)	ALK (n = 44)	Triple negative / unknown (n = 662)	Total (n = 1,126)
Age, median Sex (male) Smoking habit Non-Sq Stage III/IV	69 61 (69%) 58 (66%) 78 (89%) 51 (58%)	69 142 (40%) 142 (40%) 351 (98%) 220 (61%)	62 21 (48%) 19 (43%) 44 (100%) 35 (80%)	69 516 (78%) 544 (82%) 503 (76%) 423 (64%)	69 726 (64%) 754 (67%) 951 (84%) 714 (63%)
MST (mo) 1-yr OS rate	17.5 59%	NR 85%	NR 79%	15.1 59%	19.8 67%

B. The Subsets of HER2 aberrations**			
	IHC3+ (n = 34)	IHC2+/FISH+ (n = 34)	Mutant (n = 21)
Age, median Sex (male) Smoking habit Non-Sq Stage III/IV	71 27 (79%) 24 (71%) 30 (88%) 17 (50%)	71 27 (79%) 26 (76%) 28 (82%) 21 (62%)	65 8 (38%) 9 (43%) 21 (100%) 14 (67%)
MST (mo) 1-yr OS rate	10.5 46%	16.0 70%	NR 59%

*including 22 pts with HER2-positive tumors with EGFR mutations, 2 with both HER2- and ALK-positive tumors, and 2 had ALK-positive tumors with EGFR-mutations. ** 1 had an IHC2+/FISH+ tumor with mutation. **Conclusion:** This is the first prospective study showing a small fraction of NSCLC possessed HER2 aberrations. HER2-positive tumors had relatively poor prognosis. NSCLCs with HER2 IHC3+ and mutation seem to be distinct subsets.

Keywords: prospective cohort study, HER2, advanced NSCLC

OA 12.05 SPECTRUM OF 1,014 SOMATIC BRAF ALTERATIONS DETECTED IN CELL-FREE DNA OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Somatic *BRAF* V600E is a National Comprehensive Cancer Network clinical therapeutic target in non-small cell lung cancer (NSCLC), occurring in 6% of tumors from patients with lung adenocarcinoma. However, approximately half of BRAF alterations are non-V600E that do not respond to FDA-approved vemurafenib or dabrafenib. Emerging evidence suggests some non-V600E mutations exhibit clinical response to novel therapeutic agents. We analyzed the landscape of *BRAF* mutations in a very large cohort of patients with NSCLC who underwent somatic genomic testing utilizing a CLIA-certified/CAP-accredited/NYSDOH-approved 73 gene cell-free circulating tumor DNA (cfDNA) panel which evaluates single nucleotide variants, and selected indels, fusions, and copy number amplifications. **Method:** The Guardant Health laboratory database was queried for cfDNA tests from patients with a diagnosis of NSCLC where a *BRAF* variant was identified. Literature was queried for a description of the known function of non-V600E BRAF mutations on serine-threonine kinase activity. **Result:** A total of 1,014 *BRAF* alterations were observed in 914 tests, with 234 unique alterations identified. The majority of variants were observed only once (75.6%; N=177). 43 alterations were synonymous and excluded from analysis. Plasma-detected *BRAF* amplification was the most common alteration, observed in 484 tests. Of the remaining variants, 33 of 190 had functional consequence reported in the literature (17.4%), 18 with gain of function or predicted gain of function, 13 with loss of function or predicted loss of function and 2 with no effect. *BRAF* V600E accounted for 51.1% of occurrences of variants with gain of function or predicted gain of function (N=95 occurrences). Recurrent (>10 occurrences) non-V600E gain of function mutations included G469A (13.4%; N=25 occurrences), K601E (8.0%: N = 15 occurrences), and N581S (7.0%; N=13 occurrences). Fourteen additional gain of function variants comprised the remaining 21% of occurrences. Recurrent loss of function *BRAF* mutations (>10 occurrences) included G466V and D594G. **Conclusion:** This is the largest reported cohort of somatic *BRAF* alterations in metastatic non-small cell lung cancer. Non-V600E alterations accounted for almost 50% of the gain of function variants. The spectrum of non-V600E alterations was consistent with reports from The Cancer Genome Atlas and prior published results from tissue genomic sequencing. The recurrent non-V600E variants identified in this cohort are emerging therapeutic targets with promising early clinical data. These findings advocate for more comprehensive *BRAF* genomic profiling and identification of patients eligible for clinical trials targeting these non-V600E classic mutations and demonstrate the ability of plasma-based cfDNA to detect these alterations.

Keywords: cfDNA, NSCLC, BRAF

OA 12.06 PLASMA GENOMIC PROFILING AND OUTCOMES OF PATIENTS WITH MET EXON 14-ALTERED NSCLCS TREATED WITH CRIZOTINIB ON PROFILE 1001

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Background: *MET* exon 14 alterations occur in ~4% of non-squamous non-small cell lung cancers (NSCLCs). Treatment with the MET inhibitor, crizotinib, achieves confirmed and durable responses in patients with *MET* exon 14-altered NSCLCs, underscoring the need to test for these drivers (as of August 1, 2016, objective response rate was 39% and median duration of response was 9.1 months). Comprehensive molecular tumor profiling is required to detect *MET* exon 14 alterations that are highly heterogeneous. The utility of plasma profiling to detect these

drivers has not previously been explored in a prospective trial. **Method:** Patients with advanced NSCLCs harboring *MET* exon 14 alterations by local tumor profiling performed in a CLIA-certified or equivalent environment were treated with crizotinib at 250 mg twice daily on an expansion cohort of the ongoing phase I PROFILE 1001 study (NCT00585195). Objective response was assessed by RECIST v1.0. Prospective plasma profiling of circulating tumor DNA (ctDNA) for *MET* exon 14 alterations was performed using the PlasmaSELECT64 targeted gene panel (sequencing and analysis output by Personal Genome Diagnostics, Boston MA). **Result:** Plasma samples were obtained for *MET* exon 14 alteration analysis after study amendment approval in 20 of 52 crizotinib-treated patients, of which 18 samples were deemed sufficient for analysis. *MET* exon 14 alterations were detected in ctDNA in 11 of 18 patients (61% agreement of plasma ctDNA testing with tumor testing) mapping to the same exon 14 splice site region in 10 of the 11 cases. Of the 11 patients with ctDNA-positive tumors, all were evaluable for response. Of these evaluable patients, a confirmed partial response and stable disease were observed in 2 and 4 patients, respectively. **Conclusion:** *MET* exon 14 alterations can be detected in plasma ctDNA in a subset of patients with advanced NSCLCs that harbor *MET* exon 14 alterations by tumor testing. Responses to crizotinib were observed in patients with ctDNA-positive testing for a *MET* exon 14 alteration. Plasma profiling should be considered as an adjunct to tumor profiling in screening patients for *MET* exon 14 alterations, pending further confirmation.

Keywords: cfDNA, MET, crizotinib

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OA 12.07 LOXO-292, A POTENT, HIGHLY SELECTIVE RET INHIBITOR, IN MKI-RESISTANT RET FUSION-POSITIVE LUNG CANCER PATIENTS WITH AND WITHOUT BRAIN METASTASES

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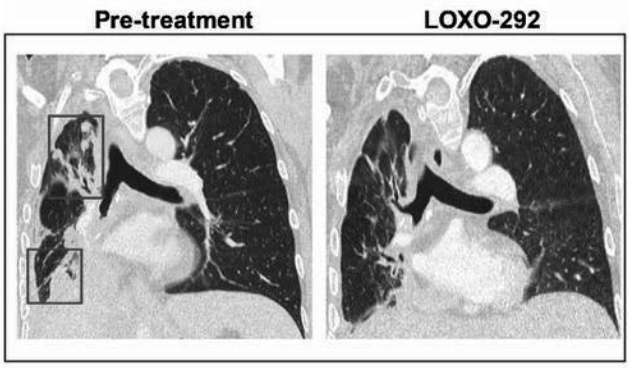
Background: *RET* fusions are validated therapeutic targets in human lung cancers. However, the clinical activity of multikinase inhibitors (MKIs) with anti-RET activity is limited by a narrow therapeutic index from off-target effects and poor pharmacokinetics (PK). Moreover, MKIs have limited RET inhibition in the central nervous system (CNS), and patients often experience disease progression in the brain. LOXO-292 is a potent and highly selective RET inhibitor, with >100-fold selectivity versus important off-targets, and anti-tumor activity in the brain and periphery in RET-dependent tumor models in vivo. **Method:** Two *RET* fusion-positive lung cancer patients were treated with LOXO-292: a patient with *CCDC6-RET*-rearranged lung cancer with acquired resistance to RXDX-105; and a patient with *KIF5B-RET*-rearranged lung cancer with progressive disease in the brain while on alectinib treated under a single patient protocol with real-time, PK- guided intra-patient dose titration. **Result:** The first patient was enrolled on cohort 1 of the Phase 1 trial (20 mg daily) and was the first lung cancer patient to receive LOXO-292. She achieved a rapid, confirmed partial response (PR) by RECIST 1.1, with a 44% reduction in target lesion size. The second patient, the first to receive LOXO-292 in the setting of brain metastases, achieved a PR with escalating doses of LOXO-292 (20-60-100 mg twice daily) that included target lesion responses in both the lungs and brain (Figure 1), and resolution of cancer-related CNS symptoms. Early clinical experience with LOXO-292 has already established drug exposures that are consistent with significant RET inhibition in vitro and RET-dependent tumor regression in vivo. Importantly, LOXO-292 has been well-tolerated, with the majority of treatment-emergent adverse events reported as Grade 1-2, and none attributed to LOXO-292. **Conclusion:** LOXO-292 has demonstrated proof-of-concept tolerability, significant exposure, and efficacy in two patients with MKI-resistant, RET-dependent cancers, including a patient with progressive brain metastases after alectinib.



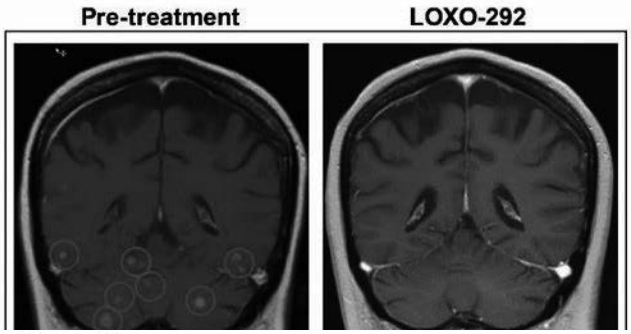


Figure 1

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OA 12.08 GENOMIC ANALYSIS OF NON-SMALL CELL LUNG CANCER (NSCLC) CASES WITH FOCAL AND NON-FOCAL MET AMPLIFICATION

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Background: *MET* amplification (*MET*amp) is a known driver and a mechanism of resistance in *EGFR*-mutated lung cancers treated with targeted therapy. However, development of therapies targeting *MET*amp has been hampered in part due to poor genomic stratification of patients. We investigated the natural distribution of the size of the *MET* amplicon and associated genomic characteristics. **Method:** Hybrid-capture based comprehensive genomic profiling (CGP) was performed prospectively on DNA isolated from FFPE samples from NSCLC. Tumor mutational burden (TMB) was calculated from 1.1 Mbp of sequenced DNA and reported as mutations/Mb, as previously described (PMID: 28420421). **Result:** We identified 545 NSCLC cases with focal, defined as <20 Mbp (n = 457, 84%), or non-focal (n = 88, 16%) amplification of the *MET* gene using CGP. Within this set, the size of the *MET* amplicon ranged from 0.095 – 158 Mbp; 25th, 50th and 75th quartiles were 1.63 Mbp, 3.46 Mbp, and 11.66 Mbp, respectively. In cases with focal *MET*amp the median *MET* copy number was 11, compared to a median of 7 copies for cases with non-focal *MET*amp (P <0.001). Median TMB in cases with focal vs. non-focal *MET*amp was 10.8 and 9.0, respectively (P=0.47). *MET* exon 14 splice site alterations co-occurred with *MET*amp in 45 cases (8%), of which 80% had focal *MET*amp (median amplicon size of 2.02 Mbp). *EGFR* mutations co-occurred with *MET*amp in 93 cases (17%) in this dataset, of which 78% had focal *MET*amp (median amplicon size: 3.77 Mbp). In contrast, cases with other co-occurring alterations described in the NSCLC NCCN guidelines (*ALK*, *ROS1* or *RET* rearrangements, BRAF V600E, or *ERBB2* mutations) *MET*amp was more commonly non-focal (3 focal and 6 non-focal cases), with a median amplicon size of 25.5 Mbp. Clinical outcomes will be presented, including a subset of cases in the setting of resistance to EGFR inhibitors. **Conclusion:** The size of the *MET* amplicon in *MET*-amplified NSCLCs is largely variable. Focal amplification is associated with a higher estimate of *MET* copy number. Neither TMB or co-occurring *MET* or *EGFR* mutations significantly correlated with size of the *MET* amplicon; however, other co-occurring known drivers were associated with non-focal *MET*amp. Additional investigation is warranted to determine the clinical significance of the size of the *MET* amplicon in NSCLC.

Keywords: focal amplification, MET, NSCLC

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OA 13.01 CD38-MEDIATED IMMUNOMETABOLIC SUPPRESSION AS A MECHANISM OF RESISTANCE TO PD-1/PD-L1 AXIS BLOCKADE

L. Chen[1], L. Diao[2], Y. Yang[1], X. Yi[3], B.L. Rodriguez[1], Y. Li[3], J. Rodriguez-Canales[4], X. Liu[3], A. Huang[5], Q. Zhao[5], D. Peng[5], J. Fradette[3], P. Tong[2], C. Ungewiss[3], Y. Fan[1], D. Peng[3], P. Villalobos[3], E. Dmitrovsky[3], V. Papadimitrakopoulou[1], J. Wang[2], L.A. Byers[1], J. Heymach[1], S. Ullrich[3], I. Wistuba[6], X. Qin[5], D. Gibbons[1]

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Background: Although immune checkpoint inhibitors of the PD-1/PD-L1 axis provide significant clinical benefit for patients with lung cancer, effective use of these agents is encumbered by a high rate of primary or acquired resistance. Strategies for optimal therapeutic application of immunotherapy require a thorough understanding of resistance mechanisms. To date, there have been only a few studies reporting potential mechanisms of resistance to PD-1/PD-L1 blockade. **Method:** In multiple immunocompetent syngeneic and spontaneous animal models of *K-ras/p53* mutant

lung cancer, we explored the resistance mechanisms to PD-1/PD-L1 blockade using both pharmacologic and genetic approaches (therapeutic antibody treatment and CRISPR/Cas9-mediated editing). The molecular and immune profiles of the tumor microenvironment were evaluated. Additionally, to determine the applicability to patients with lung cancer, we analyzed 259 tumor specimens with IHC staining and mRNA expression, and further confirmed the analyses in publically-available TCGA datasets. **Result:** In multiple models of antibody blockade and genetic knockout of PD-L1, we identified the up-regulation of CD38 on tumor cells as a marker of treatment resistance. Furthermore, by manipulating CD38 on a panel of lung cancer cell lines we demonstrated *in vitro* and *in vivo* that CD38 expression inhibits $CD8^+$ T cell proliferation, anti-tumor cytokine secretion, and tumor cell killing capability. The T cell suppressive effect is dependent upon the ectoenzyme activity of CD38 that regulates the extracellular levels of adenosine. To test whether CD38 blockade might be therapeutically efficacious to prevent anti-PD-L1/PD-1 resistance, we applied combination therapy with anti-CD38 and anti-PD-L1 and demonstrated dramatic therapeutic benefit on primary tumor growth and metastasis. Additionally, in a set of 259 resected lung cancer specimens, ~15% exhibited positive staining for CD38 on tumor cells, and the expression correlated with cytolytic T cell score and an immune/inflammatory signature across multiple large datasets. **Conclusion:** CD38 was found to be a novel mechanism for tumor escape from immune checkpoint PD-1/PD-L1 inhibitor therapy. Targeting this resistance pathway may broaden the benefit of PD-L1/PD-1 axis blockade for lung cancer treatment.

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OA 13.02 DISTRIBUTION OF PD-L1 TUMOR EXPRESSION BY ASSAY TYPE IN PATIENTS WITH METASTATIC NSCLC (MNSCLC)

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Background: Pembrolizumab was initially approved as a single agent by the US FDA on October 2, 2015, for treating patients with mNSCLC who have disease progression on or after platinum-containing chemotherapy and PD-L1 tumor expression ≥50%, as determined by the FDA-approved test (Dako 22C3). Subsequent approvals for first-line therapy and expanded second-line therapy followed in October 2016. Our aim was to study PD-L1 testing patterns in US Oncology practices from October 2015 through March 2017 and the potential impact of the PD-L1 IHC assay type on measurement of PD-L1 tumor expression. **Method:** This retrospective, observational study drew on de-identified, longitudinal data from a large electronic medical record database (Flatiron Health) representing 17% of incident oncology cases in the US. Eligible patients were adults (≥18 years) with histologically/cytologically confirmed initial diagnosis of mNSCLC (stage IV) or metastatic recurrence from October 2015 through March 2017. We determined the rate of PD-L1 testing (test date defined as the result date) and distribution of PD-L1 tumor expression (percentage of tumor cells staining for PD-L1) by IHC assay type. **Result:** The 7879 eligible patients included 4111/3768 (52%/48%) men/women; 5123 (65%) were >65 years old, and 6706 (85%) had a history of smoking. The rate of PD-L1 testing increased consistently over time from 15% in Q4/2015 to 70% in Q1/2017. Of 1728 patients with mNSCLC tested for PD-L1, 77%, 5%, 4%, and 19% were tested using Dako 22C3, Dako 28-8, Ventana SP142, and laboratory-developed tests (LDTs), respectively. Measured PD-L1 expression varied significantly (χ^2 $p<0.0001$) across the four assay types, although there was no significant difference (p=0.053) among the remaining three assays when the SP142 assay was excluded (Table**)**.

PD-L1 biomarker immunohistochemical (IHC) assay results for 1728 patients with mNSCLC whose tumors were tested from October 2015 through March 2017, by assay type.*

PD-L1 tumor expression, categorized‡	FDA-approved IHC assay, n (%)			Laboratory-developed tests, n (%) (N=323)
	Dako 22C3 (N=1335)	Dako 28-8 (N=90)	Ventana SP142† (N=75)	
<1%	478 (35.8)	37 (41.1)	46 (61.3)	127 (39.3)
1–49%	376 (28.2)	25 (27.8)	16 (21.3)	107 (33.1)
≥50%	481 (36.0)	28 (31.1)	13 (17.3)	89 (27.6)

*Some patients had more than one test and are represented in more than one column.
†Ventana SP142 results represent percentage of tumor cells staining for PD-L1.
‡$p<0.0001$ for χ^2 test comparing results across the four assay types, and p=0.053 for χ^2 test comparing results across three assay types, excluding the Ventana SP142 assay.
FDA, Food and Drug Administration.

Conclusion: We found no significant differences in measuring PD-L1 tumor expression using Dako 22C3, Dako 28-8, and LDTs; however, results of the SP142 assay appeared discordant.

Keywords: Biomarker, PD-L1, non-small cell lung cancer

OA 13 IMMUNO-BIOLOGY
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OA 13.03 WIDE EXPRESSION OF ALTERNATIVE IMMUNE CHECKPOINT MOLECULES, B7X AND HHLA2, IN PD-L1 NEGATIVE HUMAN LUNG CANCERS

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Background: Immunotherapy targeting the PD-1/PD-L1 pathway has dramatically changed the treatment landscape of non-small-cell lung carcinoma (NSCLC). We previously demonstrated that HHLA2, a recently identified B7 family immune inhibitory molecule, was widely expressed in NSCLC. To better understand the immune evasion mechanisms within the tumor microenvironment, we compared the expression profiles and functional roles of PD-L1 with potential alternative immune checkpoints, B7x and HHLA2. **Method:** Expression was assessed by immunohistochemistry using tissue microarrays consisting of 392 NSCLC tumor tissues (mostly resected stage I to III), including 195 tumors in the discovery (D) set and 197 cases in the validation (V) set. Positive PD-L1 cases were defined as samples with percentage of tumor cells revealing membranous staining of PD-L1 ≥ 1% with SP142 antibody. Human T cells were purified from eleven donors. Control human IgG, human PD-L1-Ig, human B7x-Ig and human HHLA2-Ig were used to determine the effects of PD-L1, B7x and HHLA2 on T cell proliferation and cytokine production [Human Th Cytokine Panel: IL-5, IL-13, IL-2, IL-6, IL-9, IL-10, IFN-γ, TNF-α, IL-17F, IL-17A, IL-4, IL-21 and IL-22]. **Result:** PD-L1 expression was detected in 25% and 31% of tumors in the D and V sets respectively, and was associated with higher stage and lymph node involvement in both cohorts. Multivariate analysis further showed that stage, TIL status and lymph node involvement were independently associated with PD-L1 expression. B7x was expressed in 69% and 68% of cases, while HHLA2 was positive in 61% and 64% of tumors in the two sets. Triple positive expression was detected in 13% whereas triple negative in 15% of cases. The double-expression of PD-L1 with B7x or HHLA2 was rare, 6% and 3% respectively. Interestingly, the majority (78%) of PD-L1 negative cases expressed B7x, HHLA2 or both. Moreover, the triple positive group correlated with more TIL infiltration as compared to the triple negative group (P = 0.0175). At the same concentration, B7x-Ig and HHLA2-Ig inhibited TCR-mediated proliferation of both CD4 and CD8 T cells significantly more robustly than PD-L1-Ig. All three significantly suppressed a variety of cytokine production by T cells. **Conclusion:** The majority of PD-L1 negative lung cancer cases express alternative immune checkpoint molecules (B7x, HHLA2 or both). The potential role of the B7x/HHLA2 pathway in mediating immune evasion in PDL1 negative tumors deserves to be explored to provide the rationale for an effective immunotherapy strategy in these tumors.

Keywords: Lung cancer, immune checkpoint, PD-L1

OA 13 IMMUNO-BIOLOGY
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OA 13.05 IMMUNE, MOLECULAR AND T CELL REPERTOIRE LANDSCAPE OF 235 RESECTED NON-SMALL CELL LUNG CANCERS AND PAIRED NORMAL LUNG TISSUES

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Background: Non-small cell lung cancer (NSCLC) is characterized by a high mutational load. Accordingly, it is also among the tumor types responding to immune checkpoint blockade, likely through harnessing of the anti-tumor T cell response. However, the lung is continuously exposed to the outside environment, which may result in a continuous state of inflammation against outside pathogens unrelated to the tumor microenvironment. Therefore, further investigation into the T cell repertoire and T cell phenotypes across normal lung and tumor is warranted. **Method:** We performed T cell receptor (TCR) sequencing on peripheral blood mononuclear cells (PBMC), normal lung, and tumor from 225 NSCLC patients, among which, 96 patients were also subjected to whole exome sequencing (WES) of PBMC, tumor and normal lung tissues. We further performed Cytometry by Time-of-Flight (CyTOF) on 10 NSCLC tumors and paired normal lung tissues to phenotype immune and T cell subsets. **Result:** Comparison of the T cell repertoire showed 9% (from 4% to 15%) of T cell clones were shared between normal lung and paired tumor. Furthermore, among the top 100 clones identified in the tumor, on average 57 (from 0 to 95) were shared with paired normal lung tissue. Interestingly, T cell clonality was higher in the normal lung in 89% of patients suggesting potential differences in the immune response and

immunogenicity. A substantial number of somatic mutations were also identified not only in NSCLC tumors (average 566; from 147 to 2819), but also in morphologically normal lung tissues (average 156; from 50 to 2481). CyTOF demonstrated striking differences in the immune infiltrate between normal lung and tumor, namely a lower frequency of PD-1+CD28+ T cells (both CD4+ and CD8+) in the normal lung (2.7% versus 3.0% in tumor). In addition, a unique GITR+ T cell subset (0.96%) was entirely restricted to the normal lung. Conversely, increases in regulatory T cell frequency (CD4+FoxP3+) were observed in the tumor (10.4% vs 1.7% in normal lung), further highlighting the differences in T cell phenotype and response across normal lung and tumor. **Conclusion:** These results suggest that a substantial proportion of infiltrating T cells in NSCLC tumors may be residential T cells associated with response to environmental factors. However, normal lung and NSCLC tumors carry T cells of distinct phenotypes including increases in immunosuppressive T cells within the tumor which may further highlight the differences in the anti-tumor immune response.

Keywords: NSCLC, TCR Repertoire, molecular profiling

OA 13 IMMUNO-BIOLOGY
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OA 13.06 CO-EXPRESSION OF IDO1 AND PD-L1 INDICATES MORE AGGRESSIVE FEATURES OF LUNG ADENOCARCINOMA

Y. Kozuma[1], K. Takada[1], G. Toyokawa[1], K. Kohashi[2], M. Shimokawa[3], F. Kinoshita[1], T. Matsubara[1], N. Haratake[1], S. Takamori[1], T. Akamine[1], F. Hirai[1], T. Tagawa[1], Y. Oda[2], Y. Maehara[1]

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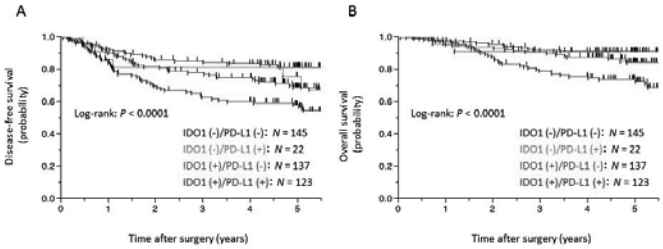
Background: Indoleamine 2, 3-dioxygenase 1 (IDO1) serves as an immunosuppressive effector and it is closely related to the prognosis in several types of cancer. We herein aim to elucidate the clinicopathological features and prognoses in patients with IDO1-expressing lung adenocarcinoma, and especially, show its correlation with the expression of programmed cell death-ligand 1 (PD-L1). **Method:** The expressions of IDO1 and PD-L1 proteins in 427 patients with surgically resected primary lung adenocarcinoma were evaluated by immunohistochemical analyses and any associations identified between IDO1 and the clinicopathological features, the prognosis and co-expression of IDO1 with PD-L1 were investigated. The expressions of IDO1 and PD-L1 at the protein and mRNA levels in lung adenocarcinoma cell lines were examined by an Enzyme-Linked Immuno Sorbent Assay, flow cytometry, and reverse transcription and real-time PCR analysis, respectively. **Result:** IDO1 was expressed in 260 patients (60.9%) at a 1% cut-off and in 63 patients (14.8%) at a 50% cut-off, respectively. PD-L1 was positive for 145 patients (34.0%). A ultivariate analysis showed IDO1 positivity (1% cut-off) to be significantly associated with a higher tumor grade, the presence of vascular invasion, and the expression of PD-L1. IDO1 and PD-L1 proteins were co-expressed in 123 patients (28.8%), and the patients whose tumor expressed both proteins exhibited significantly higher malignant traits than those whose tumor expressed only one protein or none. According to a multivariate analysis, the co-expression of both proteins was significantly associated with a shorter disease-free survival and overall survival. The expressions of IDO1 and PD-L1 in lung adenocarcinoma cell lines were elevated by treating them with interferon-γ and transforming growth factor-β.



Kaplan-Meier curves showing survival of patients with primary lung adenocarcinoma according to IDO1 and PD-L1 expression. (A) Disease-free survival and (B) overall survival among the four groups.

Conclusion: The findings of this study suggest that the co-expression of IDO1 and PD-L1 may indicate more aggressive features of lung adenocarcinoma. Combination therapy targeting both of these proteins may therefore improve the clinical outcomes in patients with lung adenocarcinoma.

Keywords: IDO, PD-L1, Immunotherapy

OA 13 IMMUNO-BIOLOGY
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OA 13.07 CONTRACTION OF T CELL CLONALITY IN LUNG CANCER METASTASES

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Background: Clonal evolution and the heterogeneity of non-small cell lung cancer (NSCLC) may affect patient outcomes through variations in treatment planning, response to therapy, and drug resistance. Even less is known about the diversity of the adaptive immune response to primary and metastatic lesions in this disease. We sought to characterize the richness, abundance and overlap of T cell clones between paired primary NSCLC lesions and brain metastases. **Method:** We identified 20 patients with NSCLC with paired, fully resected primary lesions and brain metastases with sufficient tissue available in our clinical archives. DNA was purified from formalin-fixed paraffin-embedded specimens. The complementarity determining region 3 of T-cell receptor β was profiled by next generation sequencing to identify unique T cell clones. Sample richness (including iChao1 and Efron-Thisted Estimator), and clonal abundance (Simpson's diversity index) were compared between paired lesions with the paired t test. Overlap in clonality was measured with the Morisita index. **Result:** There was a significant contraction of T cell clonality in paired metastases compared to primary lesions (mean of differences -2803, 95% CI -4202 to -1405; p=0.0005). The decreased richness in clonality in brain metastases was also supported by significant differences in iChao1 (mean of differences -20355, 95% CI -29561 to -11149; p=0.0002) and the Efron-Thisted Estimator (95% CI -21331 to -7216; p=0.0004). Simpson's diversity index was higher in brain metastases than primary lesions (mean of differences 0.002, 95% CI 0.001 to 0.004; p=0.05), but low overall. Only a fraction of T cell clones in primary lesions were also found in brain metastases (mean Morisita Index 0.23). **Conclusion:** There is greater richness but less abundance of T cell clones in primary NSCLC lesions compared to paired brain metastases. Although the blood brain barrier may restrict T cell trafficking to tumors, the minimal overlap in T cell clones may reflect the genetic divergence of metastatic tumor clones.

Keywords: T cell clones, NSCLC, Lung cancer metastases

OA 14 NEW PARADIGMS IN CLINICAL TRIALS
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OA 14.01 THE IMPACT OF MEASUREMENT VARIABILITY ON RESPONSE CATEGORIZATION IN ONCOLOGY TRIALS

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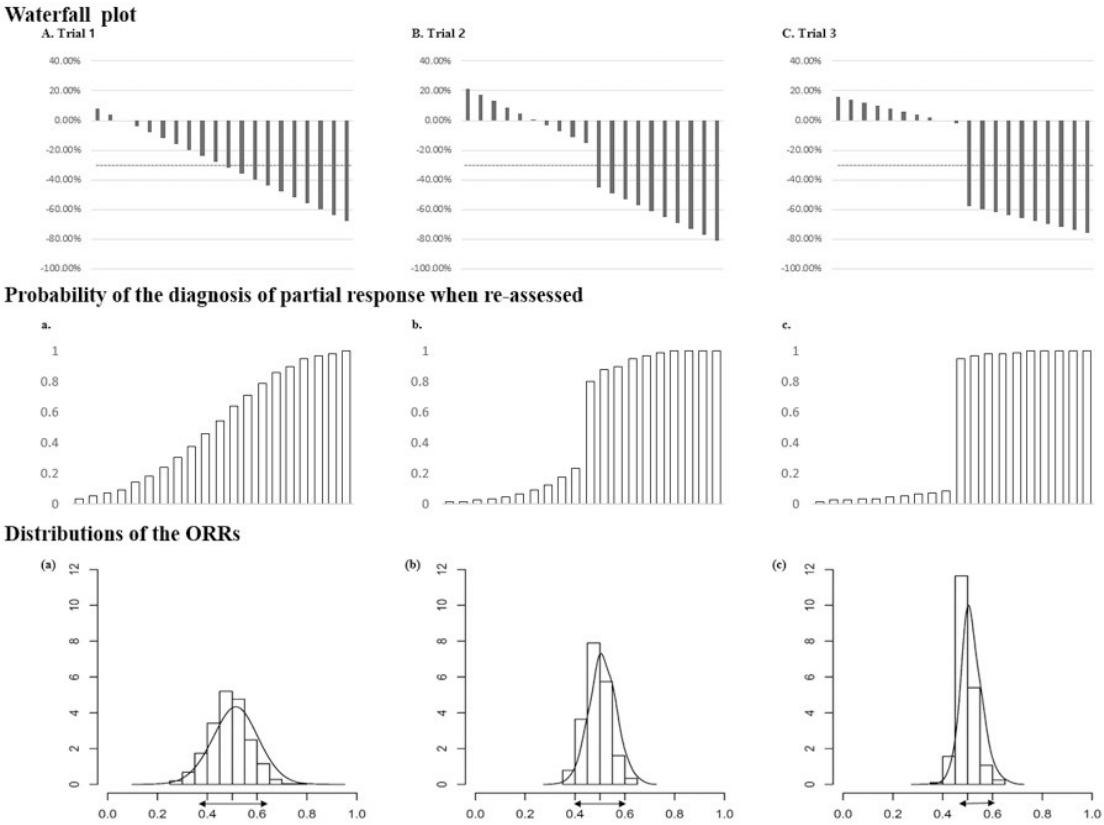
Background: Radiologic assessments of the baseline and post-treatment tumor burden are subject to measurement variability, but the impact of this variability on response categorization and the resulting overall response rate (ORR) in a specific trial has been practically unpredictable. **Method:** We built up a hierarchical model of measurement variability using a clinical trial dataset of CT scans. Simulations were then performed using the model 1) to establish the behaviour of differences between the first and the hypothetical second assessments of percent change of tumor burden in various scenarios, 2) to elaborate on the probabilistic nature of decisions about categorization, and 3) to estimate the variation in the ORR due to measurement variability. **Result:** The extent of the discrepancies between assessments of the percent change depended on the baseline burden. Smaller differences were associated with larger shrinkage of tumor burdens. The simulated probability for a specific categorization (-30% or 20%) to result from reassessment had a sigmoid shape depending on the percent change in the first set of readings, inflecting at the cutoff point for the categorization. In 3 virtual trials having the same baseline burden and the same ORR of 50%, the presence of fewer percent changes around the cutoff in a trial resulted in a more reproducible ORR (95% central range, 35%-65% vs. 40%-60% vs. 45%-60%).

(See table next page.)



Conclusion: Since determinations of partial response or progression are probabilistic outcomes due to measurement variability, quantification of the variation in the ORR by potential measurement variability is essential and will help inform decisions made on the basis of trial data**.**

Keywords: Oncology, objective response rate, Measurement Variability

OA 14 NEW PARADIGMS IN CLINICAL TRIALS
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OA 14.02 RETHINKING PROGRESSION-FREE SURVIVAL (PFS) AS A CLINICAL TRIALS SURROGATE FOR OVERALL SURVIVAL (OS)

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Background: OS assessment requires high follow-up times and patient numbers and is impacted by crossover (CO). OS hazard ratios (HRs) are generally inferior to PS HRs due to impact of post-progression survival (PPS) and CO. Some authors propose that absolute OS gains (ΔOS) should be similar to those in PFS (ΔPFS). Hence, ΔPFS might be a useful OS surrogate (Clin Cancer Res 2013;19:2646; Ann Oncol 2016;27:373).**Method:** To assess this further, we reviewed Journal of Clinical Oncology and New England Journal of Medicine 01/01/2012-06/12/2017 for randomized drug trials in incurable solid tumors. We extracted data for PFS and OS medians and HRs, calculated ΔPFS and ΔOS (experimental medians minus control medians), and did paired comparisons between 2-6 different arms in each study (245 comparisons across 201 trials). **Result:** Mean ΔOS across studies (1.03 months) was similar to mean ΔPFS (1.06 months) (n=201 evaluable, p=0.88). ΔOS correlated with ΔPFS (r=0.50, p<0.0001). With CO in <20% of patients or unstated %CO (n=144), mean ΔOS and ΔPFS were 0.93 and 0.92 months, respectively. With CO in ≥20% of patients (n=57), mean ΔOS and ΔPFS were 1.29 and 1.41 months, while with CO>50% (n=20), they were 1.4 and 1.9 months. OS HRs (mean=0.92) were inferior to PFS HRs (mean=0.82, n=196, p<0.0001), although OS and PFS HRs correlated with each other (r=0.64, p<0.0001). With CO<20% or unstated (n=135), mean OS and PFS HRs were 0.93 and 0.83, while with CO>20% (n=61), they were 0.90 and 0.80, and with CO>50% (n=20), they were 0.94 and 0.71. **Conclusion:** OS HRs were inferior to PFS HRs, probably due to PPS, competing causes of death and CO. The better mean gains and HRs in high vs low CO trials may be due to more frequently allowing CO in trials with more effective therapies. This increases risk of false-negative OS results with effective therapies if CO is permitted, but it is potentially unethical to withhold CO of effective therapies. With PFS, clinically insignificant gains may be statistically significant. Since ΔOS and ΔPFS are similar, an alternate approach would be a primary study outcome requiring PFS HR to be statistically significant and ΔPFS 95% CIs in a range considered clinically relevant for OS gains. To better understand the limitations of this approach, we are analyzing examples with minimal OS gains despite ΔPFS>2 months and examples of ΔOS>2 months but no gain in PFS, and have formulated a potential biological/statistical explanation for the latter.

Keywords: Progression-free survival

OA 14 NEW PARADIGMS IN CLINICAL TRIALS
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OA 14.03 ONTARIO'S BUNDLED PAYMENT SYSTEM FOR SYSTEMIC THERAPY SUPPORTS LUNG CANCER TRIALS

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Cancer Care Ontario, Toronto/ON/CA

Background: Clinical trials (CTs) are recognized as a key component of a quality cancer care system. When funding for systemic therapy (ST) services in Ontario transitioned in 2014/15 from a one-time payment for new cases to bundled payments for specific evidence-informed regimens, stakeholders expressed concern that the funding model could exclude patients from participation in CTs as treatment facilities would only receive funding when evidence-informed regimens were used. **Method:** A CT policy was implemented to enable public funding through the ST funding model for older and inexpensive drugs and their administration within randomized CTs at the level of the standard of care. Non-randomized CTs were to be funded at the level of best supportive care or other appropriate funding level. New and expensive drugs in a CT could be funded through a separate provincial drug reimbursement program if used according to public funding criteria with administration costs covered by the ST funding model. Each new CT is now assessed to determine the level of public funding possible. The funding model can now capture data on phase of trial, disease type, treatment regimen, trial purpose (adjuvant, palliative) and patient accrual by treatment facility **Result:** During 2015/16 and 2016/17, 43 and 44 lung CTs, respectively, were assessed and activated in Ontario. Trial accrual increased by 33% (from 311 to 413 patients) over the two years since the introduction of the funding model. Accrual varied by facility. In 2016/17, it ranged from a low of 0.25% to 37.5% of the new lung cancer (LC) patients seen at individual facilities. For the five largest cancer centres in Ontario, the percentage of patients recruited ranged from 5% to 18.3% and total accruals from these centres (n=257) comprised 63% of provincial LC trial recruitment. Five immuno-oncology trials accrued 183 patients and made up 44% of total LC trial accruals. Public funding through the ST funding model amounted to $415,000 in 2015/16 and increased to $815,000 in 2016/17. **Conclusion:** The new bundled payment system for ST and the CT policy have enabled public funding to support lung CTs. The ST funding model has facilitated the capture of CT data and trends not previously available for LC and other tumours. The new provincial CT policy and payment system do not appear to have negatively impacted participation in lung cancer CTs. The variance in trial accrual between centres warrants further study.

Keywords: bunbled payments, clinical trials, accrual

OA 14.05 PHASE 2 BASKET TRIAL OF ADO-TRASTUZUMAB EMTANSINE IN PATIENTS WITH HER2 MUTANT OR AMPLIFIED LUNG CANCERS

B. Li, R. Shen, D. Buonocore, Z. Olah, A. Ni, M. Ginsberg, G. Ulaner, W. Weber, D. Tsui, M. Offin, H. Won, M. Ladanyi, G. Riely, D. Solit, D. Hyman, C. Rudin, M. Berger, J. Baselga, M. Scaltriti, M. Arcila, M. Kris

Memorial Sloan Kettering Cancer Center, New York/US

Background: Human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) mutation and amplification each occurs in 2% of lung cancers, resulting in receptor dimerization and oncogenic signaling with in vitro sensitivity to trastuzumab. Ado-trastuzumab emtansine is a HER2 targeted antibody drug conjugate linking trastuzumab with the anti-microtubule agent emtansine. **Method:** Patients with advanced *HER2* mutant or amplified lung cancers were enrolled into separate cohorts in a basket 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. A separate cohort included patients with *HER2* mutant lung cancers assessed using PERCIST, with pre-treatment 89Zr-trastuzumab PET as correlative imaging. A Simon two stage optimal design was used with type I error rate under 2.7% (and a family wise error rate across baskets under 10%), power of 89%, H0 10%, H1 40%. Other endpoints include progression-free survival (PFS) and toxicity. HER2 testing was performed on tumor tissue by next generation sequencing (NGS), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). **Result:** A total of 33 patients were identified by NGS and enrolled. The first *HER2* mutant cohort completed accrual of 18 patients with ORR of 44% (8/18 confirmed, 95% CI 22-69%), rejecting null hypothesis. The median PFS was 4 months, and median PFS for responders was 6 months (range 4-11 months). The PERCIST measured *HER2* mutant cohort accrued 9 patients, there were 2 confirmed partial responses (PR) in 5 patients evaluated. The *HER2* amplified cohort accrued 6 patients, with 3 confirmed PR observed including 1 with concurrent *EGFR* sensitizing mutation and resistance to erlotinib. Toxicities included grade 1 or 2 including infusion reaction, thrombocytopenia and transaminitis, there were no treatment related deaths. Of the 27 patients in the *HER2* mutant cohorts, there were 18 (67%) exon 20 insertions and 9 (33%) point mutations; responders were seen across mutation subtypes (A775_G776insYVMA, G776delinsVC, V659E, S310F, L755P). Concurrent *HER2* amplification was observed in 4 of 27 patients by either NGS or FISH. IHC ranged from 0 to 3+ and did not predict response. Of the 6 patients in the *HER2* amplified cohort, 2 had concurrent *HER2* mutation and 1 had concurrent *EGFR* L858R mutation. **Conclusion:** Ado-trastuzumab emtansine is active and well tolerated in patients with advanced *HER2* mutant or amplified lung cancers as identified by NGS. While cohort expansion is ongoing, this study has met its primary endpoint in patients with *HER2* activating mutations. Further development is warranted.

Keywords: HER2 amplification, HER2 mutation, ado-trastuzumab emtansine

OA 14.06 ENTRECTINIB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC ROS1 FUSION-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Entrectinib is a potent, investigational, CNS-active, oral inhibitor of *ROS1* with a biochemical IC_{50} (0.2 nM) ~30 times more potent than crizotinib, the only agent approved for the treatment of *ROS1*-positive NSCLC. Previously, we reported an objective response rate of 85% in 13 ROS1 inhibitor-naïve NSCLC patients who were treated in Phase 1 studies (Drilon and Siena et al, Cancer Discov 2017), including 2 of 3 (67%) patients with CNS disease. Responses were durable, with 1 patient remaining on study for more than 3 years. Entrectinib was well tolerated, with predominantly Grades 1 or 2 adverse events that were reversible with dose modification. **Method:** Patients with ROS1 inhibitor-naïve NSCLC were enrolled across Phase 1 and 2 studies of entrectinib. Patients were screened for *ROS1* gene fusions either locally or centrally at Ignyta's diagnostic laboratory 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 (INV) and by blinded independent central review (BICR) using RECIST v1.1. INV results will be presented except where noted. **Result:** As of 24 May 2017, a total of 32 patients were evaluable for response (median age 52 years, 72% female). At a median follow-up of 12 months, objective responses were observed in 24 of 32 (75% [95% CI: 56.6, 88.5]; 3 complete responses) patients, including 7 of 11 (64% [95% CI: 30.8, 89.1]) patients with CNS disease at baseline. Five of 7 patients with evaluable CNS lesions by BICR experienced confirmed RECIST intracranial responses, for a CNS response rate of 71% (95% CI: 29.0, 96.3). With 19 (59%) patients remaining on study, the median duration of response was 17.2 months (95% CI: 6.5, 36.0) and progression-free survival was 19.1 months (95% CI: 6.5, 36.6). The most common (>15%) treatment-related adverse events were fatigue/asthenia (34%), dysgeusia (34%), dizziness (24%), weight increase (21%), paresthesia (19%), nausea (18%), constipation (18%), and diarrhea (16%). All data will be updated at the time of presentation. **Conclusion:** Entrectinib is well tolerated and has shown promising antitumor activity in ROS1 inhibitor-naïve NSCLC, including patients with CNS disease. Patients with ROS1+ NSCLC and other tumor types continue to be enrolled in STARTRK-2 (NCT02568267) in order to support a potential regulatory filing for entrectinib in this population.

Keywords: entrectinib, ros1, NSCLC

OA 14.07 PROGRESS IN LUNG SQUAMOUS CELL CARCINOMA FROM THE LUNG-MAP MASTER PROTOCOL (S1400) SUB-STUDIES S1400A, S1400B, S1400C AND S1400D

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Background: Lung-MAP (S1400) is a master umbrella protocol designed to establish genomic screening for previously treated squamous cell lung cancer patients (SqCCA), and independently evaluate targeted therapies with matching biomarkers and alternative therapies (designated non-match therapy) in patients without putative markers. The protocol opened June 16, 2014 with four biomarker-driven sub-studies and one non-match sub-study. **Method:** Eligibility stipulated advanced SqCCA, progressing after at least one prior platinum-based chemotherapy, PS 0–2, and EGFR/ALK wild-type. Tumor samples were required and analyzed for gene alterations by FoundationOne NGS assay (Foundation Medicine). The original biomarker and non-match studies were: S1400B evaluating taselisib for PI3K mutations, S1400C evaluating palbociclib for cell cycle gene alterations (CCGA), S1400D evaluating AZD4547 for FGFR mutations, S1400E evaluating rilotumumab and erlotinib for c-MET positive tumors, and S1400A evaluating durvalumab in patients with no matching biomarkers. The original design included randomization to a control arm, but was amended to a single-arm phase 2 design. The primary endpoint for each modified sub-study was response. **Result:** As of June 16, 2017 all original sub-studies have been closed to accrual; 1298 patients registered to the screening component of the trial and 486 patients have registered to a sub-study. Two new sub-studies have been launched and are currently accruing. Details of the completed sub-studies are included in the table.

(See table next page.)

Sub-study	Final Accrual	Biomarker prevalence /% of sub-study registrations	Closure Date	Response to investigational therapy N (%)	Status
S1400A (non-match)	Total: 116 Durvalumab: 78 Docetaxel: 38	NA/59%	12/18/15 Docetaxel arm closed: 4/22/15	11 (16%)	Administratively closed to enable activation of new non-match study.
S1400B PI3K	Total: 39 taselisib: 31 Docetaxel: 8	8%/9%	12/12/16 Docetaxel arm closed: 12/18/15	1 (4%)	Closed at interim futility analysis.
S1400C (CCGA+)	Total: 54 Palbociclib: 37 Docetaxel: 17	19%/15%	09/01/16 Docetaxel arm closed: 12/18/15	2 (6%)	Closed at interim futility analysis.
S1400D (FGFR+)	Total: 45 AZD4547: 35 Docetaxel: 10	16%/12%	10/31/16 Docetaxel arm closed: 12/18/15	2 (7%)	Closed at interim futility analysis.
S1400E (MET+)	Total: 9 R+E: 4 E: 5	N/A (closed too early)	11/26/2014	N/A	Closed d/t discontinuation of development of rilotumumab

Conclusion: Lung-MAP as a master genomic screening protocol has demonstrated feasibility with respect to accrual and evaluation of targeted therapies in lower prevalence patient populations. This dynamic, centralized, single-IRB platform is well positioned to efficiently assess multiple novel therapeutics for advanced SqCCA patients.

Keywords: Targeted therapy, Master Protocol, precision medicine

OA 15 DIAGNOSTIC RADIOLOGY, STAGING AND SCREENING FOR LUNG CANCER II
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OA 15.01 LUNG CANCER SCREENING: PARTICIPANT SELECTION BY RISK MODEL – THE PAN-CANADIAN STUDY

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Background: Retrospective studies indicate that selecting individuals for low dose computed tomography (LDCT) lung cancer screening based on a highly predictive risk model is superior to applying National Lung Screening Trial (NLST)-like criteria, which use only categorized age, pack-year and smoking quit-time information. The Pan-Canadian Early Detection of Lung Cancer Study (PanCan Study) was designed to prospectively evaluate whether individuals at high risk for lung cancer could be identified for screening using a risk prediction model. This paper describes the study design and results. **Method:** 2537 individuals were recruited through 8 centers across Canada based on a ≥2% of lung cancer risk estimated by the PanCan model, a precursor to the validated PLCOm2012 model. Individuals were screened at baseline and 1 and 4 years post-baseline. **Result:** At a median 5.5 years of follow-up, 164 individuals (6.5%) were diagnosed with 172 lung cancers. This was a significantly greater percentage of persons diagnosed with lung cancers than was observed in the NLST(4.0%)(p<0·001). Compared to 57% observed in the NLST, 77% of lung cancers in the PanCan Study were early stage (I or II) (p<0.001) and to 25% in a comparable population, age 50-75 during 2007-2009 in Ontario, Canada's largest province, (p<0·001). **Conclusion:** Enrolling high-risk individuals into a LDCT screening study or program using a highly predictive risk model, is efficient in identifying individuals who will be diagnosed with lung cancer and is compatible with a strong stage shift – identifying a high proportion at early, potentially curable stage. **Funding** This study was funded by the Terry Fox Research Institute and Canadian Partnership Against Cancer. ClinicalTrials.gov number, NCT00751660

Keywords: lung cancer screening, low dose computed tomography screening, prediction model

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OA 15.02 BENEFITS, HARMS, AND ECONOMIC EFFICIENCY OF LOW-DOSE CT LUNG CANCER SCREENING STRATEGIES IN A POPULATION-BASED SETTING

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Background: In lung cancer screening, a nodule management protocol describes nodule assessment and thresholds for nodule size and growth rate to identify patients who require immediate diagnostic evaluation or additional imaging exams. The NELSON and NLST clinical trials used different selection criteria and nodule management protocols. Several modelling studies have reported variations in screening outcomes and cost-effectiveness across selection criteria and screening intervals; however, the effect of variations in the nodule management protocol remains uncertain. This study evaluated the effects of the eligibility criteria and nodule management protocols on the benefits, harms, and cost-effectiveness of lung screening scenarios in a population-based setting in Germany. **Method:** We developed a modular microsimulation model: a biological module simulated individual histories of lung cancer development from carcinogenesis onset to death; a screening module simulated patient selection, screening-detection, nodule management protocols, diagnostic evaluation and screening outcomes. Benefits included mortality reduction, life years gained, averted lung cancer deaths. Harms were costs, false-positives, overdiagnosis. Comparator was no screening. Evaluated 57 screening scenarios included variations in selection criteria and thresholds for nodule size and growth rate. **Result:** Five years of annual screening resulted in an 11.3–12.6% lung cancer mortality reduction in the screened population. The efficient scenario included volumetric assessment, a threshold for a volume of 300 mm^3, and a threshold for a volume doubling time of 400 days. Assessment of volume doubling time is essential for reducing overdiagnosis and false-positives. Incremental cost-effectiveness ratios of the efficient scenarios were 19,389–23,804 Euro per life years gained and 178,673–285,630 Euro per averted lung cancer death. **Conclusion:** Lung cancer screening can be cost-effective in Germany. Along with the eligibility criteria, the nodule management protocol influences screening performance and cost-effectiveness. Definition of the thresholds for nodule size and nodule growth in the nodule management protocol should be considered in detail when defining optimal screening strategies.

Keywords: lung cancer, Cost-effectiveness, LDCT lung screening

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OA 15.03 GENE-BASED RISK STRATIFICATION OF NLST-ACRIN SCREENING PARTICIPANTS IDENTIFIES THE "SWEET SPOT" OF SCREENING (N=10,054)

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Background: Screening of high risk smokers with computed tomography (CT) aims to identify early stage lung cancers in screening participants amenable to curative surgery. The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer specific mortality in the CT arm compared to chest x-ray (control) arm. European screening trial results to date have failed to show any evidence of a reduction in lung cancer mortality. Reduction in lung cancer mortality comes from the combined effects of successful surgical removal of life-threatening early stage lung cancers and post-operative survival. In screening participants of the NLST, who are older chronic smokers, there exists a balance between mortality from lung cancer and mortality from non-lung cancer related causes. **Method:** This study aimed to validate a gene-based risk tool for dying of lung cancer and examine the outcomes from screening according to tertiles of risk. It also aimed to establish the utility of adding SNP-based data to risk prediction and efficacy in identifying which screening participants get the best outcomes from screening. Using prospective data from the NLST-ACRIN cohort (N=10,054), we examined the utility of combining risk genotypes with clinical risk variables in our risk model for dying of lung cancer. We then stratified screening participants into risk tertiles according to our risk model and compared the outcomes from CT versus CXR screening **Result:** The addition of risk genotypes (combined genetic risk score) to our clinical risk model for dying of lung cancer was significantly improved (AUC increased from 0.61 to 0.66, P=0.014). We show that screening participants in the middle risk tertile achieves a lung cancer specific mortality reduction of 55% and all-cause mortality reduction of 21%. In this group the number of lung cancers averted is maximised (12/1000 person screened) and number needed to screen to avert one lung cancer reduced to 84. We show that this is achieved through minimising pre-existing co-morbid disease and by maximising screen detected lung cancers amenable to CT detection and successful surgical intervention. We believe genetic data provides useful information on lung cancer biology. **Conclusion:** The "Sweet spot" of CT screening comes from identifying high risk smokers optimised according to co-existing premorbid disease (especially COPD), early stage lung cancers amenable to surgical cure and least likely to die of other

complications of smoking. Gene-based risk testing appears superior to just clinical risk models alone in prioritising high risk smokers for screening.

Keywords: "sweet spot", Gene-based risk stratification, CT screening

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OA 15.04 COMMUNITY-BASED LUNG CANCER SCREENING, TARGETING HIGH-RISK EVER SMOKERS IN DEPRIVED AREAS OF MANCHESTER: AN NHS IMPLEMENTATION PROJECT.

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Background: Lung cancer (LC) is the commonest cause of cancer-related death in the world. Screening with low-dose computer tomography (LDCT) had been shown to reduce LC specific and all-cause mortality. Benefit is greatest in those at highest risk, such as current smokers from areas of high socio-economic deprivation, yet participation in these 'hard-to-reach' populations remains a challenge and must be improved if we are to succeed with screening. The aim of this NHS implementation project was to assess LC screening within the community in deprived areas. **Method:** Ever smokers, aged 55-74, registered at 14 participating general practitioner (GP) practices in deprived areas of Manchester were invited to attend and have a free 'Lung Health Check' (LHC) in a mobile unit located at their local shopping centres. Lung cancer risk score ($PLCO_{M2012}$), respiratory symptoms and spirometry were assessed as part of the LHC with results communicated back to the GPs. Those at high risk of LC, i.e. 6-year lung cancer risk ≥1.51%, were offered immediate LDCT in a co-located mobile CT scanner. These were all reported by thoracic radiologists with an interest in pulmonary oncology. Specifically designed nodule algorithms were followed in the reporting. **Result:** The maximum available capacity of the project was filled within days of going live. 2,541 individuals attended for a LHC and consented to data analysis. The mean age was 64.1±5.5, 51.0% (n=1,296) were female, 35.1% (n=891) were current smokers and 74.5% (n=1,893) ranked in lowest deprivation quintile. Of these 56.2% (n=1,429) qualified for a LDCT scan ($PLCO_{M2012}$ risk score ≥1.51%). 46 lung cancers were detected in 42 individuals, a prevalence of 3.0%, of which 80% (n=37/46) were early stage (I+II). A treatment with curative intent was offered to 89.1% (n=41/46) of screen detected cancers and the surgical resection rate was 65.2%, which is almost fourfold the UK national average (16.8%). **Conclusion:** Taking lung cancer screening into the community can identify and target those at most risk, using the $PLCO_{m2012}$ model, resulting in a significant stage shift in screen detected lung cancers in deprived populations.(Please note this data is currently under EMBARGO and awaiting publication in the very near future. We would be grateful if this is kept confidential in line with your embargo policy. There has been a lot of excitement and anticipation around the results of this pilot study and we would greatly appreciate the opportunity to present the more detailed results in Japan with the IASLC)

Keywords: Screening, Early Detection, lung cancer

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OA 15.06 MANAGEMENT OF NONRESOLVING NEW SOLID NODULES AFTER INITIAL DETECTION IN INCIDENCE ROUNDS OF CT LUNG CANCER SCREENING

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Background: Low-dose computed tomography (LDCT) lung cancer screening is recommended by US guidelines for high-risk individuals. New solid nodules are regularly found in incidence screening rounds and have a higher lung cancer probability at smaller size than do baseline nodules, leading to the proposal of lower size cutoffs at initial new solid nodule detection. However, currently there is no evidence concerning the risk-stratification of new solid nodules at first LDCT screening after initial detection. **Method:** In the ongoing, multicenter, randomized controlled Dutch-Belgian Lung Cancer Screening (NELSON) Trial, 7,295 participants underwent the second and 6,922 participants the third screening round. We included participants with solid non-calcified nodules, that were registered by the NELSON radiologists as new or smaller than 15mm^3 (study detection limit) at previous screens and received a follow-up or regular LDCT screening after initial detection; thereby excluding high-risk nodules according to the NELSON management protocol (nodules ≥500mm^3). Nodule volume was generated semiautomatically. For assessment of the predictive performance, the area under the receiver operating characteristics curve (AUC) of nodule volume, volume doubling time (VDT), and VDT combined with a predefined 200mm^3 volume cutoff were evaluated with eventual lung cancer diagnosis as outcome. **Result:** Overall, 680 participants with 1,020 low and intermediate risk new solid nodules were included. A total of 562 (55%) new solid nodules were resolving, leaving 356 (52%) participants with a nonresolving new solid nodule of whom 25 (7%) were eventually diagnosed with lung cancer in such a nodule. At first follow-up or regular LDCT screening after initial new solid nodule detection, VDT, volume, and VDT combined with the predefined ≥200mm^3 volume cutoff had a high discriminative performance for lung cancer (VDT, AUC: 0.91; volume, AUC: 0.88; VDT and ≥200mm^3 combination, AUC: 0.94). A cutoff combination of ≤590 days VDT or ≥200mm^3 at first LDCT after initial new solid nodule detection, classifying a nodule positive when at least one criterion was fulfilled, provided 100% (95% confidence interval [CI] 84-100%) sensitivity and 84% (95%CI 80-87%) specificity for discriminating lung cancer, with positively classified nodules having a lung cancer probability of 27% (95%CI 19-37%). **Conclusion:** More than half of new solid nodules identified in LDCT lung cancer screening are resolving nodules. At first follow-up, a cutoff combination of ≤590 days VDT or ≥200mm^3 volume can be used for risk stratification.

Keywords: CT lung cancer screening, new nodules after baseline screening

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OA 15.07 VALUE OF NODULE CHARACTERISTICS IN RISK-STRATIFICATION OF NEW INCIDENT NODULES DETECTED IN CT LUNG CANCER SCREENING

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Background: New solid nodules detected in low-dose computed tomography (LDCT) lung cancer screening have a higher lung cancer probability at a smaller size than baseline nodules and lower size cutoff values for risk stratification at initial detection have been proposed. So far, it is unknown whether nodule characteristics, such as morphology or location, could improve risk stratification by size in new solid nodules. **Method:** This study forms part of the ongoing, randomized controlled Dutch-Belgian Lung Cancer Screening (NELSON) trial. This analysis included solid non-calcified nodules detected during the three incidence screening rounds and registered by the NELSON radiologists as new or previously below detection limit (15mm^3). Nodule volume was generated semiautomatically. The predictive performance of nodule characteristics (location, distribution [peripheral, nonperipheral], shape [round, polygonal, irregular], margin [smooth, lobulated, spiculated, irregular], visibility <15mm^3 in retrospect) combined with previously established volume cutoffs (<30mm^3, low risk; 30-<200mm^3, intermediate risk; ≥200mm^3 high risk) was evaluated by multivariable logistic regression analysis with eventual lung cancer diagnosis as outcome. Discrimination of lung cancer based on volume, the final parsimonious model, and the model stratified into three risk groups (low, intermediate, high) was assessed through the area under the receiver operating characteristics curve (AUC) and compared using DeLong›s Method. **Result:** Overall, 1,280 new nodules were included with 73 (6%) being diagnosed as lung cancer eventually. Of the new nodules visible <15mm^3 in retrospect and now ≥30mm^3, 22% (6/27) were lung cancer. Discrimination based on volume cutoffs (AUC: 0.80, 95% confidence interval [CI] 0.75-0.84) and continuous volume (AUC: 0.82, 95%CI 0.77-0.87) was comparable (P=0.14). After adjustment for volume cutoffs, only location in the right upper lobe (odds ratio [OR] 2.0, 95%CI 1.2-3.4), nonperipheral distribution (OR 2.4, 95%CI 1.4-4.2), and visibility <15mm^3 in retrospect (OR 4.7, 95%CI 1.7-12.8) remained significant predictors. Discrimination based on the model (AUC: 0.85, 95%CI 0.81-0.89) was superior to the volume cutoffs alone (P=0.0002), but when stratified into three risk groups (AUC: 0.82, 95%CI 0.78-0.86) discrimination was comparable (P=0.2). **Conclusion:** At initial detection, nodule volume is the strongest predictor for lung cancer in new nodules. Nodule characteristics may further improve lung cancer prediction, but only have limited incremental discriminatory value additional to volume cutoffs in a three-category stratification approach.

Keywords: new nodules after baseline screening, nodule characteristics

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OA 15.08 THOROUGHNESS OF STAGING AND THE OUTCOMES OF SURGICAL RESECTION OUTCOMES IN POTENTIALLY CURABLE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Substantial variation exists in the processes of care for potentially curable NSCLC. We examined the impact of thoroughness of staging for patients

undergoing NSCLC surgery in a large, heterogeneous population within a lung cancer endemic region of the US. **Method:** We evaluated all surgically resected patients in the Mid-South Quality of Surgical Resection (MS-QSR) cohort from 2009-2017. MS-QSR is a population-based cohort including all curative-intent NSCLC resections at 11 hospitals in the mid-south US. Patients were classified into 8 groups based on use (Yes/No) of the following staging modalities: PET/CT, pre-operative invasive staging, operative mediastinal nodal examination (MLE). We compared stage distribution, adjuvant therapy, and overall survival outcomes across groups using the chi-square test and adjusted Proportional Hazards Models. **Result:** The 2,370 patients had a median age of 67 years, were 53% male. The racial distribution was: 70% White, 25% Black, 5% Other. Clinical N-stage was similar between the 8 groups. We found statistically significant differences in pathologic stage distribution, adjuvant therapy usage, and overall survival across the 8 groups (Table 1). Patients who received PET/CT, invasive staging, and MLE (Group 1) had significantly higher pathologic N-stage distribution compared to the other groups due to substantial nodal upstaging. Group 1 had 76% eligibility and 31% use of adjuvant chemotherapy compared to 51% and 8% in the Group 8 (No PET/CT, No Invasive Staging, No MLE). Use and eligibility for adjuvant radiation therapy was also highest in Group 1. There was an overall difference in survival across the groups (p-value=0.0019) which remained significant after adjusting for age, sex, race, histology, and path stage (p-value=0.0013). After adjustment, Group 8 had a 14% increased hazard of death compared with Group 1.

	Group 1: Yes PET Yes IS Yes MLE	Group 2: Yes PET Yes IS No MLE	Group 3: Yes PET No IS Yes MLE	Group 4: Yes PET No IS No MLE	Group 5: No PET Yes IS Yes MLE	Group 6: No PET Yes IS No MLE	Group 7: No PET No IS Yes MLE	Group 8: No PET No IS No MLE	P-Value
N (%)	363 (15.3)	44 (1.9)	1234 (52.4)	319 (13.7)	46 (2.0)	9 (0.4)	265 (11.1)	75 (3.2)	
Nodal Staging	%	%	%	%	%	%	%	%	
Clinical N stage									
N0	70	59	84	88	72	78	80	76	
N1	15	16	6	4	11	0	2	1	<0.0001
N2	10	18	6	4	9	11	4	7	
N3	2	5	0	1	0	0	0	0	
Other	4	2	4	4	9	11	14	16	
Pathological N stage									
Nx	0	25	0	30	0	22	0	47	
N0	63	64	79	60	74	67	83	45	<0.0001
N1	23	11	10	10	22	11	9	8	
N2	14	0	10	0	4	0	8	0	
Adjuvant therapy									
Use of Chemotherapy									
Yes	30	16	17	9	18	22	10	8	<0.0001
No	70	84	83	92	82	78	90	92	
Eligible for Chemotherapy	75	48	61	53	74	78	53	52	<0.0001
Use of Radiation									
Yes	6	2	4	4	9	0	3	3	0.5237
No	94	98	96	96	91	100	97	97	
Eligible for Radiation	13	0	10	0	4	0	8	0	<0.0001
Survival									
Adjusted HR	1	1.00	0.87	1.37	0.96	1.15	1.00	1.14	0.0013
95% CI	----	(0.58, 1.72)	(0.71, 1.07)	(1.07, 1.74)	(0.59, 1.56)	(0.36, 3.64)	(0.76, 1.31)	(0.78, 1.68)	

Conclusion: A less thorough approach to staging may lead to less nodal upstaging and less eligibility for adjuvant therapy, which could have implications for long term survival.

Keywords: Thoroughness of staging, Surgical resection, survival

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OA 16.01 STEREOTACTIC ABLATIVE RADIOTHERAPY VERSUS SURGERY IN EARLY LUNG CANCER: A META-ANALYSIS OF PROPENSITY SCORE-ADJUSTED STUDIES

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Background: There is currently no completed randomized controlled trial data comparing stereotactic ablative radiotherapy (SABR) and surgery in operable patients with early-stage non-small cell lung cancer (ES-NSCLC). Propensity score methods are increasingly utilized in oncology to balance the baseline characteristics of non-randomized cohorts, mimicking the setting of a clinical trial. No previous meta-analysis of propensity score analyses comparing a surgical and non-surgical modality has been conducted. Our goal was therefore to perform a systematic review and meta-analysis of all propensity score analyses comparing SABR and surgery in patients with ES-NSCLC. **Method:** A systematic review was carried out according to PRISMA guidelines by querying the MEDLINE and Embase databases from inception until December 2016. Hazard ratios (HR) with confidence intervals (CI) for overall survival (OS) and disease-specific survival (DSS) were directly extracted, if available, or estimated from Kaplan-Meier curves. Meta-analysis was carried out with inverse variance-weighted random-effects models. **Result:** After reviewing 1039 records, 17 PS-adjusted studies with a total of 20151 patients were included in the final analysis. Overall survival (OS) favoured surgery over SABR (HR = 1.52 [95% CI: 1.33-1.74], p < 0.001). However, the rate at which patients died from lung cancer (DSS) was not significantly different (HR = 1.13 [95% CI: 0.86-1.49], p = 0.38). On subgroup analysis, OS was superior for both lobectomy (HR = 1.61 [95% CI: 1.27-2.03], p < 0.001) and sublobar resection (HR = 1.33 [95% CI: 1.15-1.55], p < 0.001) versus SABR while DSS again did not significantly differ (HR = 1.35 [95% CI: 0.70-2.62] and HR = 1.18 [95% CI: 0.84-1.67], respectively). On secondary analysis, meta-analysis of proportions revealed a lymph node upstaging rate of 16.0% (95% CI: 13.6%-18.6%) and adjuvant chemotherapy usage rate of 11.5% (95% CI: 8.6%-14.8%) among patients who received surgery. On meta-regression, with every increase of 0.1 in the maximum allowable difference in propensity score within a matched pair - representing increases in imbalance between cohorts, DSS outcomes increasingly favoured surgery by 1.36-fold. Critical appraisal revealed inconsistent reporting of propensity score methods. **Conclusion:** Overall survival favoured surgery over SABR in this meta-analysis of 17 propensity score analyses. However, the effectiveness of SABR was reflected in a similar DSS to surgery, supporting ongoing clinical equipoise. A direct relationship between propensity score methodology and DSS outcomes were demonstrated. Whether this observed benefit in OS for surgery is real or due to limitations in the propensity score methodology requires confirmation through randomized data.

Keywords: meta-analysis, non-small cell lung cancer, Propensity score

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OA 16.02 RISK OF RECURRENCE IN STAGE I ADENOCARCINOMA OF THE LUNG: A MULTI-INSTITUTIONAL STUDY ON INTERACTION WITH TYPE OF SURGERY AND TYPE OF NODAL STAGING

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Background: In last years, an increasing interest emerges on the role of sub-lobar resection and lobe-specific lymphnode dissection in the treatment of early stage lung cancer. The aim of our study was to define impact on Cumulative incidence of recurrence (CIR) of type of surgical resection and type of nodal staging. Furthermore, we evaluated the effect of interactions between the different kinds of procedure. **Method:** An analysis of 969 consecutive stage I pulmonary adenocarcinoma patients, operated in six Thoracic Surgery Institutions between 2001 and 2013, was conducted. Type of surgical resection included lobectomy and sub-lobar resection; pneumonectomy and bilobectomy were excluded from the analysis. Nodal staging procedures were classified in nodal sampling (NS), lobe-specific lymph node dissection (LS-ND) and systematic lymph node dissection (SND). Multivariable-adjusted comparisons for CIR was performed using Fine and Grey model, taking into account death by any cause as competing event. Test of interaction between type of surgical resection and type of nodal staging was carried out and results presented in a stratified way. Missing data were multiple-imputed, combined estimates were obtained from 5 imputed datasets. **Result:**

Multivariable-adjusted Fine and Grey model for Comulative Incidence of Recurrence (take into account age, gender, smoking habit, side of intervention, pTNM stage, vascular invasion, pTNM stage, predominant histologic pattern and histologic grade)(Results of test of interaction presented in a stratified way)

Sub-lobar resection vs. Lobectomy	**HR (95%CI)**	**P**	**INTERACTION P-value**
Overall	1.52 (1.07 to 2.17)	0.02	0.268
SND	1.98 (1.14 to 3.42)		
LS-ND	1.87 (0.94 to 3.74)		
NS	1.08 (0.61 to 1.93)		
LS-ND vs SND	**HR (95%CI)**	**P**	**INTERACTION P-value**
Overall	1.74 (1.16 to 2.6)	0.007	0.903
Lobectomy	1.66 (1.03 to 2.69)		
Sub-lobar resection	1.58 (0.75 to 3.32)		
NS vs. SND	**HR (95%CI)**	**P**	**INTERACTION P-value**
Overall	1.49 (1.12 to 1.98)	0.007	0.131
Lobectomy	1.61 (1.18 to 2.19)		
Sub-lobar resection	0.88 (0.43 to 1.82)		

Median follow-up was 63 months. Eight-hundred forty-six (87%) patients were submitted to lobectomy, while 123(13%) to sub-lobar resection. Four-hundred fifty-five (47%) patients received SND, 98(10%) LS-ND and 416(43%) NS. Two-hundred forty-seven (26%) patients developed a local/distant recurrence with a 5-year CIR of 24%. Multivariable-adjusted comparisons showed an independent negative effect of sub-lobar resection(HR 1.52;95%CI:1.07-2.17), LS-ND(HR 1.74;95%CI:1.16-2.6) and NS(HR 1.49;95%CI:1.12-1.98) on CIR(Table). Test of interaction showed an homogeneity of results among subgroups. **Conclusion:** In our series, lobectomy and systematic lymph node dissection confirmed to be the optimal strategy to achieve a favorable prognosis in stage I adenocarcinoma of the lung. The real value of sub-lobar resection and less aggressive nodal staging should be assessed by randomized clinical trial before being integrated in clinical practice.

Keywords: NSCLC, Surgery, recurrence

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OA 16.03 RECURRENCES AND 2ND PRIMARY CANCERS IN THE IFCT-0302 TRIAL ASSESSING A CT-SCAN-BASED FOLLOW-UP AFTER LUNG CANCER SURGERY

V. Westeel[1], F. Barlesi[2], P. Foucher[3], J. Lafitte[4], J. Domas[5], P. Girard[6], J. Trédaniel[7], M. Wislez[8], B. Chahine[9], J. Muir[10], S. Dehette[11], J. Virally[12], M. Grivaux[13], F. Lebargy[14], F. Al Freijat[15], N. Girard[16], E. Courau[17], R. Azarian[18], M. Farny[19], J. Duhamel[20], S. Labrune[21], F. Morin[22], P.J. Souquet[23]

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Background: The IFCT-0302 trial is the first large randomized phase III multicenter trial which compared two follow-up modalities after surgery for early stage non-small cell lung cancer (NSCLC). **Method:** After complete resection of a stage pI, II, IIIA or T4 (pulmonary nodules in the same lobe) N0-2 NSCLC (TNM 6th edition), patients were randomized (1/1) between 2 follow-up programs: - arm 1, clinical examination and Chest X-ray, - arm 2, clinical examination, Chest X-ray, thoraco-abdominal CT-scan plus bronchoscopy (optional for adenocarcinomas). In both arms, procedures were repeated every 6 months after randomization during the first 2 years, and yearly until 5 years. The primary endpoint was overall survival (OS). Distinction between lung recurrences and 2nd primary lung cancer was assessed by investigators, using the Martini and Melamed definition (J Thorac Cardiovasc Surg 1975). **Result:** 1775 patients were randomized (arm 1: 888; arm 2: 887). Patient characteristics were well-balanced between the two arms: males 76.3%, median age 63 years (range: 34-88), squamous and large cell carcinomas 39.5%, stage I 68.1%, stage II 13.7%, stage III 18.3%, lobectomy or bilobectomy 86,6%. OS and DFS were not significantly different between arms (OS: HR=0.92, 95% CI: 0.8-1.07; p=0.27). Median disease-free survival was 4.95 years (95% CI: 4.4- not reached) in arm 1 and not reached in arm 2, respectively. A recurrence was diagnosed in 245 patients (27.6%) in arm 1, and in 291 patients (32.8%) in arm 2. Recurrences were symptomatic in 203 (82.9%) and 163 (56.0%) patients, respectively. The most frequent sites of recurrence were: ipsilateral lung (42.0 and 33.0%), brain (29.4 and 23.4%), and contralateral lung (24.9 and 22.3%), respectively. Treatment of recurrence achieved complete remission in 25 (10.2%) and 52 (17.9%) patients (p=0.01), respectively. Second primary cancers (SPC) were diagnosed in 101 patients (11.4%) in arm 1, and 97 patients (10.9%) in arm 2, with symptoms at diagnosis in 64 (63.4%) and 37 (38.1%) patients, respectively. The most frequent sites of SPC were: lung (25.7 and 41.2%), prostate (14.8 and 11.3%), and ENT (11.9 and 7.2%), respectively. Treatment of SPC achieved complete remission in 30 (29.7%) and 40 (41.2%) patients (p=0.10), respectively. **Conclusion:** Although OS and DFS were not significantly increased by thoraco-abdominal CT-scan-based follow-up, recurrences or SPCs were more frequently asymptomatic and amenable to curative treatment in patients followed by thoraco-abdominal CT scan compared to those followed by chest X-ray only.

Keywords: non-small cell lung cancer (NSCLC), follow-up, early stage

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OA 16.04 EFFICACY AND SAFETY OF ERLOTINIB VS VINORELBINE/CISPLATIN AS ADJUVANT THERAPY FOR STAGE IIIA EGFR MUTANT NSCLC PATIENTS

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Background: Adjuvant chemotherapy remains the most important treatment for stage IIIA non-small cell lung cancer (NSCLC) after radical operation, but its benefits has reached plateau and high risk of recurrence. Previous studies SELECT and RADIANT have suggested a trend of improving DFS of erlotinib as adjuvant therapy for patients with activating mutations. This study is designed as prospective, open-label, randomized, multicenter phase II trial to investigate the efficacy and safety of erlotinib (E) as adjuvant therapy in comparison with vinorelbine/cisplatin (NP) chemotherapy in completely resected stage IIIA EGFR mutant patients. **Method:** Patients aged between 18 – 75 with ECOG PS 0–1, stage IIIA, *EGFR*-activating mutation (exon 19 or exon 21 L858R), reached R0 resection NSCLC were eligible. And patients were randomized(1:1) into either erlotinib (orally 150mg/day for 2 years, util relapse or unacceptable toxicity) or NP (vinorelbine 25mg/m^2 i.v. day 1, 8 and cisplatin 75mg/m^2 i.v. day 1, every 3 weeks for 4 cycles) group. Random assignment was stratified by *EGFR* mutation type (exon 19 vs exon 21), histology (adenocarcinoma vs non-) and smoking status (smoker vs non-). The primary endpoint was 2-year disease free survival rate (DFSR), secondary endpoints include disease free survival (DFS), overall survival (OS), safety (NCI CTCAE 4.0) and quality of life (QoL), and exploratory biomarker analysis. **Result:** From Sep, 2012 to May, 2015, in total 102 patients from 16 centers across China were randomized to receive E (N=51) or NP (N=51). Median follow-up time was 33 months for E and 28 months for NP. Baseline characteristics of age, sex, PS, histology, smoking status, EGFR mutation subtypes were well balanced in each arm. Two-year DFSR was 81.35% (95%CI: 69.63-93.08) in E arm and 44.62% (95%CI: 26.86-62.38) in NP arm respectively (P<0.001) in ITT population. DFS was significantly prolonged with E vs NP (median, 42.41 vs 20.96 months, HR 0.271, 95% CI: 0.137-0.535; P<0.001). OS data from our trial are still immature. In current, the number of death events were 2 (E) and 13 (NP) arm. Safety profile was similar to previous studies of each agent in NSCLC, no new unexpected AE were observed in each arms. **Conclusion:** As compared with NP, E showed superior efficacy and should be considered therapeutic option for patients with R0 resected stage IIIA NSCLC with EGFR-activating mutation. (EVAN, NCT01683175).

Keywords: Adjuvant therapy, Erlotinib, EGFR mutation

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OA 16.06 MEDIASTINAL STAGING BY VIDEOMEDIASTINOSCOPY IN CLINICAL N1 NON-SMALL CELL LUNG CANCER: A PROSPECTIVE MULTICENTRE STUDY

H. Decaluwe[1], C. Dooms[2], X. D'Journo[3], S. Call[4], D. Sanchez-Lorente[5], B. Haager[6], R. Beelen[7], V. Kara[8], T. Klikovits[9], C. Aigner[10], K. Tournoy[7], J. Moons[11], G. Brioude[3], J.C. Trujillo[4], B. Bethe[6], W. Klepetko[9], A. Turna[12], B. Passlick[13], L. Molins[5], R. Rami-Porta[14], P. Thomas[3], P. De Leyn[15]

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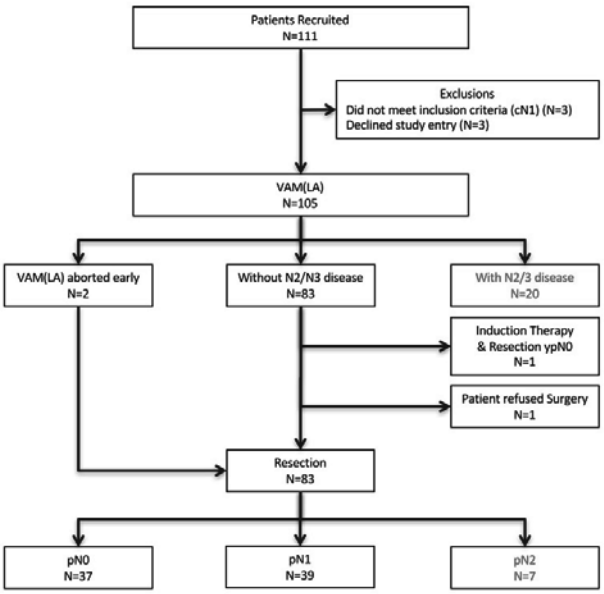
Background: A fourth of patients with cN1-NSCLC based on PET-CT imaging are at risk for occult mediastinal nodal involvement. In a previous prospective study, endosonography alone had an unsatisfactory sensitivity (38%) to detect mediastinal nodal disease. This prospective multicenter trial investigated the sensitivity of preoperative mediastinal staging by video-assisted mediastinoscopy (VAM) in patients with cN1 (suspected) NSCLC. **Method:** Consecutive patients with operable and resectable cN1 (suspected) non-small cell lung cancer (NSCLC) underwent a VAM or VAM-lymphadenectomy (VAMLA). All patients underwent FDG–PET and CT-scan. The primary study outcome was sensitivity to detect N2-disease. Secondary endpoints were the prevalence of N2-disease, negative predictive value (NPV) and accuracy of VAM(LA). **Result:** *(See next page.)*



Out of 105 patients with cN1 on imaging, 26% eventually had N2-disease. Invasive mediastinal staging with VAM(LA) reached sensitivity of 73% to detect N2-disease. The median number of assessed lymph node stations during VAM(LA) was 4. In 96% ≥3 stations were assessed. VAMLA was performed in 31%, 69% underwent VAM.

		N	Prevalence of mediastinal disease	Sensitivity OR(95%CI)	Negative Predictive Value OR(95%CI)	Negative Posttest probability OR(95%CI)
Dooms et al. Chest. 2014; 147(1): 209–15.	Endosonography alone	100	24%	0.38 (0.18-0.57)	0.81 (0.71-0.91)	0.19 (0.13-0.27)
	Endosonograpy, if negative followed by mediastionoscopy			0.73 (0.55-0.91)	0.91 (0.83-0.98)	0.09 (0.04-0.17)
Current Study	Mediastinoscopy	105	26%	0.73 (0.54-0.86)	0.92 (0.83-0.97)	0.08 (0.03-0.17)

Conclusion: VAM(LA) has a satisfactory sensitivity of 73% to detect mediastinal nodal disease in cN1-NSCLC and could be the technique of choice for pre-resection mediastinal lymph node assessment in this patient group with 26% chance of occult positive mediastinal nodes after negative PET-CT. (ClinicalTrials.gov NCT02222194)

Keywords: cN1, NSCLC, Mediastinoscopy

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OA 16.07 RADIOLOGICAL FEATURE ON TSCT FOR PREDICTING A PATHOLOGICAL LESS-INVASIVE LUNG CANCER ACCORDING TO THE 8TH TNM CLASSIFICATION

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Background: The limited resection for lung cancer has become more prevalent for patients who show a compromised pulmonary or cardiac function. As of now standard care of lung cancer is lobectomy with lymph node dissection or sampling even for early lung cancer. Japan clinical oncology group (JCOG) study 0201 has proposed the criteria to diagnose pathological less-invasive lung adenocarcinoma by using consolidation to tumor ratio (CTR) on preoperative thin-sliced computed tomography (TSCT) scan. Three clinical trials have been ongoing based on this result, but the TNM classification was drastically revised in 2016, especially in T category. The aim of this study is to propose the new radiological criteria to predict pathological less-invasive lung cancer before surgery in accordance with the new TNM classification. **Method:** We analyzed the 744 patients who have peripheral Tis-T1cN0M0 non-small cell lung cancer with 3cm or less in size and underwent complete resection by lobectomy from 2003 to 2011. We defined a lung cancer with no nodal involvement and no vessel invasion pathologically as a pathological less-invasive cancer, and investigated the radiological criteria corresponding to the new T category by using TSCT to predict a pathological less-invasive cancer with the specificity of 97% or more. We also re-evaluated the criteria by adding the parameter of CTR and presence of ground-glass opacity (GGO), and prognostic parameters; overall survival (OS) and relapse-free survival (RFS). **Result:** The cTis/T1ami/T1a patients showed no pathological invasive cancer except for only 1 patient (specificity: 99%). In the cT1b/T1c patients, the specificity of cT1b with CTR 0.5 or less, cT1b with C/T ratio 0.75 or less, and cT1b with GGO presence were 100%, 97.1%, 94.4%, respectively. The new criteria of cT1a or less and cT1b with CTR 0.75 or less showed excellent prognosis for OS and RFS. **Conclusion:** As most of the patients with cTis/T1ami/T1a and cT1b with CTR 0.75 or less showed pathological less-invasive cancers and extremely good survival, they will be more likely to be obtained good outcomes by sublobar resection including wide-wedge resection as well. The further prospective study will be required to confirm the hypothesis.

Keywords: early stage NSCLC, limited resection, Thin section computed tomography

OA 16 TREATMENT STRATEGIES AND FOLLOW UP
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

OA 16.08 A MODIFIED PATHOLOGICAL N1 CLASSIFICATION STRATEGY BASED ON SYSTEMATIC DISSECTION OF N1 NODES FROM LEVEL 10 TO 14 FOR NON-SMALL CELL LUNG CANCER

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Background: It is necessary to apply a precise standard to predict the oncological outcomes among heterogeneous subgroups of N1 disease ranging from level 10 to 14. Although International Association for the Study of Lung Cancer (IASLC) proposed a new N descriptor in the 8th edition of the TNM Classification, lack of dissection on level 13 and level 14 may affect the efficacy of new classification. In this study, we tested a hypothesized classification strategy based on systematic dissection of N1 node from level 10 to level 14. **Method:** From March 2007 to December 2014, 156 consecutive patients of non-small cell lung cancer, treating with lobectomy and systematic mediastinal lymphadenectomy, were investigated. Nodes from level 10 to 12 were dissected during operation. Intrapulmonary lymph nodes (level 13-14) were retrieved after surgery. The data were prospectively collected and retrospectively analyzed. All cases were divided into two categories according to the 8th edition of the TNM Classification: pN1a was defined as N1 at a single station, while pN1b was defined as N1 at multiple stations. Then, in our proposed classification, N1a (modified) was defined as single level of N1 station involved (not including single level 10 or 11 spread) or level 13 and/or 14 involved, while N1b (modified) was defined as single level 10 or 11 spread or multiple levels of N1 node involvement (not including level 13 and 14 spread). The association between the N1 subgroup status and survival was explored separately using 8th IASLC classification and hypothesized classification. **Result:** In the whole cohort, a mean±SD of 13.1±7.1 N2 nodes and 12.0+5.2 N1 nodes per case were collected.There were 4.7±3.1 nodes from level 13 and 14. The difference in 5-year overall survival between pN1a and pN1b was not significant (73.9% versus 65.7%, p=0.371). However, the difference in 5-year overall survival between N1a (modified) and N1b (modified) was significant (79.1% versus 60.2%, p=0.018). Multivariate analysis showed the revised N1 classification was an independent prognostic factor for NSCLC (versus N1a, the hazard ratio [HR] of N1b for OS was 2.120, 95% confidence interval [CI]: 1.083-4.151, p=0.028). However, the 8th edition IASLC N1 descriptors was not an independent prognostic factor (versus pN1a, HR of pN1b was 1.419, 95% CI: 0.710-2.837, p=0.322). **Conclusion:** The hypothesized N1 classification in present study was shown to be a better descriptor to express the outcome than 8th edition of the TNM Classification of IASLC. More data are needed to validate this proposal.

Keywords: pathological N1 non-small cell lung cancer, hypothesized classification in N1 disease, TNM classification

OA 17 IMMUNOTHERAPY II
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OA 17.01 PEMETREXED-CARBOPLATIN PLUS PEMBROLIZUMAB AS FIRST-LINE THERAPY FOR ADVANCED NONSQUAMOUS NSCLC: KEYNOTE-021 COHORT G UPDATE

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Background: Cohort G of the multicenter, open-label, phase 1/2 KEYNOTE-021 study (ClinicalTrials.gov, NCT02039674) evaluated efficacy and safety of pembrolizumab + pemetrexed and carboplatin (PC) compared with PC alone as first-line therapy for

patients with advanced nonsquamous NSCLC. At the primary analysis of cohort G (minimum follow up, 6 months; median, 10.6 months), pembrolizumab significantly improved ORR (estimated treatment difference, 26%; *P*=0.0016) and PFS (hazard ratio [HR], 0.53; *P*=0.010). The HR for OS was 0.90 (95% CI, 0.42-1.91). In a subsequent analysis (median follow-up, 14.5 months), the HR for OS was 0.69 (95% CI, 0.36-1.31). We present results from the May 31, 2017 data cutoff. **Method:** Patients with stage IIIB/IV nonsquamous NSCLC, no prior systemic therapy, and no *EGFR* mutation or *ALK* translocation were randomized 1:1 (stratified by PD-L1 TPS ≥1% versus <1%) to receive 4 cycles of carboplatin AUC 5 + pemetrexed 500 mg/m^2 Q3W with or without pembrolizumab 200 mg Q3W. Pembrolizumab treatment continued for up to 2 years; maintenance pemetrexed was permitted in both arms. Eligible patients in the PC arm with radiologic progression could cross over to pembrolizumab monotherapy. Response was assessed by blinded, independent central review per RECIST v1.1. All *P* values are nominal (one-sided *P*<0.025). **Result:** 123 patients were randomized. Median follow-up was 18.7 months (range, 0.8-29.0 months). 40 of 53 (75%) patients in the PC arm who discontinued received subsequent anti-PD-1/anti-PD-L1 therapy (including 25 who received pembrolizumab in the on-study cross over). ORR was 57% with pembrolizumab + PC versus 32% with PC (estimated difference, 25%; 95% CI, 7%-41%; *P*=0.0029). PFS was significantly improved with pembrolizumab + PC versus PC (HR, 0.54; 95% CI, 0.33-0.88; *P*=0.0067) with median (95% CI) PFS of 19.0 (8.5-NR) months versus 8.9 (6.2-11.8) months. The HR for OS was 0.59 (95% CI, 0.34-1.05; *P*=0.0344). Median (95% CI) OS was not reached (22.8-NR) months for pembrolizumab + PC and 20.9 (14.9-NR) months for PC alone; 18-month OS rates were 70% and 56%, respectively. Grade 3–5 treatment-related AEs occurred in 41% of patients in the pembrolizumab + PC arm versus 29% in the PC arm. **Conclusion:** Over the course of the 3 analyses, the HR for OS continues to improve for pembrolizumab + PC versus PC (HR: 0.90 to 0.69 to 0.59). The significant improvements in PFS and ORR with pembrolizumab + PC versus PC first observed in the primary analysis have been maintained with longer follow-up (median, 18.7 months).

Keywords: pembrolizumab, chemotherapy, NSCLC

OA 17 IMMUNOTHERAPY II
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OA 17.02 UPDATED EFFICACY RESULTS FROM THE BIRCH STUDY: FIRST-LINE ATEZOLIZUMAB THERAPY IN PD-L1–SELECTED PATIENTS WITH ADVANCED NSCLC

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Background: The anti–PD-L1 mAb atezolizumab blocks the interactions between PD-L1 and its receptors, PD-1 and B7.1, thus restoring anti-tumor immunity. A Phase II study of atezolizumab monotherapy was conducted across multiple lines of therapy in PD-L1–selected patients with advanced NSCLC (BIRCH; NCT02031458). The primary analyses showed meaningful and durable clinical benefit with atezolizumab monotherapy in 1L and 2L+ NSCLC. Here we present updated survival data (median follow-up, 29.7 months) in patients receiving 1L atezolizumab. **Method:** Eligible patients had chemotherapy-naive, locally advanced or metastatic NSCLC without CNS metastases. Prior TKI therapy was required in patients with *EGFR* mutation or *ALK* rearrangement. PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC) was centrally evaluated (VENTANA SP142 IHC assay). Patients who were TC2/3 or IC2/3 (PD-L1 expression on ≥ 5% of TC or IC) were enrolled. Atezolizumab 1200 mg was administered IV q3w until disease progression or unacceptable toxicity. The primary endpoint was independent review facility (IRF)–assessed ORR. Secondary endpoints included investigator (INV)-assessed ORR, DOR, PFS (RECIST v1.1) and OS. **Result:** With a median follow-up of 29.7 months, median OS was 26.9 months (TC3 or IC3 subgroup) and 24.0 months (all treated patients); INV-assessed ORR was 35% (TC3 or IC3 subgroup) and 26% (all treated patients; Table). Among evaluable patients, the ORR was 31% for mutant *EGFR* (4/13) vs 23% for wild-type *EGFR* patients (24/103), and 31% for mutant *KRAS* (10/32) vs 24% for wild-type *KRAS* patients (16/66). No new safety signals were observed. **Conclusion:** With more than 2 years of follow-up, atezolizumab continued to demonstrate durable clinical activity in 1L NSCLC, regardless of *EGFR* and *KRAS* mutational status. These data suggest that atezolizumab monotherapy has promising activity as a frontline therapy. Ongoing Phase III trials are evaluating atezolizumab-based regimens vs chemotherapy in 1L NSCLC.

Endpoint (95% CI)	TC3 or IC3[a] **(n = 65)**	TC2 or IC2b **(n = 73)**	**All Treated Patients (N = 138)**
INV-assessed ORR, %	35% (23.9, 48.2)	18% (9.8, 28.5)	26% (19.0, 34.2)
EGFR mutant/wild-type, %	25%/33%	33%/15%	31%/23%
KRAS mutant/wild-type, %	38%/33%	25%/15%	31%/24%
mDOR, mo	16.5 (8.5, NE)	12.5 (8.3, 17.9)	13.1 (9.9, NE)
mOS, mo	26.9 (12.0. NE)	23.5 (18.1, NE)	24.0 (18.1, 31.9)
12-mo OS rate, %	61% (49.0, 74.0)	71% (59.8, 81.5)	66% (58.1, 74.6)
24-mo OS rate, %	52% (39.3, 65.2)	49% (37.0, 61.1)	50% (41.5, 59.2)
30-mo OS rate, %	48% (35.3, 61.5)	39% (27.2, 51.2)	43% (34.3, 52.1)
mPFS, mo	7.3 (4.9, 12.0)	7.6 (4.0, 9.7)	7.6 (5.7, 9.7)
12-mo PFS rate, %	38% (25.1, 49.9)	30% (19.2, 41.2)	34% (25.3, 41.9)
24-mo PFS rate, %	28% (16.5, 40.0)	13% (4.5, 21.5)	20% (12.9, 27.5)
30-mo PFS rate, %	19% (5.4, 33.5)	9% (1.4, 16.4)	14% (6.5, 21.9)
NE, not estimable. [a]TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells. [b]TC2/3 or IC2/3 excluding TC3 or IC3.			

Keywords: Immunotherapy, advanced NSCLC, atezolizumab

OA 17 IMMUNOTHERAPY II
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OA 17.03 FIRST-LINE NIVOLUMAB PLUS PLATINUM-BASED DOUBLET CHEMOTHERAPY FOR ADVANCED NSCLC: CHECKMATE 012 3-YEAR UPDATE

R. Juergens[1], M. Hellmann[2], J. Brahmer[3], H. Borghaei[4], S. Gettinger[5], L. Chow[6], D. Gerber[7], S. Laurie[8], J. Goldman[9], F. Shepherd[10], W. Geese[11], T. Young[11], X. Li[11], S. Antonia[12]

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Background: Platinum-based doublet chemotherapy is the standard-of-care first-line treatment for most patients with advanced NSCLC, but responses are not durable (~4.5–6 mo). Chemotherapy may sensitize NSCLC tumors to immune checkpoint inhibitors. Nivolumab, a fully human programmed death (PD)-1 antibody, demonstrated long-term survival benefit in patients with previously treated advanced NSCLC. Here we report the 3-year update of safety and efficacy of first-line nivolumab combined with chemotherapy in the phase 1 CheckMate 012 study (NCT01454102). **Method:** Chemotherapy-naïve patients with stage IIIB/IV NSCLC were randomly assigned based on histology in 3 cohorts combining nivolumab Q3W with 3 platinum-based doublet chemotherapy regimens: nivolumab 10 mg/kg + gemcitabine-cisplatin (all squamous histology), nivolumab 10 mg/kg + pemetrexed-cisplatin (all non-squamous), and nivolumab 10 mg/kg or 5 mg/kg + paclitaxel-carboplatin (any histology). After 4 cycles of nivolumab plus chemotherapy, patients received nivolumab monotherapy until progression or unacceptable toxicity. The primary objective was safety. ORR, PFS, and OS were secondary/exploratory endpoints. **Result:** 56 patients were treated.

Median age was 63.5 years, 46% were male, and 14% were never-smokers; 29% of tumors had squamous histology. At database lock (September 19, 2016) the minimum follow-up was 45.5 mo. Median duration of chemotherapy treatment was ~12 weeks (4 cycles; range: 3–18 weeks) and median duration of nivolumab treatment was 17–22 weeks across cohorts (range: 3–204). No new safety signals were observed in patients receiving nivolumab maintenance compared with the September 2014 database lock. ORR was 46%. Median duration of response was 10.4 mo (95% CI: 5.1, 26.3). Median PFS was 6.0 mo (95% CI: 4.8, 8.3). Median OS was 19.2 mo (95% CI: 14.1, 23.8), and the 3-year OS rate was 25%. ORR and OS were similar in patients with tumor PD-L1 expression <1% (n=23) vs ≥1% (n=23): ORR 48% vs 52%; median OS 19.2 mo (95% CI: 12.2, 23.8) vs 20.2 mo (95% CI: 10.9, 27.2). The 3-year OS rate was 22% in both PD-L1 expression subgroups. **Conclusion:** Nivolumab plus chemotherapy resulted in prolonged survival in a subset of patients, with a 3-year OS rate of 25%. In all patients, ORR and OS were similar irrespective of tumor PD-L1 expression. These results support further evaluation of nivolumab-chemotherapy combinations as first-line treatment for advanced NSCLC, which are being explored in CheckMate 227 (NCT02477826).

Keywords: Long-term, NSCLC, PD-L1

OA 17 IMMUNOTHERAPY II
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OA 17.05 IFCT-1502 CLINIVO: REAL-LIFE EXPERIENCE WITH NIVOLUMAB IN 600 PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

O. Molinier[1], C. Audigier-Valette[2], J. Cadranel[3], I. Monnet[4], J. Hureaux[5], W. Hilgers[6], E. Fauchon[7], E. Fabre[8], B. Besse[9], P. Brun[10], D. Coëtmeur[11], E. Quoix[12], P. Mourlanette[13], F. Barlesi[14], S. Bordenave-Caffre[15], T. Egenod[16], P. Missy[17], F. Morin[18], D. Moro-Sibilot[19], N. Girard[20]

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Background: Nivolumab is a standard option for second-line treatment in pts with advanced NSCLC. Real-life data are lacking regarding the efficacy of nivolumab and post-nivolumab treatment. **Method:** This analysis included the first 600 consecutive pts with stage IIIB/IV NSCLC who received ≥1 dose of nivolumab 3mg/kg q2w through the French EAP from 01/2015 for Squamous (Sq) and 06/2015 for Non-Sq NSCLC, until 08/2015. **Result:** Median age was 64 yo, there were 409 (68%) men, 521 (87%) smokers, 478 (80%) PS0/1 pts, 230 (38%) Sq and 370 (62%) Non-Sq NSCLC, 130 (22%) pts with brain metastases. Nivolumab was administered as 2nd/3rd/≥4th-line for 26%/33%/41% pts, respectively. Best response was PR/SD/PD for 17%/30%/37% of patients, respectively, with 16% not assessable. Toxicities occurred in 187 (31%) pts, including 10% grade ≥3 events. After a median follow-up of 22.1 (95% CI 21.6-22.6) months, median PFS and OS from the initiation of nivolumab were 2.1 (95%CI 1.9-2.3) and 9.5 (95%CI 8.4-10.8) months, respectively. In the 92 pts with PS2 at initiation of nivolumab, PR/SD rates were 7%/28%; median OS was 3.6 (95%CI 2.7-5.2) months. A total of 130 pts had brain metastases at initiation of nivolumab: PR/SD rates were 12%/25%; median OS was 6.6 (95%CI 3.8-8.3) months. Post-nivolumab treatment was administered to 262 (44%) pts, and mostly consisted of gemcitabine (19%), docetaxel (18%), paclitaxel (14%), erlotinib (12%), vinorelbine (9%), platin-based doublet (8%), or pemetrexed (8%). Access to post-nivolumab treatment was higher in PS0/1 vs. PS2 pts (48% vs. 23%, p<0.001), but was not different according to histology or treatment line or disease control with nivolumab. Best response to post-nivolumab treatment was PR/SD/PD for 15%/42%/42% of pts, respectively. In the whole cohort, median post-nivolumab OS was 4.0 (95%CI 2.8-4.6) months, and was significantly higher in case of PR to nivolumab (HR=0.38; 95%CI 0.23-0.64; p<0.001), and if subsequent treatment was delivered (HR=0.30; 95%CI 0.24-0.38; p<0.001); median post-nivolumab OS in pts receiving post-nivolumab treatment was 7.5 (95%CI 6.8-8.7) months, and did not differ based on histology or treatment line. **Conclusion:** Efficacy and safety of nivolumab was in line with available data. Post-nivolumab treatment may be delivered in many pts, including pts with PS2 and brain metastases, with favorable impact on response and OS. Data on the whole cohort of 900 pts enrolled in the EAP will be presented.

Keywords: chemotherapy, non-small cell lung cancer, Nivolumab

OA 17 IMMUNOTHERAPY II
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OA 17.06 UPDATED ANALYSIS OF KEYNOTE-024: PEMBROLIZUMAB VS PLATINUM-BASED CHEMOTHERAPY FOR ADVANCED NSCLC WITH PD-L1 TPS ≥50%

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Background: KEYNOTE-024 (ClinicalTrials.gov, NCT02142738) is a multicenter, international, phase 3, randomized, open-label, controlled trial of treatment with the anti-PD-1 antibody pembrolizumab vs platinum-based chemotherapy as first-line therapy for patients with advanced NSCLC of any histology with PD-L1 tumor proportion score (TPS) ≥50% and without *EGFR* mutations or *ALK* translocations. Results from the primary analysis of KEYNOTE-024 demonstrated that after a median follow-up of 11.2 months, pembrolizumab significantly improved PFS (HR=0.50; $P<0.001$) and OS (HR=0.60; $P=0.005$) and was associated with a lower rate of treatment-related AEs compared with chemotherapy. **Method:** Patients were randomly assigned to receive either 35 cycles of pembrolizumab 200 mg every 3 weeks or 4–6 cycles of investigator's choice of carboplatin/cisplatin + gemcitabine, carboplatin + paclitaxel, or carboplatin/cisplatin + pemetrexed with optional pemetrexed maintenance (for those with non-squamous histology). Randomization was stratified by ECOG performance status (0 vs 1), histology (squamous vs nonsquamous), and geographic region (East Asia vs non–East Asia). Treatment continued until disease progression per RECIST version 1.1, intolerable toxicity, or withdrawal of consent. Patients in the chemotherapy arm who experienced disease progression could cross over to receive pembrolizumab monotherapy. Response was assessed every 9 weeks by blinded independent central review per RECIST version 1.1. The primary endpoint was PFS; secondary endpoints were OS, ORR, and safety. **Result:** 305 patients were enrolled (pembrolizumab, n=154; chemotherapy, n=151). At the time of data cutoff (July 10, 2017) after a median follow-up of 25.2 months, 73 patients (47.4%) in the pembrolizumab arm and 96 patients (63.6%) in the chemotherapy arm had died. The hazard ratio for OS was 0.63 (95% CI, 0.47–0.86; nominal $P=0.002$). Median (95% CI) OS was 30.0 (18.3–not reached) months in the pembrolizumab arm and 14.2 (9.8–19.0) months in the chemotherapy arm. The Kaplan-Meier estimate of OS at 12 months was 70.3% (95% CI, 62.3%–76.9%) for the pembrolizumab group and 54.8% (95% CI, 46.4%–62.4%) for the chemotherapy group. 82 patients allocated to the chemotherapy arm crossed over to receive pembrolizumab upon meeting eligibility criteria. Treatment-related adverse events were less frequent in the pembrolizumab arm than in the chemotherapy arm (76.6% versus 90.0%, respectively) as were treatment-related grade 3-5 adverse events (31.2% versus 53.3%). **Conclusion:** With more than half of patients having OS events and prolonged follow-up, first-line pembrolizumab monotherapy remains superior to platinum-based chemotherapy despite the crossover from the control arm to an anti-PD1 inhibitor as subsequent therapy.

Keywords: KEYNOTE-024, Non-small-cell lung cancer, pembrolizumab

OA 17 IMMUNOTHERAPY II
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OA 17.07 LONG-TERM SURVIVAL IN ATEZOLIZUMAB-TREATED PATIENTS WITH 2L+NSCLC FROM PH III RANDOMIZED OAK STUDY

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Background: Atezolizumab (anti–PD-L1) inhibits PD-L1 binding to PD-1 and B7.1, restoring anti-cancer immunity. OAK, a Phase III study of atezolizumab vs docetaxel demonstrated superior OS of atezolizumab. The characteristics of the long-term survivors (LTS) in the OAK primary population (n = 850) are evaluated and describe the largest cohort of cancer immunotherapy-treated NSCLC LTS yet reported. **Method:** Patients received IV q3w atezolizumab (1200 mg) until PD / loss of clinical benefit or docetaxel (75 mg/m^2) until PD / unacceptable toxicity. No crossover was allowed. LTS were defined as patients with OS ≥ 24 months and non-LTS as those who died within 24 months of randomization. Patients with OS censored prior to 24 months were not included. Data cutoff, January 23, 2017. **Result:** A higher 2-year survival rate was observed for the atezolizumab-arm (31%) vs docetaxel-arm (21%). After a minimum follow-up of 26 months, there were

119 LTS vs 279 non-LTS in the atezolizumab-arm and 77 LTS vs 299 non-LTS in the docetaxel-arm. Characteristics of atezolizumab-arm LTS and non-LTS are shown (Table). Atezolizumab-arm LTS were enriched for non-squamous histology and high PD-L1–expressing tumors, but also included low/no PD-L1–expressing tumors (40.3%). Atezolizumab-arm LTS had higher ORR (39.5%) than non-LTS (5.0%) but included LTS subjects with PD. 52.9% atezolizumab-arm vs 71.4% docetaxel-arm LTS received anti-cancer non-protocol therapy (NPT) after discontinuation of protocol-defined therapy. 51.9% of docetaxel-arm LTS vs 12.7% non-LTS received non-protocol immunotherapy. Median treatment exposure in atezolizumab-arm LTS was 18.0 months. Atezolizumab-arm LTS had a comparable safety profile to all atezolizumab-treated population. **Conclusion:** Atezolizumab provides superior 2-year OS benefit vs docetaxel and is well tolerated. The majority of docetaxel-arm LTS received a checkpoint inhibitor as NPT. Atezolizumab LTS appeared to have favorable prognostic factors, including non-squamous histology, but notably were not limited to patients with RECIST v1.1 response or with PD-L1 expression.

Table. Characteristics of Atezolizumab-Arm Long-Term Survivors (LTS) vs Non-Long Term Survivors (Non-LTS)

	Atezolizumab LTS (n = 119) n (%)	**Atezolizumab Non-LTS (n = 279) n (%)**
Sex		
Male	61 (51.3)	183 (65.6)
Female	58 (48.7)	96 (34.4)
Tobacco use history		
Never smoker	29 (24.4)	47 (16.8)
Current/previous smoker	90 (75.6)	232 (83.2)
Histology		
Non-squamous	101 (84.9)	195 (69.9)
Squamous	18 (15.1)	84 (30.1)
No. of prior therapies, 1	89 (74.8)	209 (74.9)
ECOG performance status at baseline		
0	60 (50.4)	89 (31.9)
1	59 (49.6)	190 (68.1)
EGFR mutation status, positive	11 (9.2)	26 (9.3)
PD-L1 IHC subgroup		
TC3 or IC3	28 (23.5)	39 (14.0)
TC1/2/3 or IC1/2/3	71 (59.7)	156 (55.9)
TC0 and IC0	48 (40.3)	119 (42.7)
Best overall response		
Complete response	5 (4.2)	0 (0)
Partial response	42 (35.3)	14 (5.0)
Stable disease	47 (39.5)	97 (34.8)
Progressive disease	25 (21.0)	142 (50.9)

IC, tumor-infiltrating immune cell; TC, tumor cell. TC3 or IC3 = PD-L1 ≥ 50% TC or 10% IC; TC1/2/3 or IC1/2/3 = PD-L1 ≥ 1% on TC or IC; TC0 and IC0 = PD-L1 < 1% on TC and IC. NCT02008227.

Keywords: atezolizumab, advanced NSCLC, cancer immunotherapy

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OA 17.08 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 additional benefit after LAT. We are running a Phase II study to evaluate the efficacy of pembrolizumab after LAT, hypothesizing that immunotherapy will be effective in the setting of a minimal disease burden. **Method:** Eligibility stipulates oligometastatic NSCLC (up to 4 sites) with completion of LAT to all known sites of disease. Within 4-12 weeks of completing LAT, pts begin pembrolizumab 200 mg every 21 days for 6 mos, with a provision to continue for a full year in the absence of progression or toxicity. Progression free survival (PFS) and overall survival (OS) are measured from the start of LAT. A sample size of 42 pts provides 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, 39 pts have been enrolled. The median age is 64 years; 54% are male; 90% Caucasian. Current and former smokers comprise 90% of the cohort, with a median of 32 pack yrs. Most common metastatic sites are lung (15 pts), brain (13), and bone (8). LAT has included surgery (24 pts), SRT (23), and concurrent chemoradiotherapy (17). Attributable adverse events (AEs) have been mostly mild and self-limited. There has been one episode of Grade 3 pneumonitis and one episode of Grade 3 adrenal insufficiency. Median follow-up from start of LAT is 16 mos. To date, 11 pts have had progression or death. The median PFS has not yet been reached. The PFS rates (±SE) at 6, 12 and 18 mos are 92%±5%, 64%±9% and 64%±9%, with 16 and 5 pts at risk beyond 12 and 24 mos, respectively. To date, 8 pts (21%) have died. The median OS has not yet been reached. The OS rates (±SE) at 6, 12 and 18 mos are 100%, 90%±6% and 75%±9%, with 22 and 5 pts at risk beyond 12 and 24 mos, respectively. **Conclusion:** Use of pembrolizumab after LAT for oligometastatic NSCLC is feasible and well tolerated. In a preliminary analysis, PFS appears favorable. Continued follow-up is necessary to confirm these findings. It is expected that accrual will be complete as of September 2017. Updated survival estimates will be presented.

Keywords: Oligometastatic, locally ablative therapy, pembrolizumab

OA 18 LUNG CANCER PATHOLOGY AND GENETICS
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OA 18.01 PAIRED TUMOR-NORMAL NEXT-GENERATION SEQUENCING (NGS) TO IDENTIFY PATHOGENIC / LIKELY PATHOGENIC GERMLINE MUTATIONS IN LUNG CANCER PATIENTS

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Background: Comprehensive NGS panel based genetic testing is becoming more common to help clinicians select appropriate therapies. It has been recommended that matched tumor-normal sequencing analyses are essential for precise identification and interpretation of genetic somatic mutations. Though it has been reported germline *EGFR* T790M mutations result in a unique hereditary lung cancer syndrome, little is known about germline mutation of other common hereditary cancer syndrome genes in lung cancer patients. **Method:** We reviewed the germline variants of 1000 consecutive lung cancer patients who had paired tumor-normal NGS panel sequencing in our institute between 2016 and 2017. Hybridization capture-based NGS panel sequencing enables simultaneously assess single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations at least 59 genes (range 59 – 1021 genes). Germline variants were interpreted following ACMG guidelines, and the variants were classified into pathogenic, likely pathogenic, variant of unknown significance, likely benign, and benign 5 classes. **Result:** Twenty-seven cases were identified to carry germline pathogenic or likely pathogenic mutations in 12 gene (2.7%): 5 with *ATM* ; 4 with *BRCA1, BRCA2* or *MSH2* respectively; 2 with *CHEK2* or *PMS2* respectively; 1 in *ATR, CDKN2A, FANCC, MSH3, PTCH2* or *RET* respectively (details in table). Mean age at diagnosis was 58 (30 – 84 years) for the patients with germline mutations and 61 (29-93 years) for those without. Interestingly, none of the patients had been diagnosed with other tumors. The incidence of actionable somatic mutations of the 27 patients was similar to others: 10 patients with *EGFR* mutation, 3 patients with *KRAS* mutation, 1 patient with *KIF5B-RET* fusion, *MET* copy number gain or *BRCA1* mutation respectively.

No.	**Gene**	**cHGVS**	**pHGVS**	**Mutation type**
1	ATM	c.1402_1403delAA	p.K468Efs*18	frameshift
2	ATM	c.1898+1G>C	.	splice
3	ATM	c.2143_2144delCT	p.L715Cfs*22	frameshift
4	ATM	c.6019dupG	p.E2007Gfs*11	frameshift
5	ATM	c.903dupT	p.A302Cfs*3	frameshift
6	ATR	c.80_81insA	p.N27Kfs*16	frameshift
7	BRCA1	c.4185+1G>A	.	splice
8	BRCA1	c.962G>A	p.W321*	nonsense
9	BRCA1	c.3340delG	p.E1114Kfs*3	frameshift
10	BRCA1	c.81-2A>G	.	splice
11	BRCA2	c.3968_3971delAATA	p.K1323Ifs*11	frameshift
12	BRCA2	c.5054C>G	p.S1685*	nonsense
13	BRCA2	c.6132_6135delCTTT	p.F2045Hfs*5	frameshift
14	BRCA2	c.6485_6486delAA	p.K2162Tfs*13	frameshift
15	CDKN2A	c.73delG	p.V25*	frameshift
16	CHEK2	c.1010delC	p.A337Efs*10	frameshift
17	CHEK2	c.1684C>T	p.R562*	nonsense
18	FANCC	c.1257_1258insC	p.T420Hfs*15	frameshift
19	MSH2	c.1165C>T	p.R389*	nonsense
20	MSH2	c.1A>T	p.0?	init-loss
21	MSH2	c.2785C>T	p.R929*	nonsense

No.	Gene	cHGVS	pHGVS	Mutation type
22	MSH2	c.340delG	p.E114Rfs*60	frameshift
23	MSH3	c.802C>T	p.R268*	nonsense
24	PMS2	c.1053delG	p.L351Ffs*5	frameshift
25	PMS2	c.943C>T	p.R315*	nonsense
26	PTCH2	c.2441_2442delCT	p.S814*	frameshift
27	RET	c.2410G>A	p.V804M	missense

Conclusion: Germline mutations in common hereditary cancer syndrome genes is not rare in lung cancer patients, and it can be identified on routine matched tumor-normal NGS sequencing. Retrospective family history analysis and genetic counseling for those patients are underway.

Keywords: lung cancer, germline mutation, next generation sequencing (NGS)

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OA 18.02 THE LANDSCAPE OF ALTERATION OF DNA INTEGRITY-RELATED GENES AND THEIR ASSOCIATION WITH TUMOR MUTATION BURDEN IN NON-SMALL CELL LUNG CANCER

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Background: A key hallmark of cancer cells is the ability to proliferate despite remarkable levels of DNA damage. Non-small cell lung cancers (NSCLC) tend to have high mutation rates, frequently related to smoking. While many genes have been functionally implicated in maintaining the integrity of the genome, for the majority of these genes there remains a lack of evidence of a direct relationship between loss-of-function and increased tumor mutation burden (TMB). Recent studies suggested an association between high TMB and cancer response to immunotherapies. The aim of this study was to comprehensively analyze the relationship between DNA integrity-related genes and TMB in NSCLC. **Method:** Whole exome DNA sequencing and copy number array data were downloaded from TCGA lung adenocarcinoma (LAC) and squamous cell carcinoma (LSCC) datasets, and mutation burdens were calculated for each of 974 tumors. We identified 150 genes across 7 pathways and 9 groups known to be involved in repairing or compensating for DNA damage. To test each gene, tumors were placed into one of three groups according to the gene's mutation status; wild-type, homozygous deleted or mutated with loss-of-function, and non-synonymous missense mutated. We then compared the average mutation burden in each of these groups. This workflow was then repeated with pathways instead of genes. **Result:** Our comprehensive analysis demonstrates a landscape of significant alterations to genes and pathways responsible for maintaining DNA integrity in NSCLC. A loss of function mutation or homozygous deletion in at least one signature gene occurred in 49% of LAC and 59% of LSCC. We searched for genes in this signature associated with significantly higher tumor mutation burdens (one sided t-test, $p < 0.05$) and found 4 in LAC (RRM1 1%, TP53 17%, FANCE 1%, and MLH1 2%) and 8 in LSCC (NEIL1 0.5%, POLE 4%, POLG 0.5%, FANCE 3%, GEN1 1%, MLH1 4%, MSH6 1%, and RPA1 2%) datasets. Of note, tumors with nonsense mutations, indels, or homozygous deletions in the FANCE or MLH1 genes have significantly higher TMB in both LAC and LSCC. We repeat this process to find pathways significantly associated with increased TMB. **Conclusion:** We present a comprehensive study of the association between genes responsible for maintaining DNA integrity and TMB in NSCLC. These findings are important to the search for potential predictive biomarkers for immunotherapy.

Keywords: Mutation burden, DNA integrity, NSCLC

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OA 18.03 GENOMIC PROFILING REVEALS HEDGEHOG PATHWAY ALTERATIONS IN VISMODEGIB SENSITIVE LUNG SQUAMOUS CELL CARCINOMA

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Background: The objective response rate of squamous cell carcinoma of the lung (SCCL) to checkpoint inhibitors, as well as the frequency of known NSCLC oncogenic drivers, is low. We performed comprehensive genomic profiling (CGP) on a large set of SCCL cases to identify new opportunities for potential benefit from targeted or immunotherapies. **Method:** Hybrid-capture based CGP of up to 315 genes was performed prospectively on DNA isolated from tissue-based FFPE samples of SCCL, and tumor mutational burden (TMB) was assessed as described previously (PMID: 28420421). **Result:** From a dataset of 958 unique SCCL cases, we identify 2.6% of cases harboring alterations in *PTCH1*, 0.3% in *SMO1*, and 01.2% in *SUFU*, which were primarily mutually exclusive Genes known to be oncogenic drivers in NSCLC were altered at the following frequencies in SCCL 8.0% *KRAS*, 6.8% *EGFR*, 3.4% *MET*, 1.9% *BRAF*, and less than 1% each for *ALK*, *ROS*, and *RET*. In *PTCH1*-mutated cases 96% did not harbor alterations in these driver genes (1/23 positive for co-occurrence). The overall SCCL population has a median TMB of 9.0, with 11.3%) cases higher than 20 mutations/Mb (m/Mb). Two index cases with *PTCH1* mutations and no alterations in established NSCLC driver genes were identified. A year 77-year-old male with a 40 pack-year smoking history was diagnosed with metastatic SCCL, basaloid variant, harboring PTCH1 s799fs*29 with TMB of 3.7 m/Mb, and he had a year-long complete response to vismodegib. A 69-year-old male with poorly differentiated SCCL harboring *PTCH1* W197* and W460* had a 7 month response to vismodegib. On progression, biopsy of recurrent disease after vismodegib failure demonstrated the same *PTCH1* alterations as well as acquisition of the 11q13 (*CCND1/FGF3/FGF4/FGF19*) amplicon. Both biopsies had TMB > 45 m/mb. Nine additional cases not in this series identified as the basaloid variant of SCCL by expert thoracic pathology review were assayed by CGP and 11% (1/9) harbored *PTCH1* mutation, but no other alterations of the hedgehog pathway were identified. **Conclusion:** The index cases presented here suggest a subset of *PTCH1*-mutated SCCL may see clinical benefit from hedgehog inhibitors, regardless of TMB. In a small series of expert diagnosed basaloid histology in SCCL cases, this histology may enrich for hedgehog pathway alterations. Further investigation of underlying *PTCH1* LOH and TMB will be undertaken to assess which SCCL cases can respond to respond to hedgehog pathway inhibitors.

Keywords: squamous, Hedgehog, tumor mutational burden

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OA 18.04 WHOLE GENOME TUMOR-NORMAL SEQUENCING REVEALS POTENTIAL FALSE POSITIVES VERSUS STANDARD CGP SEQUENCING IN PATIENTS WITH NSCLC

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Background: Matched tumor-normal sequencing analyses are essential for precise identification and interpretation of somatic and germline alterations. A 2015 study of 815 paired tumor and normal genomes showed that both genomes are required for precise identification and interpretation of both somatic and germline variation. In this study, we further demonstrate the critical importance of both tumor and germline sequencing using a selected panel of genes that are relevant to cancer prognosis and treatment. **Method:** Tumor and normal (germline) genomes were sequenced using the Illumina HiSeqX platform. Data was aligned to GRCh37 using methods described previously. Tumor versus matched-normal variant analysis was performed using the NantOmics Contraster analysis pipeline to determine somatic and germline genomic variants. RNA-Seq libraries were prepared from tumor samples using KAPA stranded RNA-Seq with RiboErase kit and sequencing on the Illumina platform. RNA sequencing reads were aligned and variants were identified using methods that have been previously described. **Result:** 44 patients with NSCLC with tumor-normal sequencing were analyzed. 29 patients also had RNA-Seq whole transcriptome data available for analysis. Focusing on somatic SNVs in ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, KMT2A (MLL), NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET; 427 germline plus somatic variants were detected in these 25 genes in 44 patients; 386 out of 427 (90%) variants detected in somatic tissue were also present in germline (true positive germline variant, false positive somatic variant). 5 out of 29 patients (17%) did not have detectable expression in at least one somatic variant. Focusing on germline SNVs in APC, MYH, MLH1, MSH2, MSH6, PMS2, EPCAM, POLE, POLD1, BMPR1A, PTEN, STK11; 350 germline plus somatic variants were detected in these 12 genes in 44 patients, 10 out of 44 patients (23%) had at least one variant detected in their tumor DNA in these 12 genes that was not detected in the patient's germline DNA (false positive germline variant, true positive somatic variant). **Conclusion:** Somatic-only sequencing may lead to false positive variant calls which has important clinical implications for highly actionable targets and for the veracity of mutational load algorithms. Calling germline variants from somatic DNA has a false positive risk---called variants may truly be somatic mutations. This is further complicated by the presence of circulating tumor DNA which may also lead to a false positive "germline" result in the absence of a true normal comparator.

Keywords: Genomics, DNA sequencing, lung cancer

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OA 18.06 THREE-DIMENSIONAL ASSESSMENT OF SPREAD THROUGH AIR SPACES IN LUNG ADENOCARCINOMA: INSIGHTS AND IMPLICATIONS

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Background: Tumor spread through air space (STAS) is a newly recognized form of invasion in lung adenocarcinoma and squamous cell carcinoma and growing evidence shows it is associated with recurrence and survival. The observation that

tumor STAS clusters/nests or single cells within air spaces on two-dimensional H&E slides raised the question of how these cells could survive within air spaces without a vascular supply and this has led some to speculate STAS is an artifact. Herein, we perform the high resolution-high quality 3D reconstruction and visualization of normal lung and tumor in a lung adenocarcinoma to investigate the invasive pattern of STAS. **Method:** A formalin-fixed paraffin embedded block of invasive adenocarcinoma with micropapillary pattern and extensive STAS was studied. Following our histology 3D reconstruction standard procedure, 3D reconstruction was performed for analysis from 200 serial sections of H&E stained 20x (0.5um/pixel resolution) whole slide images. The relationship to alveolar walls between micropapillary structures within the tumor and STAS clusters in lung parenchyma distant from the tumor was evaluated. **Result:** 3D reconstruction and analysis demonstrated the following novel features – a) in the main tumor area, micropapillary structures within airspaces were connected to alveolar walls, b) unlike in 2D evaluation where STAS appeared as 'free-floating' micropapillary clusters, in 3D evaluation many STAS clusters within air spaces are attached to alveolar walls, and c) STAS clusters that appear ring-like in 2D by 3D evaluation they are actually balls of tumor cells surrounding a central space. **Conclusion:** Our 3D reconstructed image analysis for the first-time demonstrates that most STAS cells are not 'free-floating', rather attached to the alveolar walls. In addition within the main tumor micropapillary clusters are attached to alveolar walls. These findings raise an intriguing hypothesis that STAS cells are clusters of tumor cells spread within alveolar spaces in a non-contiguous fashion to reattach to the alveolar walls at a distance possibly by co-option of alveolar wall capillaries to support their growth. This form of spread is analogous to the phenomenon of vascular spread where tumor cells spread freely within blood vessels to distant sites where they attach to endothelium and extravasate through the vessel walls to form metastases. It is possible the ball-like configuration of STAS clusters may facilitate movement through alveolar spaces distant from the main tumor. The frequent alveolar wall attachment of STAS observed on serial 3D imaging disputes the concept this is an artifact.

Keywords: Adenocarcinoma, Three-Dimensional Assessment, Spread Through Air Spaces

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OA 18.07 3D LOW-ATTACHMENT CULTURE: A PUTATIVE MODEL FOR STAS AND "FLOATING" CANCER CELLS

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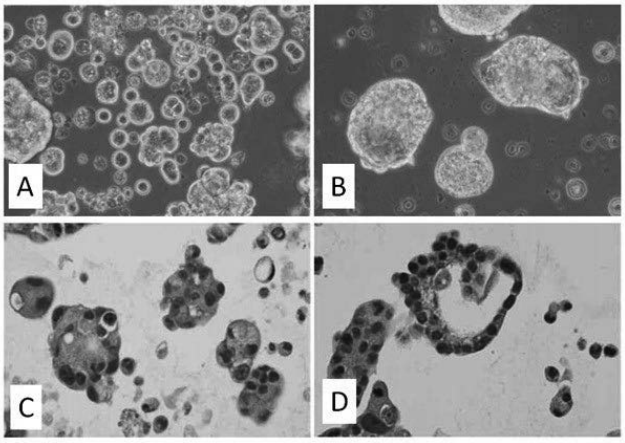
Background: Cancer cells "floating" in stroma, air space, or lymphovascular channels are often found in aggressive lung adenocarcinomas. Recently, the concept of STAS (spread through alveolar space) has been proposed, and studies have shown that STAS predicts early recurrence and poor patient prognosis. However, the biologic basis for the aggressive phenotype of the tumor with these histologic features remains elusive. In this study, we tested whether 3D (three-dimensional) low-attachment culture could be an in vitro model for STAS and "floating" cancer cells. **Method:** Lung adenocarcinoma cell lines harboring diverse driver mutations (EGFR, KRAS, BRAF, HER2, RET) were used. Cells were subjected to detached condition by using low-attachment culture dishes to generate "floating" cancer cells in vitro. Cell growth assay, immunohistochemistry and Western blotting were used to characterize the biologic properties of "floating" cancer cells. Cancer cells were inoculated in pleural cavity or left ventricle of the heart of NOD/SCID mice to test their metastatic potential in vivo. **Result:** Upon detachment, cancer cells formed solid, micropapillary, or hollow ring-like structures, admixed with single cells, recapitulating a histologic spectrum of STAS in primary tumors. Outlining with MUC1, a feature of micropapillary lung adenocarcinoma, was also demonstrated in the in-vitro-generated micropapillary clusters as well. Detached cells initially showed retarded cell growth, but some cell lines regained growth potential with time in culture. Expression analysis of various biomarkers revealed that detached cells showed features of cell stress and altered metabolism, as indicated by increased expression of phospho-p38 (a stress-activated MAP kinase) and GLUT-1 (glucose transporter-1), respectively, and these findings were confirmed by analysis of primary tumors. Finally, cancer cells that adapted to detached conditions exhibited increased metastasis in vivo.



"Floating" cell clusters generated by low-attachment culture. (A), (B) Phase contrast image. (C), (D) H&E stain.

Conclusion: 3D low-attachment culture may be a convenient model to study the biology of aggressive lung cancer with STAS and "floating" cancer cells.

Keywords: metastasis, model, 3D culture

OA 18 LUNG CANCER PATHOLOGY AND GENETICS
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

OA 18.08 FLI1 CIRCULAR RNAS PROMOTE METASTASIS OF SMALL CELL LUNG CANCER CELLS BY DIRECT BINDING TO MIR-584-3P

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Background: Small cell lung cancer (SCLC) is regarded as the most devastative type of human lung malignancies, with their rapid growth and we have discovered that there are FLI1 circular RNAs (circFLI1s) aberrantly expressed in SCLC tissues, such as circFLI1E2-4 and circFLI1E2-5 which are derived from exon 2-exon 4 and exon 2-exon 5 of FLI1, respectively. This study investigated the role of circFLI1s in the biological processes of SCLC. **Method:** The expression level of circFLI1s was evaluated by fluorescence in situ hybridization(FISH) in 54 primary SCLC and 50 non-small cell lung cancer (NSCLC) patients with known follow-up data. Correlation between circFLI1s expression and clinical characteristics was assessed with logistic regression. Cellular proliferation, apoptosis, cell cycle, migration and ability of colony formation were used to investigate the function of circFLI1s in SCLC. Ulteriorly, we explored the possible mechanism of circFLI1s via luciferase reporter assay, RT-PCR and FISH. **Result:** The expression of circFLI1E2-4 and circFLI1E2-5 were up-regulated in SCLC tissues compared with NSCLC tissues . The high expression of these circFLI1s was significantly associated with positive lymph nodal involvement ($p<0.05$). The silencing of circFLI1E2-4 and circFLI1E2-5 but not FLI1 mRNA significantly inhibited migration of highly aggressive SCLC cell lines in vitro and vivo, while did not affect their proliferation, cell cycle, apoptosis and colony formation. Via bioinformatic analysis and luciferase screening assay, circFLI1s were observed to sponge to 2 miRNAs with 6 potential binding sites. Specifically, we showed that these circFLI1s directly binded to miR-584-3p and inhibited miR-584-3p activity, further to regulate the transcriptional activity of its target gene ROCK1 and the RhoA/ROCK1 signal pathway. **Conclusion:** This study uncovers that circFLI1s is an important driving factor that promotes tumor metastasis in SCLC through , and may serve as an attractive target for therapeutic intervention of SCLC.

Keywords: small cell lung cancer, FLI1 circular RNAs, miR-584-3p

MA 01 SCLC: RESEARCH PERSPECTIVES
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MA 01.01 METASTATIC BEHAVIOR OF PULMONARY NEUROENDOCRINE CARCINOMAS IS ASSOCIATED WITH EPITHELIAL TO MESENCHYMAL TRANSITION GENE PROFILE

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Background: The new 2015 WHO classification broadly divided pulmonary neuroendocrine tumor (NET) of the lung in low-grade typical carcinoid (TC) and atypical carcinoid (AC), to the high-grade large-cell neuroendocrine carcinoma (LCNEC) and the small-cell carcinoma (SCLC). The molecular alterations underlying the pathogenesis of these tumors have been studied showing two blocks of entities with independent cellular mechanisms. Many of the differences between the two NETs blocks can be ascribed to tobacco consumption, which induces epithelial to mesenchymal transition activation, responsible for invasive and metastatic behavior. These correlations further highlight the difference in OS for patients with low and high grade metastatic NETs. Therefore, epithelial to mesenchymal transition (EMT) genes profile emerge promise as indicator of invasion and metastasis in NETs. **Method:** Fresh frozen tissue from SCLC (n = 10), LCNEC (n = 4), AC (n = 5), TC (n = 5) and matched normal tissue samples were collected for qRT-PCR analysis carried out on StepOnePlus™ Real-Time PCR System (Applied Biosystems) with RT² Profiler PCR Array System for the EMT pathway with 84 target genes (Qiagen, Dusseldorf, Germany). Linear regression was done to evaluate association between gene expressions. Clinical variable such as age, gender, tobacco history, lymph node metastasis and histologic types were associated with gene expression. Differences were regarded as statistically significant at $P < 0.05$. **Result:** High expression of membrane receptor EGFR (p = 0.003), protein of the matrix metalloproteinase MMP3 (p = 0.044), transcriptional factor TCF3 (p = 0.022) and signaling pathway factor WNT5A (p = 0.013) were observed in patients with tobacco history. Metastatic LCNEC and SCLC presented significant lower expression of JAG1 gene and higher level of EGFR (p<0.01), transmembrane protein DSP (p = 0.03), TCF3 (p = 0.01), TGF-B3 (p = 0.04) and WNT5A (p = 0.01) compared to TC and AC. In addition to these genes, AKT1 and MAP1B were equally high expressed in metastatic NE carcinomas. Importantly, increased expression of these genes added of MMP2 gene was significantly associated with poor OS of the patients. **Conclusion:** A panel of 84 EMT genes was tested and the best biomarkers included EGFR, MMP2, MMP3, TCF3, WNT5A, JAG1, TGFB3, AKT1 and MAP1B with impact on unfavorable prognostic and overall survival of patients, highlight that EMT play a fundamental role in pathogenetic pathway of metastasis in NETs. Supported by CNPQ project 301411/2016-6; FAPESP 2013/10113-7.

Keywords: metastasis, epithelial to mesenchymal transition, Pulmonary Neuroendocrine tumors

MA 01 SCLC: RESEARCH PERSPECTIVES
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 01.02 MULTIGENE MUTATION PROFILING AND CLINICAL CHARACTERISTICS OF SMALL-CELL LUNG CANCER IN NEVER-SMOKERS VERSUS HEAVY SMOKERS

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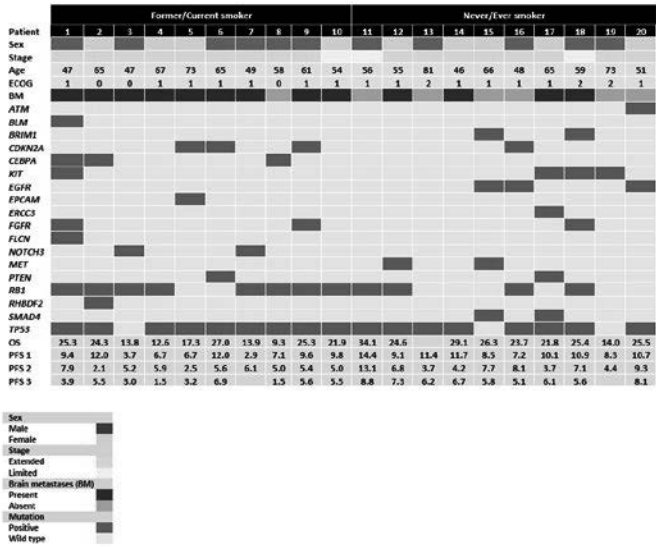
Background: Small-cell lung cancer (SCLC) has been occasionally detected in never-smokers as smoking rates decrease worldwide. We investigated the clinical and genetic characteristics of SCLC in never-smokers (Geno1.3-CLICaP) **Method:** A cohort of patients diagnosed with SCLC were grouped into smokers (n=10) and ever/never-smokers (n=10). For both groups, somatic mutation profiling was carried out using a comprehensive NGS assay (TruSight Tumor 170) targeting the full coding regions of 170 cancer-related genes. Epidermal growth factor receptor (EGFR) mutation was confirmed by RT-PCR (Cobas™). The clinical outcomes of the two groups were compared using Kaplan-Meier and Cox proportional models. **Result:** Median age was 58 years (r, 46-81), 55% (n = 11) were men, most patients had extended disease (85%) and the dominant tumor involvement site was pleura and lungs (65%). No significant differences were found in age, disease distribution, baseline performance status and cerebral metastases in relation to tobacco exposure. The ORR to first-line therapy were 50% and 90% between smokers and ever/never-smokers, respectively (p=0.032). The median overall survival (OS) was 29.1 months in ever/never-smokers (95%CI 23.5-34.6) versus 17.3 months in smokers (95%CI 4.8-29.7; p=0.0054). Never-smoking history (HR 0.543, 95%CI 0.41-0.80), limited stage disease (HR 0.56, 95%CI 0.40-0.91) and response to first line platinum based chemotherapy (HR 0.63, 95%CI 0.60-0.92) were independently related with good prognosis. Among ever/never smokers main genetic mutations were TP53 (80%), RB1 (40%), CYLD (30%), EGFR 30%), MET (20%), SMAD4 (20%) and BRIP1 (20%). None of the smokers had mutations in EGFR, MET or SMAD4, but there was a greater involvement in RB1 (80%, p=0.04), CDKN2A (30%, p=0.05), CEBPA (30%, p=0.05), FANCG (20%), GATA2 (20%), and PTEN (20%). **Conclusion:** Never-smokers with SCLC are increasingly prevalent and have a better prognosis than their smoker counterpart. EGFR, MET and SMAD4 are frequent mutations among SCLCs of ever/never smokers, and RB1, CDKN2A and CEBPA among smokers.

Graphical abstract



Keywords: tobacco exposure, small cell lung cancer, next-generation sequencing

MA 01 SCLC: RESEARCH PERSPECTIVES
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MA 01.03 THE POTENTIAL OF CTDNA SEQUENCING IN DISEASE MONITORING AND DEPICTING GENOMIC EVOLUTION OF SMALL-CELL LUNG CANCER UNDER THERAPY

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Background: Although small cell lung cancer (SCLC) is sensitive to initial therapy, almost all patients relapse and survival remains poor. Outgrowth of treatment-resistant subclones could be responsible for recurrence. However, genomic evolution of SCLC after treatment hasn't been well investigated, partially due to the challenge of obtaining longitudinal samples. CT is the standard modality for response assessment and disease monitoring. But it doesn't always accurately assess the disease status. SCLC is characterized by early hemagenous spread, which makes circulating tumor DNA (ctDNA) analysis a promising modality for genomic profiling and disease monitoring of SCLC. **Method:** Targeted-capture deep sequencing (mean target coverage 538x-1866x) of 545 cancer genes was performed to 44 ctDNA samples collected before therapy as baseline and at different timepoints during treatment from 23 SCLC patients. Pretreatment tumor biopsies from 8 patients were also sequenced (mean target coverage 348x-1281x) of the same gene panel. DNA from peripheral blood mononuclear cells was served as the germline control. **Result:** Mutations were identified in all 44 ctDNA samples with a median of 16 mutations per sample (average mutation burden of 6.6/Mb). TP53 and RB1 were the most frequently mutated genes, detected in 91% (21/23) and 65% (15/23) patients, respectively. 74 mutations were identified from the 8 tumor biopsies, among which, 69 (93.2%) were detected in matched ctDNA. We inferred subclonal architecture of each ctDNA sample based on cancer cell fraction derived using PyClone. A median of 10 (ranging 2-26) subclones was inferred from each ctDNA sample and only 17% (2% to 60.%) of mutations were clonal mutations suggesting substantial genomic heterogeneity. Single gene mutations were not associated with survival. However, mean variant allele frequency of clonal mutations (clonal-VAF) at baseline was associated with progression-free survival (PFS) and overall survival (OS) independent of stage, age, or platinum sensitivity. The median PFS of patients with higher versus lower than median clonal-VAF was 5.2 months (95% CI, 4.6 to 5.8 months) versus 10.0 months (95% CI, 9.3 to 10.7 months),

p=0.002. The median OS was 8.1 months (95% CI, 5.5 to 10.7 months) versus 24.9 months (95% CI, 0.0 to 51.2 months) in patients with higher versus lower than median clonal-VAF, respectively, p=0.004. Analysis of serial ctDNA before and during treatment showed that clonal-VAF closely tracked closely with treatment responses. **Conclusion:** ctDNA sequencing is a promising modality for genomic profiling and disease monitoring for SCLC patients. Clonal VAF may be a better ctDNA metric than single gene mutations.

Keywords: ctDNA, small cell lung cancer, biomarker

MA 01 SCLC: RESEARCH PERSPECTIVES
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MA 01.05 ACTIVITY AND SAFETY OF THE COMBINATION OF PM01183 AND DOXORUBICIN IN RELAPSED SCLC. FINAL RESULTS OF A PHASE IB TRIAL.

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Background: Lurbinectedin (PM01183) 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:** Multicenter, phase I clinical trial to determine the recommended dose (RD) of the combination of PM01183 and DOX. An expansion cohort was recruited after finding striking activity in second-line small cell lung cancer (SCLC) patients. Due to hematological toxicity, the trial was amended to use a lower DOX dose and thus improve safety of the combination in selected indications. SCLC patients <75 years with ECOG performance status (PS) 0-1 and pretreated with no more than one chemotherapy line were included. Stable brain metastases were allowed. DOX was interrupted after 10 cycles and PM01183 could be continued as single-agent. Primary G-CSF prophylaxis was not mandatory. **Result:** 48 patients were treated: 21 in Cohort A (PM01183 3-5 mg flat dose [FD] Day (D)1 + DOX 50 mg/m2 D1 every 21 days [q21d]), and 27 in Cohort B (PM01183 2 mg/m2 D1 + DOX 40 mg/m2 D1 q21d). Males: 74%; median age: 64 (48-77) years, ECOG 0-1: 37%-63%; known central nervous system (CNS) involvement: 10%; bulky disease (>50 mm): 67%. 85% responded to first line, including 4% with complete response (CR). Median chemotherapy free interval (CTFI): 3.4 months. Refractory (CTFI<30 days) 23%; resistant (CTFI 30-90 days) 34%; sensitive (CTFI>90 days) 43%. RD: PM01183 4 mg FD (or 2 mg/m2) + DOX 50 mg/m2 D1 q21d. Confirmed ORR: 50% (95CI: 35-65%) with 6% CR in both cohorts; ORR=69% (95CI: 49-85%) with 10% CR in sensitive patients. Cohort A: ORR=67% (95%CI: 43-85%) with 10% CR; ORR=92% (95%CI: 62-100%) in sensitive patients. Cohort B: ORR=37% (95%CI: 19-58%) with 4% CR; ORR=53% (95%CI: 28-77%) in sensitive patients. Median PFS (mPFS) 4.6 months (95%CI: 3.1-5.8), with mPFS 1.5 months (95%CI: 1.2-3.8) in resistant patients and 5.8 months (95%CI: 3.6-7.9) in sensitive patients. In both cohorts, grade 4 neutropenia/anemia/ thrombocytopenia appeared in 73%/4%/15% of patients and febrile neutropenia in 21% (11% at RD). Non-hematological toxicity was mainly fatigue (G3=14%) and nausea (G3=5%). **Conclusion:** PM01183/DOX combination showed remarkable activity as second line in SCLC, especially in patients with CTFI>90 days, regardless of dose. Activity is higher than reported for CAV or topotecan in this setting. Reversible myelosuppression was the most frequent and expected side effect. A phase III trial with this combination in relapsed SCLC is ongoing.

Keywords: Phaese I, Second Line, SCLC

MA 01 SCLC: RESEARCH PERSPECTIVES
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MA 01.06 A PHASE II STUDY OF ETIRINOTECAN PEGOL (NKTR-102) IN PATIENTS WITH CHEMOTHERAPY-RESISTANT SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) has poor prognosis and systemic chemotherapy is the standard treatment. Irinotecan is a topoisomerase-I inhibitor that has been used in treating SCLC. Etirinotecan pegol (NKTR-102) is a polyethylene glycol conjugate of irinotecan uniquely designed for prolonged tumor cell exposure by using the polymer conjugate technology. This is a single arm phase II study to evaluate single agent etirinotecan pegol in patients with relapsed SCLC (NCT01876446). In WCLC 2016 we reported its promising activity with an acceptable toxicity profile in treatment of chemotherapy-sensitive SCLC. Here we report the results in chemotherapy-resistant SCLC. **Method:** A total of 38 patients who have received only one prior systemic therapy for SCLC were enrolled. There were 2 patient cohorts: those progressing on first-line chemotherapy <3 months after completion of treatment (Group A: chemotherapy-resistant, N=20) and those progressing on first-line chemotherapy ≥3 months after completion of treatment (Group B: chemotherapy-sensitive, N=18). Etirinotecan pegol was administered at 145 mg/m^2 IV once every 3 weeks. Cycles were repeated every 21 days until disease progression, unacceptable toxicity, or withdrawal from study. The primary endpoint was the 18-week progression free survival (PFS) rate. The secondary endpoints were objective response rate (ORR), duration of response (DOR), overall survival (OS) and toxicity. A single-stage design was used to assess the primary endpoint separately for each patient group. **Result:** Group A has completed targeted enrollment of 20 patients and the results are presented here. Median age was 60.4 (46.1-74.8) years, with 50% male and ECOG PS 0 (9/20) or 1 (11/20). Prior chemotherapy included cisplatin/etoposide (25%) or carboplatin/etoposide (70%). Patients received a median of 2 (1-10) cycles of etirinotecan pegol, with dose reduction in 15%. PFS rate at week 18 was 35% (7/20, 95% Confidence Interval (CI): 16-55%). ORR was 20% (4/20), all of which were partial response. Another 30% (6/20) of patients had stable disease. Median DOR was 4.8 (1.6-10.5) months. Median PFS was 9.4 (95% CI: 5.8, 21.6) weeks, and OS was 8.1 (95% CI: 2.9, 11.9) months. The most common treatment-related adverse events (AEs) of any grade were diarrhea (50%), fatigue (35%), weight loss (35%), nausea (30%), and vomiting (30%). The most common AEs ≥grade 3 were diarrhea, leukopenia and neutropenia (2 cases each, all grade 3). **Conclusion:** Etirinotecan pegol has demonstrated promising activity with an acceptable toxicity profile and a convenient schedule in treatment of patients with chemotherapy-resistant relapsed SCLC and therefore warrants further investigation.

Keywords: small cell lung cancer, Etirinotecan, NKTR-102

MA 01 SCLC: RESEARCH PERSPECTIVES
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MA 01.07 LANREOTIDE MAINTENANCE IN SCLC EXPRESSING SOMATOSTATINE RECEPTORS: EFFICACY RESULTS OF MULTICENTER RANDOMIZED G04.2011 TRIAL.

S. Pilotto[1], E. Bria[1], D. Galetta[2], F. Grossi[3], G. Fasola[4], G. Romano[5], L. Bonanno[6], A. Bearz[7], M. Papi[8], A. Caprioli[9], A. Catino[2], A. Follador[4], E. Rijavec[3], A. Misino[2], G. Surico[5], A. Favaretto[10], L. Giannone[1], G. Tortora[1], D. Giannarelli[11], A. Santo[1]

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Background: SCLC is featured by both a rapid response and progression during/after standard upfront therapy. Thus, maintenance strategies emerged as potential treatment opportunities, although to date all drugs failed to significantly improve prognosis. SCLC cells harbor a neuroendocrine phenotype, frequently expressing somatostatine (SST) receptors. This study aimed to investigate the efficacy of somatostatine (SST) analogue Lanreotide (LAN) as a maintenance strategy for SCLC patients (pts) after response to standard upfront treatment. **Method:** A multicentre, randomized, open-label, no-profit national trial was conducted, randomizing (1:1) SCLC (limited/extended disease, L/ED) pts expressing SST receptors (by SST receptor scintigraphy) with objective response (CR or PR) after upfront platinum-based chemotherapy plus/minus radiotherapy to receive maintenance LAN 120 mg subcutaneously every 28 days, up to progressive disease (PD) for 1 year (Arm A), versus observation (Arm B). Primary end-point was 1-year Progression-Free Survival (PFS). Primary intention-to-treat (ITT) analysis was planned (power: 80%; 2-tailed alpha-error: 5%) after 47 PFS events. **Result:** Seventy-one pts (median age 66 [37-82]; male/female 72/28%; L/ED 39/61%; ECOG-PS 0-1/2 97/3%; previous best response CR/PR 6/94%) were randomized in 9 Italian centers. Median time from diagnosis and end-of-1st line to inclusion was 5.7 months (3-160) and 30 days (0-119), respectively. Median number of LAN doses and treatment duration (Arm A) was 4 (1-12) and 83 days (1-392), respectively. With a median follow-up of 9.4 months and 62 events, median PFS was 3.6 (95% CI 3.2-3.9) versus 2.3 months (95% CI 1.7-2.9), for Arm A and B (log-rank p=0.11; HR 1.51, 95% CI 0.90-2.50), with a 1-year PFS of 10.3% versus 7.3%, respectively. At the cox-proportional multivariate modelling, stage (ED versus LD, HR 2.88 [95% CI 1.64-5.04, p<0.0001) and treatment arm (B versus A, HR 1.63 [95% CI 0.97-2.72], p=0.06) were independent predictors for PFS. Median PFS of arm A and B was 7.0 [95% CI <1-13.5] and 3.8 months [95% CI <1-8.6] in LD pts (p=0.21), and 3.0 (95% CI 2.2-3.8) and 2.2 (95% 1.7-2.7) in ED pts (p=0.19). Median OS was 9.5 (95% CI 4.8-14.3) and 4.7 months (95% CI 1.7-16.6), for Arm A and B (log-rank p=0.47), respectively. LAN was well-tolerated: serious treatment-related adverse events were grade 3 abdominal pain and electrolyte disorder in overall 2 pts. **Conclusion:** Although the primary end-point was not met, the overall efficacy of LAN as a maintenance strategy after response to standard upfront treatment for SCLC deserves future investigations, particularly in pts with LD.

Keywords: maintenance treatment, SCLC, Lanreotide

MA 01.09 TREATMENT PATTERNS IN EXTENSIVE DISEASE SMALL CELL LUNG CANCER ACROSS THE UNITED STATES, EUROPE, AND JAPAN

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Background: Small cell lung cancer (SCLC) comprises ~10-15% of lung cancers. The majority of patients with SCLC present with extensive disease (ED) and have extremely poor outcomes; <5% survive 2 years. Although first-line (1L) treatment is typically platinum-based, many patients are platinum-resistant with few effective options after relapse. The study objective was to compare treatment patterns across regions and by platinum resistance/sensitivity. **Method:** This study used data from the Oncology Monitor (Ipsos Healthcare), a global clinical database of oncology patients collected through retrospective medical chart reviews. Treating physicians were invited to submit information on their patients with SCLC treated from January 2014 through December 2016 in the United States (US), the European Union 5 (EU5; France, Germany, Italy, Spain, and the United Kingdom), or Japan. **Result:** A total of 5849 patients with SCLC were included (2605 in the US, 2203 in the EU5, and 1041 in Japan). Mean age was 65.6 years (standard deviation: 8.8); 66.3% were male and 94.0% diagnosed with ED. In all, 73.4% of patients were receiving 1L, 19.8% second-line (2L), and 6.8% third-or-later-line therapy. Platinum/etoposide was the most frequently prescribed 1L therapy, although it was significantly more common in the US (87.0%) than the EU5 (82.1%) or Japan (73.3%) (P<0.05). Cisplatin/etoposide was prescribed more often in 1L in the EU5 (40.8%) than in the US (26.6%) or Japan (23.7%) (P<0.0001). Platinum/irinotecan was an uncommon 1L treatment in the US (2.0%) and EU5 (0.5%) but common in Japan (22.7%; P<0.0001). Platinum-resistance (relapse within ≤3 months of 1L treatment completion) was observed in >40% of patients (US: 45.4%, EU5: 40.9%, Japan: 56.1%). Regardless of platinum-resistance versus sensitivity, the most common 2L treatment in the US and EU5 was topotecan (42.3% vs 47.6%) and (59.5% vs 56.1%), and amrubicin in Japan (52.1% vs 53.1%). Among platinum-resistant patients in the US, EU5, and Japan, 27.3%, 10.8%, and 36.4% received a platinum-based 2L therapy. Additionally, 52.3%, 66.7%, and 44.9% of platinum-sensitive patients did not receive 2L platinum re-challenge. **Conclusion:** Current NCCN and ESMO guidelines (endorsed by JSMO) recommend platinum-resistant patients receive non–platinum-based 2L therapies. The guidelines also recommend that platinum-sensitive patients (relapse >6 months) receive the original 1L regimen as a 2L re-challenge. However, this real-world study found that a significant proportion of platinum-resistant patients were re-challenged with a 2L platinum-based therapy. Conversely, in patients where platinum re-challenge is recommended, a large proportion did not receive platinum-based therapies in 2L.

Keywords: Real-world, small cell lung cancer, platinum-based therapy

MA 01.10 OUTCOME BASED ON BASELINE TOTAL LYMPHOCYTE COUNT & NEUTROPHIL-TO-LYMPHOCYTE RATIO IN EXTENSIVE STAGE SMALL-CELL LUNG CANCER

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Background: The prognosis for patients with extensive stage small-cell lung cancer (ES-SCLC) is dismal. Immune suppression and systemic inflammation have been linked with outcomes for patients with a variety of malignancies, including lung cancer. The purpose of this study was to investigate the impact of baseline immune suppression and systemic inflammation as assessed with hematologic markers such as total lymphocyte count (TLC) and neutrophil-to-lymphocyte ratio (NLR) on overall survival (OS) in patients with ES-SCLC. **Method:** We retrospectively investigated 253 consecutive patients with pathologically and radiographically proven ES-SCLC treated at a single tertiary cancer center from 1998 through 2015. Potential correlations between initial complete blood counts & differential and other clinicopathologic characteristics were sought. Hematologic markers such as pretreatment TLC, NLR, platelet count, and platelet-to-lymphocyte ratio and other clinical characteristics including age, sex, performance status, race, TNM stage (M1a vs. M1b), weight loss, smoking status, number of initial chemotherapy cycles (<4 vs. ≥4 cycles), thoracic radiation therapy (TRT) dose (<45 Gy vs. ≥45 Gy), and receipt of prophylactic cranial irradiation (PCI) were evaluated for correlation with OS. Median values for each hematologic marker were used as cutoffs. Factors identified as important by univariate analysis were selected as covariates to construct a multivariate Cox model for OS. **Result:** Pretreatment TLC was below the lower limit of normal (i.e., <1.0×10^3/μL) in 58 patients (23%). Median OS was 11.0 months for the entire cohort. Median OS time was significantly worse in patients with lower pretreatment TLC (TLC ≤1.5×10^3/μL: 9.8 months, 95% confidence interval [CI] 8.9 10.7 vs. TLC >1.5×10^3/μL: 11.6 months, 95% CI 9.3 13.9) and higher pretreatment NLR (NLR >4.0: 9.3 months, 95% CI 8.8 9.8 vs. NLR ≤4.0: 13.9 months, 95% CI 11.2 16.6). Multivariate analysis identified lower pretreatment TLC (hazard ratio [HR] 0.735, 95% CI 0.561 0.962, P=0.025) and elevated pretreatment NLR (HR 1.534, 95% CI 1.182 1.991, P=0.001) as being independent predictors of inferior survival. Six other clinicopathologic factors (age >63 years, being male, performance status score ≥2, having <4 initial chemotherapy cycles, TRT <45 Gy, and no PCI) were also shown to be independent predictors of worse OS in multivariate analysis (P<0.05). **Conclusion:** Pretreatment TLC and NLR are useful prognostic markers for OS in patients with ES-SCLC. These findings have important implications for stratifying patients with ES-SCLC for various treatment approaches, possibly including immune modulation.

Keywords: extensive stage small-cell lung cancer, hematologic markers, prognostic factor

MA 01.11 TIMING OF THORACIC RADIOTHERAPY IS MORE IMPORTANT THAN DOSE ESCALATION IN PATIENTS WITH LIMITED-STAGE SMALL CELL LUNG CANCER

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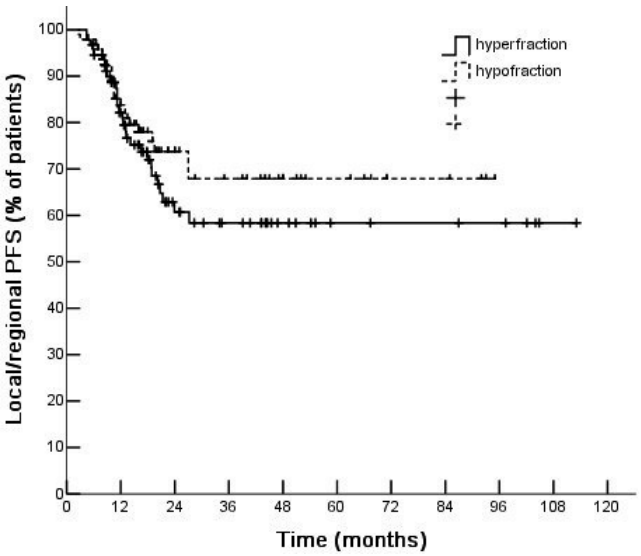
Background: The optimal thoracic radiation dose/fraction for limited-stage small cell lung cancer (SCLC) is still in debate. This study mainly aims to retrospectively compare the impact on local/regional progression-free survival (LRPFS) of different thoracic radiation dose/fraction schedules from two prospective trials. **Method:** Patients in the hyperfractionated arm received thoracic radiotherapy consisted of 1.5 Gy twice a day in 30 fractions to 45 Gy. Patients in the hypofractionated arm received 2.5 Gy daily in 22 fractions to 55 Gy. Kaplan-Meier method was used to estimate survival data. Multivariate prognosis analysis was made by Cox proportional hazard regression analysis. **Result:** Nighty-two and 96 patients were accrued into to the hyperfractionated and hypofractionated arm respectively. The 1-year, 2-year LRPFS rates of the two arms were 82.1%, 60.7% and 84.9%, 68.8% respectively (P=0.27). The median OS time (months) of the two arms were 28.3 and 22.0 respectively, while 1-year, 3-year, 5-year OS rates were 85.2%, 40.8%, 27.1% and 76.9%, 34.3%, 26.8% respectively (P=0.37). On multivariate Cox regression study, the time (days) from the initiation of chemotherapy to thoracic radiotherapy (TCT) ≤ 43 (HR: 0.397, 95%CI: 0.207-0.762, P=0.005) was independently associate with improved LRPFS. The time (days) from the start of chemotherapy to end of thoracic radiotherapy (SER) ≤ 63 (HR: 0.508, 95%CI: 0.322-0.762, P=0.044) and PCI (HR: 0.433, 95%CI: 0.298-0.630, P=0.000) were favorably related to OS. Grade 2 and 3 acute radiation esophagitis were observed in 28.3%, 8.7% and 15.5%, 2.1% of patients in hyper- and hypofractionated arm respectively (P=0.009).



Conclusion: Both hyperfractionated and hypofractionated radiotherapy had achieved good LRPFS and OS in this study, although there was no statistical significance between the two arms. Keep TCT ≤ 43, SER ≤ 63 resulted in better LRPFS and OS. However, the incidence of acute radiation induced esophagitis was significantly more common in the hyperfractionated arm than in hypofractionated arm.

Keywords: small cell lung cancer; limited-stage; thoracic radiotherapy, radiation dose; timing of radiotherapy; study on the prognosis

MA 02.01 EVIDENCE OF CLINICAL ACTIVITY OF SITRAVATINIB IN COMBINATION WITH NIVOLUMAB IN NSCLC PATIENTS PROGRESSING ON PRIOR CHECKPOINT INHIBITORS

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Background: Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy (CIT) is a rational approach to restoring or improving the efficacy of CIT in patients with immunotherapy resistant NSCLC. Sitravatinib is a spectrum-selective TKI which targets TAM receptors (Axl, MER), split family receptors (VEGFR2 and KIT), and MET. Inhibition of these target classes by sitravatinib may enhance anti-tumor activity through targeted depletion of immunosuppressive Type 2 tumor associated macrophages, regulatory T cells and myeloid-derived suppressor cells (MDSCs) and increasing antigen presentation capacity of dendritic cells in the tumor microenvironment (TME) thereby enhancing anti-tumor T effector and NK cell responses. Given these pleiotropic immune activating effects, the combination of sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of CIT in patients with immunotherapy resistant NSCLC. **Method:** MRTX-500 is a Phase 2 Study of sitravatinib in combination with nivolumab in non-squamous NSCLC patients who have experienced progression of disease on or after treatment with CIT. The primary objective is to assess the clinical activity of the combination using ORR by RECIST 1.1. Enrollment into the Phase 2 treatment arm is stratified by prior outcome of CIT (e.g., clinical benefit versus progression of disease in ≤12 weeks). The investigational agent sitravatinib is administered orally in continuous regimen; nivolumab is administered intravenously, 240 mg every 2 weeks. The sample sizes for the treatment arms are based on two-stage Simon Optimal Design. **Result:** The recommended phase 2 dose of the combination is 120 mg of sitravatinib orally, once daily with nivolumab given at a flat dose of 240 mg IV Q 2 weeks. As of June 20, 2017, the study has enrolled 11 patients and 6/11 patients have had at least one on-study tumor assessment. Two patients out of 6 have achieved PR by RECIST. The first patient is a 72 yo female with pan-wild type metastatic NSCLC with history of treated brain metastases with multiple prior therapies who previously received pembrolizumab (stable disease for 14 months) and obtained confirmed PR at first disease evaluation. The second patient is a 71 yo female with pan-wild type metastatic NSCLC with multiple prior therapies who previously received nivolumab (progressive disease as best overall response) but who obtained unconfirmed PR at first disease evaluation. Treatment has been associated with manageable side effects to date. **Conclusion:** This study is ongoing and actively accruing patients.

Keywords: NSCLC, Sitravatinib, Nivolumab

MA 02.02 PHASE 2 STUDY OF PEMBROLIZUMAB PLUS CC-486 VS PEMBROLIZUMAB PLUS PLACEBO IN PREVIOUSLY TREATED PATIENTS WITH ADVANCED NSCLC

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Background: Studies have demonstrated that epigenetic modifiers, such as azacitidine, may sensitize tumor cells to treatment with checkpoint inhibitors, such as pembrolizumab (pembro). Efficacy and safety results from a phase 2, randomized, double-blind study of pembro in combination with CC-486, an oral formulation of azacitidine, vs pembro+placebo (PBO) for 2L treatment of advanced NSCLC are reported. **Method:** Patients aged ≥ 18 years with stage IIIB/IV NSCLC with only 1 prior platinum-based chemotherapy were randomized 1:1 (stratified by histology) to pembro 200 mg day 1 plus either CC-486 300 mg or placebo days 1-14 of a 21-day cycle. Primary endpoint was PFS. Key secondary endpoints included OS, ORR and safety. **Result:** 51 and 49 patients were randomized to the pembro+CC-486 and pembro+PBO arms. Baseline characteristics were generally balanced between treatment groups. Efficacy results are shown in Table 1. Median duration of treatment for pembro+CC-486 vs pembro+PBO was 14 vs 24 weeks, and median number of cycles was 5 vs 7. The most common grade 3/4 TEAEs associated with pembro+CC-486 were nausea (14%), vomiting (12%), asthenia (10%), and diarrhea (8%), vs diarrhea (6%), asthenia (6%) and pneumonia (6%) with pembro+PBO. Patients treated with pembro+CC-486 vs pembro+PBO experienced a higher rate of pembro dose interruptions (29% vs 16%) and discontinuations (20% vs 10%), and a higher rate of CC-486 or PBO dose interruptions (61% vs 24%) and discontinuations (33% vs 12%). Gastrointestinal events, asthenia/fatigue, and elevated transaminase levels were the most common TEAEs leading to discontinuations. **Conclusion:** The addition of CC-486 to pembro did not improve the primary endpoint of PFS compared with pembro+PBO. PD-L1 expression did not appear to be predictive of CC-486 treatment efficacy. The increase in TEAEs in the combination arm, particularly gastrointestinal (nausea and vomiting), which are known to be associated with CC-486, may have influenced treatment exposure.

Efficacy Endpoints	**Pembro + CC-486 n = 51**	**Pembro + PBO n = 49**
Overall		
PFS, median, months	3.1	4.0
ORR, n (%)	10 (19.6)	7 (14.3)
By PD-L1 Level at Baseline	**n = 45**	**n = 44**
PFS, median, months ≥ 50% ≥ 1%-49% 0%	5.5 1.6 3.6	8.0 1.4 3.9
ORR, % ≥ 50% ≥ 1%-49% 0%	37.5 20.0 18.5	37.5 0.0 7.1

Keywords: pembrolizumab, CC-486, NSCLC

MA 02.03 SELECTIVE HISTONE DEACETYLASE INHIBITOR ACY-241 PLUS NIVOLUMAB FOR REFRACTORY ADVANCED NSCLC: RESULTS FROM A PHASE 1B STUDY

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Background: ACY-241, an oral inhibitor of histone deacetylase 6, has demonstrated activity in preclinical NSCLC models in combination with immunotherapy. The objectives of this study are to evaluate safety, dose-limiting toxicities (DLTs), the maximum-tolerated dose (MTD), and preliminary antitumor activity of ACY-241 in combination with the immune checkpoint inhibitor nivolumab. **Method:** In the 3+3 dose-escalation design, previously treated patients with advanced NSCLC and ECOG PS of 0 or 1 will receive ACY-241 on days 1 to 28 of each 28-day cycle at 3 dose levels (180, 360, and 480 mg) in combination with nivolumab 240 mg on day 15 of cycle 1 and days 1 and 15 of each subsequent cycle. Antitumor activity will be assessed per RECIST v1.1 and immune-related response criteria (irRC). **Result:** As of 16 June 2017, 13 patients have been treated in the 3 dose-escalation cohorts. All patients had received first-line treatment with platinum-based chemotherapy. The median age of all patients was 66 years, 62% were male, 54% had an ECOG PS of 0, 54% had stage IV disease, and 85% had adenocarcinoma (15% had squamous histology). No DLTs were observed in the 180- or 360-mg ACY-241 cohorts. The 480-mg cohort is currently under investigation. The most common all-grade adverse events (AEs) in all cohorts were cough (15%), arthralgia (15%), and fatigue (15%, including grade 3 in 1 patient). One patient experienced a grade 3 cerebrovascular accident related to a brain metastasis but unrelated to study drug. No immune-related AEs have been observed. Six patients were evaluable for response: 2 experienced objective responses (1 complete and 1 partial); 2 patients had stable disease; 2 patients had disease progression. Two patients were not evaluable for efficacy, and 5 patients have not yet undergone a response assessment. **Conclusion:** No DLTs have been observed with ACY-241 at 180 or 360 mg. Preliminary antitumor activity has been observed with the combination treatment. Updated pharmacokinetic data will be presented at the meeting. NCT02635061

Keywords: ACY-241, Nivolumab, NSCLC

MA 02.05 NIVOLUMAB IN ADVANCED NON-SQUAMOUS NSCLC PATIENTS WITH KRAS MUTATIONS: RESULTS FROM THE ITALIAN EXPANDED ACCESS PROGRAM (EAP)

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Background: Nivolumab significantly improved overall survival (OS) versus docetaxel in patients (pts) with previously treated non-squamous non small cell lung cancer (non-Sq-NSCLC) in the Checkmate 057 study. In a pre-specified subgroup analysis of this trial, this advantage was confirmed also in patients (pts) with KRAS-mutation (KRAS+). However, since the number of KRAS+ pts enrolled in the trial was too small to draw definitive conclusions, the Italian nivolumab expanded access program (EAP) for non-Sq-NSCLC might represent an important source of information about this subpopulation. Here we report the results of the use of nivolumab in pts with

KRAS mutation treated in the Italian EAP. **Method:** Nivolumab was provided upon physicians' request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months. Pts included in the analysis received ≥1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events. **Result:** Overall, 1588 pts with advanced non-Sq-NSCLC, enrolled in 168 sites, received at least one dose of nivolumab in the Italian EAP. Among 532 pts evaluated for KRAS mutation, 206 (39%) resulted positive. In this subgroup of pts, the best overall response rate (BORR) was 20%, including 2 pts with complete response and 39 pts with partial response. The median OS was 10.7 months (8.6-12.8), with a median follow-up of 7.7 months (0.1-21.2) and a median number of 8 doses (1-45). These results were in line with those ones showed in the overall population (18% BORR and 11 months median OS, respectively). Overall, among pts with KRAS mutation, 166 discontinued treatment for any reason, with only 14 (8%) pts who discontinued treatment due to adverse events, in line with what observed in the general population and in previous studies. **Conclusion:** To date, no direct targeted therapy is available for pts with KRAS mutation. This analysis seems to confirm, in a real word setting and in a larger number of pts, the results obtained with nivolumab in KRAS-positive pts in CheckMate 057, thus representing a potentially effective therapeutic option for this subpopulation.

Keywords: Advanced NSCLC, Immunotherapy, Second line

MA 02 EMERGING TARGETS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 02.06 BRAF MUTANT NSCLC: CORRELATION WITH PD-L1 EXPRESSION,TMB, MSI AND RESPONSE TO ICPI AND ANTI-BRAF THERAPY

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Background: The efficacy of immune check-point inhibitors (ICPi) in BRAF mutant non-small cell lung cancer (NSCLC) is largely unknown. The correlation with different parameters predicting efficacy of ICPi (e.g., PD-L1 expression, tumor mutational burden (TMB) and microsatellite instability status (MSI) in these tumors needs further evaluation. **Method:** A retrospective analysis of 30 patients with BRAF mutant advanced NSCLC treated between Aug 2013 and May 2017 was performed. The patients were divided into 2 groups: BRAF V600 E (Group A, N=16), non-V600E BRAF (Group B, N=14). PD-L1 was assessed by immunohistochemistry using 22C3 Dako antibody clone on Dako or Ventana›s platform in 16 patients. TMB and MSI were assessed in 9 and 11 patients, respectively. Median progression-free survival (mPFS) with ICPi and targeted agents as well as median overall survival (mOS) were assessed in each group by Kaplan-Meier method. **Result:** Baseline characteristics of the cohort: median age 66y (range 39-98); males 53%; current/past smokers/never smokers/NA 13%/44%/40%/3%; adenocarcinoma/other histology 80%/20%; ECOG PS 0/1/2/3/4/NA 27%/33%/10%/13%/0%/17%. The distribution of TMB, PD-L1 expression and MSI status between the 2 groups is presented in Table 1. Ten patients received ICPi (nivolumab-8, pembrolizumab-2), and thirteen patients received anti-BRAF therapy (dabrafenib+trametinib-6, dabrafenib-4, vemurafenib-3). mOS and mPFS with ICPi and anti-BRAF therapy are summarized in Table 1. Four patients with BRAF V600 E PD-L1 ≥ 50% tumors were included in the series; one patients responded to dabrafenib+trametinib combination (response ongoing, 7.1months+); in two patients ICPi were initiated, response assessment pending. One patient with a non-V600E BRAF mutant NSCLC responded to dabrafenib for 6.7 months. **Conclusion:** BRAF mutant NSCLC tumors are associated with high level of PD-L1 expression, low/intermediate TMB and MSI stable status. ICPi may induce prolonged responses both in BRAF V600E and non-V600E BRAF mutant NSCLC. Some non-V600E BRAF mutant NSCLC may benefit from anti-BRAF targeted therapy.

Keywords: BRAF mutant NSCLC; PD-L1 expression; immune check-point inhibitors

MA 02 EMERGING TARGETS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 02.07 A PHASE II STUDY OF PEMBROLIZUMAB IN EGFR MUTANT, PD-L1+, TYROSINE KINASE INHIBITOR (TKI) NAÏVE PATIENTS WITH ADVANCED NSCLC

A. Lisberg, J. Hunt, N. Reese, T. Wang, P. Coluzzi, M. Spiegel, K. Bornazyan, J. Carroll, J. Madrigal, B. Ledezma, M. Mendenhall, J. Bui, H. Lu, A. Cummings, Z. Noor, J.W. Goldman, E. Garon

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Background: Pembrolizumab, a humanized monoclonal antibody that inhibits the interaction between programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) has demonstrated significant antitumor activity and produced durable responses in non-small cell lung cancer (NSCLC). However, data to date suggests that responses are less frequent in patients whose tumors harbor mutations in the epidermal growth factor receptor (EGFR) gene. Our single center experience with the KEYNOTE-001 trial suggested that EGFR mutation positive NSCLC patients with a history of prior tyrosine kinase inhibitor (TKI) therapy had worse clinical outcomes than those who were TKI naïve. However, that analysis was limited by small sample size. As a result of this observation, we are currently enrolling an open-label, phase II trial, of front-line pembrolizumab in EGFR mutation positive NSCLC patients that are PD-L1+. **Method:** This is an open-label, phase II trial of pembrolizumab in patients with EGFR mutation positive NSCLC whose tumors are PD-L1 positive [>1% tumor membranous staining by immunohistochemistry (IHC), 22C3 pharmDx test in a CLIA certified laboratory]. Patients receive pembrolizumab 200mg by IV infusion every three weeks and are evaluated every 9 weeks +/- 1 week with radiographic imaging to assess response to treatment for a maximum of 35 trial treatments of pembrolizumab. After progression on pembrolizumab, patients are followed for evaluation of EGFR TKI efficacy. The primary end point of the study is objective response rate (ORR) to pembrolizumab, per RECIST 1.1. Secondary endpoints include safety and efficacy [progression-free survival (PFS), overall survival (OS)] of front-line pembrolizumab in this population, as well as efficacy [PFS, OS, ORR] of subsequent EGFR TKI after progression on pembrolizumab. Correlative analyses include whole exome sequencing and IHC of patient specimens. To date, 8 out of the 25 planned patients have been enrolled. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: EGFR, NSCLC, anti-PD-1 therapy

MA 02 EMERGING TARGETS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 02.09 A PH I/II STUDY OF BGB324, A SELECTIVE AXL INHIBITOR AS MONOTHERAPY AND IN COMBINATION WITH ERLOTINIB IN ADVANCED NSCLC

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Background: BGB324 is an orally available selective inhibitor of the receptor tyrosine kinase AXL (Biochemical IC50 0.4nM). In animal models of NSCLC exposure, BGB324 restricts cellular plasticity and prevents the development of resistance to Epithelial Growth Factor Receptor (EGFR) inhibitors through mesenchymal transformation. **Method:** BGB324 was administered at an oral loading dose (600 mg) on days one and two followed by a daily maintenance dose (200 mg) to eight patients with previously treated NSCLC (EGFR mutant or wildtype). The tolerability of two different loading doses BGB324 (600 mg on days one and two or 400 mg on days one two and three) were then explored in combination with erlotinib at a dose of 150 mg daily in patients with EGFR mutated NSCLC. **Result:** Two of eight patients treated with BGB324 monotherapy achieved at least six months of stable disease. Both dose levels of BGB324 were tolerated in combination with erlotinib although most patients experienced a transient worsening in gastrointestinal toxicity during the loading dose prior to returning to baseline. A three day loading dose was preferred. Treatment with BGB324 was accompanied by increases in patient serum levels of soluble AXL receptorconsistent with receptor inhibition. One patient who previously experienced progression during treatment with another EGFR inhibitor remains on treatment with erlotinib plus BGB324 for more than eighteen months with a best response of stable disease. The most common treatment related adverse events were increased serum creatinine, diarrhea, nausea and dysguesia. **Conclusion:** BGB324 can be safely administered to patients with advanced NSCLC for prolonged periods at doses that abrogate AXL signalling either as monotherapy or in combination with erlotinib. A proportion of patients achieve durable disease stabilisation following treatment with BGB324 alone further exploration of the efficacy of the combination is ongoing.

Keywords: Erlotinib, Axl, NSCLC

MA 02 EMERGING TARGETS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 02.10 PHASE I STUDY OF ABBV-399 (TELISOTUZUMAB VEDOTIN) AS MONOTHERAPY AND IN COMBINATION WITH ERLOTINIB IN NSCLC

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Background: The c-Met receptor is overexpressed in ~50% of patients (pts) with non-small cell lung cancer (NSCLC). ABBV-399 is a first-in-class antibody-drug conjugate composed of ABT-700, an anti–c-Met antibody, conjugated to monomethyl auristatin E (a microtubule inhibitor). Preclinical data demonstrate that ABBV-399 can deliver a potent cytotoxin directly to c-Met+ tumor cells. **Method:** ABBV-399 was administered at doses ranging from 2.4 to 3.0 mg/kg (dose expansion and combination cohorts at 2.7 mg/kg) once every 21 days to 29 pts with advanced c-Met+ (immunohistochemistry [IHC] H-score ≥150) NSCLC both as monotherapy (ABBV-399/monotherapy; 16 pts) and in combination with oral erlotinib 150 mg daily

(ABBV-399/ERL; 13 pts) (NCT02099058). c-Met expression was assessed by IHC utilizing the SP44 antibody (Ventana; Tucson, AZ, USA). **Result:** As of April 26, 2017, 16 pts with c-Met+ NSCLC received ≥1 dose of ABBV-399/monotherapy. Monotherapy treatment-related adverse events (TRAEs) occurring in ≥10% of pts (all dose levels and all grades) were fatigue (43.8%), nausea (37.5%), neuropathy (25.0%), vomiting (18.8%), anemia, constipation, and diarrhea (12.5% each). Three of 16 (19%) ABBV-399–treated c-Met+ NSCLC pts had a confirmed partial response (PR) with duration of response (DOR) 3.1, 4.8, and 11.1 months. At week 12, 9 of 16 pts (56.3%) had disease control. TRAEs in ABBV-399/ERL occurring in ≥10% of pts (all grades) were neuropathy (46.2%), nausea (23.1%), fatigue, acneiform rash, dry skin, and diarrhea (15.4% each). Four of 13 (31%) evaluable ABBV-399/ERL–treated c-Met+ pts had a PR (3 confirmed, 1 unconfirmed) with DOR 2.8, 5.3, 4.2+, and 9.1+ months. Three of the 4 pts with PR had EGFR-mutated tumor and recently progressed on TKI. At week 12, 10 of 13 pts (76.9%) had disease control. There were no treatment-related deaths as monotherapy or in combination with erlotinib. Responses were seen in both squamous and non-squamous histology. **Conclusion:** ABBV-399 is well tolerated at 2.7 mg/kg once every 21 days and has demonstrated antitumor activity in pts with c-Met+ NSCLC both as monotherapy and in combination with erlotinib. Early evidence suggests that ABBV-399 represents a novel treatment paradigm effective against multiple c-Met+ NSCLC molecular subtypes and histologies. Updated efficacy/safety data and c-Met IHC status will be presented. Safety and efficacy data from Q2week dosing of ABBV-399 will also be presented.

Keywords: Antibody-drug conjugate, non-small cell lung cancer, c-Met

MA 02 EMERGING TARGETS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 02.11 A PHASE I TRIAL OF ERLOTINIB AND ONALESPIB IN EGFR-MUTANT NSCLC: FOCUS ON EGFR EXON 20 INSERTIONS

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Background: Onalespib (AT13387) is a non-ansamycin small molecule that inhibits heat shock protein-90 (Hsp90). Hsp90 inhibitors (Hsp90i) preferentially degrade overexpressed and mutated oncoproteins including those that mediate resistance to EGFR-TKIs. Previous Hsp90i studies demonstrated activity in EGFR-mutant NSCLC including EGFR Exon 20 insertions (EGFRex20ins) - uncommon EGFR mutations typically refractory to 1st and 2nd generation EGFR-TKIs. A phase I study of onalespib plus erlotinib was conducted to determine the MTD, DLT, RP2D, pharmacokinetics (PK) and preliminary antitumor activity for a planned phase 2 trial in EGFR-mutant NSCLC including EGFRex20ins. **Method:** Using a 3 + 3, dose escalation design, onalespib was examined at 2 dose levels (DL) from 150 (DL0) to 120 (DL-1) mg/m^2 IV weekly (D1, D8, D15 on a q28 day cycle). Daily erlotinib was given at 150 mg at both DL. Key eligibility: NSCLC with EGFR activating mutation including EGFRex20ins, age ≥ 18, ECOG PS≤2, acceptable organ function, and ≥1 systemic therapy for advanced disease (platinum-based chemotherapy for EGFRex20ins and EGFR-TKI for other EGFR-mutations). Plasma for PK and ctDNA for next-generation sequencing of ~70 cancer related genes was collected at relevant timepoints. **Result:** 9 pts have been treated on 2 DL (3 DL0, 6 DL-1). Pt characteristics: median age 65, M/F (2/7), ECOG PS 0-1 (4/5), EGFRex20ins (8), EGFR E19del (1). 7 pts completed ≥1 cycle. Two DLTs (grade (Gr) 3 maculopapular rash and Gr 3 hypophosphatemia) occurred in DL0. Common drug-related adverse events (AE) of any Gr were diarrhea (100%) and rash (44%), fatigue (55%), increased bilirubin (22%), nausea (44%) and vomiting (33%). Drug-related Gr 3 AEs were diarrhea (55%), maculopapular rash (11%) and hypophosphatemia (11%). At the planned 2-month evaluation, 5 pts had SD, 3 PD, and 1 had withdrawn for toxicity. Of the 5 pts continuing, 2 had SD and 1 PD at the 4-month evaluation. Kaplan-Meier estimate on therapy without progression at the second evaluation is 30% (95% CI: 10 to 87%). **Conclusion:** In patients with EGFR-mutant NSCLC, onalespib plus erlotinib is feasible, tolerable and demonstrates disease control in EGFRex20ins, thereby addressing a key unmet need in NSCLC. The RP2D is erlotinib 150 mg PO daily and onalespib 120 mg/m^2 weekly (D1, D8, D15 q28days). Diarrhea was the most common AE, and generally manageable with supportive care and dose reduction to DL-1. Updated results including PK as well as ctDNA for EGFR-mutation and relevant bypass tracts mediating EGFR-TKI resistance will be presented.

Keywords: EGFR Exon 20 Insertion

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.01 NAB-PACLITAXEL ± CC-486 AS SECOND-LINE TREATMENT OF ADVANCED NSCLC: RESULTS FROM THE ABOUND.2L+ STUDY

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Background: CC-486 (oral azacitidine) is an epigenetic modifier with potential effect as a priming agent for chemotherapy in patients with NSCLC. Outcomes of nab-paclitaxel+CC-486 vs nab-paclitaxel as second-line treatment of advanced NSCLC are reported. **Method:** Patients with advanced nonsquamous NSCLC and no more than 1 prior chemotherapy line (including platinum doublet combination) were randomized (1:1) to nab-paclitaxel 100 mg/m^2 d8, 15 + CC-486 200 mg qd d1-14 or nab-paclitaxel 100 mg/m^2 d1, 8, both administered q3w until progressive disease/unacceptable toxicity. Primary endpoint was PFS. Secondary endpoints: DCR, ORR, OS, and safety. QoL, an exploratory endpoint, was assessed on d1 of each cycle. **Result:** The nab-paclitaxel+CC-486 arm was discontinued in October 2016 due to demonstrated futility vs nab-paclitaxel monotherapy upon completion of a protocol-specified interim analysis. Overall, 161 patients were randomized (nab-paclitaxel+CC-486, 81; nab-paclitaxel, 80). Baseline characteristics were balanced between arms. The median number of cycles was 4 for each arm, and the median nab-paclitaxel cumulative dose was 600 mg/m^2 and 800 mg/m^2 in the nab-paclitaxel+CC-486 and nab-paclitaxel arms, respectively. Rates of grade 3/4 (G3/4) treatment-emergent AEs were 59.5% and 54.4% for the combination and monotherapy arms, respectively. The most frequent hematologic G3/4 AEs were neutropenia (16.5% vs 10.1%) and anemia (1.3% vs 7.6%). G3/4 peripheral neuropathy was reported in 2.5% and 7.6% of patients, respectively. The addition of CC-486 to nab-paclitaxel did not improve ORR, DCR, PFS, or OS (Table). When assessed by Lung Cancer Symptom Scale, nab-paclitaxel monotherapy was associated with improvement in the global QoL, average symptom burden index, and lung cancer symptoms except for hemoptysis. **Conclusion:** The addition of CC-486 to nab-paclitaxel did not clinically benefit patients with previously treated NSCLC. However, single-agent nab-paclitaxel appears to be a promising therapy based on safety, efficacy, and QoL data. Updated efficacy and safety data will be presented. NCT02250326

	***nab*-Paclitaxel + CC-486** **n = 81**	***nab*-Paclitaxel** **n = 80**
Median PFS, months	3.2	4.2
HR (95% CI)	1.3 (0.9 - 2.0)	
1-year PFS, %	4.1	18.3
Median OS, months	8.4	12.7
HR (95% CI)	1.4 (0.88 - 2.31)	
1-year OS, %	39.2	54.3
ORR, n (%)a	11 (13.6)	11 (13.8)
Response rate ratio (95% CI)	0.99 (0.45 - 2.15)	
CR PR SD PD DCR (≥ SD)	0 11 (13.6) 41 (50.6) 22 (27.2) 52 (64.2)	0 11 (13.8) 43 (53.8) 19 (23.8) 54 (67.5)

CR, complete response; DCR, disease control rate; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease. [a]Response rate was based on the intent-to-treat population; however, 14 patients did not have a response assessment.

Keywords: nab-paclitaxel, Second-line, CC-486

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.02 TIMING OF B12/FOLATE SUPPLEMENTATION IN NSCLC PATIENTS ON PEMETREXED BASED CHEMOTHERAPY: FINAL RESULTS OF THE PEMVITASTART RANDOMIZED TRIAL

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Background: Vitamin B12 and folic acid supplementation(B12-FAS) reduces the incidence and severity of hematological toxicity[HTox] in pemetrexed-based chemotherapy. It is recommended to initiate B12-FAS 5-7 days before the first cycle. Observational and prospective single-arm studies have not shown any increase in HTox when pemetrexed was started earlier than the recommended duration of B12-FAS. **Method:** An open-label, randomized trial (PEMVITASTART; NCT02679443) was conducted to evaluate differences in HTox between patients initiated on pemetrexed-platinum chemotherapy following 5-7 days of B12-FAS (Delayed Arm;

DA) versus those receiving B12-FAS simultaneously(≤24 hours) with chemotherapy initiation (Immediate Arm; IA). Eligible patients had locally advanced/metastatic non-squamous NSCLC AND ECOG PS=0-2. Block randomization was 1:1 into DA and IA. All enrolled patients received 3-weekly pemetrexed-platinum doublet [500mg/m^2 AND cisplatin(65mg/m^2) OR carboplatin(AUC 5.0mg/mL/min) each on D1] for maximum of six cycles. Supplementation was 1000µgm FA PO daily and 3-weekly 1000µgm i/m vitamin B12. Primary outcome was any grade HTox while secondary outcomes were grade 3/4 HTox, relative dose intensity(RDI) delivered, inter-cycle delays(ICDs), supportive therapies usage (ESA/G-CSF/PRBC transfusions) and changes in serum levels of B12/FA/homocysteine. **Result:** Of 161 patients recruited (81 IA, 80 DA), 150 patients (77 IA, 73 DA) received ≥1 cycle and were included in modified ITT analysis. Baseline parameters were matched except for gender (IA=10.4%, DA=23.3%, p=0.03) and baseline thrombocytopenia (IA=7.8%, DA=0%, p=0.03). Baseline anemia(Hb<12gm/dL) was present in 34.7% (IA=32.5%, DA=37.0%; p=0.56). Incidence of any grade anemia, leukopenia, neutropenia and thrombocytopenia was 87.0% vs. 87.7%(p=0.90), 37.7% vs. 28.8%(p=0.25), 20.8% vs. 15.1%(p=0.36) and 31.2% vs. 16.4%(p=0.04) in IA and DA respectively. Grade 3/4 anemia was 18.2% vs. 12.3%(p=0.32) in IA and DA respectively while other cytopenias were similar (<5% in each arm). Supportive therapies usage in IA vs. DA were 22.1% vs. 12.3% for PRBC transfusions (p=0.12), 3.9% vs. 6.8% for G-CSF (p=0.49) and 10.4% vs. 1.4% for ESAs (p=0.03). ICDs occurred in 14.3% of IA vs. 8.2% in DA (p=0.24). RDI delivered (median 93.5% for pemetrexed and 91.0% for platinum) was similar in both arms. Following continued B12-FAS, after C3(compared to baseline), serum homocysteine was lower (median 10.0µmol/L vs. 17.6µmol/L;p<0.001) while FA (median 17.9ng/ml vs. 5.7ng/ml;p<0.001) and B12 levels (mean 1926.3pg/ml vs. 880.2pg/ml;p<0.001) were higher. In DA, serum FA and B12 on Day1 of C1(following 5-7days of B12-FAS) were significantly higher than baseline but homocysteine levels were similar. **Conclusion:** Simultaneous B12-FAS initiation with pemetrexed-based chemotherapy is feasible with acceptable HTox profile. Serum homocysteine levels are unaffected by 5-7 days of B12-FAS.

Keywords: vitamin supplementation, hematological toxicity, pemetrexed

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.03 NEDAPLATIN PLUS DOCETAXEL VERSUS CISPLATIN PLUS DOCETAXEL AS FIRST-LINE CHEMOTHERAPY FOR ADVANCED SQUAMOUS CELL CARCINOMA OF THE LUNG

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Background: A previous phase III randomized trial improved overall survival of patients with advanced or relapsed squamous cell lung carcinoma, compared with cisplatin plus docetaxel. However, evaluation of nedaplatin plus docetaxel's effect on progression free survival (PFS) and time to progression (TTP) was limited. **Method:** To compare the efficacy and safety of nedaplatin plus docetaxel and cisplatin plus docetaxel. In this randomized, open-label, multicenter trial, patients diagnosed with advanced or relapsed squamous cell carcinoma pathologically or cytologically were enrolled in China. All the patients have no previous oncology medication. Patients were randomly assigned (1:1) to 80 mg/m^2 nedaplatin and 75 mg/m^2 docetaxel intravenously, or 75 mg/m^2 cisplatin and 75 mg/m^2 docetaxel, every 3 weeks for four cycles. The primary end points was PFS. Secondary endpoints included TTP and best overall response. The efficacy endpoint were analyzed in the intention-to-treat set and in the per protocol set. Clinical trial number: NCT02088515; Funding:Jiangsu Simcere Pharmaceutical Co., Ltd. **Result:** From December 2013 to December 2015, 286 patients were randomly assigned. Two hundred and eighty patients were included in the modified intention-to-treat analysis (141 in the nedaplatin group and 139 in the cisplatin group). In the intention-to-treat analysis set, median PFS was 4.63 months (95% confidence interval (CI), 4.43-5.10) in the nedaplatin group and 4.23 months (95% CI, 3.37-4.53) in the cisplatin group. PFS did not differ significantly between two groups (log-rank test, p =0.056). In per protocol set, PFS was significantly longer in the nedaplatin group (median 4.63 months, 95% CI, 4.43-5.10) than in the cisplatin group (median 4.27 months, 95% CI, 3.37-4.53; hazard ratio 0.760, 95% CI 0.585-0.989; p=0.039, log-rank test). Best overall response and TTP were improved in nedaplatin group than in cisplatin group (p= 0.002, median 4.57(4.30-4.80) vs 3.67(3.13-4.43) p= 0.020, respectively) in the intention-to-treat analysis set. Grade III or IV adverse events was more frequent in the cisplatin group than in the nedaplatin group (46 of 141 patients in the nedaplatin group and 62 of 139 in the cisplatin group, p=0.039). Grade 3 or worse nausea (0 vs 7) and fatigue (1 vs 3) were more frequent in the cisplatin group than in the nedaplatin group. **Conclusion:** There was no significant difference of PFS between cisplatin group and nedaplatin group. However, more adverse events was observed in the cisplatin group than in the nedaplatin group. Nedaplatin plus docetaxel could be a new treatment option for advanced or relapsed squamous cell lung cancer.

Keywords: Nedaplatin, Squamous cell lung carcinoma, randomized trial

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.05 BEVACIZUMAB COMBINED WITH CHEMOTHERAPY FOR PATIENTS WITH ADVANCED NSCLC AND BRAIN METASTASIS. A FRENCH COHORT STUDY

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Background: Although brain metastases (BM) are a very common and clinically challenging for NSCLC progression, there are few prospective studies addressing the safety and efficacy of bevacizumab in combination with chemotherapy in patients with BM. This study aimed to describe the characteristics of patients receiving bevacizumab in combination with first-line metastatic chemotherapy for advanced NSCLC (aNSCLC), with BM or not, in routine clinical practice. **Method:** For this French non-interventional, prospective, and multicenter study, data were collected every 3 months over an 18-month period, from bevacizumab initiation. End points were progression-free survival (PFS), overall survival (OS), treatment use, and safety. **Result:** Amongst the 407 aNSCLC patients analyzed, the 84 patients (21%) with BM at bevacizumab initiation had poorer general health than patients without BM (ECOG 2: 16% versus 11%). All except for 2 patients received bevacizumab (7.5 or 5 mg/kg/3 weeks in 99% of patients) in combination with doublet chemotherapy. After a median follow-up of 10.8 months (range: 0.2-34.1), median PFS and OS were not significantly different between patients with or without BM. BM was not found as PFS prognosis factor in multivariate analysis (HR=1.03; 95% CI=[0.79; 1.33], p=0.85). At least one serious adverse event (SAE) was reported in 30% of aNSCLC patients with BM (n=25) and in 32% of patients without BM (n=106); 13% (n=11) and 12% (n=40) of patients experienced at least one bevacizumab-related SAE, respectively. Three patients in each group died from bevacizumab-related events.

	aNSCLC patients with brain metastasis - N=84 (months, [CI 95%])	**aNSCLC patients without brain metastasis - N=423 (months, [CI 95%])**	**Logrank test *p value***
Median PFS	6.5 [5.7; 8.1]	6.9 [5.9; 7.6]	0.57
Median OS	14.5 [10.0; -]	12.5 [10.1; 14.7]	0.33

Conclusion: In this study, no differences were observed between advanced NSCLC patients with and without brain metastasis in terms of clinical benefit (survival and safety) from first-line chemotherapy combined with bevacizumab. Nature, severity and outcome of AEs were consistent with the known safety profile of bevazicumab.

Keywords: Brain metastasis, bevacizumab, Non-small-cell lung carcinoma

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.06 EFFECT OF 2L RAMUCIRUMAB AFTER RAPID TIME TO PROGRESSION ON 1L THERAPY: SUBGROUP ANALYSIS OF REVEL IN ADVANCED NSCLC

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Background: In REVEL, ramucirumab+docetaxel in the second-line (2L) treatment of patients with advanced NSCLC led to improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), independent of histology. This exploratory, post-hoc analysis focuses on patients who progressed rapidly on first-line (1L), and who traditionally have a poor prognosis in the 2L setting. In REVEL, treatment benefit was observed in patients with progressive disease as their best overall response to 1L and in patients who were on 1L for only a short time (Reck M, ASCO 2017, Abstr 9079). Here, we report outcomes from patients who participated in REVEL according to their time to tumor progression (TTP) on 1L (ClinicalTrials.gov, NCT01168973). **Method:** Patients with advanced NSCLC of squamous or nonsquamous histology with disease progression during or after 1L platinum-based chemotherapy were randomized (1:1) to receive docetaxel 75 mg/m^2 and either ramucirumab 10 mg/kg or placebo on day 1 of a 21-day cycle. OS was the primary endpoint. Secondary endpoints included PFS, ORR, safety, and patient-reported quality-of-life (QoL). Response was assessed according to RECIST v1.1. QoL was assessed with the Lung Cancer Symptom Scale. TTP on 1L, defined as the time

from start of 1L until progressive disease, was assessed for the REVEL intent-to-treat population. **Result:** Of 1253 patients in REVEL, 11% had TTP ≤9 weeks, 17% had TTP ≤12 weeks, and 28% had TTP ≤18 weeks on 1L therapy. Baseline characteristics of each subgroup generally were balanced between treatment arms. Efficacy, safety, and QoL outcomes by TTP are shown in the table *(See next page).*

Outcomes in Patients From the REVEL Study by Time to Tumor Progression on First-Line Therapy						
	≤9 Weeks		≤12 Weeks		≤18 Weeks	
INTENT-TO-TREAT POPULATION	**Ramucirumab +Docetaxel N = 71**	**Placebo +Docetaxel N = 62**	**Ramucirumab +Docetaxel N = 111**	**Placebo +Docetaxel N = 98**	**Ramucirumab +Docetaxel N = 182**	**Placebo +Docetaxel N = 172**
Median OS, months (95% Confidence Interval [CI])	8.28 (5.19, 10.84)	4.83 (3.09, 6.90)	9.10 (6.70, 10.84)	5.78 (4.30, 7.49)	8.51 (6.97, 9.95)	5.95 (4.44, 6.97)
Unstratified Hazard Ratio (HR) (95% CI)	0.69 (0.47, 1.01)		0.74 (0.54, 1.00)		0.80 (0.63, 1.01)	
12-month survival rate, % (95% CI)	47 (35, 58)	32 (20, 44)	34 (25, 43)	23 (15, 32)	30 (23, 37)	24 (18, 31)
18-month survival rate, % (95% CI)	20 (11, 31)	12 (5, 24)	17 (10, 26)	13 (6, 22)	17 (11, 23)	13 (8, 20)
Median PFS, months (95% CI)	3.01 (2.66, 4.07)	1.48 (1.41, 1.87)	3.61 (2.76, 4.21)	1.61 (1.45, 2.60)	3.22 (2.79, 4.14)	1.61 (1.48, 2.60)
Unstratified HR (95% CI)	0.69 (0.48, 0.98)		0.73 (0.55, 0.97)		0.72 (0.58, 0.89)	
ORR (complete response [CR]+partial response [PR]), %, (95% CI)	18.3 (10.1,29.3)	3.2 (0.4, 11.2)	18.9 (12.1, 27.5)	9.2 (4.3, 16.7)	19.2 (13.8, 25.7)	10.5 (6.3, 16.0)
Disease Control Rate (CR+PR+stable disease), % (95% CI)	50.7 (38.6, 62.8)	30.6 (19.6, 43.7)	49.5 (39.9, 59.2)	37.8 (28.2, 48.1)	50.5 (43.1, 58.0)	36.0 (28.9, 43.7)
Average Symptom Burden Index, time to deterioration HR (95% CI)	0.60 (0.30, 1.22)		0.49 (0.27, 0.88)		0.74 (0.49, 1.12)	
Total Score Lung Cancer Symptom Scale, time to deterioration HR (95% CI)	0.89 (0.45, 1.78)		0.71 (0.41, 1.23)		0.90 (0.60, 1.36)	
SAFETY POPULATION	**Ramucirumab +DocetaxelN = 70**	**Placebo +DocetaxelN = 61**	**Ramucirumab +DocetaxelN = 109**	**Placebo +DocetaxelN = 97**	**Ramucirumab +DocetaxelN = 179**	**Placebo +DocetaxelN = 171**
Any Treatment-Emergent Adverse Event (TEAE), n (%)	67 (95.7)	58 (95.1)	105 (96.3)	92 (94.8)	173 (96.6)	159 (93.0)
Grade ≥3	50 (71.4)	46 (75.4)	80 (73.4)	69 (71.1)	134 (74.9)	113 (66.1)
TEAE leading to discontinuation	4 (5.7)	2 (3.3)	5 (4.6)	3 (3.1)	13 (7.3)	6 (3.5)
TEAE leading to dose adjustment	24 (34.3)	19 (31.1)	39 (35.8)	28 (28.9)	70 (39.1)	47 (27.5)
TEAE leading to death	5 (7.1)	4 (6.6)	7 (6.4)	6 (6.2)	9 (5.0)	8 (4.7)
TESAE	25 (35.7)	30 (49.2)	46 (42.2)	46 (47.4)	80 (44.7)	71 (41.5)

Conclusion: Efficacy, toxicity, and QoL outcomes among ramucirumab+docetaxel patients who have aggressive disease with rapid TTP on 1L therapy appear consistent with the intent-to-treat population. The benefit/risk profile for these rapid progressors suggests that such patients may derive meaningful benefit from ramucirumab+docetaxel in the 2L setting.

Keywords: ramucirumab, REVEL, non-small cell lung cancer

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.07 THE PREDICTIVE VALUE OF INTERFERON-Γ RELEASE ASSAYS (IGRA) FOR CHEMOTHERAPY RESPONSE IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: INF-γ had recently been known to take part in cancer immunology and its interactions with chemotherapy were also described. Our previous study had showed that impaired PHA-stimulated INF-γ (PSIG) response from peripheral lymphocytes was associated with lower one-year overall survival in advanced non-small cell lung cancer (NSCLC) patients. In this study, we aimed to evaluate the correlation between PSIG and chemotherapy response. **Method:** Form January 2011 to August 2012, 340 newly-diagnosed lung cancer patients from 4 referral centers in Taiwan were enrolled in a prospective latent TB observational study. Patients who had advanced NSCLC and had been treated with chemotherapy were included in this study. The pretreatment PSIG levels were evaluated by Interferon-Gamma Release Assay (IGRA) with QuantiFERON-TB In-Tube (Qiagen, Germany). Patients were grouped into high PHA response group if their PSIG levels were above the median level; the others were grouped into low PHA response group. Their demographic characteristics, tumor response, and survival were investigated and correlated with PSIG levels. **Result:** Eighty-four patients were enrolled in this study. The response rate in high PHA response group was 45.2%, versus 35.7% in lower PHA response group (p=0.999190). The disease control rate in high PHA response group was 76.2%, versus 52.4% in low PHA response group (p=0. 023999). In multivariate analysis, PSIG response was an independent predictor for disease control rate (OR=3.017, 95% CI= 1.115-8.165). Also, the Kaplan-Meier curves and estimates survival analysis demonstrated both longer progression-free survival (p=0.008) and overall survival (p=0.003) in high PHA response group. **Conclusion:** Higher pre-treatment PSIG response, assayed by IGRA testing, was associated with better disease control rate and survival among advanced NSCLC patients treated with chemotherapy.

Keywords: Interferon-Gamma, non-small cell lung cancer, chemotherapy

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.09 THE COST AND THE BENEFIT: FRONT-LINE IMMUNOTHERAPY FOR NON-SMALL CELL LUNG CANCER

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Background: The U.S. Food and Drug Administration approved pembrolizumab in combination with carboplatin/pemetrexed for patients with untreated, metastatic, non-squamous, non-small cell lung cancer based on KEYNOTE 021G. This trial randomized 123 patients to carboplatin/pemetrexed versus carboplatin/pemetrexed/pembrolizumab with maintenance pembrolizumab. Maintenance pemetrexed was optional in both arms. Progression-free survival (PFS) was longer for carboplatin/pemetrexed/pembrolizumab (not reached vs. 8.9 months, HR 0.49, 95% CI 0.29-0.83, p=0.0035). No statistically significant improvement in overall survival (OS) has yet been demonstrated (HR 0.69, 95% CI 0.36-1.31, p=0.13), with neither arm reaching median OS. Frontline pembrolizumab improves PFS and OS in comparison to chemotherapy in patients with high PD-L1 expression. Drug cost information should be available to providers to better inform decision-making and assess value. **Method:** Dose calculations were based on the following: GFR 125, BSA 2.00 m2, carboplatin AUC 5, pemetrexed 500mg/m2, and pembrolizumab 200mg. Drug costs were obtained via the Centers for Medicare & Medicaid Services Pricing File. **Result:** Four cycles of carboplatin/pemetrexed/pembrolizumab followed by maintenance pembrolizumab and pemetrexed cost $618,889. Four cycles of carboplatin/pemetrexed followed by pemetrexed maintenance cost $249,972. Pembrolizumab alone for an equivalent number of cycles cost $368,917. Table 1: Regimen Cost Calculations

Induction, 4 cycles (Cost)	Maintenance, 24 months, 35 cycles (Cost)	Total Medication Cost
Carbo AUC 5 + Pemetrexed 500mg/m2 + Pembro 200mg q3w ($63,666)	Pembro 200mg + Pemetrexed 500mg/m2 q3w ($555,223)	$618,889
Carbo AUC 5 + Pemetrexed 500mg/m2 + Pembro 200mg q3w ($63,666)	Pembro 200mg q3w ($331,079)	$394,745
Carbo AUC 5 + Pemetrexed 500mg/m2 + Pembro 200mg q3w ($63,666)	Pemetrexed 500mg/m2 q3w ($224,143)	$287,809
Pembro 200mg q3w ($37,838)	Pembro 200mg q3w ($331,079)	$368,917
Carbo AUC 5 + Pemetrexed 500mg/m2 ($25,828)	Pemetrexed 500mg/m2 ($224,143)	$249,972

Conclusion: While the addition of pembrolizumab to front-line therapy resulted in an improvement in PFS in a phase II study of 123 patients, it increased medication costs 2.4 fold, from $249,972 to $618,889. Phase III trials are underway to more definitively assess the benefit of immunotherapy administered with chemotherapy in a broad population of patients. Treatment with carboplatin/pemetrexed/pembrolizumab cost 1.7 times that of pembrolizumab alone, and the addition of chemotherapy is of unclear benefit for patients with high PD-L1 expression. Further defining patient subsets who will benefit the most from this costly regimen should be undertaken. It is crucial healthcare professionals and patients understand the cost implications of front line therapy options.

Keywords: Immunotherapy, Non-small cell carcinoma, cost

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.10 PROGNOSTIC FACTORS IN NSCLC PATIENTS TREATED WITH A FOURTH-LINE THERAPY

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Background: Emergence of new active drugs and improvement in supportive care make it more likely for patients with advanced NSCLC to receive a fourth-line therapy. However, no survival benefit of such treatment has ever been demonstrated yet, although some studies suggest that it may be effective in selected patients. A better selection could avoid exposing patients to futile and toxic treatments. We conducted a study aiming at identifying prognostic factors in patients with advanced NSCLC treated with a fourth-line therapy. **Method:** In this retrospective, multicentric study, patients with advanced NSCLC receiving a fourth-line therapy were included. Factors associated with prolonged overall survival (OS, defined as OS >6 months) were identified by univariate and multivariate analysis using a Forward method. **Result:** 151 patients were included in this study between Jan 2015 and Dec 2016. Median age was 60 (range 55-64). Most patients were male (70%) and had adenocarcinoma (72%). Most common prior treatments included platinum-based chemotherapy (92%), single-agent chemotherapy (81%), targeted therapies (46%) and immunotherapy (9%). Median OS was 7.39 months (6.7-9.43). Nine factors were significantly associated with OS >6 months: current smoker (Hazard Ratio (HR) 1.99, 95% confidence interval[1.16-3.41]), former smoker (HR 0.51[0.30-0.98]), Karnofsky Index (KI) ≥ 90% at the start of fourth-line therapy (HR 0.35[0.19-0.65]), weight loss since first-line therapy (HR 1.85[1.06-3.23]), early stage at diagnosis (HR 0.48[0.24-0.96]), number of cycles and delay since first-line therapy (HR 0.94[0,89-0,99]and 0.99[0.99-1]), Progressive Disease (PD) as Best Objective Response (BOR) in the first 3 lines of treatment (HR 2.92[1.9-5.37]), absence of grade ≥ 3 Adverse Events (AEs) during first-line therapy(HR 0.54[0.31-0.94]). Among them, 4 independent variables were found to be statistically significant by multivariate analysis, including early stage at diagnosis (HR 0.37[0.16-0.58]), absence of grade ≥ 3 AEs during first-line therapy (HR 0.56[0.32-0.98]), PD as BOR in the first 3 lines of treatment (HR 3.06[1.64 -5.73]) and KI ≥ 90% at the start of fourth-line therapy (HR 0.31[0.16-0.58]). **Conclusion:** We highlighted 4 factors significantly associated with OS >6 months in patients treated with fourth-line advanced NSCLC. These factors need to be prospectively assessed to confirm if they could help identifying patients who may benefit from fourth-line therapy.

Keywords: Fourth-line, Prognostics factors, NSCLC

MA 03 CHEMOTHERAPY
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 03.11 TARGETING CDCA3 ENHANCES SENSITIVITY TO PLATINUM-BASED CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related mortality worldwide with a 5 year survival rate of 15%. Non-small cell lung cancer (NSCLC) is the most commonly diagnosed form of lung cancer. Cisplatin-based regimens are currently the most effective chemotherapy for NSCLC, however, chemoresistance poses a major therapeutic problem. New and reliable strategies are required to avoid drug resistance in NSCLC. Cell division cycle associated 3 (CDCA3) is a key regulator of the cell cycle. CDCA3 modulates this process by enabling cell entry into mitosis through degradation of the mitosis-inhibitory factor WEE1. Herein, we describe CDCA3 as a novel prognostic target to delay or prevent cisplatin resistance in NSCLC. **Method:** CDCA3 expression was investigated using bioinformatic analysis, tissue microarray immunohistochemistry and western blot analysis of matched NSCLC tumour and normal tissue. CDCA3 function in NSCLC was determined using several in vitro assays by siRNA depleting CDCA3 in a panel of three immortalized bronchial epithelial cell lines (HBEC) and seven NSCLC cell lines. To determine strategies to suppress CDCA3 activity the phosphorylation status of CDCA3 was assessed using mass spectrometry analysis. Kinases that phosphorylate CDCA3 were identified using a siRNA screen and high content immunofluorescence and microscopy approaches. **Result:** We have

previously shown that CDCA3 transcripts and protein levels are elevated in resected NSCLC patient tissue, high mRNA levels being associated with poor survival. CDCA3 depletion markedly impairs proliferation in seven NSCLC cell lines by inducing a G2 cell cycle arrest. Silencing of CDCA3 also greatly sensitises NSCLC cell lines to cisplatin. Consistently, NSCLC patients with elevated CDCA3 levels and treated with cisplatin have a poorer outcome than patients with reduced CDCA3 levels. To aid patient response to cisplatin, we have been looking at strategies to suppress CDCA3 expression in tumour cells. Accordingly, in response to cisplatin, CDCA3 is phosphorylated (S^{222}) via casein kinase 2 (CK2) which prevents CDCA3 degradation in NSCLC cells. Moreover, the CK2 inhibitor CX-4945 reduces CDCA3 levels in cisplatin treated cells. CX-4945 increased cisplatin-induced cell death in control cells. The efficacy was further enhanced in CDCA3 depleted NSCLC cells. **Conclusion:** Our data highlight CDCA3 as a novel factor in the pathogenesis of NSCLC. We propose that preventing cisplatin-induced CDCA3 phosphorylation by targeting CK2 is a worthwhile and novel strategy in treating NSCLC and may ultimately benefit patient outcome by preventing cisplatin resistance.

Keywords: non-small cell lung cancer, prognostic factor, cisplatin chemotherapy

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.01 PROSPECTIVE COMPARATIVE EVALUATION OF PATIENT AND CAREGIVER PERSPECTIVES ON A MULTIDISCIPLINARY MODEL OF LUNG CANCER CARE

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Background: Coordinated multidisciplinary (MD) lung cancer care, with all key specialists concurrently providing early input to develop a consensus care plan in collaboration with patients and their caregivers, may improve patient-centered outcomes over the usual serial care (SC) model, but needs rigorous evaluation. **Method:** Prospective, longitudinal study comparing newly-diagnosed lung cancer patients receiving MD vs. SC within the same US healthcare system. The MD intervention was implemented from lung cancer care initiation until definitive treatment decision. After that, both cohorts of patients received their actual cancer treatments within the same environments. At baseline and 6 months, patients completed treatment-related satisfaction measures from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) and the Functional Assessment of Cancer Therapy- Lung (FACT-L) quality of life instrument. All measures were coded so that larger scores are better. Time-specific comparisons were made with the Wilcoxon-Mann-Whitney test and changes from baseline to 6 months were compared between MD vs. SC patients in mixed linear models. **Result:** The 463 patients who participated (156 MD, 307 SC) were similar in sex and health insurance. MD cohort was slightly older (69 v 66 years), with more racial minorities (37% v 29%). Patients receiving MD care reported greater satisfaction with the treatment plan ($p=0.0266$) and overall quality of care ($p<0.0010$) at 6 months. Additionally, satisfaction with the treatment plan showed greater improvement over time for MD vs. SC (p-value for trend=0.0046). SC patients showed more improvement in satisfaction with overall care than MD patients, but did not reach the level of satisfaction of MD patients at 6 months (p-value for trend=0.0018). Caregivers of MD patients perceived receiving better quality of care compared to other lung cancer patients than caregivers of SC patients ($p=0.0049$). Caregiver satisfaction did not differ between MD and SC in the communication measures or overall quality, and did not have significant differences in the trend over time. Patient reported Health-Related Quality of Life (HRQOL) improved from baseline to 6 months for the lung cancer-specific scale compared with no change with SC (p-value for trend= 0.0334). Other HRQOL scales were similar between groups **Conclusion:** Compared with SC patients, MD patients experienced improved lung cancer-specific HRQOL and greater satisfaction with both treatment plan and quality of care received. MD patients' caregivers were more likely than SC patients' caregivers to think their care was better than that of other patients.

Keywords: Patient Perspectives, Multidiciplinary Care, Patient Satisfaction

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.02 ASSESSING THE PSYCHOSOCIAL NEEDS OF NEWLY DIAGNOSED NSCLC PATIENTS: IDENTIFYING THE POPULATION MOST AT-RISK

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Background: The Psychosocial Screen for Cancer (PSSCAN-R) questionnaire and the Canadian Problem Checklist (CPC) are validated screening tools used to identify the psychosocial needs of patients with cancer. The questionnaire identifies at-risk patients requiring timely psychosocial intervention and the CPC comprises of patient-reported support needs in 6 psychosocial domains. The study goal was to review reported needs of patients with NSCLC to facilitate the development of programs and resources specific to those identified as at-risk for psychosocial distress. **Method:** All patients with NSCLC referred to BC Cancer Agency centres from 2011-2015, who completed a prospective PSSCAN-R and CPC questionnaire at the time of their first visit, were included in the study. Demographics and baseline disease characteristics were collected retrospectively. Univariate analysis using the Chi-squared test and Fisher's exact test were used to compare patient groups based on gender, age and stage of disease. **Result:** 4313 patients completed the PSSCAN-R and CPC questionnaire. The median age was 70 (21-99), with 50% female and 51% of patients with stage IV disease. 29% of patients live alone with 13% having lost their spouse/partner. However, 93% of patients report regular contact with friends/relatives and 85% have someone who can provide assistance with daily tasks (shopping, cooking, transportation). Female patients, patients aged 65 or younger, and those with advanced disease were more likely to report significantly higher levels of anxiety and depression, and reported higher number of needs on the CPC.

	Total	Female (n=2179)	Male (n=2134)	p	Age <65 (n=1816)	Age ≥ 65 (n=2997)	p	Stage I-III (n=2098)	Stage IV (n=2215)	p
Anxiety Moderate/Severe	1918 (44%)	1075 (49%)	843 (40%)	<0.001	721 (55%)	1197 (40%)	<0.001	819 (39%)	1099 (50%)	<0.001
Depression Moderate/Severe	1348 (31%)	766 (35%)	582 (27%)	<0.001	508 (39%)	840 (28%)	<0.001	593 (28%)	755 (34%)	<0.001
CPC Domains										
Emotional (Fears/worries, sadness, frustration/anger, changes in appearance, intimacy/sexuality)	2998 (70%)	1646 (76%)	1352 (63%)	<0.001	1018 (77%)	1980 (66%)	<0.001	1370 (65%)	1628 (74%)	<0.001
Informational (understanding my illness/ treatment, talking with the health care team, making treatment decisions, knowing about available resources)	2885 (70%)	1529 (70%)	1356 (64%)	<0.001	963 (73%)	1922 (64%)	<0.001	1323 (63%)	1562 (30%)	<0.001
Social/Family (feeling a burden to others, worry about family/friends, feeling alone)	2320 (54%)	1292 (59%)	1028 (48%)	<0.001	832 (63%)	1488 (50%)	<0.001	1046 (50%)	1274 (58%)	<0.001
Physical (concentration/memory, sleep, weight)	2675 (62%)	1375 (63%)	1300 (61%)	0.140	894 (68%)	1781 (59%)	<0.001	1199 (57%)	1476 (67%)	<0.001
Practical (work/school, finances, getting to & from appointments, accommodation)	1704 (40%)	877 (40%)	827 (39%)	0.319	697 (53%)	1007 (34%)	<0.001	793 (38%)	911 (41%)	0.027
Spiritual (meaning/purpose in life, faith)	851 (20%)	435 (20%)	416 (20%)	0.702	281 (21%)	570 (21%)	0.081	389 (19%)	462 (21%)	0.061

Conclusion: Newly diagnosed patients with NSCLC report clinically higher levels of anxiety and depression and have greater number of concerns in multiple psychosocial domains. Resources should be developed for lung cancer patients based on their care needs with careful consideration of patients' age, gender and disease stage to optimally support their psychosocial needs during treatment and follow up.

Keywords: Psychosocial Needs, lung cancer, supportive care

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.03 PHYSICIAN EMPATHY AND SENSITIVITY TO A PATIENT'S EMOTIONAL JOURNEY CAN BE CRITICAL TO PATIENT OPTIMISM AND EMPOWERMENT

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Background: A lung cancer diagnosis can be devastating for the patient and their family. In most cases patient perception of the disease is that of a "death sentence" and based on anecdotal or direct experience with a family member or friend where "nothing could be done." These sentiments are especially true among smokers and former smokers. Few patients are aware of the treatment option landscape that is emerging today in lung cancer. At the time of diagnosis, a patient not only relies heavily on the medical recommendations of their physician but also on the attitude their physician projects to guide their treatment journey. **Method:** The Addario Lung Cancer Foundation (ALCF) conducted a qualitative market research study to map the emotional journey of patients diagnosed with lung cancer to identify opportunities to improve patient engagement and empowerment and to identify trusted sources of information and education. A total of 26 1-hour patient interviews were conducted by an independent market research firm in a blinded format. **Result:** One of the key findings of this study is that patient disease outlook closely mirrors their physician interactions. At the point of diagnosis patients are very reliant upon their physician and are overwhelmed and reluctant to question information from their medical staff. Patients reported that physician attitude made a difference in their care and optimism. One patient recalled "My first oncologist came in and said, 'It's not curable. We'll try a few things and nothing will work.' And I thought to myself, 'What am I doing here?'" For smokers/former smokers many patients were met with feelings of blame and shame based on the interactions with medical staff collecting their histories. Those who sought out second opinions from more supportive physicians were more optimistic going into treatment. **Conclusion:** Physician empathy and sensitivity to a patient's emotional journey can be critical to patient optimism and empowerment. Opportunities exist to educate physicians on the role they play for patients at this vulnerable time. Creating a cadre of key opinion leaders dedicated to empathetic patient care, changing the stigma around smoking and minimizing biases can impact

the lung cancer community. These findings also highlight the role that advocacy groups, such as ALCF can play in reaching patients early, empowering patients to seek second opinions and providing education that gives them options and hope.

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.05 THE IMPACT OF THE MESO FOUNDATION ON ADVOCACY EFFORTS FOR FUNDING MESOTHELIOMA RESEARCH

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Background: The Mesothelioma Applied Research Foundation is the nonprofit collaboration of patients and families, physicians, advocates, and researchers dedicated to eradicating the life-ending and vicious effects of mesothelioma. The Meso Foundation's Advocacy Program objective is to obtain federal funding for mesothelioma research. **Method:** An analysis was performed of the Meso Foundation's advocacy efforts and grant funding from years 2000- 2015. **Result:** The Meso Foundation has funded 103 projects from 8 countries for a total awarded amount of 9.8 million dollars. From 2000- 2015, the Meso Foundation grant program has funded research that has produced over 240 publications in peer reviewed journals. As a direct result of Foundation advocacy, the Department of Defense has awarded a total of $12.4 million to mesothelioma research since 2008. The Meso Foundation's grant program has funded the basic science research that helped lay the groundwork for several mesothelioma clinical trials. A few of the more notable trials include the measles virus and the WTI Vaccine. Several of the proposals funded by Meso Foundation grants have extended to global levels through presentations at international conferences including but not limited to International Association for the Study of Lung Cancer (IASLC), American Society of Clinical Oncology (ASCO), and American Association for Cancer Research (AACR). **Conclusion:** Through actively engaging members of congress, the Meso Foundation has successfully advocated for increased funding for mesothelioma research. The Meso Foundation is committed to leveraging the knowledge we gain from our own research, as well as discoveries made by our collaborations with academic institutions and industry partners to work toward the development of innovative treatments and care platforms for mesothelioma patients and their families.

Keywords: Mesothelioma, Advocacy

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.06 DEVELOPING A LUNG CANCER CLINICAL QUALITY REGISTRY FRAMEWORK TO COLLECT LONGITUDINAL PATIENT-REPORTED OUTCOMES

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Background: When captured by psychometrically-sound patient-reported outcomes measures (PROMs), patients' appraisals of their symptoms, quality of life and functional status can provide powerful data to better inform clinicians about the impact of health conditions and the consequences of medical care. Reviewing and reporting on integrated PROMs alongside clinical data may translate to health service improvements and efficiencies. There are, however, many challenges including the need to find sustainable and cost-efficient methods for the routine collection of PROMs across the whole patient journey. This two-phase study set out to develop a lung cancer clinical quality registry framework to collect longitudinal patient-reported outcome measures. Phase 1 focused on the development of the data collection framework and phase 2 sees a 12-month implementation and mixed-method evaluation of the feasibility of implementing the framework. We will report on development of the framework and provide preliminary results on the implementation phase. **Method:** The development phase utilised a formative evaluation method to decide on essential aspects of the PROMs framework. Specifically, a Delphi process was employed to seek consensus on PROMs to administer and the schedule of assessments, with a specific focus on clinical relevance and feasibility of administration. The first Delphi round consisted of individual interviews with lung cancer clinical experts to generate a list of domains to be included in the PROMs. In the second round, aggregated results were presented to the panel and domains of interest were considered alongside PROMs meeting minimum measurement standards. Then, four patients previously treated for lung cancer were invited to provide feedback on the content of PROMs and data collection methods. **Result:** From Delphi findings, it was determined that the EORTC QLQ-C30 and the lung cancer-specific module (QLQ LC13) would be administered at baseline and two, six and 12 months after baseline, and a brief social isolation measure (PROMIS) would be administered at baseline only. A clearly defined subset of patients about to commence chemo-radiation treatment for lung cancer was chosen for the implementation phase and commenced on October 31 2016. To date, 74% (14/19) of eligible patients have been recruited thus far. Preliminary data indicate high adherence to baseline assessments (100%). Adherence is much lower at two months (50%), with non-adherence frequently due to side effects or ill health (38%). **Conclusion:** Identifying and deciding which PROMs to collect, the overall purpose of PROMs collection, data completeness and utility requires careful consideration and evaluation to determine framework sustainability.

Keywords: Patient-reported outcomes, clinical quality registry, feasibility

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.07 UNDERSTANDING PATIENT BARRIERS TO UTILIZATION OF LOW DOSE CT LUNG CANCER SCREENING

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Background: Despite evidence that lung cancer disproportionately affects minority populations, there is a paucity of data describing the impact of lung cancer screening. Results of NLST may not be generalizable to all populations given that 91% of the participants were Caucasians. Further study of lung cancer screening in a diversity of racial and ethnic groups is a necessary step in the implementation of lung cancer screening. Before underrepresented populations can be screened, community perceptions about lung cancer screening must be explored and barriers to screening must be identified. The purpose of our study was to identify potentially correctable barriers to obtaining LDCT for lung cancer screening in a diverse, but predominantly African American population. **Method:** We developed a questionnaire consisting of 22 items. Five questions assessed patient demographics including socioeconomic status and insurance coverage. Two questions assessed patient access and utilization of health care. Three questions assessed smoking history and prevalence in interpersonal relationships. One questions assessed patient concern about lung cancer. Two questions measured patient knowledge about lung cancer. One question addressed patient willingness to go to a doctor's appointment to learn more about lung cancer screening. One question elicited whether LDCT had been mentioned by a healthcare provider. Six questions assessed awareness and knowledge about LDCT lung cancer screening. One question addressed reasons for non-adherence to appointments. **Result:** The questionnare was complete by 100 patients. Almost all of our patients reported having health insurance and a primary care doctor (96%). 50% of patients are current or former smokers. 83% are current or former smokers or have friends and/or family members who are heavy/long time smokers. 90% of patients knew that smoking is the most common cause of lung cancer. 56% of patients know that lung cancer can be treated successfully at least sometimes. 81% of patients reported to be at least somewhat concerned that they or someone they know can die of lung cancer. 87% of patients are willing to go to a doctor's appointment to learn more about lung cancer screening. 100 % of patients reported to have not heard about LDCT from their doctors. The average score was 2/6 (33%) on items accessing knowledge about lung cancer screening. Cost was the most frequently reported reason (52%) for nonadherence to appointments. **Conclusion:** Our study was able to identify potentially correctable barriers to utilization of low dose CT lung cancer screening such a lack of primary care support and perceived cost.

Keywords: lung cancer screening, Population barriers, low dose CT

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.09 A STUDY ON THE DAMAGE OF PASSIVE SMOKING TO JAPANESE LUNG CANCER PATIENTS

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Background: Japan's measures to prevent passive smoking are considered to be among the world's worst. Creating smoke-free environments is an urgent task for Japan as it prepares to host the 2020 Tokyo Olympics and Paralympics Games. In spring of 2017, discussions on a draft bill to strengthen measures against passive smoking were stalled due to opposition from within the ruling party. One lawmaker remarked that "(Cancer patients) don't have to work", indicating that patients can choose their occupation and avoid secondhand smoke as they wish. Against this backdrop, the Japan Lung Cancer Alliance conducted a survey on damage by secondhand smoke to cancer patients. Based on the survey' result, this study aims to shed light on the problems experienced by lung cancer patients including the impact of secondhand smoke on their employment. **Method:** For 5 days from 28 May to 1 June 2017, a survey by questionnaires was conducted on lung cancer patients. The announcement of the survey was made by ten patient advocacy groups. **Result:** There were 231 responses, among which valid responses were 215. 91 percent of the respondents considered passive smoking "unpleasant" due to fears or anxieties for recurrence of lung cancer and/or hatred. It was found that among those respondents who were employed at the time of the survey, about 31 percent had been exposed to secondhand smoke at their workplace, and 4.2 percent had quitted their job. Not only at the work place, 6.2 percent of the respondents were exposed to the secondhand smoke at home, event after they were diagnosed as lung cancer. **Conclusion:** It is understood that working cancer patients worry about recurrence of cancer and/or hatred. Moreover, the experiences of those lung cancer patients who had left their job because of passive smoking reveal a lack of the freedom to choose their occupation. The urgent countermeasure is also required to prevent the passive smoking at home.

Japan's delay in adopting measures against passive smoking appears be related to an insufficient level of understanding in the society about difficulties faced by cancer patients. It is hoped that this study will draw attention to the damage by passive smoking to lung cancer patients and foster international support for the advocacy of legislation enacting stricter measures.

Keywords: passive smoking from family, patient advocacy, working with cancer

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.10 AN ASSESSMENT OF THE WILLINGNESS TO PROVIDE SERIAL BIO-SPECIMENS: EXPERIENCE FROM AN IRISH TERTIARY CANCER CENTRE

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Background: The rising imperative to improve our understanding of cancer heterogeneity and individualised drug response has led to a high demand for biopsy material. With improvements in technologies, there is now a move away from more traditional tissue based sampling to liquid based biopsies. 'Liquid biopsies' provide a non-invasive means for molecularly profiling patients with cancer, thus benefiting patients and clinicians in terms of treatment choice and shared decision-making. We assessed the willingness of patients to undergo repeated tissue and/or 'liquid' based sampling. **Method:** Detailed questionnaires, assessing patients' perceptions of, and willingness to undergo serial biopsies were distributed to ambulatory patients at a tertiary cancer referral centre (St. James's Hospital, Dublin). Multivariate analysis was performed using ordinal logistic regression analysis. **Result:** The questionnaire response rate was 97% (247/255). Respondents were primarily female (73%), aged between 51-70 yrs (51%), with breast (39%), colorectal (16%), oesophagogastric (13%), and lung cancer (12%). Of those that responded, repeat biopsy of an easily accessible lesion was acceptable to 203 (82%) patients if recommended by an oncologist. However this reduced to 102 (41%) patients, if the purpose was solely for clinical trial. Acceptability decreased to 168 (68%) and 81 (33%) patients respectively for more invasive biopsies. Additionally, 79 (32%) patients were willing to undergo additional biopsy for research purposes only, with 54 (21%) patients uncertain of its utility in research. Lower performance status (OR=0.44, p=0.04) and the belief that biopsy was unimportant for research (OR=0.74, p=0.04) negatively impacted on willingness to undergo biopsy, while a prior invasive biopsy increased acceptance (OR=1.02, p=0.02). In terms of blood sampling, 82% of patients would consent to repeated blood sampling over the course of their treatment, with >5 samples considered acceptable by 51.5% of patients. Patients with lung cancer had 3.38 greater odds (OR=3.38, p=0.047) of consenting to a repeated blood sample for purely research purposes (compared to any other type of cancer); however their willingness to undergo repeat biopsy was similar to that of other patients (OR=1.99, p=0.129). Data analysis is currently on-going. **Conclusion:** Patients with cancer are willing to participate in serial sampling of blood and urine but are less likely to consent to repeated tissue biopsies. Patients with lung cancer were particularly amenable to repeated blood sampling compared to patients with other cancer types. This is significant given the recent data supporting the use of 'liquid' biopsy for real-time monitoring of resistance mutations and treatment response dynamics in patients with lung cancer.

Keywords: patient experience, repeated biopsy, liquid biopsy

MA 04 ADVOCACY: LISTEN TO THE PATIENTS
MONDAY, OCTOBER 16, 2017 - 11:00-12:30

MA 04.11 A COMPREHENSIVE VISION TO REDUCE LUNG CANCER STIGMA: CHANGING CULTURAL PERSPECTIVES ON LUNG CANCER

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Background: Lung cancer stigma has wide-reaching effects and impacts treatment, quality of life, survival, societal attitudes, research funding, and advocacy efforts. Those affected by lung cancer commonly feel hopeless, isolated, reluctant to share their diagnosis in addition to feelings of guilt, shame, anxiety and depression. Stigma responses can hinder information seeking information related to treatment options and psychosocial support and, tragically, can cause delays in diagnosis and even refusal of treatment. Major pan-cancer organizations, those dedicated to all lung diseases as well as lung cancer-specific organizations conduct awareness raising campaigns designed to confront lung cancer stigma, all working in some measure to create a more compassionate and empathic environment for those at-risk and diagnosed. These efforts have not been coordinated and to date, no known comprehensive vision to address lung cancer stigma in its entirety has been developed. **Method:** HIV/AIDS and mental health advocates have devoted extensive efforts to developing coordinated stigma reduction plans. While not always applicable, their approaches can inform our efforts in lung cancer. To develop a comprehensive framework to address lung cancer stigma, a synthesis of relevant strategies used in other disease-states, a review of lung cancer stigma literature and exploration of the efforts of organizations and individuals from around the world was conducted. **Result:** Awareness-raising, myth-busting and public health advocacy are featured prominently in other stigma-reduction plans. Lung cancer, like HIV/AIDS and other smoking-related cancers, must also address nihilism from medical professionals and work to ensure non-judgmental discussions and compassionate treatment environments that explore appropriate treatment options become the norm. Founded on seven key areas of opportunity, the plan includes multiple areas of impact that need to be addressed. Included are suggested remediation methods and real-world examples from all over the globe to illustrate creative ways lung cancer stigma reduction can be approached. This comprehensive, multi-level, multi-pronged vision allows individuals, systems and organizations to find points of convergence and work collaboratively on addressing the stigma so closely associated with lung cancer. **Conclusion:** Through a comprehensive approach, lung cancer stigma can be reduced and ultimately eliminated. To initiate a global conversation and better unite the lung cancer community, we offer this unifying strategy to address lung cancer stigma. Through the menu of stigma-reduction strategies, we hope to spark conversation, collaboration, and convergence. Dedicated medical professionals, survivors, loved ones, advocacy organizations and others can use the vision to apply appropriate strategies in their regions/countries and work collaboratively toward this all-important goal.

Keywords: stigma

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MA 05.01 INTEGRATING INDEL MUTATIONS INTO NEOANTIGEN PREDICTION IN LUNG CANCER: DEVELOPING PERSONALIZED CANCER VACCINES

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Background: Mutant neoantigens generated from genetic alterations that are exclusively present in tumors represent highly promising cancer vaccine targets. However, publically available neoantigen prediction algorithms only identify and utilize single nucleotide mutations (SNVs) but not short insertion and deletions (INDELs). Short INDELs can lead to the generation of novel junctional or frameshift neoantigens which may be more immunogenic than neoantigens that result from single nucleotide missense mutations. **Method:** We developed a bioinformatics pipeline for neoantigen prediction using paired normal tissue and tumor exome sequencing, RNA sequencing and HLA binding prediction. 536 lung adenocarcinoma (LUAD) and 466 lung squamous cell carcinoma (LUSC) cases were analyzed using our bioinformatics pipeline. The non-synonymous somatic SNVs and short INDELs mutations were identified to generate a list of mutation neoantigen-derived and, when possible, their corresponding wild-type epitopes. Binding affinities of the paired wild-type and mutant peptides to HLA class I were then predicted and compared. **Result:** On average, 8.65 (range1-158) mutant neoantigen peptides per sample were identified in 395 out of 536 (73.6%) LUAD samples. Among them, 63.7% were SNVs and 36.3% were INDELs. On average, 8.54 (range 1-504) mutant neoantigen peptides per sample were identified in 360 out of 466 LUSC samples. Among those, 67% were SNVs and 33% were INDELs. Most neoantigen peptides are private in both LUAD and LUSC. The mutant neoantigen peptides identified from INDELs were predicted to have 3.9 (p= 2.42E-74) and 1.14 (p =5.44E-67) fold higher HLA class I binding affinity than wild type peptide compared to those from SNVs in LUAD and LUSC respectively. **Conclusion:** Tumor INDELs may be a rich source of neoantigens with a higher predicted high HLA binding affinity in lung cancers that warrant consideration in development of a personalized cancer vaccine.

Keywords: INDEL mutation, lung cancer, mutant neoantigen

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
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MA 05.02 STK11/LKB1 LOSS OF FUNCTION GENOMIC ALTERATIONS PREDICT PRIMARY RESISTANCE TO PD-1/PD-L1 AXIS BLOCKADE IN KRAS-MUTANT NSCLC

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Background: The genomic landscape of primary resistance to PD-1 blockade in lung adenocarcinoma (LUAD) is largely unknown. We previously reported that co-mutations in STK11/LKB1 (KL) or TP53 (KP) define subgroups of KRAS-mutant LUAD with distinct therapeutic vulnerabilities and immune profiles. Here, we present updated data on the clinical efficacy of PD-1/PD-L1 inhibitors in co-mutation defined KRAS mutant and wild-type LUAD patients and examine the relationship between genetic alterations in individual genes, tumor cell PD-L1 expression and tumor mutational burden (TMB) using cohorts form the SU2C/ACS Lung Cancer Dream Team and Foundation Medicine (FM). **Method:** The cohorts included 924 LUAD with NGS (FM cohort) and 188 patients with KRAS non-squamous NSCLC (SU2C cohort) who received at least one cycle of PD-1/PD-L1 inhibitor therapy and had available molecular profiling. Tumor cell PD-L1 expression was tested using E1L3N IHC (SU2C) and the VENTANA PD-L1 (SP142) assay (FM). TMB was defined as previously described and was classified as high (TMB-H), intermediate (TMB-I) or low (TMB-L). **Result:** 188 immunotherapy-treated (83.5% nivolumab, 11.7% pembrolizumab, 4.8% anti-PD1/PD-L1 plus anti-CTLA-4) pts with KRAS-mutant NSCLC were included in the efficacy analysis. The ORR differed significantly between the KL (8.8%), KP (35.9%) and K-only sub-groups (27.3%) (P=0.0011, Fisher's exact test). KL LUAC exhibited significantly shorter PFS (mPFS 1.8m vs 2.7m, HR=0.53, 95% CI 0.34-0.84, P<0.001, log-rank test) and OS (mOS 6.8m vs 15.6m, HR 0.53, 95% CI 0.34 to 0.84, P=0.0072, log rank test) compared to KRAS-mutant NSCLC with wild-type STK11. Loss-of function (LOF) genetic alterations in STK11 were the only significantly enriched event in PD-L1 negative, TMB-I/H compared to PD-L1 high positive (TPS≥50%), TMB-I/H tumors in the overall FMI cohort (Bonferroni adjusted $P=2.38x10^{-4}$, Fisher's exact test) and among KRAS-mutant tumors (adjusted P=0.05, Fisher's exact test) . Notably, PD-1 blockade demonstrated activity among 10 PD-L1-negative KP tumors, with 3 PRs and 4SDs recorded. In syngeneic isogenic murine models PD-1 blockade significantly inhibited the growth of Kras mutant tumors with wild-type LKB1 (K), but not those with LKB1 loss (KL), providing evidence that LKB1 loss can play a causative role in promoting PD-1 inhibitor resistance. **Conclusion:** Loss of function genomic alterations in STK11 represent a dominant driver of de novo resistance to PD-1/PD-L1 blockade in KRAS-mutant NSCLC. In addition to tumor PD-L1 status and tumor mutational burden precision immunotherapy approaches should take into consideration the STK11 status of individual tumors.

Keywords: KRAS, STK11, Immunotherapy

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
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MA 05.03 THE EARLY MONITORING OF DERIVED NEUTROPHIL-TO LYMPHOCYTE RATIO (DNLR) COULD BE A SURROGATE MARKER OF BENEFIT OF IMMUNOTHERAPY IN NSCLC

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Background: Baseline high derived NLR (dNLR>3, neutrophils/(leucocytes-neutrophils) ratio) has recently correlated with no benefit to immune checkpoint inhibitors (ICI) in advanced NSCLC, but the dynamic monitoring of dNLR has not been assessed in this population. **Method:** dNLR at baseline, at 2nd cycle and at progressive disease were retrospectively collected in advanced NSCLC patients treated with ICI from November 2012 to April 2017, in a multicentric cohort (N= 292) from 4 European centers. The primary endpoint was overall survival (OS), and secondary endpoints were progression free survival (PFS), response rate (RR) and disease control rate (DCR). **Result:** Out of 292 patients (67%) were males, 264 (92%) smokers and 239 (83%) with PS ≤1, with median age 64 years; 153 (52%) had adenocarcinoma and 114 (30%) squamous; 44 (15%) were KRASmut, 11 (4%) EGFRmut and 3 (1%) ALK positive. PDL1 was ≥ 1% by immunohistochemistry in 67 (76%), negative in 21 (24%) and unknown in 204 patients. The median of prior lines was 1 (0-10). The median follow-up was 12 months (m) [11-14]. The median PFS and OS were 4m [3-5] and 11m [9-15]. Baseline dNLR was>3 in 106 patients (36%) and at 2nd cycle in 90 patients (32%). dNLR>3 at baseline and at 2nd cycle were associated with poor PFS (p<0.0001 and p=0.0008, respectively), poor OS (both p<0.0001) and progressive disease (p=0.002 and p=0.005, respectively). At 2nd cycle of ICI, the dNLR status (> high or ≤ 3 low) changed in 63 patients: in 38 (14%) dNLR decreased; in 25 (9%) dNLR increased. According to the dNLR monitoring (combining dNLR at baseline et at 2nd cycle), the median OS was 17m (95%CI 13-NA) when dNLR remained low (n=153), 10m (95%CI 7-NA) when dNLR changed (n=64) and 4m (95%CI 3-7) when dNLR remained high (dNLR>3, n=64, p<0.0001).The dNLR monitoring was also associated with PFS (p=0.002), RR and DCR (p=0.003 and p=0.013, respectively). **Conclusion:** Monitoring dNLR at baseline and at 2nd cycle could be a routinely tool to early assess benefit to ICI in NSCLC patients on treatment. The dNLR monitoring showed a strong correlation with OS and PFS. Modification of dNLR between baseline and 2nd cycle impacts outcomes in NSCLC patients treated with ICI.

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MA 05.04 DISTINCT IMMUNOSUPPRESSIVE MICROENVIRONMENT DETERMINES POOR PROGNOSIS OF NONSMOKERS WITH ADENOCARCINOMA OF NON-SMALL CELL LUNG CANCER

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Background: Recent clinical trials have demonstrated the efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer (NSCLC). However, not all the patients receive survival benefit from these immunotherapies. In an attempt to refine the current strategy of cancer immunotherapy to treat NSCLC, we examined the influence of tumor-infiltrating lymphocytes (TILs) on postoperative survival. **Method:** We evaluated the prognostic significance of TILs ($CD4^+$, $CD8^+$, and $FOXP3^+$) comprehensively by immunohistochemical (n = 234) and immune-related gene expression analysis (n = 58), and explored the relationship between immune features and clinical characteristics including histological types, smoking habit, epidermal growth factor receptor mutation, and postoperative survival. **Result:** Compared with non-adenocarcinoma (non-AD) patients, adenocarcinoma (AD) tumors had significantly higher number of tumor-infiltrating $CD4^+$ T cells ($P < 0.05$) but lower $CD8^+$ T cells and $FOXP3^+$ T cells ($P < 0.01$). We found higher accumulation of $CD8^+$ T cells in non-AD patients was correlated with longer survival, indicating it is a better prognostic factor ($P < 0.02$). On the contrary, high accumulation of $CD8^+$ T cells and $FOXP3^+$ T cells were identified as unfavorable prognostic factors ($P < 0.05$) in AD patients, particularly in AD nonsmokers ($P < 0.02$). The expression of activated T cell-related genes including interferon gamma and granzyme was associated with $CD8^+$ T-cell accumulation in non-AD patients, but not in AD patients, especially in AD nonsmokers. Infiltrating $CD8^+$ T cells were significantly less activated in immunosuppressive microenvironment with high expression of immunoregulation related genes including GATA3, IL13, CCR4 and CCL17 in AD nonsmokers ($P < 0.05$). In AD nonsmokers, there are possibly immunodysfunctional $CD8^+GATA3^+$ T cells ($P < 0.01$) and immunoregulatory $CD8^+$ $FOXP3^+$ T cells ($P < 0.01$), accompanied by immunoregulatory $CD4^+FOXP3^+CCR4^+$ T cells ($P < 0.01$) that may be recruited by CCL17 produced by tumor-associated $CD163^+$ macrophages ($P < 0.05$) in IL13-associated tumor microenvironments ($P < 0.05$). **Conclusion:** In contrast to presence of activated $CD8^+$ T cells in non-AD, $CD8^+$ T cells are not activated, and may include dysfunctional and immunoregulatory T cells, accompanied by $FOXP3^+$ regulatory T cells and M2-like macrophages in IL13-associated tumor microenvironment of AD nonsmokers. Our study suggests that modulation of such immunosuppressive condition may be an attractive strategy for treatment of AD nonsmokers including immune-checkpoint blockade.

Keywords: Adenocarcinoma, smoking, Immunosuppression

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
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MA 05.06 COMPARISON STUDY OF PD-L1 IMMUNOHISTOCHEMISTRY ASSAYS WITH 22C3 AND 28-8: ANALYSIS ON SURGICAL SPECIMENS OF NSCLC.

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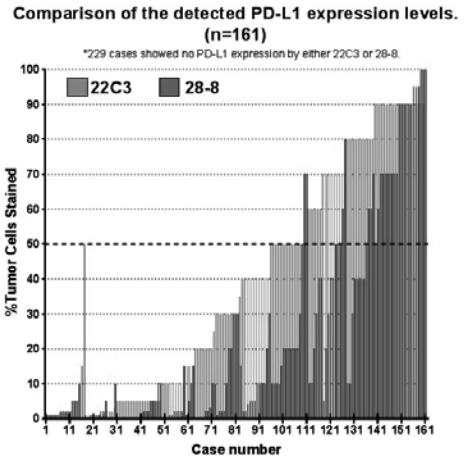
Background: The checkpoint inhibitors programmed cell death and its ligand (PD-L1) antibodies are promising treatment agents for patients with advanced non-small cell lung cancer (NSCLC). Their clinical efficacy is predicted by drug-tailored PD-L1 immunohistochemistry (IHC) assays. We aimed to identify the similarity and distinction of 22C3 and 28-8 IHC tests. **Method:** Three hundred and ninety consecutive cases of completely resected NSCLC between January 2009 and September 2014 that had adequate tissue samples were investigated. From the archived samples, 5-μm thick sections were cut and stained with PD-L1 IHC 22C3 PharmDx and 28-8 PharmDx (Dako, Santa Clara, CA). The staining and evaluation in 22C3 and 28-8 test were performed by two separate laboratories. PD-L1 expression and high PD-L1 expression were defined as ≥1% and ≥50% of tumor cells stained, respectively. Statistical significance was defined as a p-value of <0.05. **Result:** The

study population included 288 patients with adenocarcinomas, 70 with squamous cell carcinomas, 18 with large cell carcinomas, 9 with adenosquamous carcinoma and 5 with pleomorphic carcinoma. Two hundred and ninety-three patients had pStage I; 47, pStage II; and 46, p Stage IIIA tumors. Two hundred and twenty-nine specimens showed no PD-L1 expression with either 22C3 or 28-8. The detection rate of PD-L1 expression was 36.9% (144 cases) with 22C3 and 35.6% (139 cases) with 28-8, respectively (p= 0.710). The detection rate of high PD-L1 expression was 16.9% (66 cases) with 22C3 and 9.0% (35 cases) with 28-8 (p= 0.0013). The Spearman correlation coefficient was 0.866 (95% confidence interval, 0.838–0.890; p< 0.0001).



Conclusion: 22C3 IHC assay may be more sensitive to detect high PD-L1 expression in NSCLC compard to 28-8 IHC assay, whereas 22C3 and 28-8 showed no significant difference to detect PD-L1 expression. Further investigation is necessary to reveal clinical, pathological and molecular background. This approach will help better interpretation of PD-L1 IHC results.

Keywords: PD-L1, Immunohistochemistry, non-small cell lung cancer

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MA 05.07 WHOLE BODY PD-1 AND PD-L1 PET IN PTS WITH NSCLC

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Background: Tumor PD-L1 IHC relates moderately with treatment outcome following anti-PD1 therapy in pts with NSCLC and single biopsies do not account for tumor heterogeneity. Aim: 1. Assess safety of the PET procedures. 2. Quantify ^{89}Zirconium-labeled nivolumab (^{89}Zr-nivo) and ^{18}F-labeled BMS-986192 (^{18}F-PD-L1) uptake. 3. Assess tracer uptake heterogeneity. 4. Correlate tracer uptake with PD-1/PD-L1 IHC in tumor, stroma and with treatment outcome. **Method:** NSCLC pts eligible for treatment with nivolumab were included. Pts received whole body ^{18}F-PD-L1 and ^{89}Zr-nivo PET scans. Baseline tumor biopsy was required to assess PD-(L)1 IHC status (28.8 assay). SUV_{peak} was calculated for delineable lesions and correlated to PD-(L)1 IHC and response after 12 wks of nivolumab treatment. **Result:** 10 pts (3 ≥50%, 5 ≥1%, 5 negative by PD-L1 IHC) were enrolled and 37 lesions analysed. No toxicity related to radiotracer was observed. Tumor uptake of both tracers was visualized in all pts, but not in all lesions. Tracer uptake varied among pts with mean ^{18}F-PD-L1 SUV_{peak} 4.6, range 0.5 - 14.4 and mean ^{89}Zr-nivo SUV_{peak} 5.0, range 1.6 – 11 (p=0.03) and within pts with mean SUV_{peak} difference 3.6-fold (±2.1) and 2.4-fold (±0.77) between lesions for ^{18}F-PD-L1 and ^{89}Zr-nivo, respectively. For lesions with ≥50% PD-L1 IHC, mean ^{18}F-PD-L1 SUV_{peak} was 8.0 (±4.7) as compared to 3.5 (±1.6) for lesions with <50% PD-L1 IHC (p=0.03). For tumors with high TIL/ stromal PD-1 expression, mean ^{89}Zr-nivo SUV_{peak} was 8.6 (±2.4) as compared to 6.1 (±2.1) for lesions with low PD-1 expression (p=0.1). Mean SUV_{peak} for ^{18}F-PD-L1 was 8.4 (±5.4) for pts with PR and 4.5 (±2.9) for pts with PD/SD (p=0.3). Mean SUV_{peak} for ^{89}Zr-nivo was 7.8 (±1.8) for pts with PR and 5.4 (±2.2) for pts with PD/SD (p=0.2). **Conclusion:** 1. PET-imaging with both tracers is safe and feasible, with good tumor-to-normal tissue contrast. 2. Tumor uptake showed heterogeneity among pts and among tumors within pts. 3. Pts with ≥50% tumor PD-L1 expression showed higher ^{18}F-PD-L1 uptake. 4. Pts with high PD-1 expression showed higher ^{89}Zr-nivo uptake, and pts with PR demonstrated higher ^{18}F-PD-L1 and ^{89}Zr-nivo tracer uptake than pts with PD/SD, although these are without statistical significance which may be due to the small dataset.

Keywords: immuno-PET, Nivolumab, NSCLC

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
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MA 05.08 VERY EARLY RESPONSE OF CIRCULATING TUMOR DERIVED DNA PREDICT THE EFFICACY OF TREATMENT BY NIVOLUMAB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy has become one of the options among the treatments of lung cancer. Nivolumab was first proven to have the utility as a second line treatment for non-small cell lung cancer. However, predictive factor of its efficacy is unknown. In recent years, studies have evolved on circulating tumor DNA (ctDNA). Clinical applications expanded and included prediction of prognosis, monitoring treatment effects and acquired resistance of driver genes, and assessment of residual tumor burden of resected cancer. In this study, we took cases in which tumor tissue was surgically resected or obtained by biopsy and the corresponding somatic mutations in plasma were studied. Then, we used these somatic mutations presumably derived from original tumor tissue as "tumor markers". We took serial blood samples before and after starting nivolumab and examined to see whether early change of the level of ctDNA can predict long term treatment outcomes. **Method:** Fourteen patients who were treated by nivolumab from February 1st to September 30th in 2016 were studied. Peripheral blood samples were collected from the patients before, 1, 2, 4, 6 and 8 weeks after the initiation of nivolumab treatment. To identify somatic mutations in tissue and total plasma DNA, we performed targeted sequencing using "lung cancer panel" spanning whole exons of these 53 genes, and next generation sequencing was performed. Gene mutations detected in both tumor tissue and plasma were defined here as circulating tumor DNA (ctDNA). Early response of the level of ctDNA after starting nivolumab was evaluated to see whether it could predict treatment outcome. **Result:** Of 14 cases, 6 cases were Responders, and 8 Non-responders. ctDNA was detected more often in the serial plasma samples of patients carrying high tumor burden (p=0.02). In addition, basal and serial ctDNA analysis revealed that decrease of allelic frequency (AF) level within 2 weeks correlated with the good durable response, and on the contrary, the increase with no or poor response. **Conclusion:** In patients carrying high tumor burden, plasma analysis of ctDNA which was validated by tumor tissue, revealed the durable good response of nivolumab could be predicted within 2 weeks.

Keywords: Nivolumab, Circulating Tumor DNA, Immunotherapy

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
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MA 05.09 PRE-EXISTING IMMUNITY MEASURED BY TEFF GENE EXPRESSION IN TUMOR TISSUE IS ASSOCIATED WITH ATEZOLIZUMAD EFFICACY IN NSCLC

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Background: Association between T-effector (Teff) gene expression (GE), a marker of pre-existing immunity, and OS benefit with atezolizumab (anti–PD-L1) was demonstrated in the Phase II study POPLAR of atezolizumab vs docetaxel in 2L+ NSCLC. We analyzed Teff GE association with atezolizumab efficacy in a larger Phase III study, OAK. **Method:** Patients with 2L+ NSCLC were randomized to receive atezolizumab or docetaxel. Teff signature was defined by 3 genes (PD-L1, CXCL9, and IFNγ), and Teff GE was measured by averaging the normalized expression of each gene. Teff GE subgroups were defined by quartiles. PD-L1 expression was assessed using the SP142 IHC assay; the TC1/2/3 or IC1/2/3 subgroup had ≥ 1% PD-L1 expression on tumor cells (TC) or tumor-infiltrating immune cells (IC). **Result:** 753 of 850 patients from the OAK primary analysis constituted the biomarker evaluable population (BEP) for Teff GE. Expression of the Teff signature was associated with PD-L1 expression by IHC ($P = 7.3\times10^{-45}$). Although no significant PFS benefit with atezolizumab vs docetaxel was observed in the BEP (HR, 0.94 [95% CI: 0.81, 1.10]) or the TC1/2/3 or IC1/2/3 subgroup (HR, 0.93 [95% CI: 0.76, 1.15]), a gradient of improved PFS benefit with atezolizumab was observed with increasing Teff GE. Significant PFS benefit occurred with ≥ median Teff GE cutoff (HR, 0.73 [95% CI: 0.58, 0.91]; Table). Teff GE also enriched for improved OS; however, a trend toward OS benefit was still observed in patients with low Teff GE (Table).

Table. PFS and OS with atezolizumab vs docetaxel by PD-L1 IHC and Teff GE subgroups		
	PFS, HR (95% CI)	**OS, HR (95% CI)**
OAK primary population (N = 850)a		
ITT[a]	0.95 (0.82, 1.10)	0.73 (0.62, 0.87)
TC1/2/3 or IC1/2/3[a] (n = 463)	0.91 (0.74, 1.12)	0.74 (0.58, 0.93)
TC2/3 or IC2/3[a] (n = 265)	0.76 (0.58, 0.99)	0.67 (0.49, 0.90)
OAK BEP for Teff GE (N = 753)		
BEP	0.94 (0.81, 1.10)	0.71 (0.59, 0.85)
TC1/2/3 or IC1/2/3 (n = 420)	0.93 (0.76, 1.15)	0.74 (0.58, 0.95)
Teff GE subgroups		
≥ 25% (n = 570)	0.91 (0.76, 1.09)	0.67 (0.54, 0.83)
< 25% (n = 183)	1.11 (0.82, 1.49)	0.87 (0.63, 1.21)
≥ 50% (n = 379)	0.73 (0.58, 0.91)	0.59 (0.46, 0.76)
< 50% (n = 374)	1.30 (1.05, 1.61)	0.87 (0.68, 1.11)
≥ 75% (n = 190)	0.66 (0.48, 0.91)	0.60 (0.42, 0.87)
< 75% (n = 563)	1.10 (0.92, 1.31)	0.76 (0.62, 0.92)
[a]Rittmeyer A. et al. Lancet, 2017;389:255-265. NCT02008227.		

Conclusion: This is the first demonstration of the association between markers of Teff biology and clinical outcomes with cancer immunotherapy in a randomized Phase III trial. Teff GE may reflect pre-existing immunity and be a more sensitive biomarker compared with PD-L1 IHC, identifying more patients (50% prevalence) likely to experience PFS benefit with atezolizumab.

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MA 05.11 ENDOTHELIAL ADHESION MOLECULE OVEREXPRESSION CORRELATES TO DECREASED CD8 T CELLS AND INCREASED B/TREG CELLS IN LUNG CANCER

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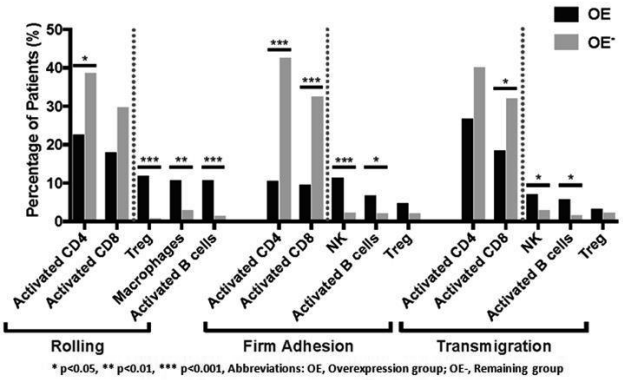
Background: Immunotherapy has become a promising recourse for lung cancer therapy. The endothelium separates circulating immune cells and the tumor microenvironment, and it is necessary for immune cells to penetrate this barrier to accost the tumor. This requires cell-matrix interactions via endothelial adhesion molecules(EAM) such as selectin and integrin. While it is expected that higher expression of EAM is linked to greater immune cell infiltration in general, little is known as to its actual effect on various types of immune cells in human lung cancer. **Method:** Based on the TCGA database, mRNA-seq values of genes related to the leukocyte recruitment cascade were analyzed in 504 patient samples with lung squamous cell carcinoma(SCC) and 522 patient samples with lung adenocarcinoma. The genes were divided into 3 sets: rolling, firm adhesion, and transmigration. Immune cell infiltration of each set was analyzed using Gene Set Enrichment Analysis(GSEA), and p values were derived from Fisher's exact and Chi-squared tests. **Result:** In lung SCC, overexpression(z score>2.0) of the above genes was statistically significantly correlated with decreased infiltration of activated CD4/CD8 T cells, but increased infiltration of activated B/Treg cells (Figure1). Similar trend was also observed in lung adenocarcinoma. Macrophage, dendritic cells, and natural killer cells showed increased infiltration in the EAM overexpression groups of both SCC and adenocarcinoma. Overall survival showed no significant difference in all three EAM gene overexpression groups in both types of lung cancer.

Figure 1. Immune cell infiltration landscape by adhesion molecule status in human lung squamous cell carcinoma.



Conclusion: We demonstrate for the first time that overexpression of EAM genes is linked to differential infiltration of various immune cells (including decreased CD4/CD8 T cells and increased activated B/Treg cells) in human lung cancer tissue. Recruitment of B/Treg cells by EAM may have an impact on inactivation of infiltrated T cells in the tumor microenvironment. This suggests that EAM status may serve as a predictive biomarker for T cell-mediated immunotherapy.

Keywords: NSCLC, CD8 T cell, integrin

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MA 05.12 ONCOGENIC DRIVERS INDUCE PRODUCTION OF CCL5 TO RECRUIT REGULATORY T-CELLS EARLY IN LUNG CANCER PROGRESSION

E. Franks[1], E. Halvorsen[1], E. Melesse[2], A. Unni[3], J. Collier[1], M.H. Oh[1], V. Lam[4], G. Krystal[4], J.C. English[5], W. Lam[6], S. Lam[6], N. Abraham[2], K. Bennewith[6], W. Lockwood[1]

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Background: Lung cancer development is driven by the expression of mutant oncogenes, with EGFR and KRAS the most frequent in lung adenocarcinoma. However, these mutations alone are not sufficient for tumorigenesis suggesting additional factors influence tumour development and progression, including the balance of anti-tumour immune effector cells and pro-tumorigenic immune suppressor cells. Tumour cells can evade immune surveillance by producing cytokines to recruit immune modulatory cells that promote an immune suppressive environment, such as regulatory T cells (Tregs). We hypothesized that oncogene signaling regulates the production of cytokines by tumour cells in order to recruit immune suppressive cells and promote lung tumour development. **Method:** We used CIBERSORT to quantify 22 immune cell types in over 300 human lung adenocarcinoma and 100 matched normal lung tissues, and validated findings with immunohistochemistry. Cells expressing doxycycline inducible $EGFR^{L858R}$ and $KRAS^{G12V}$were analyzed for cytokine production using a multiplex assay (LUMINEX). EGFR (Afatinib) and MEK (Trametinib) inhibitors were used in lung cancer cell lines harbouring EGFR or KRAS mutations and cytokine production was quantified using ELISA. Conditioned media from $EGFR^{L858R}$and $KRAS^{G12V}$ expressing cells were used in a trans-well assay to determine if secreted cytokines could induce Treg migration. Transgenic mouse models of lung adenocarcinoma and bronchoalveolar lavage (BAL) from patients with and without lung cancer were used to assess CCL5 and Tregs in vivo. **Result:** Treg cells were significantly enriched in lung tumours and not normal tissue. CCL5 production is increased rapidly upon oncogene induction and subsequent transformation of normal cells and is dependent on sustained ERK signaling for continued expression. Conditioned medium from $EGFR^{L858R}$ expressing cells increased Treg migration, which was mitigated by an anti-CCL5 antibody. Transgenic mice expressing $EGFR^{L858R}$ or $KRAS^{G12D}$ in the lung epithelium recruited Tregs to the lung upon tumor induction. Assessment of CCL5 in BAL from patients with and without lung cancer is currently in progress. **Conclusion:** Oncogene driven ERK signaling may regulate expression of CCL5 from lung tumour cells, and oncogene induced CCL5 production stimulates Treg migration ex vivo. These data suggest CCL5-mediated Treg recruitment to lung tumours may occur in early stages of lung tumour development and that targeted inhibition of CCL5 or ERK signaling may represent therapeutic strategies to block recruitment of immunosuppressive Tregs by lung tumours.

Keywords: oncogene singling, cancer progression, immune evasion

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MA 05.13 SCAVENGER RECEPTOR MARCO DEFINES A TARGETABLE TUMOR-ASSOCIATED MACROPHAGE SUBSET IN LUNG CANCER

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Background: Tumor-associated macrophages (TAMs) with immunosuppressive and tumor promoting features are attractive targets for immunotherapy. MARCO is a scavenger receptor expressed on a subpopulation of macrophages in secondary lymphoid organs. A recent study performed in animal models concluded that treatment with an anti-MARCO antibody results in reprogramming of the TAMs and inhibition of tumor growth and metastatic spread. The expression and function of MARCO in lung cancer TAMs is not known. **Method:** The infiltration of TAMs expressing MARCO, CD68, CD163 and MSR1, in the tumor and stromal compartments, was analyzed by immunohistochemistry in a non-small cell lung cancer (NSCLC) cohort (n=352). In addition, PD-L1 expression was assessed on tumor cells. Immunofluorescence was performed on selected cases to evaluate marker co-expression. Associations to immune cells and regulatory inflammatory pathways were studied in a subset of cases (n=174) with available RNA-seq data. **Result:** A large variance in TAM density could be observed between cases as well as a strong correlation between CD68 and CD163, indicating a pro-tumor phenotype of infiltrating macrophages. Correlation to clinical data showed a trend towards worse survival for patients with high macrophage infiltration. TAM expression of MARCO was seen on a subpopulation of pro-tumor macrophages. The majority of MARCO expressing TAMs were found to be located within tumor cell nests. Interestingly, stromal macrophages expressing MARCO tended to aggregate in close proximity to the tumor nests. On the transcriptomic level, increased MARCO gene expression correlated to genes linked to immunosuppressive TAMs, T-cell infiltration and immune checkpoint molecules like PD-L1 and CTLA-4. The association between macrophage infiltration and tumor cell PD-L1 expression was confirmed by immunohistochemistry. Also, co-expression of PD-L1 and MARCO could be detected on certain macrophages within the tumor cell nests. **Conclusion:** MARCO expression characterizes a specific subpopulation of pro-tumor macrophages that are enriched in PD-L1 positive NSCLC cases. Patients with significant infiltration of MARCO positive TAMs could benefit from treatment with anti-MARCO antibodies, possibly in combination with available immune checkpoint inhibitors.

Keywords: PD-L1, MARCO, Tumor-associated macrophages

MA 05 IMMUNO-ONCOLOGY: NOVEL BIOMARKER CANDIDATES
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MA 05.14 DIFFERENTIAL EXPRESSION OF IFN-STIMULATING DNA SENSORS STING AND CGAS IN LUNG CANCER SUBTYPES

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Background: STING is a protein that promotes type I IFN production (IFNα/β) essential for activation of dendritic cells and antigen presentation and priming of T-cells. The cytoplasmic DNA sensor cGAS (cGAMP Synthase) is able to detect tumor DNA, and in response will synthesize cGAMP. cGAMP binds STING specifically, resulting in production of type I IFN. STING is therefore referred to as an adaptor protein essential for immune signaling following detection of tumor DNA. Analysis of the TCGA database indicates decreased survival in lung adenocarcinoma patients lacking STING expression. STING expression is decreased in tumor tissues and can be lost as the tumor progresses. One reported mechanism of loss of STING or cGAS in tumors is due to hypermethylation, a common occurrence in lung cancer. Agonists of STING show potent immune response and are currently in clinical trials. Importantly, recent studies show that expression of STING and cGAS proteins are essential for response to PD-1:PD-L1 blockade. **Method:** Section not applicable **Result:** We analyzed 55 NSCLC and 39 SCLC cell lines, and 317 NSCLC and 78 SCLC tissues for STING and cGAS expression using immunohistochemistry. 14/55 (25.45%) NSCLC cell lines and 25/39 (64.10%) SCLC cell lines showed no STING expression. Separated in to adenocarcinoma (AC) and squamous cell carcinoma (SCC) subsets, STING expression in AC shows loss of STING as tumor stage increases (Positive: 70% Stage I, 65% Stage II, 52% Stage III, 40% Stage IV, 71% total; n=156) while STING expression is low at all stages of SCC (Positive: 29% Stage I, 18% Stage II, 36% Stage III, 13% Stage IV, 27% total; n=161). SCLC tissues stained showed widespread loss of STING (Positive: 40% Stage I, 27% Stage II, 31% Stage III, 100% Stage IV, 37.18% total, n=78). Expression of cGAS was higher in AC (94%) than SCC (75%) and showed no correlation with stage. TCGA analysis of STING methylation shows hypermethylation in AC (0.15- ± 0.13 tumor vs 0.05 ± 0.02 normal, n=422) and SCC (0.23 ± 0.16 tumor vs 0.04 ± 0.03 normal, n=359). cGAS shows slight methylation in AC (0.05 ± 0.07 tumor vs 0.05 ± 0.01 normal, n=422) but a large increase in SCC (0.19 ± 0.24 tumor vs 0.04 ± 0.01 normal, n=359). **Conclusion:** This study indicates drastic differences in STING and cGAS expression in AC, SCC, and SCLC. Differential expression of these proteins could impact the efficacy of STING agonists, radiation therapy, and immunotherapy in lung cancer.

Keywords: STING, Immunology, Interferon

MA 06 LUNG CANCER BIOLOGY I
MONDAY, OCTOBER 16, 2017 - 15:45-17:30

MA 06.01 CANCER TESTIS ANTIGENS AND MUTATIONAL LOAD IN RELATION TO THE IMMUNE LANDSCAPE OF NON-SMALL CELL LUNG CANCER

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Background: The avoidance of immune surveillance by tumor cells is an accepted hallmark of cancer. The aim of this study was to describe the natural immune landscape of NSCLC tissue, to identify important regulatory associations and potential targets of immune response. This includes mutational load and cancer testis antigen (CTA) expression, and the comprehensive analysis of tumor infiltrating immune cells in connection with immune signaling and clinical information. **Method:** Tissue microarrays including duplicate cancer samples of 357 NSCLC patients were stained with antibodies against CD3, CD4, CD8, CD45RO, FoxP3, CD20, CD138, and CD44 to analyze the protein expression in the stroma and tumor compartment. For 197 of these cases, corresponding RNA-seq data were available. The immunological data were correlated to the transcriptomic data and to patients' clinical outcome. The mutation status and the mutational load was based on a targeted next-generation sequencing panel of 82 genes (HaloPlex). **Result:** The immune cell infiltration was predominantly in the stroma, although CD8 and FoxP3 cells also showed relevant infiltration of the tumor cell compartment. The amount of T-cells of different subsets and CD20-positive B-cells correlated positively to each other. A higher mutational load was associated with higher CD8 T-cell infiltrates, CD45RO cells, FoxP3 regulatory cells as well as CD20-positive B-cells in the tumor compartment. In contrast, the number of expressed CTAs were associated with an abundance of CD45RO-positive cells in the stromal compartment. Only CD44-positivity (HR = 0.61, $p < 0.01$) as well as high CD20 positive B-cells (HR = 0.34, $p < 0.01$) and plasma cell (CD138, HR = 0.71, $p < 0.05$) counts in the tumor, and for plasma cells also the stromal (HR = 0.61, $p < 0.01$), compartment were associated with longer overall survival. **Conclusion:** Here we describe natural immune profiles in a large clinical NSCLC patient cohort. Interestingly both mutational load and CTA expression is associated with the abundance of distinct immune cell infiltrates. We could not confirm the impact of tumor infiltrating T-cells on survival. However, the consistent prognostic impact of both B-cell markers indicates a major role of the humoral immune response in lung cancer.

Keywords: NSCLC, PD-L1, immune profiles

MA 06 LUNG CANCER BIOLOGY I
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MA 06.02 CYTOLOGY AND SURGICAL PATHOLOGY SPECIMENS ARE COMPARABLE TESTING SUBSTRATES FOR PD-L1 IMMUNOHISTOCHEMISTRY IN LUNG CANCER

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Background: Immunohistochemical (IHC) testing for programmed death ligand 1 (PD-L1) expression by non-small cell lung cancer (NSCLC) specimens has become standard of care to help select immune checkpoint inhibitor therapy. The companion IHC assay for pembrolizumab has been validated and approved for use on surgical pathology specimens; however, the performance of this assay when applied to cytology specimens is not well characterized. **Method:** Following IRB approval, all NSCLC cytology or surgical pathology specimens obtained from 11/2015 to 5/2017 at our institution that were tested for PD-L1 expression by a commercial vendor (Integrated Oncology/LabCorp, NY) using the FDA-approved companion diagnostic PD-L1 clone 22C3 pharmDx kit on the Dako Automated Link 48 platform (Dako, Carpenteria, CA) were identified. Patient cohorts where testing was performed on diagnostic cytology vs. surgical pathology specimens were compared. Tumor PD-L1 expression was stratified by clinically relevant groups: <1%, 1-49%, and ≥50%. Tumor genotyping results for EGFR, KRAS, ALK, and ROS1 were also collected. **Result:** Cytology formalin-fixed paraffin-embedded (FFPE) cell blocks included endobronchial ultrasound transbronchial needle aspirates (57%), pleural/pericardial fluids (28%), fine needle aspirates (13%), and bronchial washings/lavages (2%). Surgical FFPE specimens included small core/incisional biopsies (60%), bronchial biopsies (12%), and large resections (28%). PD-L1 testing was successful for over 96% (223/232) of specimens (Table). Overall, EGFR mutations were more frequent with no/low PD-L1 expression, ALK rearrangements with high PD-L1 expression, but no relationship between KRAS mutations and PD-L1 expression.

PD-L1 Tumor Proportion Score Stratified by Specimen Type		
	Cytology Cell Block	**Surgical Pathology**
<1% PD-L1 TPS	35 (37.2%)	52 (37.7%)
1-49% PD-L1 TPS	20 (21.3%)	35 (25.4%)
≥50% PD-L1 TPS	33 (35.1%)	48 (34.8%)
Failed Analysis	6 (6.4%)	3 (2.2%)
Total	**94 (100%)**	**138 (100%)**

Chi-squared value=2.95, p>0.39 (not significant); TPS=tumor proportion score **Conclusion:** For NSCLC, no statistically significant differences in PD-L1 expression patterns were observed between cytology cell block and surgical pathology specimens, implying that in clinical practice any adequate cytology cell block or surgical pathology specimen could be utilized for testing. Importantly, analysis of clinical outcomes with use of first line pembrolizumab based on cytology vs surgical pathology specimen PD-L1 ≥50% expression is currently ongoing.

Keywords: PD-L1, cytology, Specimen testing

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MA 06.03 PROGRAMMED DEATH-LIGAND 1 (PD-L1) EXPRESSION IN CLINICAL PRACTICE: COMPARISON OF TEMPORALLY OR SPATIALLY SEPARATED TEST RESULTS

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Background: Advances in understanding of immune checkpoint inhibitors, have resulted in FDA approvals of anti-PD-1/PD-L1 inhibitor therapies for clinical use in nonsmall cell lung cancer (NSCLC). Detecting PD-L1 expression, as a predictive biomarker using companion diagnostic test (PD-L1 IHC 22C3 pharmDx), helps us identify NSCLC patients eligible for anti-PD-1 therapy (Pembrolizumab). Tumor Proportion Score (TPS) ≥50% and TPS ≥1% qualitatively estimated, by PD-L1 IHC 22C3 pharmDx test, are cut-offs which indicate use of Pembrolizumab as monotherapy in first line (TPS ≥50%) or second line (TPS ≥1%) settings for NSCLC. Intratumoral heterogeneity of PD-L1 expression in NSCLC is known. Approximately 60% of NSCLC present with advanced stage of disease. Tissue sampling of metastatic sites for initial diagnosis using core needle biopsy or fine needle aspiration techniques is common clinical practice. Significant body of literature is not available to address the issue of PD-L1 expression at metastatic sites and its concordance/discordance with primary lung tumor. We decided to look at cases with repeat request for PD-L1 testing at alternate sites or on subsequent tumor resections. **Method:** Our departmental anatomic pathology database was queried to search for NSCLC cases wherein PD-L1 immunohistochemistry was performed in our laboratory using companion diagnostic test (PD-L1 IHC 22C3 pharmDx) on AutoLink 48 autostainer as per protocol, and reported by one of our pathologists. Analysis was performed to determine additional PD-L1 IHC test requests for same patient and subsequent subgroup analysis to determine test results and other parameters such as type of specimens, tumor sites, and concordant/discordant results. **Result:** PD-L1 IHC 22C3 pharmDx test request was received on 460 NSCLC patient specimens in last six months. Of these, in twenty-five patients testing was attempted/performed on two tissue specimens, with final results reported in eighteen patients. Discordant results are noted in four patients (22.22%). In an additional patient, reported level of PD-L1 expression (low) was concordant; however reported TPS (5% & 45%) was different. **Conclusion:** Currently, in routine clinical practice, PD-L1 IHC test results are usually reported on a single tissue specimen. However, when tested on separate site/s or specimen type/s, our results suggest, that one can observe discordant results. At the lower end of results (PD-L1 negative or low expression), this can impact therapeutic decisions. Though a larger study is necessary to address this issue, one can suggest, that PD-L1 IHC testing should be performed on multiple site specimens, especially when temporally separated, in best interests of patient care.

Keywords: clinical practice, PD-L1, Immunohistochemistry

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MA 06.04 DEVELOPMENT OF NEXT-GENERATION SEQUENCING BASED CANCER PANEL AND ITS CLINICAL IMPLICATIONS IN LUNG CANCER

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Background: To search actionable driver mutations, various cancer panels using next-generation target sequencing technologies are rapidly developed and adopted in the treatment of lung cancer. We developed a new cancer panel to detect 313 coding gene mutations, 30 fusion and 3 exon-skipping genes including either known or potential target genes. Performance of the panel was tested on our archived lung cancer tissue bank samples. **Method:** Two hundreds and two samples were tested (male 118, female 84, median age 63 (30-84) years). Histologic cell types were mainly adenocarcinoma (adenocarcinoma 158, squamous cell 25, large cell 6, sarcomatous 3, small cell 1, and mixed cell types 9). **Result:** With our cancer panel, 139 samples (68.8%) were identified to have mutations including 88 EGFR, 23 KRAS, 8 MET mutations, 7 ALK, 6 RET, 3 ROS1, 6 rare fusions (PTEN, BRAF, MET, CBFB, EWSR1, BCR), and 18 CNV alterations. Medical records revealed that traditional single-site tests including Sanger sequencing of EGFR, KRAS mutations and either immunohistochemical stain or FISH test for ALK or RET fusion had been performed in 191 patients. Among those patients, we identified 102 pathogenic mutations (53.4%) including 80 EGFR, 14 KRAS mutations, 6 ALK, and 2 RET fusions. Conventional single-site test results matched with that of cancer panel in 139 samples (72.8%). Cancer panel detected additional mutations in 48 samples (25.1%; 38 from the single-site test negative and 10 from positive samples). In two samples, the results showed discrepancy while in the other two, mutations were detected only in single-site test. However additional tests revealed cancer panel results to be correct. Excluding 4 patients with M1 stage, 198 patients' long-term survival were analyzed according to the mutational status. In Cox's proportional hazard model, presence of EGFR mutation was the only prognostic marker that predicted long-term survival along with clinical variables such as age, pT-stage, and pN-stage. **Conclusion:** In our results, we confirmed superior accuracy of our cancer panel compared to the traditional single-site tests. Furthermore, the new cancer panel discovered novel mutations, of which significance requires future functional investigation and potential development of new target agents.

Keywords: cancer panel, target sequencing, mutation

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MA 06.06 ASSESSMENT OF RANK PREVALENCE AND CLINICAL SIGNIFICANCE IN THE NSCLC EUROPEAN THORACIC ONCOLOGY PLATFORM LUNGSCAPE COHORT

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Background: Receptor Activator of Nuclear Factor κappa-B (RANK) is a pathway involved in bone homeostasis. Recent evidence suggests that RANK signalling may also play a role in bone metastasis, and primary breast and lung cancers. The European Thoracic Oncology Platform (ETOP) Lungscape project allows evaluation of the prevalence of RANK expression and its clinical significance in a cohort of surgically-resected NSCLCs. **Method:** RANK expression was assessed on tissue microarrays (TMAs) using immunohistochemistry. Up to 4 cores per patient were analysed based on sample acceptance criteria. An H-Score (staining intensity + % cells stained) was used to assess RANK expression (positivity), as defined by at least 1 core with any degree of positive staining. Prevalence of RANK positivity and its association with clinicopathological characteristics, other cancer-related biomarkers (IHC ALK/MET/PTEN/PD-L1 expression and EGFR/KRAS/PIK3CA mutations) and patient outcome [Relapse-free Survival (RFS), Time-to-Relapse (TTR), Overall Survival (OS)] was explored in a subset of the ETOP Lungscape cohort. The prevalence of RANK overexpression (proportion of positive cancer cells ≥50%) was also investigated. **Result:** RANK expression was assessed in patients from 3 centers, a total of 402 from the 2709 patients of the Lungscape cohort, with median follow-up 44 months; 32.6% female, 40.8/54.2/5.0% adenocarcinomas (AC)/squamous cell carcinomas (SCC)/other, 44.8/28.4/26.9% with stage I/II/III, 20.6/57.7/18.9% current/former/never smokers (and 2.7% with unknown smoking status). Median was 74 months for both RFS and OS, while median TTR was not reached. Prevalence of RANK positivity was 26.6% (107 of the 402 cases), with 95% confidence interval (95%CI):22.4%-31.2%; significantly higher in AC: 48.2% (79 of 164 cases), 95%CI:40.3%-56.1%; vs SCC: 9.2% (20 of 218 cases), 95%CI:5.7%-13.8%; (p<0.001). RANK positivity was more frequent in females (38.9% vs 20.7% in males, p<0.001) and tumors≤4cm (30.7% vs 21.1% in tumors>4cm, p=0.031). Significant associations were also detected between RANK and PTEN expression in AC (RANK positivity 57.4% in PTEN expression vs 30.5% in PTEN loss; p=0.0011) and with MET status in SCC (RANK positivity 27.8% in MET+ vs 7.6% in MET-; p=0.016). No association with outcome was found. RANK overexpression was identified in 43 (10.7%; 95%CI: 7.9%-14.1%) cases. **Conclusion:** In this early-stage NSCLC cohort, RANK positivity (26.6% overall) is found to be significantly more common in adenocarcinomas (48.2%), females, patients with tumors of smaller size, with PTEN expression (in SCC) and MET positivity (in AC). No prognostic significance of RANK expression was found. Analysis of additional cases is ongoing and results will be presented.

Keywords: RANK, ETOP Lungscape, NSCLC

MA 06.07 JAK PSEUDOKINASE DOMAIN VARIANTS HIGHLIGHT NRTK NSSNPS IDENTIFIED WITH NEXT-GENERATION SEQUENCING IN NSCLC PATIENTS

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Background: Non-receptor tyrosine kinase (nRTK) pathways are aberrantly activated in cancer, and mutations in nRTKs have potential therapeutic and prognostic importance. Tumor profiling with next-generation sequencing (NGS)enables a gene's entire coding sequence to be evaluated, facilitating the identification of novel non-synonymous single nucleotide polymorphisms (nsSNPs) in nRTKs. **Method:** We searched nsSNPs in 14 nRTKs in the tumors of advanced NSCLC patients (pts) at our institution that received NGS with Caris from 2013-2015. All mutations test-defined as pathogenic (PATH) or nsSNPs labelled variants of undetermined significance (VUS) were included. To classify VUS, nsSNPs underwent PolyPhen-2's in silico analysis to predict pathogenicity. Any VUS predicted-damaging with PolyPhen-2 we denote pnsSNP. nsSNPs were then classified as occurring within or outside of the tyrosine kinase domain (TKD); JAK1-3 pseudokinase domain (PSKD) lesions were also described. **Result:** 157 NSCLC pts were identified with median age 65 (range 26-85); 51% were male; 65% Caucasian, 35% African-American. 98 nRTK variants were found (93 nsSNPs and 5 PATHs). 5/5 PATHS were PIK3CA. 31/93 (33%) nsSNPs were pnsSNPs and spread among 30 pts. pnsSNPs were found in 12/14 nRTKs with median 2 (range 0-6). The most frequent were JAK3 (6/20 nsSNPs were pnsSNPs), BTK (5/8), ABL1 (3/12), JAK2 (3/11), CDK12 (3/9) and JAK1 (3/3). 66% were extra-TKD (28% were pnsSNP), 23% TKD-restricted (44%) and 11% PSKD of JAK1-3 (100%). There were 6 N-lobe PSKD, 3 C-lobe PSKD and 1 C-lobe TKD JAK1-3 pnsSNPs (Table 1) at PSKD-TKD contact sites known to harbor the majority of activating JAK mutations. 6/12 JAK pnsSNPs were in pts whose tumors were EGFR-/KRAS-/ALK-/ROS-/PDL1-. **Table 1:** JAK1-3 pnsSNPs in NSCLC patients.

VUS; allele frequency	Location	Accession Number; Minor allele frequency (ExAC)	Histology	Age, race, gender	Genomics (EGFR, KRAS, ALK or ROS1-rearranged, PDL1 (%))
D660N; 66%	PSKD; N-lobe	rs368904859; T=2.0e-5	Adeno-carcinoma	66, C, M	Negative
P674S; 9%	PSKD; N-lobe	None	Squamous	76, C, M	PDL1+ (5%)
D739N; 47%	PSKD; N-lobe	rs759709239; T=3.3e-5	Large cell	43, C, M	KRAS+
E621D; 30%	PSKD; N-lobe	None	Unspecified	65, AA, M	Negative
D686H; 13%	PSKD; N-lobe	None	Adeno-carcinoma	55, C, M	Negative
C1105F; 41%	TKD; C-lobe	None	Adeno-carcinoma	73, C, F	KRAS+, ROS1-rearranged
V55E; 13%	FERM	None	Adeno-carcinoma	74, C, F	Negative
Y105H; 21%	FERM	None	Squamous	68, C, F	PDL1+ (20%)
R537Q; 47%	PSKD; N-lobe	rs587778413; T=4.1e-5	Adeno-carcinoma	60, C, F	PDL1+ (65%)
L702P; 53%	PSKD; C-lobe	rs772117537; G=1.7e-5	Squamous	80, C, M	Negative
P745L; 50%	PSKD; C-lobe	rs776106625; A=8.3e-6	Adeno-carcinoma	68, C, M	EGFR+ (E746_A750del)
L788I; 7%	PSKD; C-lobe	None	Squamous	68, AA, M	Negative

Conclusion: >19% NSCLC pts held a pnsSNP with 77% occurring outside of the TKD-proper. The majority of JAK1-3 pnsSNPs localized to the PSKD; their frequency and functional impact should be examined on a larger scale.

Keywords: Non-receptor tyrosine kinase, Janus kinase, Pseudokinase domain

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MA 06.08 LUNG CANCER PATIENTS WITH GERMLINE MUTATION: A RETROSPECTIVE STUDY

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Background: Genetic testing for alterations of oncogenic driver genes has become essential and standard in clinical practice. Germline mutations predisposing to lung cancer are rare, but there have been reports regarding germline mutations in EGFR, HER2, BRCA2, CDKN2A, BAP1, SFTPA2, and PARK2. Next generation sequencing is being introduced to clinical practice of lung cancer, enabling investigation of multiple oncogenic driver genes simultaneously. In addition, liquid biopsy, which analyzes cell free DNA in blood, increases the opportunity to detect germline mutations in lung cancer patients. We examined the frequency and characteristics of lung cancer patients with germline mutations. **Method:** Between February 2012 and January 2017, 3,869 patients with a diagnosis of lung cancer were seen by Division of Medical Oncology in Ohio State University. Of these, seven were found to have germline mutations. The patient characteristics and treatment outcomes were retrospectively investigated. **Result:** Table 1 shows characteristics and treatment outcomes of the seven lung cancer patients with germline mutations. Median age was 50 (range, 34-72). Three had BRCA2 germline mutations, two had germline TP53 mutations (of which one patient also had a PARK2 mutation), one had a BRCA1 mutation, and one had an EGFR mutation. Testing for other oncogenic drivers were done in five patients, and interestingly, four patients had oncogenic driver mutations. The frequency of detecting germline mutations in lung cancer patients has been increasing in recent years, but is often unrecognized by providers. In our series, one patient was found to have a germline mutation by Foundation ONE, and another was found to have a germline mutation by Foundation ACT. *(See next page.)*

Year	Age	Sex	Histology	Stage	Smoking hisory	Other cancer	Germline mutation	Other somatic gene alteration	Targeted therapy	Respnse
2014	37	F	Ad	IA	former smoker (2py)	No		not evaluated	—	—
2014	72	F	Ad	IV	former smoker	breast cancer, lung cancer	EGFR T790M	EGFR G719S	rociletinib	SD
2015	69	F	Ad	IIIA	former smoker	breast cancer, uterine cancer		EGFR L858R	—	—
2015	50	F	SCLC	IA	never smoker	breast cancer	TP53 Y236*, PARK2 Q347*	FGFR2amplification	—	—
2016	34	F	Ad	IV	former smoker	No	BRCA2 L3061*	MET 3028+2T>C	crizotinib	PR
2016	44	F	Ad	IV	never smoker	orbital rhabdomyosarcoma		ALK fusion	crizotinib	PR
2017	62	F	SCLC	IV	former smoker	breast cancer		not evaluated	—	—

Conclusion: Introduction of next generation sequencing technology and liquid biopsies to clinical practice can raise the probability of detecting germline mutations in lung cancer patients. Clinicians should be alert to the potential existence and importance of germline mutations in their lung cancer patients.

Keywords: lung cancer, germline mutation

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MA 06.09 DETECTION OF EGFR T790M MUTATIONS BY FOUR TESTING PLATFORMS IN CTDNA FROM CHINESE PATIENTS WITH ADVANCED NSCLC

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Background: Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI) targeting sensitizing mutations and T790M mutation, which causes ~60% of acquired resistance after first-line TKI treatment. T790M testing provides guidance for second-line treatment decisions. This study evaluated four T790M detection platforms using plasma circulating tumor DNA (ctDNA). **Method:** ADELOS is a multicentre, open-label, single-arm study (NCT 02997501) of Chinese patients with advanced non-small cell lung cancer (NSCLC) and progression on previous EGFR-TKI treatment. Plasma ctDNA testing for T790M was performed by Cobas® real-time polymerase chain reaction (PCR), super amplification refractory mutation system (Super-ARMS) PCR, capture-based next-generation sequencing (NGS, 168 gene panel), and QuantStudio3D digital PCR (3D dPCR). T790M-positive patients detected by these platforms received osimertinib 80 mg/day orally until progression. Matched tissue re-biopsy samples were also tested by Cobas® or NGS. The primary objectives were to evaluate concordance between the Cobas® test and the other three platforms and to assess the efficacy of osimertinib in ctDNA T790M-positive patients. **Result:** Of 256 patients enrolled, 181 were ctDNA T790M-positive, among which 167 received osimertinib monotherapy. T790M plasma positive rate was from 37.4% to 63.5% (Cobas®< Super-ARMS<NGS<3D dPCR). Using Cobas® as a reference, plasma T790M test concordance ranged from 67% with 3D dPCR to 91% with Super-ARMS PCR. Sensitivity was >90% for all three platforms. Specificity was between 53% (3D dPCR) and 89% (Super-ARMS). Compared with paired tissue testing results (n=73), NGS showed the highest concordance and sensitivity, while Cobas® showed the highest specificity (Table 1). **Table 1.** Comparison of different platforms for T790M detection

	Cobas® PCR n=254	**Super-ARMS PCR n=256**	**NGS n=256**	**3D dPCR n=255**
T790M detected, n (%)	95 (37.4)	108 (42.2)	138 (53.9)	162 (63.5)
Comparison vs Cobas plasma test (n=254)				
Concordance %, (95% CI)	--	91.3 (87.2, 94.5)	82.7 (77.5, 87.1)	66.8 (60.6, 72.6)
Sensitivity %, (95% CI)	--	94.7 (88.1, 98.3)	98.9 (94.3, 100.0)	90.5 (82.8, 95.6)
Specificity %, (95% CI)	--	89.3 (83.4, 93.6)	73.0 (65.3, 79.7)	52.5 (44.4, 60.5)
Comparison vs Tissue (n=73)				
Concordance %, (95% CI)	67.1 (55.1, 77.7)	64.4 (52.3, 75.3)	69.9 (58.0, 80.1)	61.6 (49.5, 72.8)
Sensitivity %, (95% CI)	57.1 (42.2, 71.2)	61.2 (46.2, 74.8)	71.4 (56.7, 83.4)	69.4 (54.6, 81.7)
Specificity %, (95% CI)	87.5 (67.6, 97.3)	70.8 (48.9, 87.4)	66.7 (44.7, 84.4)	45.8 (25.6, 67.2)

Conclusion: Super-ARMS showed highest concordance and NGS showed highest sensitivity compared with Cobas® plasma T790M testing. Concordance and specificity of 3D dPCR was lower using other ctDNA tests or tissue as reference. Subsequent osimertinib treatment in these patients will justify the effectiveness of T790M testing by different technologies.

Keywords: Circulating Tumor DNA, osimertinib, T790M

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MA 06.11 DISTINCT MUTATIONAL LANDSCAPE AND EVOLUTIONARY TRAJECTORIES OF BRAIN METASTASIS AND LIVER METASTASIS IN LUNG ADENOCARCINOMA

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Background: Distant metastases confer mainly resistance to improving the long-term survival of patients with lung cancer. The major reason was that the genetic heterogeneity and evolutionary patterns between primary tumor and their distant metastases or among distinct metastatic sites remains poorly understood. The current study aimed to depict the distinct mutational landscape of primary lung adenocarcinoma and their distant metastases (brain or liver) and reconstruct the evolutionary history of metastases. **Method:** Seventeen patients with primary lung adenocarcinoma and distant metastases [5 with primary lesion and matched brain metastases (BM), 6 with primary lesion and matched liver metastases (LM), 6 with sole BM] were included. All tissues (by either biopsy or surgical resection) and matched peripheral blood samples were collected before systemic treatment. We performed whole-exome (150×) and targeted 416-gene panel sequencing for these

samples. **Result:** In the matched cases, the mutational landscape of primary lesions for BM was distinctly different from those for LM. Compared to the primary lesions, BM had the significantly different patterns of somatic genome alterations while LM had the similar ones. In six cases with sole BM, both intratumoral and intertumoral genetic homogeneity of BM were observed. By using a set of genes which were frequently found in the primary lesions, we can clearly segregate the copy number variations (CNV) pattern of patients with BM from those with LM. Moreover, when we performed the hierarchical clustering based on these genes, we saw clear segregation between BM and LM. Patients with BM had dramatically higher tumor mutational burden (TMB) than those with LM in both primary ($P < 0.01$) and metastatic lesions ($P < 0.001$). Significant differences in TMB were also observed between primary and metastatic lesions in patients with BM ($P < 0.001$) instead of LM ($P > 0.05$). Phylogenetic analysis showed that LM followed the liner progression whereas BM followed the parallel progression. In patients with sole BM, both intratumoral and intertumoral lesions have a monoclonal origin and descend from a common 'metastatic precursor'. **Conclusion:** The current evidence suggested that BM had distinctly different mutational landscape from LM in lung adenocarcinoma. Patients with BM had higher TMB than those with LM. BM followed the parallel progression whereas LM followed the liner progression. Intratumoral and intertumoral lesions of BM had genetic homogeneity and originated from the same precursor. These results had profound clinical implications for application of immunotherapy and improvement of prognosis in patients with lung adenocarcinoma and distant metastases.

Keywords: Brain metastasis, Liver Metastasis, lung adenocarcinoma

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MA 06.12 GENOMIC REARRANGEMENTS OF LUNG ADENOCARCINOMAS WITH FUSION DRIVER GENE

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Background: A subset of lung adenocarcinoma is transformed by fusion genes, i.e. EML4-ALK, KIF5B-RET. Practically, fusion genes are detected using PCR, FISH and/or RNAseq. Although TCGA project sequenced many lung cancer genomes, little is known about the genomic landscape of driver-fusion positive lung adenocarcinoma. In particular, we wondered the frequency and impact of complex genomic rearrangements, such as chromothripsis, chromoplexy, and chromoanasynthesis, in the pathogenesis of lung adenocarcinomas. **Method:** We performed whole-genome sequencing analyses for 38 pairs of driver-fusion-positive lung adenocarcinoma and its normal counterpart samples. These 38 tumors harbored one driver fusion genes such as EML4-ALK, KIF5B-RET, and CD74-ROS1. We mapped reads using Burrows-Wheeler Aligner, and processed aligned reads with Picard and Genome Analysis Toolkit. We analyzed tumor purity, ploidy and copy number variations using Sequenza. We called point mutations and indels using Mutect and Strelka. And we also called structural variations using Delly. **Result:** The number of somatic point mutations of these samples was lower than general lung adenocarcinomas. Mutational signature analysis revealed that signature 1 and 5 are major factors in these samples. More than 70% of driver fusion genes were established by complex genomic rearrangements rather than simple events. Based on the copy number change and the microhomology, replication-based mechanism is presumed to be a main cause of these complex events. Somatic mutation on TP53 was rare in these samples. **Conclusion:** Much of driver fusion genes in lung adenocarcinomas are made by complex genomic rearrangements. TP53-independent replication-based mechanism is critical to these phenomena.

Keywords: fusion gene, lung adenocarcinoma, Genomic rearrangement

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MA 06.13 DIRECT METABOLOMIC PROFILING OF LUNG CANCERS

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Background: Lung cancers rely on metabolites to fuel growth and to signal to surrounding tissues. Systematic study of these molecules may identify biomarkers for early diagnosis and novel pathways tractable to therapy. Previous studies of the metabolome in lung cancer have been confined to the serum and to sputum. We have therefore interrogated biochemical profiles in human lung cancers and matched adjacent normal tissues with the aim of identifying metabolites and metabolic signatures associated with lung cancer. **Method:** Global biochemical profiles were determined in human lung tumour and adjacent normal tissue. 12 tumours and 12 matched normal samples were tested from adenocarcinoma (ADC) patients, and 12 tumour/normal pairs were similarly tested from squamous cell carcinoma (SCC) patients. Samples were analysed on the Metabolon GC/MS and LC/MS/MS platforms, with the inclusion of technical replicates. **Result:** Application of PCA as a function of the tissue metabolome demonstrated that the normal, ADC and SCC groups were clearly distinguishable. We observed general metabolic changes associated with tumour tissue ($q<0.10$ throughout), with reductions in glucose and concomitant elevations in sorbitol and lactate indicative of Warburg metabolism in both ADC and SCC. Levels of reduced glutathione (GSH) were higher in SCC compared to ADC and normal tissue, indicating elevated antioxidant capacity in SCC. Conversely, alternative antioxidants including taurine, biliverdin, ascorbate, alpha- and gamma-tocopherol, and ergothioneine were higher in ADC than SCC. The neurotransmitters serine, NAA, GABA, and NAAG were also significantly elevated in ADC but not SCC. Finally, elevations in prostaglandin D2 and 6-keto prostaglandin F1alpha were confined to SCC and prostaglandin E2 was elevated to a much greater extent (8-fold versus 3-fold) in SCC vs. ADC, as compared respectively to normal lung tissue. **Conclusion:** Results from this pilot global profiling study confirm greater glucose utilization and lactate production, increased fatty acid synthesis, and changes in membrane biology in ADC and SCC. However, changes in glutathione metabolism, antioxidant capacity, neuroactive metabolites, and inflammation appear to vary according to tumour type. A larger scale study may identify differential therapeutic avenues and response to therapy. Profiling of matched serum/plasma from lung cancer patients may allow for identification of disease-specific biomarkers to supplement histological-based diagnostic techniques.

Keywords: metabolome, NSCLC, profiling

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MA 06.14 ONCOGENIC SOS1 MUTATIONS IN LUNG ADENOCARCINOMA

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Background: Lung adenocarcinomas are characterized by genetic alterations along receptor tyrosine kinase pathways. Around 50% of lung adenocarcinomas contain alterations in KRAS and EGFR alone. Nonetheless, genetic drivers in a large proportion of other cases remain to be determined. Recent exome sequencing analysis of lung adenocarcinomas in our lab has identified SOS1, a guanine nucleotide exchange factor, as being significantly mutated in lung cancers lacking canonical oncogenic mutations. However, the functional significance of the mutations is unclear. **Method:** In vitro cellular assays as well as in vivo transplatation experiments were performed to determine the phenotype of SOS1 mutants. Biochemical approaches were used to determine the mechanism by which SOS1 mutants confer an oncogenic phenotype. RNA sequencing of SOS1 mutant cells was performed to transcriptionally profile the cells, and inhibitors of the RTK/Ras/MAPK pathway were tested for their efficacy against SOS1 mutants. **Result:** We demonstrate that ectopic expression of mutated SOS1 induces anchorage-independent cell growth in vitro and tumor formation in vivo. Biochemical experiments suggest mutant SOS1 drives over-activation of the Ras pathway, and through RNA sequencing, we identify an upregulation of MYC targets in cells expressing mutant SOS1. Furthermore, we demonstrate that cancer cells with mutant SOS1 are dependent on SOS1 for survival and are also sensitive to inhibitors of the MAPK pathway. **Conclusion:** Our work provides experimental evidence for the role of SOS1 as a novel oncogene and suggests possible therapeutic mechanisms to target SOS1-mutated cancers.

Keywords: SOS1, novel oncogene, therapeutic target

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MA 07.01 PATIENTS WITH ALK IHC-POSITIVE/FISH-NEGATIVE NSCLC BENEFIT FROM ALK TKI TREATMENT: RESPONSE DATA FROM THE GLOBAL ALEX TRIAL

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Background: Patients with ALK-positive NSCLC have seen significant advances and increased options in ALK targeted therapies recently, and therefore rely on high quality, robust ALK status testing. Fluorescence in-situ hybridization (FISH) and immunohistochemistry (IHC) are the most common methods to determine ALK status for ALK tyrosine kinase inhibitor (TKI) treatment. However, availability of clinical

outcome data from randomized trials linked directly to specific methods is limited. The ALEX trial (BO28984, NCT02075840) provides a unique dataset to assess ALK IHC- and FISH-based assays regarding clinical outcome for alectinib and crizotinib, particularly for the subset of patients with IHC-positive/FISH-negative NSCLC. **Method:** The VENTANA ALK (D5F3) CDx Assay (ALK IHC) performed in central laboratories was used as an enrollment assay for the selection of patients with ALK-positive NSCLC for inclusion in the ALEX trial. Additional samples from these patients were retrospectively tested in central laboratories with the Vysis ALK Break Apart FISH Probe Kit (ALK FISH). **Result:** Overall, 303 patients all with ALK IHC-positive NSCLC were randomized in the ALEX trial, of those 242 patients also had a valid ALK FISH result, with 203 patients having ALK FISH-positive disease and 39 patients having ALK FISH-negative disease (alectinib, n=21; crizotinib, n=18). For 61 of 303 (20.1%) patients with an ALK IHC-positive result, a valid ALK FISH result could not be obtained due to the test leading to an uninformative FISH result (10.9%), or not having adequate/no tissue available (9.2%). Ventana IHC staining success rates were higher than for Vysis FISH testing for the ALEX samples. Exploratory analysis of investigator-assessed progression-free survival (PFS) in patients with a FISH-positive result (HR 0.40, 95% CI 0.27–0.61; p<0.0001; median not reached [alectinib] versus 12.7 months [crizotinib]) was consistent with the primary endpoint analysis in the Ventana ALK IHC-positive population. Patient outcome data show that 28% of central ALK IHC-positive/ALK FISH-negative samples were from patients who responded to ALK TKI treatment (complete response or partial response) and 33% had stable disease according to investigator assessment. **Conclusion:** This analysis shows that ALK IHC is a robust testing approach, which may identify more patients with a valid ALK testing result who benefit from ALK TKI treatment than ALK FISH testing. While PFS of patients with ALK FISH-positive NSCLC was similar to that of patients with ALK IHC-positive NSCLC, the analysis also revealed that the majority of patients with ALK IHC-positive/ALK FISH-negative NSCLC may derive clinical benefit from ALK TKI treatment.

Keywords: FISH, Alectinib, NSCLC

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MA 07.02 RESPONSE TO ENSARTINIB IN TKI NAÏVE ALK+ NSCLC PATIENTS

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Background: Ensartinib is a novel, potent anaplastic lymphoma kinase (ALK) small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1, and SLK. Ensartinib has demonstrated significant anti-tumor activity in both ALK TKI-naïve and crizotinib-resistant NSCLC patients. We report on data from ALK TKI treatment naïve patients. **Method:** Pts with advanced solid tumors and ECOG PS 0-1 were treated with ensartinib 225 mg qd on a continuous 28-day schedule. In expansion phase, pts were required to have measurable ALK+ NSCLC with tissue confirmed centrally via FISH or IHC. Asymptomatic brain metastases were allowed. Targeted NGS of cfDNA was performed retrospectively at baseline and on study and compared with tissue results. **Result:** As of 01Apr2017, 102 pts enrolled. In the ALK TKI naïve cohort, 15 (8 female, 7 male) ALK+ NSCLC pts treated at doses ≥ 200 mg evaluable for response. 4 pts had received prior chemotherapy. Median age 59 (34-80) yrs, 60% had ECOG PS 1. Partial response (PR) achieved in 13 pts (87%). Six pts had ALK detected via plasma NGS. In two patients who did not respond to ensartinib, tissue was positive via FISH and plasma was negative. Seven patients had insufficient plasma for NGS evaluation. Median PFS in the initial 13 evaluable ALK+ pts was 25.6 mos with the longest being 44+ mos. The PFS for all patients is still maturing. In 3 pts with central nervous system (CNS) target lesions and no prior radiation, 1 had a complete response (CR) and 2 had PR for an ORR of 100%. Most common drug-related AEs (≥20% of pts) included rash (54%), nausea (34%), pruritus (26%), vomiting (25%), and fatigue (21%). Most AEs were Grade (G) 1-2. Most common G3 tx-related AE was rash (12 pts). **Conclusion:** Ensartinib was well-tolerated and induced responses in ALK TKI naïve ALK+ NSCLC pts, including pts with CNS lesions. Enrollment is ongoing in the phase 3 study of ensartinib vs. crizotinib in ALK TKI naïve NSCLC patients.

Keywords: NSCLC, ALK+, lung

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MA 07.03 INCIDENCE, PREDICTORS AND PROGNOSTIC SIGNIFICANCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH ADVANCED ALK-REARRANGED NSCLCS

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Background: The incidence of venous thromboembolic events all along the course of the disease in advanced-stage lung adenocarcinomas is approximately 15 %. It is plausible that the different molecular subtypes might influence on the risk of thrombosis. Based on our clinical observation, and supported by limited data from isolated small series, patients bearing ALK rearranged tumors could be at a particularly high-risk of thromboembolic disease. **Method:** We included consecutive patients diagnosed with advanced-stage ALK fusion positive non-small cell lung cancers (NSCLC) between January 2012 and December 2016. Clinical data were contributed by 29 Medical Centers from Spain and one large Academic Cancer Center from Portugal. Investigators at each institution retrospectively reviewed patients' medical records. A thromboembolic event was defined as any venous or arterial thromboembolism, or both, at any site, documented by appropriate imaging studies, that occurred at the time or after advanced-stage cancer diagnosis. **Result:** A total of 241 ALK-rearranged NSCLCs were included in our study. Half of the patients were never smokers (52 %), and most had stage IV pulmonary adenocarcinomas (n=204, 85%). Baseline brain and liver metastasis were detected in 22 % and 25 % of the patients respectively. Seventy-three patients (30 %) developed thromboembolic disease. In 54 patients (74 %) thromboembolic complications occurred within the first 6 months from diagnosis. In the multivariate competing-risk regression analysis, the presence of baseline liver metastases (HR of 1.85, CI 95 % 1.09-3.15; p = 0.021) and baseline leukocyte counts > 11.0000 cells/mm3 (HR of 2.34, CI 95 % 1.43-3.82; p = 0.001) were independent predictors of thromboembolic disease. Remarkably, 50 % of the patients with either liver metastases or leukocytosis at diagnosis developed thromboembolic disease. Patients experiencing thromboembolic events had shorter median overall survival (OS) (20 months) than patients without thrombosis (36 months) (p = 0.035). In the multivariate Cox Model, thromboembolic disease remained associated with worse OS (HR of 1.70, CI 95 % 1.10-2.62; p = 0.016) when considered as a time-varying covariate. The presence of baseline thromboembolic disease (n = 24) was associated with a numerical non-significant increased risk of death (HR 1.67, CI 95 % 0.96-2.91; p = 0.068). **Conclusion:** Venous and/or arterial thromboembolic complications occur in a high proportion of patients with advanced-stage ALK fusion positive NSCLCs, particularly in the presence of baseline liver metastasis or leukocytosis. The development of thromboembolic disease is associated with a lower OS in these patients.

Keywords: ALK fusions, thromboembolic disease, liver metastases

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MA 07.04 CLINICAL IMPACT OF CRIZOTINIB ON BRAIN METASTASES IN PATIENTS WITH ADVANCED ROS1-REARRANGED NON-SMALL CELL LUNG CANCER

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Background: Brain metastases are common in patients with advanced non–small cell lung cancer (NSCLC). Approximately 1% of NSCLC patients have ROS1-rearranged, and these patients achieved prolonged survival when treated with crizotinib, which is approved for the treatment of ROS1-rearranged NSCLC. However, this efficacy might not translate to intracranial control of disease. Herein, we evaluated the clinical impact of crizotinib on brain metastases in patients with advanced ROS1-rearranged

NSCLC. **Method:** Between April 2014 and October 2016, 53 ROS1-rearranged NSCLC patients treated with crizotinib were retrospectively evaluated for baseline characteristics, brain metastases status, progression patterns and the overall prognosis. **Result:** Of the 53 ROS1-rearranged NSCLC patients who received crizotinib as treatment, 13 (24.5%) patients had baseline brain metastases before crizotinib treatment. Among patients without baseline brain metastases who developed progressive disease after initiation of crizotinib (n=27), 22.2% were diagnosed with brain metastases. Among patients without baseline brain metastases, systemic progression-free survival (PFS) and overall survival (OS) after initiation of crizotinib was significantly longer than that of patients with brain metastases (median PFS: 20.4 months vs. 11.0 months, p = 0.003; median OS: not reached vs. 16.5 months, p = 0.027). There was no significant difference in systemic PFS and OS between patients developing brain metastases before and after crizotinib treatment (median PFS: 11.0 months vs. 6.4 months, p = 0.469; median OS: 16.5 months vs. not reached, p = 0.605). Among the patients with baseline brain metastases, 6 had received prior brain radiotherapy and 7 had received no prior radiotherapy. A total of 2 patients in the treated group had an event of brain metastases progression, as compared with 4 patients in the untreated group (33.3% vs 57.1%, p = 0.592). There was no significant difference in intracranial PFS in the previously brain treated patients versus the untreated patients before crizotinib treatment (median intracranial PFS: 12.5 months vs. 11.0 months, p = 0.790). **Conclusion:** Brain metastases status before crizotinib treatment was significantly associated with both PFS and OS in crizotinib-treated ROS1-rearranged NSCLC patients. Patients with brain metastases received prior radiotherapy have not prolonged survival compared with the patients treated with crizotinib alone.

Keywords: non-small cell lung cancer(NSCLC), ros1 rearrangement, Brain metastasis

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MA 07.06 DETECTION OF MECHANISMS OF RESISTANCE TO ALK INHIBITORS IN ROUTINE PRACTICE: A RETROSPECTIVE STUDY

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Background: Treatment of ALK-rearranged Non-Small Cell Lung Cancer (NSCLC) relies on ALK tyrosine kinase inhibitors (TKI). However, efficacy of ALK TKI is limited by the emergence of drug resistance. ALK molecular alterations (amplification or mutation) account for about 40% of mechanisms of resistance to ALK TKI. Even though clinical and fundamental data suggest variability in drug efficacy according to the mechanism of resistance, these mutations are rarely investigated in routine practice. While targeted next-generation sequencing (t-NGS) is increasingly used for detecting molecular abnormalities, the impact of this tool in routine detection of ALK alterations is unknown. **Method:** We performed a retrospective multicentric study aiming at determining the frequency of ALK alterations using t-NGS in metastatic ALK-rearranged NSCLC patients progressing upon ALK TKI. Clinical, pathological, molecular characteristics, and patients outcome were collected. **Result:** We identified 22 patients with metastatic ALK-rearranged NSCLC who underwent a rebiopsy at progression on first ALK TKI, between January 2012 and May 2017. There were 12 females and 10 males, median age was 55, 18 patients (82%) were never smokers. Crizotinib was the first ALK TKI in 21 patients (95%). 15 patients (68%) received a second-generation ALK inhibitor and 3 patients (14%) received a third generation of ALK inhibitor. t-NGS on rebiopsy was performed in 16 patients. 6 ALK mutations (37.5%) were identified, including 3 G1202R, 1 C1156Y, 1 V1180L and 1 L1196M mutations . An ALK amplification (6%) was detected in a rebiopsy (6%) by FISH, with no concomitant ALK mutation. All ALK mutations were detected in solid biopsy, 2 ALK mutation was also detected in liquid biopsy. Median Overall Survival from first ALK TKI was 797 days (IC 95% 460-1135) and tended to be longer in patients with a known mechanism of resistance (1135 days Vs 543 days p=0.2). **Conclusion:** Targeted NGS is feasible in routine practice for detection of mechanisms of resistance to ALK TKI in ALK-rearranged NSCLC patients and may help selecting the best treatment at progression upon ALK TKI.

Keywords: NSCLC , EML4/ALK , Resistance , NGS .

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MA 07.07 CLINICAL OUTCOMES AND ALK RESISTANCE MUTATIONS IN ALK+ NON-SMALL CELL LUNG CANCER ACCORDING TO EML4-ALK VARIANT

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Background: Advanced ALK+ non-small cell lung cancers (NSCLCs) are effectively treated with ALK tyrosine kinase inhibitors (TKIs). However, clinical outcomes among patients treated with ALK TKIs vary, and the clinical benefit of TKI therapy is limited due to acquired resistance. To date, emerging data suggest that the specific EML4-ALK variant may impact clinical outcome, but whether variant is associated with mechanisms of TKI resistance is unknown. **Method:** We identified 108 advanced ALK+ NSCLC cases with known ALK fusion variants. Progression-free survival (PFS) on ALK TKIs and resistance mechanisms were retrospectively evaluated according to ALK variant. **Result:** The 108 ALK+ cases consisted of: 42 (39%) EML4-ALK v1 (E13;A20), 8 (7.4%) v2 (E20;A20), 45 (41.7%) v3 (E6;A20), 3 (2.8%) v5 (E2;A20), 4 (3.7%) v5' (E18;A20), 1 (0.9%) v7 (E14;A20), and 5 (4.6%) non-EML4-ALK variants. Given the small numbers of non-v1/v3 cases, v1 and v3 cases were selected for further analysis. Among the 21 v1 and 25 v3 cases treated with first-line crizotinib, there was no significant difference in PFS (HR = 0.81 [95% CI, 0.42-1.57], p = 0.526). Similarly, there was no difference in PFS on second-generation ALK TKIs among 35 v1 and 35 v3 patients who received ceritinib, alectinib, or brigatinib following first- or later-line crizotinib (HR = 1.32 [95% CI, 0.77-2.26], p = 0.308). Interestingly, among 12 v1 and 17 v3 patients who received the third-generation TKI lorlatinib after failure of a second-generation TKI, v3 was associated with significantly longer PFS than v1 (HR = 0.250 [95% CI, 0.09-0.72], p = 0.006). From our cohort, we identified 11 v3 and 14 v1 post-crizotinib biopsies. No difference was noted in the presence of ALK resistance mutations (27% and 21%, respectively; p = 1.000). In contrast, among 30 v3 and 18 v1 post-second generation TKI biopsies, ALK resistance mutations were more common among v3 vs v1 cases (66% vs 44%, respectively; p = 0.147). Furthermore, the ALK G1202R solvent front mutation occurred more frequently in v3 vs v1 (47% vs 0%, respectively; p = 0.001). **Conclusion:** Our findings suggest that EML4-ALK variants 1 and 3 may not be associated with significantly different PFS outcomes on crizotinib or second-generation ALK TKIs. However, ALK resistance mutations, particularly G1202R, occur more frequently in v3 vs v1 post–second generation TKI. Patients with this variant may therefore derive particular benefit from third-generation, pan-inhibitory ALK TKIs. Larger, prospective studies will be needed to confirm these findings.

Keywords: tyrosine kinase inhibitor (TKI), Resistance, ALK variant

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MA 07.08 CLINICAL IMPLICATIONS OF ALK RESISTANCE MUTATIONS: INSTITUTIONAL EXPERIENCE AND LAUNCH OF REMOTE PARTICIPATION STUDY

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Background: ALK resistance mutations are detected in 30-50% of the patients with ALK-positive non-small cell lung cancer (NSCLC) and resistance to ALK tyrosine kinase inhibitors (TKIs). Preliminary data suggests that TKI-resistant patients benefit from further ALK inhibition based on the specific resistant mutations, but clinical data are limited. **Method:** Patients with ALK-positive NSCLC were identified from our institutional database with IRB approval. Tumor specimens from patients with TKI-resistance were analyzed using next-generation sequencing (NGS). We aimed to study the relationship between specific ALK-resistant mutations, patient characteristics and clinical outcomes. **Result:** Among 82 ALK-positive NSCLC patients, we identified 29 cases with advanced disease, TKI resistance, and specimens available for NGS. Twenty-two specimens from 19 patients were adequate for genomic analyses. Patients received a median of 4 lines of treatment for advanced disease including a median of 2 ALK TKIs, with a median overall survival (OS) of 3.3 years. In 9 of 22 specimens, crizotinib was the only TKI received. Ten specimens (45.5%) showed an ALK resistance mutation: one G1128A, one L1152R, four I1171N/T, two F1174V and two G1202R. ALK-resistance mutations were more common with EML4-ALK variant 3 (4/5) than variant 1 (1/5). Three cases with sequential biopsies showed features of tumor evolution, such as a compound mutation (I1171N + C1156Y) or a mutational change (L1152R to G1128A). One case initially had an EGFR L858R mutation, then acquired an ALK rearrangement, then acquired a G1202R mutation. OS was longer in 8 patients with secondary ALK mutation (5.5y) compared to 11 patients without (1.8 y). Using these learnings from an institutional cohort of ALK resistant patients, we designed and are launching a prospective study to characterize ALK TKI resistance, which uses remote-participation and plasma NGS to enroll patients from across the US. Patients with systemic progression while on a next-generation ALK TKI submit blood to a central lab for analysis and banking. Plasma NGS results are returned to the patient and their provider, and including expected TKI sensitivities for any identified ALK-resistance mutations. Through monitoring outcomes, this study can assess if molecularly-guided therapy for ALK TKI-resistance is feasible and effective. **Conclusion:** ALK resistance mutations arise in a large portion of patients and are associated with longer survival. The SPACEW-ALK study (Study of Plasma next-generation sequencing for remote Assessment, Characterization, Evaluation of patients With ALK drug resistance) uses plasma NGS and remote consent to assess ALK resistance and the feasibility of precision resistance therapy for these patients.

Keywords: ALK resistance, Plasma NGS

MA 07.09 ALK/ROS1/TRK INHIBITOR TPX-0005 EFFECTIVELY OVERCOMES CLINICAL RESISTANCE SOLVENT FRONT MUTATIONS

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Background: ALK, ROS1 and TRK kinase inhibitors have achieved tremendous success in the treatment of lung cancer patients with abnormal ALK, ROS1 or NTRK gene. However, the emergence of drug resistance limits their long term clinical applications. An ever increasing number of acquired resistance mutations are being reported from the clinic. In addition to the gatekeeper mutations, the solvent front mutations have been recently recognized as common resistance mutations to many kinase inhibitors. For example, the solvent front ALK G1202R mutant conferred resistance to many clinical ALK inhibitors in lung cancer including crizotinib, ceritinib, alectinib, and brigatinib. The same position mutations ROS1 G2032R, TRKA G595R and TRKC G623R rendered resistance to the ROS1 inhibitor crizotinib in lung cancer, pan-TRK inhibitor entrectinib and larotrectinib in colon cancer, and larotrectinib in infantile fibrosarcoma, respectively. **Method:** A conserved glycine residue at the hinge C-terminal forms a hydrophobic sandwich with the kinase beta 1 sheet. Kinase inhibitors often use an aromatic ring or a flat motif to fit through this narrow glycine sandwich to the solvent. Alterations at the conserved glycine or the nearby residues, commonly referred to as solvent-front mutations, clash with the inhibitor motif and induce clinical resistance. Here, we designed TPX-0005, a novel three-dimensional macrocycle with a much smaller size than current ALK, ROS1, and TRK inhibitors in the clinic to avoid the steric clash inside the sandwich. **Result:** TPX-0005 resides at the center of the highly conserved ATP site without direct contact with the solvent front glycine sandwich. As expected, TPX-0005 potently inhibited WT EML4-ALK and solvent front mutant EML4-ALK G1202R with similar activities in both enzymatic (WT Ki 0.87 nM vs G1202R 0.81 nM) and Ba/F3 cell proliferation assays (WT IC_{50} 21.1 nM vs G1202R 20.5 nM). TPX-0005 showed potent activities against CD74-ROS1 G2032R (IC_{50} 8.4 nM), LMNA-TRKA G595R (IC_{50} 0.4 nM), TEL-TRKB G639R (IC_{50} 1.9 nM) and TEL-TRKC G623R (IC_{50} 0.4 nM) in Ba/F3 cell proliferation assays. In the xenograft tumor model studies, TPX-0005 dramatically caused tumor growth inhibition and tumor regression in the tumors carrying WT and solvent-front mutations of ALK, ROS1 or TRKA fusion genes, respectively. **Conclusion:** Taken together, preclinical results demonstrated that TPX-0005 is a novel ALK/ROS1/TRK inhibitor overcoming the profound solvent front kinase mutations. TPX-0005 will bring new methods for the treatment of resistance patients with solvent front mutations in ALK, ROS1, or TRK fusion genes. A phase 1/2 study of TPX-0005 in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements (TRIDENT-1) is actively pursued (NCT03093116).

Keywords: ros1, TRK, ALK

MA 07.11 A PHASE II STUDY OF TRASTUZUMAB EMTANSINE IN HER2-POSITIVE NON-SMALL-CELL-LUNG CANCER

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Background: Trastuzumab emtansine (T-DM1), an anti-HER2 antibody conjugated with vinca-alkaloid, has been approved for clinical use in HER2-positive breast cancer. HER2-alterations are detected even in non-small-cell lung cancer (NSCLC). We have launched a phase II trial of T-DM1 monotherapy for patients with HER2-positive lung cancer. **Method:** Eligible patients had pathologically diagnosed NSCLC with documented HER2-positivity (immunohistochemistry [IHC] 3+, both IHC 2+ and fluorescence in situ hybridization [FISH] +, or exon 20 insertion mutation) and were previously treated with standard chemotherapy. Thirty patients would receive T-DM1 3.6 mg/kg every 3 weeks. The primary endpoint is the overall response rate (ORR) per RECIST v1.1. **Result:** This study was early terminated due to the limited efficacy, leading that only 16 patients were registered. The demographics of the 15 evaluable patients were as follows: age (median; 67, range: 45-77), sex (male; 47%), performance status (0-1; 80%), histology (non-squamous; 100%), HER2 status (IHC3+; 33%, IHC2+/FISH; 20%, and mutation; 47%) and number of prior chemotherapeutic regimens (median; 4, range: 1-7). Of 15 patients, one, who possessed HER2 mutation achieved a partial response, resulting in ORR of 6.7%. None of the 15 patients experienced treatment-related deaths. Survival data would be presented at the meeting. **Conclusion:** T-DM1 has a limited efficacy for HER2-positive NSCLCs in our cohort. Additional molecular approaches are warranted for the precision medicine in HER2-positive tumors. UMIN registration number 000019446.

Keywords: NSCLC, HER2, T-DM1

MA 07.12 SHORT-TERM CULTURE OF PATIENT DERIVED TUMOR ORGANOIDS IDENTIFY NERATINIB/TRASTUZUMAB AS AN EFFECTIVE COMBINATION IN HER2 MUTANT LUNG CANCER

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Background: There are currently no effective targeted therapies for HER2 mutant lung cancer. Both neratinib alone or in combination with temsirolimus both have low response rates. One challenge is the lack of patient derived HER2 mutant cell line models and a platform in which to identify the most effective therapeutic strategy. Patient derived xenografts (PDXs) are emerging as an alternative tool to screen for drug efficacy, but can take months to generate and are impractical for screening of large sets of drug combinations. Here we report on a novel 3D microfluidic platform that allows for evaluating ex vivo responses to targeted therapies or targeted therapy combinations from patient derived tumor spheroids (xDOTS). **Method:** We generated xDOTS from DFCI 359, a PDX derived from a HER2 mutant (InsYVMA) NSCLC patient under an IRB approved protocol. Tumor organoids (<100 μm and >40μm) were treated with: HER2 covalent inhibitors (neratinib, afatinib); an EGFR inhibitor (gefitinib), and combinations of HER2 inhibitors and other compounds (neratinib/trastuzumab or neratinib/temsirolimus) at known peak plasma concentrations for 3 days in our 3D microfluidic cell culture device. Live/death quantification was performed by dual labeling de-convolution fluorescence microscopy using acridine orange for live and propidium iodide for dead cells. Cell type characterization was performed by immunofluorescence. The most effective combination was used to treat the DFCI 359 PDX and a HER2 InsYVMA genetically engineered mouse model (GEMM). **Result:** Both neratinib alone and afatinib alone, but not gefitinib, induced high degree of cell death in the DFCI 359 xDOTS. The combinations of neratinib/trastuzumab, and neratinib/temsirolimus enhanced the therapeutic benefit compared to neratinib alone, with the former combination being more effective than the latter. Using fluorescence microscopy we demonstrate that the effects are specific to the tumor cells, rather than the stromal component. We then went on to confirm these findings in a concomitant in-vivo efficacy experiment using the DFCI 359 PDX and the HER2 InsYVMA GEMM. In both in vivo models, the neratinib/trastuzumab combination led to significant tumor regressions and was superior to either single agents or the neratinib/temsirolimus combination. **Conclusion:** Our findings demonstrate the ability to use a 3-D in vivo microfluidic system to identify combination therapies for HER2 mutant NSCLC. Based on our studies, neratinib/trastuzumab is a promising combination for a clinical trial for HER2 mutant lung cancer.

Keywords: HER2 mutant lung cancer, targeted therapy combinations, Tumor organoids

MA 07.13 NGS SEQUENCING BASED LIQUID / TISSUE BIOPSY IDENTIFIED COEXISTENCE OF HER2 AMPLIFICATION AND MUTATION IN ADVANCED NSCLC PATIENTS

R. Chen[1], J. Zhao[2], G. Lin[3], L. Liu[4], L. Chen[5], X. Hu[6], X. Ai[7], Z. Fan[8], C. Xu[9], W. Wang[10], W. Zhuang[3], M. Fang[11], Y. Zhu[12], G. Chen[13], Y. Guan[1], L. Yang[1], X. Xia[1], X. Yi[1]

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Background: Human epidermal growth factor 2 (HER2, ERBB2) mutations / amplifications have been identified as oncogenic drivers in 2-5% of lung cancers. It has been reported that hybridization capture-based next-generation sequencing (NGS) could reliably detect HER2 amplification in qualified breast and gastroesophageal tumor tissue samples. However, there is little data in lung cancer, especially for advance NSCLC with only ctDNA samples available. **Method:** We reviewed 2000 consecutive samples from advanced NSCLC patients sequenced in our institute between 2015 and 2016. Tumor biopsy and/or ctDNA samples were analyzed using hybridization capture-based NGS ER-Seq method, which enables simultaneously assess single-nucleotide variants, insertions/deletions, rearrangements, and somatic copy-number alterations at least 59 genes (range 59 – 1021 genes). **Result:** We identified 54 samples from 48 patients with HER2-mutation or amplification in the cohort (54/2000=2.7%). The 54 samples included 14 tissue biopsy samples, 37 ctDNA samples, and 3 pleural effusion samples. Thirty-six samples carried HER2 mutations, and 23 samples carried HER2 amplification with 5 samples have concurrent HER2 mutation and amplification. A 9-base pair (bp) in-frame insertion in exon 20 (Y772_A775dup) was detected in 18 samples (18/36=50%). In addition, there were 5 other insertions in exon 20; eight single bp

substitutions (S310F) in exon 8; three exon 17 V659E mutations (from the sample patient with 3 ctDNA samples submitted at different time); one exon 19 D769H mutation; and one exon 21 V842I mutation. Amplification were identified in 23 samples, with copy number range from 3.8 to 19.6 in tissue samples (n=7, medium 11.6); from 4.3 to 51.8 in ctDNA samples (n=16, medium 7.3); 3.2 and 6 in the 2 pleural effusion samples. Interestingly, the allele frequency (AF) of HER2 mutation was the maximal in 4 of the 5 patients with concurrent HER2 mutation and amplification. Two patients were EGFR-TKI resistant with EGFR L858R mutation remaining and HER2 mutation and amplification might be the major reason for the resistance. **Conclusion:** HER2 mutations might coexist with HER2 amplification in advanced NSCLC patients, and it could be detected simultaneously with hybridization capture-based NGS sequencing both in tissue and liquid biopsy samples. Further quantative analysis of HER2 amplification / mutation and anti-HER2 therapeutic effects are underway.

Keywords: HER2 amplification and mutation, ctDNA, next generation sequencing (NGS)

MA 07 ALK, ROS AND HER2
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 07.14 CHANGE IN PRACTICE PATTERNS FROM AN ONLINE NSCLC TREATMENT DECISION SUPPORT TOOL

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Background: Therapeutic options for advanced NSCLC have changed dramatically in recent years, greatly increasing the complexity of therapeutic decision-making. Treatment guidelines are sub-optimal for extrapolation to individual patient care. We have previously published results of an online decision support tool designed to provide clinicians with education and expert guidance. Here we report results of the third version, capturing the impact of rapidly expanding new treatment options. **Method:** A panel of 5 experts provided treatment recommendations for 241 case scenarios across 1st- and 2nd-line settings for advanced NSCLC. Individual scenarios were defined by key patient and disease characteristics including histology, driver mutations, performance status, and previous therapy among others. For each patent scenario, participating oncologists entered patient and disease factors and their treatment recommendation, selected from a menu of treatment choices. Expert choices for that scenario were then provided to participants for reconciliation. **Result:** 708 cases were entered by 492 oncologists; 79% non-USA, 21% USA. Highlights: In the 1st-line setting, an EGFR TKI was selected in 89% of EGFR-mutated cases (n = 113), an increase of 22% from the 2014 tool. In contrast to 100% of experts selecting crizotinib for ROS1 cases, participating oncologists chose crizotinib in only 25% (n = 16). Immunotherapy (IO) was commonly selected by experts for 2nd-line therapy in cases without actionable mutations (see Table). Participants chose IO less frequently in both PD-L1-positive and negative cases. Participants changed their choice after viewing expert recommendations in 48% of cases.

	Participants' Treatment Choice	Experts' Treatment Choice
Nonsquamous		
• PD-L1 positive (≥1%)	54% anti-PD-1 agent (n = 35)	100% anti-PD-1 agent
• PD-L1 negative (<1%)	28% anti-PD-1 agent, 65% Chemotherapy (n = 104)	40% anti-PD-1 agent, 55% Chemotherapy
Squamous		
• PD-L1 positive (≥1%)	62% anti-PD-1 agent (n = 24)	100% anti-PD-1 agent
• PD-L1 negative (<1%)	28% anti-PD-1 agent, 65% Chemotherapy (n = 74)	85% anti-PD-1 agent, 15% Chemotherapy

Conclusion: This decision-making tool integrates recent changes to the treatment landscape, including IO. Compared to the 2014 version, practicing oncologist use of 1st-line EGFR targeted therapy now closely tracks experts, while selection of IO and targeted therapy for ROS1 disease lagged behind expert recommendations. A detailed analysis of expert versus online user data capturing evolving practice trends will be presented.

Keywords: Practice patterns

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.01 INCORPORATING THE REVIEW OF PATIENTS ON IMMUNOTHERAPY INTO AN ESTABLISHED LUNG CNS NURSE LED REVIEW CLINIC

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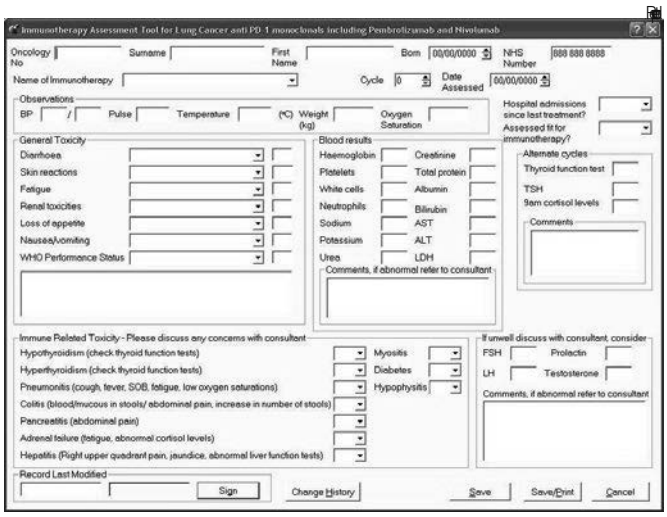
Background: The Kent Oncology Centre has been instrumental and innovative in the development of nurse-led services since 2005. The Lung CNS's have been conducting oncology clinics since 2009 reviewing patients on TKI's and chemotherapy. With Immunotherapy now available to some lung cancer patients, the Lung CNS's needed to incorporate immunotherapy review into their established clinics. The Lung CNS's worked collaboratively to develop a patient-centred electronic assessment tool. The tool would ensure standardised practise, patient safety and assess toxicities whilst on Immunotherapy. The aim is for the Lung CNS's to utilise the electronic tool and roll out through an educational programme thus increasing knowledge and confidence and empowering nurses to safely review patients on immunotherapy. **Method:** To incorporate immunotherapy patients to an established CNS Nurse-led review clinic: **Agreement** between Consultant and Senior Nurses. **Discussions** with Computer Sciences, Lung Cns's, Oncologists, Chemotherapy Lead Nurse. **Educational Requirements** - Consultation and Physical Examination Skills, Non-Medical Prescribing, Chemotherapy Competence, IRMER. **Protocols -** Agreed for the Nurse Led Oncology review clinic. **Competence -** The Lung CNS requires a set of practice and competence in judgement and decision making. How the clinic works Consent by the consultant. Consultant toxicity assessment pre cycle 2. Reviewed thereafter by lung CNS or Chemotherapy Nurse prior to each treatment. Electronic Toxicity assessment completed. Weight/Observations recorded. Bloods FBC, U&E's, LFT's. Thyroid 8 weekly. 9am cortisol LH and FSH Direct access to consultant. Consultant review with CT scan. **Result:**



Toxicities. Adisonian Crisis Hypothyroidism Diarrhoea/Colitis Fatigue Hepatitis Skin Reactions Pneumonitis **Conclusion:** The number of patients on Immunotherapy treatment is set to rise. Incorporating the review of Immunotherapy into an established Lung CNS Nurse-led Review clinic enabled standardised practise, enhanced patient safety and provided continuity of care. Through education and training and by using an electronic assessment tool; chemotherapy nurses can be empowered to review patients on Immunotherapy.

Keywords: Immunotherapy Electronic assessment tool, Immunotherapy, Nurse-led review

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.02 EFFICACY OF SINGLE-DOSE NEPA VERSUS 3-DAY APREPITANT REGIMEN FOR PREVENTION OF CINV: A PHASE 3 LUNG CANCER SUBSET ANALYSIS

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Background: Cisplatin, a systemic treatment component for many lung cancer types, is highly emetogenic (HEC). The guideline-recommended antiemetic combination for patients receiving HEC includes a NK_1 receptor antagonist (NK_1RA), a 5-HT_3RA, and dexamethasone (DEX). NEPA is the first oral fixed combination of an NK_1RA (netupitant) and a 5-HT_3RA (palonosetron). The approval of oral NEPA was based on studies demonstrating superior prevention of chemotherapy-induced nausea and

vomiting (CINV) over oral palonosetron; an intravenous formulation of NEPA is under FDA evaluation. A new Phase 3 study in Asia has reached its primary objective: a single day oral dose of NEPA is non-inferior to a 3-day regimen of aprepitant (APR) and granisetron (GRAN) [both combined with DEX] in preventing CINV in patients receiving cisplatin. This post-hoc analysis explores the efficacy of NEPA vs APR/GRAN within the lung cancer subset of that study. **Method:** Chemotherapy-naïve lung cancer patients in this double-blind, parallel group study received either a single oral dose of NEPA prior to cisplatin-based HEC or a 3-day regimen of APR/GRAN, both with oral DEX on days 1-4. Efficacy endpoints were complete response (CR: no emesis/no rescue medication), no emesis, and no significant nausea (<25 mm on 100 mm visual analog scale) during the acute (0-24h), delayed (25-120h) and overall (0-120h) phases post-chemotherapy. The risk difference for NEPA – APR/GRAN and associated 95% confidence intervals (CIs) were analyzed for each endpoint using the Cochran-Mantel-Haenszel test. **Result:** 542 (65%) of the 828 patients had lung cancer. Mean age was 56.1; 73% males. Response rates were comparable for both arms during the acute phase, and favored NEPA in delayed phase (**Table -** *see next page*).

% of Patients	NEPA (N = 275)	APR/GRAN (N = 267)	Risk Difference % (95% CI)
Complete Response			
Acute	87.6%	89.5%	-1.6% (-6.9%, 3.7%)
Delayed	82.9%	76.0%	7.2% (0.5%, 13.9%)*
Overall	78.9%	74.9%	4.3% (-2.7, 11.4%)
No Emesis			
Acute	88.4%	90.3%	-1.6% (-6.9%, 3.7%)
Delayed	84.4%	78.7%	6.1% (-0.4%, 12.7%)
Overall	80.0%	77.2%	3.3% (-3.6%, 10.2%)
No Significant Nausea			
Acute	89.5%	88.0%	1.6% (-3.7%, 6.9%)
Delayed	80.4%	74.2%	6.4% (-0.6%, 13.5%)
Overall	77.1%	71.5%	5.8% (-1.5%, 13.2%)

*statistically significant difference – exploratory analysis

Conclusion: As a fixed oral combination of an NK_1RA and $5HT_3RA$ in a single capsule/cycle, NEPA offers a convenient and effective prophylactic antiemetic in lung cancer patients receiving cisplatin-based HEC regimens.

Keywords: CINV, aprepitant, NEPA

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.03 DISCUSSING POTENTIAL RECURRENCE AFTER LUNG CANCER SURGERY: COMPLEXITY AND CHALLENGES

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Background: Increasing numbers of patients are being treated with potentially curative surgery for lung cancer. Pathological staging gives an indication of 5-year survival and whether further treatment is recommended. Patients undergo a period of post-operative clinical surveillance to monitor for potential recurrence of cancer. The process of discussing potential recurrence and its early warning signs has not been well researched. This study examines how clinical teams and patients manage information disclosure about possible cancer recurrence following lung cancer surgery. The aim is to identify some of the practice implications for lung cancer teams. **Method:** This qualitative project used case study methodology to explore how information regarding possible recurrence was presented to patients. Twelve patients were recruited at two thoracic surgical centres. Observation of the first post-operative surgical and subsequent oncology or follow-up clinic was conducted and consultations audio recorded. In-depth, one-to-one interviews were completed with clinical staff (surgeon, oncologist, physician and/or nurse specialist) who saw the patients to ascertain their perspective and understand rationale for particular information giving. Framework Analysis methods were used to identify key themes. **Result:** Staff varied in the extent and explicitness that long-term surgical outcomes were communicated to patients. Explicit information was presented in terms of recurrence risk or survival and the terms were frequently used interchangeably. Clinicians were often reluctant to give a numerical estimate of risk of recurrence or survival at the post-operative clinic. Information about early warning signs of recurrence was sporadic, with some clinicians preferring to delay such discussions until later on in the follow-up pathway, due to fear of damaging patients' perceived fragile hope for cure. Information was aimed at supporting hope, aiding treatment understanding, or facilitating decision-making. Choices made by staff regarding information giving were complex and largely tacit, but appeared to be linked to individual professionals' underlying optimistic or realistic approach. Staff talked about the importance of balancing hope and realism. **Conclusion:** These findings give unique insight and reveal how challenging and complex it is for clinicians to discuss recurrence following lung cancer surgery. The next stage of the project will examine the patient's perspective of this process. These data will then be combined to identify ways to improve communication of recurrence

Keywords: Communication, recurrence, lung cancer surgery

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.05 SURVIVING LUNG CANCER, AN ANALYSIS OF THE PATIENT CONCERNS IDENTIFIED IN A NURSE-LED FOLLOW-UP CLINIC AFTER THORACIC SURGERY

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Background: Using evidence based follow up guidelines, our nurse led follow-up clinic was established in December 2012. All post-operative thoracic surgery patients are seen, including patients with primary lung cancer. We evaluated problems and issues patients identified related to their post-operative recovery and follow-up period **Method:** Data was collected prospectively from December 2012 to March 2017. This included information for each patient on surgery, pathology, TNM stage, follow-up plan and smoking status. We recorded additional issues raised by patients. Data was analysed to generate descriptive statistics of post-operative problems. There were 546 patient episodes in 189 clinics for 285 patients with primary lung cancer **Result:** Of the 285 patients 70 (25%) were smokers in the 6 weeks prior to surgery. 171 (60%) were ex-smokers and 44 (15%) had never smoked. 32 (11%) patients smoked after surgery, all except one were pre-operative smokers. Smoking cessation was a concern after surgery with 44% of the pre-operative smokers restarting smoking post-operatively. The number of patients seen at each follow-up interval and the issues identified are shown in the table below. The most frequent issues reported by patients after thoracic surgery are pain, respiratory issues and anxiety. 80% of patients report problems at their first follow-up appointment after surgery, decreasing to 59% at five years. Respiratory issues are common in this group of patients who often have co-existing lung disease. Anxiety, most commonly associated with fears about recurrence of disease, remains a problem throughout the follow-up period. 31% of patients had abnormal imaging at one or more appointments.

Issues identified in the nurse led thoracic surgery follow-up clinic							
	Number of patients % of the total patients seen in each survillance period						
Time since surgery	**Total**	**Pain**	**Respiratory issues**	**Anxiety**	**Imaging issues**	**Other issues**	**No issues**
1st follow-up	120	33 27.5%	23 19%	24 20%	18 15%	16 13%	24 20%
6 months	118	21 18%	20 17%	11 9%	33 28%	14 12%	31 26%
12 months	79	10 13%	20 25%	8 10%	19 24%	8 10%	14 18%
18 months	66	9 14%	15 23%	8 12%	14 21%	7 11%	22 33%
2 years	65	9 14%	12 18%	7 11%	10 15%	10 15%	19 29%
3 years	48	7 15%	7 15%	7 15%	11 23%	8 17%	13 27%
4 years	28	0	7 25%	5 18%	5 18%	8 29%	7 25%
5 years	22	0	6 27%	2 9%	4 18%	2 9%	9 41%
Totals	546	89 16%	110 20%	72 13%	114 21%	71 13%	139 25%

Conclusion: The findings indicate the extent of physical, psychological and lifestyle (e.g. smoking) concerns in post-operative follow-up. A new telephone follow-up clinic has recently been introduced to address these needs. Further investigation with objective assessment and scoring of symptoms would improve the quality of the data collected.

Keywords: Thoracic Surgery, survivorship, nursing

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.06 ASSESSMENT TO PROGRAMMING: RESPONDING TO THE NEEDS OF THE US LUNG CANCER COMMUNITY

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Background: Research shows people diagnosed with lung cancer have greater unmet supportive care, physical and emotional needs compared to those diagnosed with other cancers. Much of this research is older and primarily focused on small numbers of newly diagnosed patients. Other research has focused on the relative lack of treatment options and does not address practical and psychosocial needs. **Method:** To more fully understand the current unmet needs of lung cancer survivors, an online survey was distributed between 11/9/2015 and 2/8/2016. Of

820 respondents, 471 were lung cancer patients/survivors with 349 loved ones. Queried on treatment histories, respondents were asked to identify the most prevalent and problematic symptoms and side effects experienced during treatment, shortly after treatment ended and at 5+ years post-diagnosis. They were also asked which were most problematic during each time period. **Result:** The survey had an overall 72% completion rate with 21% of survivor-respondents indicating a diagnosis 5+ years prior. Patients/survivors rated anxiety, fatigue and shortness of breath as most challenging in the immediate, post-treatment, and long-term. During treatment, gastrointestinal issues including constipation, diarrhea and nausea were also highly problematic. All groups reported physical effects were significantly more problematic during treatment but deemed emotional effects more difficult to manage post-treatment and in the long-term. In open-ended questions, nearly 25% of respondents indicated they received inadequate information/assistance to manage physical and emotional reactions, both during and after treatment. Only 27% of respondents had a discussion about palliative care with just over 20% having received it. The survey affirmed that assistance to manage lung cancer's symptoms and treatment side effects is an unmet need in the lung cancer community. In response, a four-part educational series, including webinars and accompanying print materials, was developed. The series is the only to focus specifically on lung cancer and helps participants understand the causes of the top four reported symptoms and side effects, including potential medical interventions and holistic, practical tips that can used immediately. **Conclusion:** Those diagnosed with lung cancer are the experts and we can only understand their unmet needs by asking them. This large, extensive survey provided insight into their needs during, immediately after and long after treatment. Our initial four-part webinar series is only the beginning--through our results and querying webinar participants, we are developing additional educational programming to help those diagnosed with lung cancer and their loved ones understand and manage their specific disease and treatment-related challenges.

Keywords: symptoms, side effects, Education

MA 08 SUPPORTIVE CARE AND COMMUNICATION
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MA 08.07 CAN THE EARLY INTERVENTION OF THE LUNG CANCER CNS REDUCE THE LENGTH OF STAY FOR PATIENTS ADMITTED VIA THE EMERGENCY ROUTE ON FIRST PRESENTATION?

J. Draffen[1], K. Clayton[2], P. Shepherd[3], S. Bolton[4], V. Beattie[5], P. Rees[6], J. Roberts[7], J. Mcphelim[8], S. Kefyalew[9], Y. Jeffs[10], D. Denby[11]

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Background: The National Lung Cancer Audit 2015 reported 40% of patients with Lung cancer are diagnosed following an emergency admission. The National Lung Cancer Forum for Nurses Workshop 2016 undertook a review of how the Lung Cancer CNS's (LCNS) early intervention can have a positive impact on the reduction in the length of stay for those patients admitted via the emergency route at their first presentation. **Method:** A prospective and a retrospective review of a cohort of patients admitted by the emergency route was undertaken, n=51 in both cohorts, across 13 UK sites over a 2 month period. A standardised Data Collection Tool was developed to ensure consistency and avoid bias. In the prospective cohort the LCNS actively identified patients at an early stage following their admission, whereas the retrospective cohort was a random sample of patients admitted and diagnosed via the emergency route irrespective of the LCNS involvement. **Result:** Demographics and baseline characteristics were found to be similar in both cohorts. 31% of patients were never seen by the LCNS in the retrospective cohort whereas all patients were seen in the prospective cohort 76% of patients in the prospective cohort were seen within 0-5 days following admission by a LCNS compared with 43% in the retrospective cohort Average length of stay in the prospective cohort was 9.7 days V 17.6 days in the retrospective cohort. **Conclusion:** This review suggests the early intervention of a LCNS is associated with a reduced length of stay following an emergency admission when Lung Cancer/Mesothelioma is diagnosed.

Keywords: LUNG CANCER, CLINICAL NURSE SPECIALIST, EMERGENCY PRESENTATION

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.09 POSTOPERATIVE MOBILISATION AND REHABILITATION REQUIREMENTS FOR LUNG CANCER PATIENTS UNDERGOING MINIMALLY INVASIVE SURGERY

P. Agostini[1], S. Lugg[2], K. Adams[1], T. Smith[3], M. Kalkat[4], P. Rajesh[4], R. Steyn[4], B. Naidu[4], A. Rushton[3], E. Bishay[4]

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Background: Video-assisted thoracoscopic surgery (VATS) is now increasingly performed and recommended in early-stage NSCLC resection. Early postoperative mobilisation, rehabilitation and physiotherapy can improve subsequent reduction in lung volumes, aid clearance of secretions and independent mobility, although there is much variation in how lung cancer patients are currently managed in this respect. The objective of this study was to observe capability for early mobility and frequency of issues potentially amenable to physiotherapy rehabilitation following VATS lobectomy for lung cancer. Any preoperative factors associated with increased rehabilitation needs were also identified, thus enabling early recognition of lung cancer patients needing rehabilitation. **Method:** A prospective observational study was performed including all consecutive cancer patients undergoing VATS lobectomy in a regional centre over 4 years (2012-2016). Standard postoperative care included early mobilisation where patients were sat out by nursing staff from postoperative day 1 (POD1) and assisted to mobilise as able. Physiotherapy assessment of all patients on POD1 determined presence of issues potentially amenable to rehabilitation, and this was commenced as deemed necessary. Outcome measures included development of postoperative pulmonary complication (PPC), hospital and high dependency unit (HDU) length of stay (LOS) and intensive therapy unit admission (ITU). **Result:** 285 lung cancer patients were observed; 76 (27%) patients did not requiring specialised rehabilitation or physiotherapy, and engaged with nursing staff successfully in early mobility and becoming independently mobile. These patients had a significantly lower hospital and HDU length of stay ($p<0.001$), reflecting uncomplicated recovery. The remaining 209 patients (73%) received physiotherapy rehabilitation to assist/improve reduced mobility. Of these patients 23 (8%) also received chest physiotherapy for sputum clearance and 65 (23%) for lung volume loss. amongst those requiring this therapy were all patients who developed PPC, and all those admitted to the ITU. Despite surgery being non-invasive the frequency of development of PPC was higher than that for other VATS surgery at 7%, and this was associated with poorer outcomes. Logistic regression identified that COPD, BMI, preoperative mobility and age were associated with increased postoperative rehabilitation needs for mobility or respiratory issues ($p=0.013$). **Conclusion:** We recommend that all lung cancer patients receive early mobilisation and routine postoperative rehabilitation following this surgery ensuring issues amenable to physiotherapy and the need for rehabilitation is detected early. Associated preoperative baseline factors included COPD, poor preoperative mobility, and increasing BMI and age; such patients may benefit from preoperative rehabilitation as well as routine physiotherapy for better postoperative outcome.

Keywords: physiotherapy, VATS, Rehabilitation

MA 08 SUPPORTIVE CARE AND COMMUNICATION
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 08.10 FAVORABLE CLINICAL STATUS PREDICTS BENEFIT FROM EARLY-PALLIATIVE CARES & OS IMPROVEMENT IN NSCLC: A RANDOMIZED CLINICAL STUDY

O. Arrieta, L. Ramirez-Tirado, D. Michel-Tello, J. Turcott, J. Martinez-Hernandez, A. Beck-Magaña, E. Montes-Servin, E. Verastegui, S. Allende-Perez

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Background: Early-palliative care (EPC) after lung cancer diagnosis is essential for a better quality-of-life (QoL), and even offers a substantial improvement in survival outcomes. We prospectively assessed the effect of EPC in overall survival (OS) and patient-reported outcomes in non-small cell lung cancer (NSCLC) patients. **Method:** Newly-diagnosed and treatment-naïve NSCLC patients were included and randomly assigned (1:1) to receive either EPC with oncologic, nutritional, and psychological care, or standard oncologic care alone. Assessments were performed at baseline, second, fourth and sixth cycle of chemotherapy, with evaluations including: QoL, evaluated by The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, depression and anxiety which were evaluated using the Hospital Anxiety and Depression Scale, and oncologic symptomatology, which was evaluated with the Edmonton System Assessment Scale. NCT01631565 [013/020ICI(CV773/13)]. **Result:** Ninety-six NSCLC patients were enrolled; 42 patients were allocated to EPC while 54 patients were allocated to standard-care. Overall, patients receiving EPC have lower self-reported symptoms, depression and anxiety. Median OS of patients with EPC was 11.1 months (95% CI: 8.4–13.9), while in patients with standard-care was 5.9 months (95% CI: 4.8 – 7.1); $p=0.049$. In the multivariate analysis, factors associated with worse OS were: patients in standard-care arm (HR, 95% CI 1.6 (0.9 – 2.7); $p=0.05$), male patients (HR, 95% CI 1.8 (1.1 – 3.0); $p=0.028$) and worse ECOG performance status (≥2) (HR, 95% CI 1.9 (1.0 – 3.5); $p=0.039$).In a subgroup analysis, patients who reaped the most benefit from EPC included those with better ECOG performance status (<2) (8.9 vs. 5.7 months; $p=0.05$); those without depression at baseline (14.8 vs. 6.5 months; $p=0.05$) and those Corroborar que si sea mayor ansiedad basal-mayor beneficio **Conclusion:** EPC might provide benefit in the clinical symptomatic burden and OS of NSCLC patients. Benefits from EPC in OS might be associated to favorable global clinical status.

Keywords: clinical trial, early-palliative cancer care, non-small cell lung cancer

MA 08.11 DO PATIENTS TREATED WITH CHEMOTHERAPY FOR ADVANCED NSCLC REGRET HAVING RECEIVED TREATMENT? A PROSPECTIVE EVALUATION IN 164 PATIENTS

P. Hollen[1], R. Gralla[2], B. Coyne[1], R. Hall[3], R. Genzler[4], H. Cheng[5], G. Weiss[4], J. Gildersleeve[6], I. Hinton[6], J. Crawford[7], L. Rosen[8], M. Lesser[8]

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Background: While many thousands of patients per year receive chemotherapy for advanced NSCLC with first-line or subsequent chemotherapy, little is known about patients' views on their decision to receive that treatment. In that median survival results generally do not exceed one year, there are many potential risks for regret. Given the highly symptomatic nature of NSCLC coupled with patient, family and oncologist desires to decide rapidly on treatment, many challenges exist affecting quality decision making for patients and their supporters facing treatment. Among 59 studies dealing with regret in a recent systematic review (Becerra Perez 2016), none analyzed patients with lung cancer (66% of studies were in oncology). A clinical profile of the extent of regret, and factors contributing to that regret is lacking in those undergoing chemotherapy for lung cancer. **Method:** All patients were entered into a phase III, two-arm, prospective, randomized trial in patients receiving chemotherapy for lung cancer. Patients were randomly assigned to either usual care (UC), or enhanced care (EC) using the DecisionKEYS decision aid coupled with every 3 week PRO assessment using the electronic LCSS measure. All patients were offered the Decision Regret Scale ("DRS," O'Connor 1999), at 11 weeks (+/- 2 weeks) after starting treatment. The DRS is a categorical scale with 5-items in 5 categories (ranging from "strongly disagree" to "strongly agree"). Patients completed assessment for decisional conflict; the patients' supporters completed similar measures. **Result:** 164 patients were entered, 160 received chemotherapy. Characteristics: 43% women; 92% Stage IV; 73% first-line therapy. Means: age 63; KPS 81. ECOG 1 = 56%; ECOG 2 = 42%. 46% represented minority groups. 22 different chemotherapy regimens were used. First-line patients received combination regimens with the majority being platinum-based with 2 or 3 drugs. 128 patients (80%) completed the DRS. Results combined the two top categories indicating the greatest extent of regret. Only 9 patients (7%) expressed regret as the maximum of the 5 DRS questions. 94% expressed that the decision for chemotherapy was a wise one. This low degree of regret did not differ by first-line or subsequent chemo or by EC versus UC groups. **Conclusion:** Patients receiving chemotherapy for advanced NSCLC, at 3 months after starting treatment, rarely (7%) have regret, and 98% expressed that they made the right decision. Other factors associated with the few patients with regret, such as decisional conflict or reduced quality of life, will also be presented. Support: NIH/NCI R01 CA-157409

Keywords: decision making, quality of life, Regret

MA 09.01 A PROPENSITY-MATCHED ANALYSIS OF LOBECTOMY AND STEREOTACTIC BODY RADIOTHERAPY FOR EARLY STAGE NON-SMALL CELL LUNG CANCER

Y. Xu[1], Q. Lin[1], X. Sun[1], J. Liu[2], Q. Chen[1], W. Mao[3]

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Background: Lobectomy is the preferred treatment for patients with early stage non-small cell lung cancer (NSCLC). However, stereotactic body radiation therapy (SBRT) is an attractive option due to its promising efficacy reported recently. Given that prospective comparative data on lobectomy and SBRT are limited, we compared the two treatments for early stage NSCLC. **Method:** All patients undergoing treatment with lobectomy or SBRT for clinical early stage (T size≤5cm) NSCLC between January 2012 and June 2017 were reviewed. Age, gender, tumor characteristics, Charson Comorbidity Index, pulmonary function, local control rate (LCR), recurrence-free survival (RFS), overall survival (OS) data were collected and propensity matching performed. **Result:** For the entire lobectomy cohort, 3-year OS, DFS, and LCR were 87.9%, 84.9%, and 96.4% respectively. For the entire SBRT cohort, 3-year OS, RFS and LCR were 84.4%, 60.7% and 93.4%, respectively. A total of 246 patients underwent surgery, and 117 received SBRT. There were statistically difference between surgical patient and SBRT patients in tumor histology(P<0.000). Surgical patients had tendency that have longer tumor size than SBRT patients (2.4±1.0 vs. 2.1±0.8, P=0.092). There were no statistically difference between lobectomy and SBRT group with age (68.9±6.6 vs.69.0±9.2, P=0.980), Eastern Coorperative Oncology Group performance scores, Charlson comorbidity Index, pulmonary function test result (FEV1 and predict FEV1), gender, T stage, and tumor location. A propensity matched comparison in a blinded manner (1:1 ratio, caliper distance=0.0025) based on age, gender, WHO performance status score, pulmonary function (forced expiratory volume in 1 second [FEV1] % and FEV1), and T stage resulted in 49 matched pairs. The follow-up period ranged from 0.3 to 60.0 months, with a median of 21.4 months. There were no differences between lobectomy and SBRT in LCR, respectively 97.1% and 100% (p=0.355) at 4 year. Also the 4-year RFS was comparable between groups, as 68.6% after lobectomy, versus 81.9% at 4 year after SBRT (p=0.963). The 4-year OS was similar in both groups, with 58.1% vs. 75.2% for lobectomy and SBRT (p=0.774). No patient experienced treatment-related death in both groups. **Conclusion:** This retrospective analysis found no significant difference in LCR, RFS and OS between lobectomy and SBRT. This study indicated matching these disparate cohorts of patients remains challenging. Participation in clinical trials is essential to define the indications and relative efficacy of lobectomy and SBRT in a high-risk population.

Keywords: NSCLC, lobectomy, SBRT

MA 09.02 ULTRA-CENTRAL TUMOURS TREATED WITH STEREOTACTIC BODY RADIOTHERAPY: A SINGLE INSTITUTIONAL EXPERIENCE

V. Yau[1], S. Raman[1], S. Pineda[1], L. Le[1], A. Lau[1], A. Bezjak[2], J. Cho[1], A. Sun[3], A. Hope[4], M. Giuliani[4]

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Background: Stereotactic body radiotherapy of "ultra-central" (UC) lung tumours, PTV directly abuts/overlaps the proximal bronchial tree (PBT), trachea, esophagus, pulmonary vein/artery, are considered to be at higher risk of toxicity. The purpose of this study is to review the outcomes and toxicities of Ultra-central lung tumours, compared to central tumours. **Method:** A retrospective review based on a prospective database of patients treated with lung SBRT from January 2006- December 2015 was conducted. Patients with central tumours defined using RTOG 0813 criteria and ultracentral tumours were included. 115 patients (53%) received 60Gy/8 and 61 (28%) received 48Gy/4. At our institution, the recommended Dmax for esophagus is 45Gy and 40Gy for 8 and 4 fractions, respectively. The Dmax and D10cc constraints for trachea, proximal bronchial tree, heart, and major vessels (including pulmonary artery and vein) are 48Gy and 40Gy for 4 fractions and 64 and 60Gy for 8 fractions. Toxicity was graded using CTCAE v3.0. Log-rank test was used to compare overall and cause-specific survival. Local, regional, and distant recurrence were compared using Gray's test. **Result:** 215 tumours were analyzed (189 C and 26 UC). The median age for C and UC were 75 years and 72.5 years. Median tumour size and PTV volume were 2.2 cm (range 0.9-5.7) and 41.7 cm3 (range 9.7-246.3) (C group) and 2.5 cm (0.8-5.5) and 58.2 cm3 (16.8-238.3) (UC group). The percentage of squamous cell carcinoma was higher in the UC group (15%, n=29 in C; 38%, n=10 in UC). The median follow-up was 20.3 months (24.5 mo for patients still alive). Median overall survival (OS) and cause-specific survival (CSS) was 34 mo and 53.8 mo for C and 20.1 mo and 28.2 mo for UC, respectively. Differences in OS and CSS between the two groups did not meet statistical significance (p=0.24 and p=0.14, respectively). Local, regional, and distant failure rates were 3%, 8% and 18% in the central tumour group and 0%, 9% and 25% in the ultra-central tumour group at 2 years. There was no statistically significant difference found in the rates of recurrence between the two groups. The rates of any grade 2 or higher toxicity (hemoptysis, esophageal toxicity, cough, dyspnea, pneumonitis) was 9% (n=17) in the C and 7.7% (n=2) in UC group (p=0.89). There were no known grade 4 or 5 toxicities. **Conclusion:** In our experience, SBRT to ultra-central tumours resulted in effective local control and no excessive risk of toxicity compared to central tumours.

Keywords: Ultra-central, stereotactic radiotherapy, central

MA 09.04 INCREASINGLY ABNORMAL PRE-TREATMENT DIFFUSION CAPACITY IS ASSOCIATED WITH GREATER LOCAL FAILURE AFTER LUNG SBRT

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Background: We hypothesized that impaired pulmonary functions tests might predict for altered lung density which would interfere with the efficacy of radiotherapy. We therefore sought to determine if there are associations between pre-treatment [preTx] forced expiratory volume in 1 second (FEV1, in L and as % predicted [%p]) and diffusion capacity (DLCO, as %p) with local failure (LF) rates seen with lung stereotactic body radiotherapy (SBRT) for medically inoperable lung cancer. **Method:** From an IRB-approved institutional prospective SBRT registry of 1330 patients, we identified 557 treated definitively for medically inoperable early stage T1-T3N0M0 non-small cell lung cancer (NSCLC) between 2003 and 2016 for whom both preTx FEV1 and DLCO were available. Lung SBRT dose/fractionation for a given pt was at the discretion of the treating physician. LF was defined as progressive and increasing CT scan abnormalities confirmed by progressive and incremental increases in lesion SUVs on serial PET imaging, with or without biopsy. Predictors of LF were determined using competing risks regression and rates of local control were determined from cumulative incidence analysis. **Result:** Pt characteristics included: female gender (52.6%); median age 74 years (range 42-95); median KPS 80 (range 50-100); median preTx FEV1 and DLCO: 1.39L (range 0.26-3.87), 60 %p (range 13-

151) and 52 %p (range 10-143), respectively. Tumor characteristics included: median diameter 2.2 cm (range 0.7-7.2); median PET SUVmax 7.7 (range 0.8-56); % as T stage 1a, 1b, 2a, 2b, 3: 40.2; 35.5; 18.9; 4.5; 0.9, respectively; "central" location (per RTOG 0813) 22.6%. Median follow up was 18.3 months. At analysis, 46.9% pts were alive. Treatment characteristics included 50 Gy/5 fractions (fx) for 235 pts (42.2%), 60 Gy/3 fx for 167 pts (30%), and other schedules for 155 pts (27.8%), with the latter excluded from analysis due to variability in schedules, leaving 402 pts (72.2%). Only dose was significantly associated with LF on multivariable analysis [p=0.0057; HR =3.416, 95% CI 1.429-8.166]. Three-year cumulative incidence of LF post-SBRT for 50 Gy/5fx and 60 Gy/3 fx was 15.2% and 2.3% [p=0.024], respectively. In subset analysis of the 50 Gy/5 fx, DLCO was significant for LF both as a continuous variable and as a categorical variable. The significant cut-off for DLCO was 45%p, such that 3-year LF at <45 was 24.7% (95% CI 13.6-35.8) and at > 45 was 10.6% (95% CI 5.3-16.0), [p=0.0234; HR =0.441, %95 CI 0.217-0.895[CR1]]. There were no significant associations between LF and pulmonary functions tests for 60 Gy/3 fx. **Conclusion:** As preTx DLCO drops below 45 %p, our findings suggest local failure increases when lung SBRT is delivered as 50 Gy/5 fx for early stage NSCLC. This warrants validation in prospective series.

Keywords: Lung SBRT, pulmonary function tests, local control

MA 09 THE CURRENT STATUS OF RADIATION ONCOLOGY
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MA 09.05 EVIDENCE IN FAVOR OF OR AGAINST THE USE OF TKIS WITH CONCURRENT CRANIAL RADIOTHERAPY IN PATIENTS WITH NSCLC AND CNS INVOLVEMENT

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Background: Central nervous system (CNS) metastases, including brain metastases (BM) and leptomeningeal metastases (LM) represent a frequent complication of non-small cell lung cancer (NSCLC). Patients with CNS metastases comprise a heterogeneous group, with a median survival that ranges from 3 to 14 months. Local therapies, such as whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or surgical resection, are available treatment strategies for BM. Introduction of tyrosine kinase inhibitors (TKIs) in clinical practice has led to individualization of therapy based upon the presence of the exact abnormality, resulting in a major therapeutic improvement in patients with NSCLC who harbor epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK) gene rearrangements, respectively, but their role in combination with radiotherapy is controversial **Method:** We performed a systematic literature review of published data in PUBMED, SCOPUS and COCHRANE databases, as well as a manual search of reported data in major congresses, using the terms "EGFR-TKIs", "ALK-TKIs", "CNS", "BM" or ""LM" and "concurrent radiotherapy" or "stereotactic radiotherapy" from January 2000 through May 2017. Only prospective or retrospective clinical trials and meta-analyses reported in English language were included **Result:**

Author/ year	Phase	No of pts	EGFR status	Treatment groups	Control	Outcomes
Lind et al 2009	I	11	NA	Cohort 1: Erlotinib 100 mg +WBRT Cohort 2: Erlotinib 150 mg +WBRT		-Grade 3-5 toxicity in cohort 2 -High IDCR
Welsh et al 2013	II	40	EGFR mutant: 9 of 15 pts tested	Erlotinib 150 mg + WBRT		-ORR 86%, -Median OS 11.8 m -Median OS 19.1 m in EGFR mutant
Sperduto et al 2013	III	126 (closed early)	NA	Arm 2: TMZ+ WBRT+ SRS Arm 3: Erlotinib 150 mg + WBRT +SRS	Arm 1: WBRT +SRS	OS not improved with addition of drugs -No difference in CNS-TTP between the three arms -49% grade 3-5 toxicity in arm 3
Lee et al.2014	II	80	EGFR mutant 1 out of 35 pts tested	WBRT + Erlotinib	WBRT	No difference in OS
Ma et al. 2009	II	21	NA	WBRT +Gefitinib		ORR 86% -Median OS 13 m -No significant grade 3 toxicity
Pesce et al 2012	Random-ized Phase II	59	NA	WBRT + Gefitinib vs WBRT+ TMZ		Median OS 6.3 m (Gefitinib arm), 4.9 m (TMZ arm) -No relevant toxicity
Zeng et al 2012	Retro-spective	90	NA	WBRT +Gefitinib	Gefitinib	Higher ORR and OS with WBRT+ Gefitinib
Luo et al 2015	Meta-analysis	980 (8 trials)	NA	Radio-therapy + TKI (TKI group)	Radio-therapy or Radio-therapy+ chemo-therapy (non-TKI group)	-Higher RR, CNS-TTP and OS in radio-therapy +TKI group -No difference is serious AEs
jiang et al 2016l	Meta-analysis	1552 (15 trials)	NA	Radio-therapy + TKI	Radio-therapy or Radio-therapy+ chemo-therapy	Higher RR, DCR, CNS-TTP and OS in radio-therapy +TKI group -Increased rate of any grade AEs

Conclusion: At this time, concurrent use of TKIs with radiotherapy, although appearing to be safe, is not recommended outside of a clinical trial. Interestingly, data in EGFR mutant patients treated with an EGFR-TKI alone prompt the question whether this could be a front line approach in patients with asymptomatic BM, reserving WBRT for symptomatic cases. In clinical practice, burden of extracranial disease might also guide treatment decisions; physicians might select not to discontinue a TKI during WBRT in case of extensive extracranial organ involvement

Ongoing clinical trials are currently evaluating the effectiveness of concomitant use of radiotherapy and TKIs.

Keywords: NSCLC with CNS, concurrent brain radiotherapy, Small molecule inhibitors

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MA 09.06 PULMONARY OLIGOMETASTASES TREATED BY STEREOTACTIC BODY RADIATION THERAPY (SBRT): A NATIONWIDE SURVEY OF 1,378 PATIENTS

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Background: The treatment outcomes of patients with pulmonary oligometastases treated by SBRT were evaluated; the oligometastases were classified into three

groups (oligo-recurrence, sync-oligometastases, and unclassified oligometastases) and the outcomes compared. **Method:** This study was limited to patients who had a BED10 ≥75 Gy. Oligo-recurrence was defined as a primary lesion that was controlled, the number of metastases or recurrences in the lung was one to five, and the disease-free interval (DFI), the interval between initial therapy of the primary lesion and the date of recurrence in the lung, was ≥6 months. Sync-oligometastases were defined as: the primary lesion was active; the number of metastases or recurrences in the lung and the active primary lesion was one to five; and the DFI was zero. The definition of unclassified oligometastases was similar to that of oligo-recurrence, but the DFI was <6 months. All oligomtastases in this study were treated by local therapy for all active lesions including primary and metastatic lesions. **Result:** Between 2004 and 2015, 1378 patients (male/female = 893/485; PS 0/1/2/3 = 746/474/85/17) meeting the study definition of pulmonary oligometastases were treated by SBRT in 68 institutions in Japan. Their median age was 72 years (16-93 years). The primary region was lung in 421, colorectal in 348, head and neck in 113, and others in 618. Histopathology showed adenocarcinoma in 761, squamous cell carcinoma in 358, and others in 186. Oligostatus was oligo-recurrence in 1013, sync-oligometastases in 118, and unclassified oligometastases in 122. The median maximum tumor diameter (MTD) was 1.5 cm (0.3-6.5 cm). The number of target tumors was solitary in 1037 and multiple in 341. The median BED10 was 105.6 Gy (75-289.6 Gy). The median DFI was 17.9 months (0-424 months). The median follow-up time was 24.3 months (0.1-143.7 months). The 3-year overall survival (OS), relapse-free survival, and local control rates were 60.3% (95%CI: 57.1-63.3%), 32.6% (95%CI: 29.7-35.5%), and 81.4% (95%CI: 78.8-83.7%). Univariate analysis showed only oligostatus, sex, PS, DFI, MTD, primary region, and histopathology were significant. The 3-year OS was 64.0% (95%CI: 60.4-67.5%) for oligo-recurrence and 50.6% (95%CI: 42.9-57.8%; p<0.001) for the others. Multivariate analysis of OS showed that only oligostatus (others/oligo-recurrence: HR 1.43), MTD (≥2 cm/<2 cm, HR 1.45), histopathology (others/adenocarcinoma: HR: 1.47), and sex (male/female: HR 1.38) were significant. **Conclusion:** Pulmonary oligometastases, oligo-recurrence, female sex, adenocarcinoma, and small-sized tumor could be factors associated with longer survival.

Keywords: oligometastases, oligo-recurrence, sync-oligometastases

MA 09 THE CURRENT STATUS OF RADIATION ONCOLOGY
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 09.08 RECEIPT OF CHEST RADIATION AND IMMUNE-RELATED PNEUMONITIS IN PATIENTS WITH NSCLC TREATED WITH ANTI-PD-1/PD-L1

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Background: Immune-related pneumonitis (IR-pneumonitis) is a potentially fatal toxicity of anti-PD-1/PD-L1. This study investigates the role of chest radiotherapy (RT) and the development of IR-pneumonitis in NSCLC patients treated with anti-PD-1/PD-L1. **Method:** Between January 2011 and April 2017, NSCLC patients treated with anti-PD-1/PD-L1 either as part of a clinical trial or as standard-of-care at a tertiary academic cancer center, were identified. Patient demographics, treatment, adverse event and RT data including type of RT (SBRT, 2D/3D conformal RT, IMRT, multiple), timing of RT (pre or post PD-1/PD-L1), location of RT (chest/non-chest), and number of courses of chest-RT, were collected in an IRB-approved institutional database. IR-pneumonitis was diagnosed clinically by the treating investigator; patients with confirmed RT pneumonitis, progressive NSCLC, or active infection were excluded. Associations between patient, treatment and RT parameters, and development of any grade IR-pneumonitis were evaluated using Student's t-test and Fisher's exact tests. **Result:** Of 184 NCSLC patients identified: median age was 67 years (range: 39-88); 57% (n=105) were male, 75% (n=137) were former/current smokers, 64% (n=118) had adenocarcinoma histology, and 59% (n=109) had advanced NSCLC at diagnosis. Anti-PD-1/PD-L1 monotherapy was received in 74% (n=136, nivolumab: 107, pembrolizumab: 14, durvalumab: 7, other: 8) and combination therapy in 26% of patients (n=48, PD-1/CTLA-4: 13, PD-L1/CTLA-4: 5, PD-1/chemotherapy: 4, PD-1/other: 25, PD-L1/other; 1). Any RT was received by 129 patients (70%), and 96 patients received chest-RT (52%). Thirty-eight (21%) patients developed IR-pneumonitis of any grade. IR-pneumonitis incidence was numerically higher in patients receiving combination therapy compared with monotherapy (29%, n=14/48 vs. 18%, n=24/136, p=0.1). Former/current smokers had a higher incidence of pneumonitis compared with never smokers (25% vs. 12%, p=0.03). IR-pneumonitis incidence was numerically higher in patients receiving chest-RT compared with non-chest/no RT (25%, n=24/96 vs. 16%, n=14/88, p=0.15). Of 129 patients who received any RT, there was a trend towards increased IR-pneumonitis in patients who received chest RT compared with those who received non-chest RT (25%,n=24/96 vs 9%, n=3/33; p=0.08). Overall, there were no significant associations between chest-RT type, chest-RT timing, nor receipt of more than one chest-RT course, and development of IR-pneumonitis (p>0.05). **Conclusion:** IR-pneumonitis incidence is 21% and may be higher than reported in clinical trials. Smoking status is associated with the development of IR-pneumonitis. Receipt of chest-RT was numerically higher, but not statistically associated with, development of IR-pneumonitis after receipt of anti-PD-1/PD-L1 in patients with advanced NSCLC. Radiation parameters did not associate with the development of IR-pneumonitis.

Keywords: Chest Radiation, pneumonitis, Anti-PD-1/PD-L1

MA 09 THE CURRENT STATUS OF RADIATION ONCOLOGY
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 09.09 ISOTOXIC DOSE-ESCALATED RADIOTHERAPY (RT) IN NON-SMALL CELL LUNG CANCER (NSCLC) WITH DEEP INSPIRATION BREATH HOLD (DIBH)

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Background: With interest in the use of isotoxic dose-escalated RT in treatment of inoperable NSCLC, this study investigated the impact of DIBH using the Active Breathing Coordinator™ (ABC- Elekta, Stockholm, Sweden) device on isotoxic dose escalation potential. **Method:** Following informed consent, a four-dimensional (4D) planning CT scan and a DIBH scan using the ABC device were acquired in patients sequentially in the same session. A motion-encompassing target volume on the 4D scan and a motion-managed target volume on the DIBH scan were created. The RayStation radiotherapy treatment planning system (research version 5.99.0.16) was used to generate two corresponding volumetric modulated arc therapy (VMAT) plans for each patient, following the guidelines of the isotoxic IMRT trial (NCT01836692). The target dose was escalated up to a maximum of 79.2 Gy in 44 twice daily fractions and plans optimised to minimise dose to normal tissues. Potential to escalate target dose and differences in dose-volume metrics between the plans were compared using the Wilcoxon signed-rank test. **Result:** 21 patients were included. The mean total lung volume was significantly higher with DIBH compared to 4D scans with an increase of 44.7 % ± 17.4 % (mean ± standard deviation), p < 0.001). In 20/21 patients, the maximum target dose of 79.2 Gy was achievable in both plans, however in one patient 61.2 Gy was achieved with 4D compared to 75.6 Gy with DIBH planning. In the 20 patients achieving equivalent target dose-escalation, the mean lung dose was 17.0 Gy (± 0.3Gy) with 4D versus 14.6 Gy (± 0.3 Gy) with DIBH (p < 0.001). There was a significant mean reduction in heart dose between the DIBH compared to 4D plans of 0.3 Gy (± 0.2 Gy, p< 0.001) and significant reductions in heart D100 %, D66 % and D33 %(p < 0.01). Mediastinal envelope and oesophageal doses were similar using both techniques. **Conclusion:** The use of DIBH compared to 4D planning aids lung and cardiac sparing in isotoxic dose escalated RT and for a small number of patients may allow an increase in target dose. Particularly given the interaction between lung and cardiac toxicity in locally advanced NSCLC treated with radical RT, use of DIBH for treatment may lead to a reduction in toxicity compared to a 4D approach. In acknowledgement of the use of a mid-ventilation technique in some institutions, comparison with this method is planned.

Keywords: Breath-hold, Isotoxic, Radiotherapy

MA 09 THE CURRENT STATUS OF RADIATION ONCOLOGY
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 09.10 TOWARD A RADIOLOGICAL SCORING SYSTEM OF RADIOTHERAPY-INDUCED LUNG DAMAGE

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Background: There is no objective criteria to quantify radiotherapy-induced lung damage (RILD), leading to under-reporting of toxicity across centres and trials. Our objective is to build a radiological scoring system of RILD that correlates with decline in lung function. **Method:** Baseline and 12-month CT scans and formal respiratory function tests (FVC, FEV1 and DLCO) from 23 patients enrolled in an isotoxic chemoradiation clinical trial (IDEAL CRT) were available for central review. First, the presence of new CT findings of RILD was qualitatively scored into eleven sub-categories: consolidation, ground-glass opacities, traction bronchiectasis, reticulation, pleural thickening, pleural effusion, reduction in lung height, distortions of the diaphragm, fissures, anterior junction line and major airways. From these, three main categories were derived: parenchymal change, pleural changes and volume reduction. The correlation between number of features scored and decline in breathing function was investigated. Later, twelve imaging markers were defined to quantify the severity of the radiological findings. The correlation between each imaging marker and decline in breathing scores was also investigated. **Result:** Each patient scored either two or three (out of three) categories of damage. Differences in variation of FVC, FEV1 and DLCO between these two groups were statistically significant (p≤0.02). The number of sub-categories scored was moderately correlated with decline in FVC (ρ=-0.67, p<0.01), FEV1 (ρ=-0.41, p=0.05) and DLCO (ρ=-0.50, p=0.01). Six of the twelve imaging markers were moderately correlated with changes in FVC and FEV1 (ρ=-0.5, p<0.05); five were weakly correlated (ρ=-0.2, p<0.05). The strongest correlations were found for imaging markers that quantify change in lung volume and shape, mediastinal shift and pleural reaction.

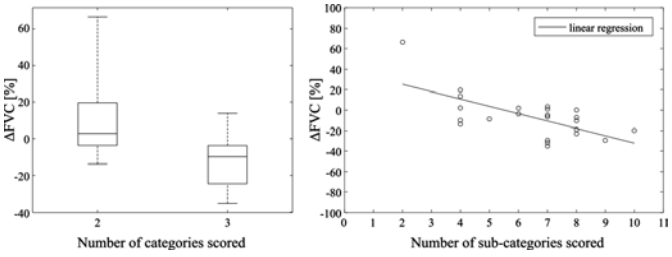

Figure- Relationship between radiological findings of RILD and changes in FVC. **Conclusion:** We investigated the relationship between radiological findings of RILD and decline in lung function. Our findings suggest that a scoring system can be proposed when investigated in a larger cohort.

Keywords: computed tomography, radiation-induced lung damage, breathing scores

MA 09 THE CURRENT STATUS OF RADIATION ONCOLOGY
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 09.11 ISOTOXIC INTENSITY MODULATED RADIOTHERAPY (IMRT) IN STAGE III NON-SMALL CELL LUNG CANCER (NSCLC) – A FEASIBILITY STUDY

K. Haslett[1], N. Bayman[1], K. Franks[2], N. Groom[3], G. Hanna[4], S. Harden[5], C. Harris[1], S. Harrow[6], M. Hatton[7], P. Mccloskey[8], F. Mcdonald[9], L. Ashcroft[10], D. Ryder[10], C. Faivre-Finn[11]

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Background: The majority of stage III patients with non-small cell lung cancer (NSCLC) are unsuitable for concurrent chemoradiotherapy. Alternative treatment options include sequential chemoradiotherapy and radiotherapy (RT) alone. As the rate of local failure is high there is a rationale for treatment intensification. **Method:** Isotoxic Intensity Modulated Radiotherapy (IMRT) is a multicentre feasibility study combining a number of intensification strategies; dose escalation, acceleration and hyperfractionation. Patients with inoperable stage III NSCLC, ECOG performance status (PS) 0-2, unsuitable for concurrent chemoradiotherapy were recruited. A minimum of 2 cycles of induction chemotherapy was mandated before RT. The dose of radiation was increased until one or more of the organs at risk (OAR) met predefined constraints or the maximum dose of 79.2Gy was reached. RT was delivered twice-daily in 1.8 Gy fractions. A RT quality assurance programme was in place. The primary end point was feasibility (>80% of patients achieving >60Gy EQD2 i.e. total biologically equivalent in 2 Gy fraction), with acute/late toxicity (CTCAE version 4.0), local control and overall survival as secondary end points. **Result:** Between June 2014 and March 2016, 37 patients were enrolled from 7 UK centres. Median age = 67 years (range 46-86). Male:female ratio = 18:19. ECOG PS=0, 5 (13.51%), PS=1, 29 (78.38%), PS=2, 3 (8.11%). Stage IIIa:IIIb ratio 23 (62.2%):14 (37.8%). Out of 37 patients, 2(5.4%) failed to achieve EQD2 >60Gy due to large tumour size and inability to meet OAR constraints, they received standard RT. This was due to large tumour size and inability to meet OAR constraints. Median prescribed tumour dose was 77.4Gy (61.2 – 79.2Gy) with the maximum dose of 79.2Gy delivered to 14 (37.8%) patients. All patients completed RT as scheduled except one due to disease progression. Grade (G)3 acute toxicities included: dysphagia 1 (2.9%), dypsnoea 2 (5.7%), lung infection 3 (5.7%) and radiation oesophagitis 2 (5.7%). There were three G5 events: radiation pneumonitis, trachea-oesophageal fistula and bronchopulmonary haemorrhage, which were probably treatment related. G3 late toxicities included: fatigue 1 (2.9%), dyspnoea 3 (8.6%) and 1 (2.9%) case of late G4 lung infection. At time of analysis median follow-up was 12.8 months for 20 survivors. Overall survival and progression-free survival at 1 year was 75% and 59% respectively. **Conclusion:** In the majority, treatment intensification using isotoxic IMRT is feasible. This regime will be tested alongside other intensified treatments against standard sequential chemoradiotherapy in the ADSCAN study (ISRCTN47674500).

Keywords: Personalised, Intensification, Radiotherapy

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.01 DURVALUMAB ± TREMELIMUMAB WITH PLATINUM-DOUBLETS IN NON-SMALL CELL LUNG CANCER: CANADIAN CANCER TRIALS GROUP STUDY IND.226

R. Juergens*[1], D. Hao[2], S. Laurie[3], P. Ellis[1], M. Mates[4], P. Bradbury[5], M. Tehfe[6], C. Kollmannsberger[7], A. Arnold[1], J. Goffin[1], P. Wheatley-Price[3], J. Hilton[3], A. Robinson[4], D. Tu[8], P. Brown-Walker[8], L. Seymour[8]

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Background: Anti-PD1-monotherapy has activity in NSCLC with improved outcomes compared to chemotherapy. Preclinical, and early clinical data, suggests that combining immune checkpoint inhibitors and platinum-based chemotherapy may be synergistic. We examined the cohort of patients (pts) with metastatic NSCLC, with no prior therapy for advanced disease, from this multicentre phase Ib trial. The primary objective was to establish the recommend phase II doses of durvalumab (Du) ± tremelimumab (Tr) in combination with platinum-doublet chemotherapy. Secondary objectives included assessing safety, tolerability, and antitumour activity of the 4-drug combination. **Method:** Pts were treated with Du±Tr at one of 4 dose levels (DL) concomitantly with either pemetrexed (Pem) +cisplatin/carboplatin followed by maintenance Pem for nonsquamous histology or gemcitabine (Gem) +cisplatin/carboplatin for squamous tumours. At DL0 Du 15 mg/kg IV q3wks was added; DL1 added Du 15mg/kg q3wk + Tr 1mg/kg x1 dose; DL2a added Du 15mg/kg q3wk + Tr 1 mg/kg q6wk x multiple doses; DL2b added Du 15mg/kg q3wk + Tr 3 mg/kg q6wk (1 dose with cycle 1 and 2 doses with maintenance pem), DL3 and DL4 added a fixed doses of Du 1125mg/Tr 56 mg and Du 1500 mg/ Tr 75 mg q3wk respectively. Du could continue until 1 year or unacceptable toxicity. **Result:** To date, 45 pts (median age=62 (range 36-78); 44% male, 100% ECOG PS≤1) have received 346 cycles in the Pem-platinum cohort while 9 pts (median age=64 (range 57-80); 78% male, 100% ECOG PS≤1) have been received 55 cycles in the Gem-platinum group. Most adverse events were ≤grade 2 and attributed to chemotherapy. Immunotherapy-related adverse events (irAEs) ≥ grade 3 were observed in 27% of patients and were more commonly reported with the addition of Tr. In the Pem-platinum cohort, diarrhea (n=5), fatigue (n=4) and elevated lipase (n=4) were the most come irAEs ≥ grade 3, while rash, pneumonitis and hypothyroidism occurred in 1 pt each after the introduction of Tr. In the Gem-platinum cohort, irAEs ≥ grade 3 were fatigue and rash (1 pt each at DL2b) and elevated lipase (1 pt at DL3). The objective response rate in 35 evaluable patients receiving Pem-platinum was 57.1% (95% CI=39.4, 73.7) and 37.5% (95% CI=8.5, 75.5) in the 8 evaluable patients receiving Gem-Platinum. **Conclusion:** The combination of Du±Tr can be safely administered with platinum-doublet chemotherapy with encouraging preliminary response data. Adding Tr may increase ≥ grade 3 irAE hence patient selection and early intervention is key to managing irAEs.
*contributed equally

Keywords: immunotherapy, chemotherapy, non-small cell lung cancer

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.02 NAB-PACLITAXEL + DURVALUMAB AS SECOND- OR THIRD-LINE TREATMENT OF ADVANCED NSCLC: RESULTS FROM ABOUND.2L+

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Background: Chemotherapy may enhance immunotherapeutic effects by causing tumor antigen release, which primes the immune system to kill tumor cells. Early clinical data on nab-paclitaxel + carboplatin in combination with immune checkpoint inhibitors (ICI) demonstrated promising activity without compounding toxicities in patients with non-small cell lung cancer (NSCLC). ABOUND.2L+ evaluated nab-paclitaxel–based regimens in previously treated patients with advanced NSCLC. Here we report the efficacy and safety of nab-paclitaxel + durvalumab as second/third-line treatment. **Method:** Patients with advanced NSCLC were assigned to receive second/third-line (immunotherapy allowed in prior line, including platinum doublet combination) nab-paclitaxel 100 mg/m^2 on days 1 and 8 + durvalumab 1125 mg on day 15, in 21-day cycles, administered until unacceptable toxicity/progression per immune-related RECIST v1.1. Primary endpoint is progression-free survival (PFS). Secondary endpoints are overall survival (OS), overall response rate (ORR), disease control rate (DCR), and safety. **Result:** Seventy-nine patients were enrolled. Median age was 63 years, 68% of patients were male, 23% had Eastern Cooperative Oncology Group performance status of 0, and 70% had nonsquamous NSCLC; 11% of

patients received prior ICIs. Median PFS (Table) and OS were 4.5 (3.4-5.8) months and NE (7.3-NE). ORR was 27% (1 complete response) and DCR was 71%. Grade 3/4 treatment-emergent adverse events of special interest occurring in ≥ 5% of patients included neutropenia (6%) and dyspnea (5%); grade 3/4 peripheral neuropathy and anemia each occurred in 4% of patients. Median treatment duration was 24 weeks; median number of treatment cycles was 7. For nab-paclitaxel and durvalumab, median dose intensities were 59.05 mg/m^2/week and 326.61 mg/week, respectively; median percentages of per-protocol dose were 88.58% and 87.10%. **Conclusion:** The combination of durvalumab with nab-paclitaxel demonstrated antitumor activity with manageable toxicity in the second/third-line setting. Further details will be presented. NCT02250326

Nab-P Durva	Median PFS (range), months
Overall (n = 79)	4.5 (3.4-5.8)
ICI pretreated (n = 9)[a] ICI naive (n = 69)[a]	6.9 (1.4-NE) 4.4 (3.0-5.7)
Squamous (n = 23)[a] Nonsquamous (n = 55)[a]	5.9 (3.0-7.8) 4.2 (2.9-5.7)
ICI, immune checkpoint inhibitor; NE, not estimable; PFS, progression-free survival. [a] Data pending for 1 patient.	

Keywords: durvalumab, nab-paclitaxel, Second-line

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.03 3-YEAR SURVIVAL AND DURATION OF RESPONSE IN RANDOMIZED PHASE II STUDY OF ATEZOLIZUMAB VS DOCETAXEL IN 2L/3L NSCLC (POPLAR)

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Background: Atezolizumab (anti–PD-L1) has demonstrated OS benefit over docetaxel in a randomized Phase II study, POPLAR, in patients with advanced NSCLC. This benefit has been confirmed in the randomized Phase III study OAK (Rittmeyer, 2017). The 3-year survival analysis of the POPLAR study presented here describes the longest survival follow-up reported to date of an all-comer randomized PD-L1/PD-1 immunotherapy trial in 2L+ NSCLC. **Method:** Patients were randomized 1:1 to receive atezolizumab (1200 mg) or docetaxel (75 mg/m^2) IV q3w. Tumors were prospectively evaluated for tumor cell (TC) or tumor-infiltrating immune cell (IC) PD-L1 expression using the VENTANA SP142 IHC assay. Landmark OS was estimated using the Kaplan-Meier method. Data cutoff, April 7, 2017; minimum follow-up, 3 years. **Result:** The 2-year and 3-year survival with atezolizumab vs docetaxel were 32.2% vs 16.6% and 18.7% vs 10.0%, respectively. The long-term OS benefit of atezolizumab vs docetaxel was observed across histology and PD-L1 expression subgroups (Table). While the TC3 or IC3 subgroup derived the greatest OS benefit, the TC0 and IC0 subgroup also had improved long-term OS with atezolizumab vs docetaxel. The ITT ORR was 15% in both atezolizumab and docetaxel arms, but the median duration of response was 3 times longer with atezolizumab (22.3 months [95% CI: 11.6, 31.1] vs 7.2 months [95% CI: 5.8, 12.2] with docetaxel). Seven of the 11 docetaxel-arm 3-year survivors received subsequent non-protocol therapy with anti–PD-L1/PD-1 agents. Atezolizumab had a favorable safety profile compared with docetaxel that was consistent with previous reports. **Conclusion:** Atezolizumab demonstrates superior 2-year and 3-year OS benefit compared with docetaxel, and this benefit is observed across histology and PD-L1 expression subgroups (including TC0 and IC0). Atezolizumab is well tolerated, and responses are highly durable. These results are consistent with long-term OS results from OAK, presented separately.

Table. Landmark OS in the ITT, PD-L1 expression, and histology subgroups in POPLAR

Population (n, atezolizumab vs docetaxel)	2-year OS rate, %			3-year OS rate, %		
	Atezolizumab	Docetaxel	*P* valuea	Atezolizumab	Docetaxel	*P* valuea
ITT (144 vs 143)	32.2%	16.6%	0.0027	18.7%	10.0%	0.0419
PD-L1 Expression Subgroups						
TC3 or IC3 (24 vs 23)	41.7%	19.9%	0.1003	37.5%	14.9%	0.0724
TC2/3 or IC2/3 (50 vs 55)	36.1%	13.8%	0.0082	21.2%	9.9%	0.1166
TC1/2/3 or IC1/2/3 (93 vs 102)	36.0%	19.8%	0.0124	18.0%	11.0%	0.1759
TC0 and IC0 (51 vs 41)	25.0%	6.8%	0.0202	20.5%	6.8%	0.0693
Histology Subgroups						
Non-squamous (95 vs 95)	32.2%	21.1%	0.0960	23.3%	12.4%	0.0585
Squamous (49 vs 48)	32.7%	7.8%	0.0020	9.4%	5.2%	0.4603

[a]For descriptive purpose only. TC3 or IC3 = PD-L1 ≥ 50% TC or 10% IC; TC2/3 or IC2/3 = PD-L1 ≥ 5% TC or IC; TC1/2/3 or IC1/2/3 = PD-L1 ≥ 1% on TC or IC; TC0 and IC0 = PD-L1 < 1% on TC and IC. NCT01903993.

Keywords: atezolizumab, cancer immunotherapy, advanced NSCLC

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.05 IMPROVED OUTCOME FOR IMMUNE CHECKPOINT INHIBITORS (ICI) IN PATIENTS PREVIOUSLY TREATED WITH BAVITUXIMAB IN THE SUNRISE TRIAL

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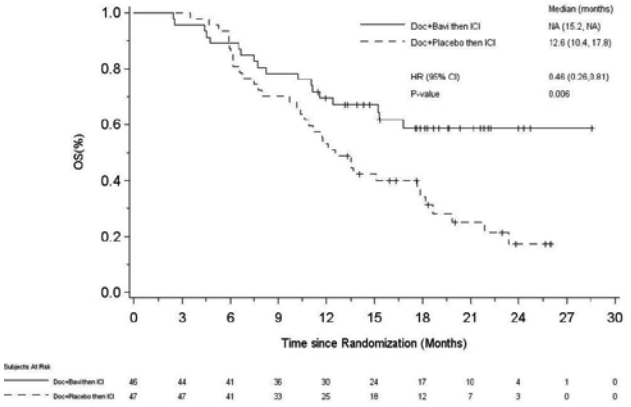
Background: Bavituximab targets exposed phosphatidylserine (PS) in the tumor microenvironment, resulting in repolarization of myeloid suppressor cells/M2 macrophages to M1, production of pro-inflammatory cytokines such as IFNγ and IL-12, dendritic cell maturation, and tumor specific cytotoxic T-cell activation. SUNRISE was a Phase III trial of docetaxel with bavituximab (D+B) or placebo (D+P) in patients with treated Stage IIIb/IV non-squamous NSCLC. Recent correlative analyses from SUNRISE suggest bavituximab is more active in PD-L1 negative, immune cold tumors and thus may complement PD-1/PD-L1 ICI. **Method:** This subgroup analysis included all patients who received subsequent ICI after discontinuing SUNRISE study drug. We calculated overall survival (OS) both from randomization and start of subsequent ICI. **Result:** Ninety-three of 597 randomized patients (16%) received ICI as next line of therapy after SUNRISE assigned treatment. Baseline characteristics were balanced between the treatment groups and consistent with the ITT population. From randomization, mOS was not reached (95% confidence interval [CI], 15.2-NA) in D+B (N=46) and 12.6 months (95% CI, 10.4-17.8) in D+P (N=47) (hazard ratio [HR], 0.46; P=0.006) (Figure). From start of ICI, mOS was not reached (95% CI, 10.2-NA) in D+B and 6.2 months (95% CI, 3.9-8.7) in D+P (HR, 0.42; P=0.002). The mPFS was 6.0 months (95% CI, 3.5-6.5) in D+B and 4.4 months (95% CI, 2.6-6.3) in D+P (HR, 1.00; P=0.991). ORR was 20% vs. 13% (Odds ratio 0.6; P=0.41) for D+B and D+P, respectively. The safety profile was similar between groups and no immune related (IR) toxicities (colitis, pneumonitis, hypothyroidism) were reported. **Conclusion:** Within

the limits of a subgroup analysis, a significant improvement in OS was observed for patients previously treated with D+B. Furthermore, bavituximab has not been associated with IR toxicities and might serve as a useful drug in combination with ICI for the treatment of immune cold tumors.



Keywords: bavituximab, Checkpoint Inhibitor, NSCLC

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.06 REAL-WORLD RESULTS IN NON-SQUAMOUS NON-SMALL CELL LUNG CANCER PATIENTS: ITALIAN NIVOLUMAB EXPANDED ACCESS PROGRAMME

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Background: Nivolumab monotherapy has shown survival benefit in patients (pts) with different tumors, including melanoma, lung cancer, renal cell carcinoma, head and neck cancer and Hodgkin lymphoma. Controlled clinical trial setting differs from what experienced by pts and physicians in routine clinical practice. Here, we report efficacy and safety results of nivolumab in pts with non-squamous non-small cell lung cancer (Non-Sq-NSCLC) treated in the Expanded Access Programme in Italy. **Method:** Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Squamous NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received at least one dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events. **Result:** Overall, 1588 pts were enrolled in the EAP across 168 Italian centers. Baseline characteristics of pts were representative of Non-Sq-NSCLC population, in the advanced disease setting. As of March 2017, median overall survival (OS) was 11 months (10.0-12.0), with a median follow-up of 7.8 months (1-21.9) and a median of 7 doses (1-46). The best overall response rate (BORR) was 18%, including 10 pts (<1%) with complete response and 280 pts (17.6%) with partial response. Stable disease has been defined for 414 pts (26.0%) and totally 274 (17.2%) patients were treated beyond progression. Response rates and survival were comparable among pts regardless age (< and ≥ 75 years), presence of brain metastasis and number of prior therapies. Overall, among 1588 pts, 1254 discontinued treatment for any reason, with only 93 (7%) pts who discontinued treatment due to adverse events, in line with what observed in previous studies. **Conclusion:** To date, this is the largest clinical experience with nivolumab in a real-world setting and these EAP data are in line with what reported in the registrative phase 3 clinical trial. According to these results, nivolumab seems to be an effective and safe therapy for pre-treated patients with non-squamous NCSLC, supporting its use in current clinical practice.

Keywords: Expanded Access Programme, Nivolumab, Anti-PD-1

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.07 ELDERLY LUNG CANCER PATIENTS ON IMMUNOTHERAPY: PRELIMINARY RESULTS FROM THE ELDERS STUDY

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Background: Immunotherapy is revolutionising the way many cancer types are treated. The immunosenescence and the high heterogeneity of the elderly raises questions on the benefits with such treatments and real-world data is lacking. **Method:** ELDERS is a prospective, observational pilot study on the use of checkpoint inhibitors in patients with advanced/metastatic non-small cell lung cancer (NSCLC) or malignant melanoma. The study was designed with 2 arms, the elderly (≥ 70 years) and the non-elderly (45-69 years) with 2 co-primary endpoints, immune-related toxicity (irAE) profile and health-related quality of life (HRQoL) through the EORTC QLQ-C30. A comorbidity score (CIRS) was applied at baseline (score 0-56) and serial geriatric assessments were performed for stratification with a screening tool (G8) and further geriatric assessment as needed. A total of 110 patients of a planned 120 have been recruited. This interim analysis is of the NSCLC cohort with a minimum of 3 months on study/follow-up. **Result:** 32 patients were included, with 96% treated with pembrolizumab (9% first-line) and 40.6% enrolled on the elderly arm. In both arms, 45% had a tumour PD-L1 expression of ≥50%. The elderly arm had more advanced disease with 69% staged M1b vs. 42.1% in younger arm (p=0.05). 69% of patients, in both arms, were performance status 0/1 at the start of treatment. The median CIRS total score was 12 for the elderly and 7 for the younger arm. 46% of elderly patients had an abnormal geriatric screening (G8≤14), requiring further assessments. With a median follow-up of 6 months, the objective response rate (ORR) was overall 19% with a median time to response of 8 weeks. The ORR was numerically higher in the elderly with 30.8% vs. 10.5% (p=0.09). 9.4% of patients on study had a grade 3/4 irAE, with no difference between study arms. Elderly patients had a numerically higher rate of admissions, 53.8% vs. 36.8% (p=0.18). No statistically significant correlation was identified between higher comorbidity score or abnormal geriatric assessment and the incidence of irAEs. No significant negative impact on the global HRQoL was detected in either arm during treatment with immunotherapy. **Conclusion:** Despite the small number of patients and the limited follow-up time, there is no signal in this interim analysis to indicate that elderly patients have less benefit or higher risk of irAE compared with younger patients, despite more comorbidities and geriatric syndromes. These results help to inform clinical practice in the absence of trials dedicated to the elderly population.

Keywords: elderly, Immunotherapy, NSCLC

MA 10 IMMUNOTHERAPY I
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 10.09 INCREASED T FOLLICULAR HELPER CELL INFILTRATION IN LUNG ADENOCARCINOMA TERTIARY LYMPHOID ORGANS

E. Marshall, K. Ng, K. Enfield, S. Martin, K. Milne, S. Kung, C. Macaulay, W. Lam

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Background: T follicular helper cells (Tfh) are an antigen-experienced CD4+ T cell subset that have been found to play crucial roles in the development of humoral immunity. In particular, their presence in the B cell-rich germinal centre of secondary and tertiary lymphoid tissue aids in B cell maturation through selection of B cells producing high-affinity antibodies. Tfh cells have known roles in autoimmune disease and B cell malignancies; however, their role in many solid tumours, including those of the lung, remains unclear. **Method:** We analyzed 83 paired tumour-normal lung adenocarcinoma samples from the BC Cancer Agency (BCCA) as well as 576 unpaired samples from The Cancer Genome Atlas (TCGA). Relative immune cell content was obtained from gene expression data using a linear support vector regression deconvolution approach (CIBERSORT). Spatial positioning of B and T cells within selected tumour sections was examined through IHC. The impact of Tfh infiltration on patient survival was analyzed using a Cox Proportional Hazard model. **Result:** T follicular helper cells are increased in tumour tissue, accompanied by global upregulation of Tfh markers PDL1 and CXCR5 in both the BCCA and TCGA cohorts. Histological analysis revealed localization of Tfh cells within tertiary lymphoid organs, with direct contact with B cells in the follicular zone observed. Importantly, Tfh recruitment appears to be an early event in tumour development and a function of neoantigen exposure, indicative of an active anti-tumour response rather than a result of chronic inflammation of the tumour microenvironment. **Conclusion:** T follicular helper cells are required for B cell maturation and subsequent antibody responses. As such, it is not surprising that Tfh infiltration in tumour-resident ectopic lymphoid structures correlates with patient survival in various cancer types. Given the importance of tumour-specific antibody responses in natural and therapeutic immunity, further investigation of Tfhs may show prognostic utility and be a marker of early-stage lung tumours.

Keywords: T follicular helper cell, Immunology

MA 10.10 TUMOR DRAINING LYMPH NODE IMMUNOPHENOTYPE CORRESPONDS WITH PRIMARY TUMOR CHARACTERISTICS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

V. Murthy[1], J. Tsay[1], J. Minehart[2], K. Mangalick[2], J. Bessich[1], G. Michaud[1], M. Curotto De Lafaille[1], K. Wong[3], C. Goparaju[4], H. Pass[4], D. Sterman[1]

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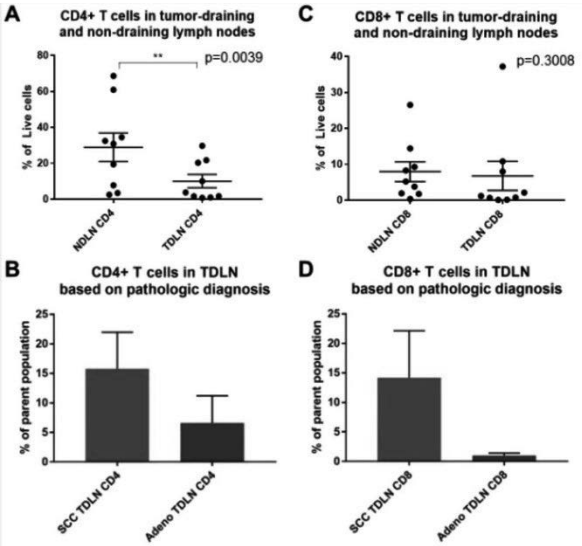
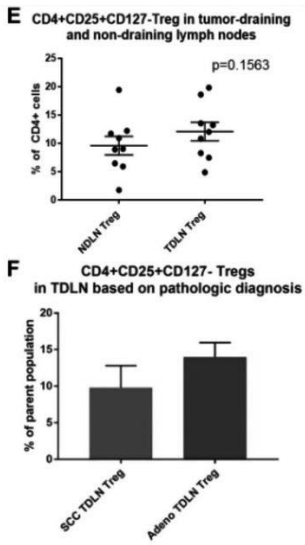
Background: There is growing appreciation for the role of tumor-draining lymph nodes (TDLN) in the dynamic of immunoediting orchestrated by non-small cell lung cancers (NSCLC). By comparing T-cell subsets and gene expression in TDLN and non-draining lymph nodes (NDLN), we aim to determine whether there is tumor-regional variation in immunophenotype. **Method:** Patients undergoing endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis/staging of NSCLC were recruited. Aspirates were obtained from TDLN (N1/N2 nodes with increased fluorodeoxyglucose-F-18 (FDG) avidity and/or enlarged >1cm) and NDLN (non-enlarged/non-FDG-avid N2/N3 nodes) along with peripheral blood. Samples were stained with fluorophore-conjugated antibodies (CD4-FITC, CD8-V450, CD25-PECy7, CD127-APCR700, CD45RO-PECF594) and analyzed by flow cytometry. CD4+CD25- and CD8+ effector T-cells (Teff) were sorted. Gene expression profiling was performed on sorted Teff using the Nanostring™ platform to measure differential expression between TDLN and NDLNs. **Result:** We compared T-cell subpopulations in TDLN and paired NDLN from 16 subjects. There were significantly fewer CD4+ T-cells in TDLN vs NDLN (10.1% vs 28.9%, p=0.0039), with more Tregs (12.1% vs 7.3%, p=0.1563) suggesting a pattern of tumor-regional immunosuppression in the TDLN. This was more consistent when tumor histology was adenocarcinoma compared to squamous cell cancer with respect to both depletion of Teff and higher proportion of Tregs (Figure 1). A more immunosuppressive TDLN phenotype was also observed with high tumor PD-L1 expression (>50%), with 36% fewer CD4+ T-cells in TDLN relative to paired NDLN when PD-L1 expression was high relative to just 3.2% fewer CD4+ T-cells with low PD-L1 expression. Gene expression in Teff has preliminarily demonstrated upregulation of genes mediating T-cell exhaustion (CTLA-4, PD-1, TGF-β) and downregulation of co-stimulatory/recruitment factors (CD28, ICOS, ICAM2) in TDLN suggesting impaired activation of tumor-regional Teff.





Conclusion: Our findings suggest that TDLNs in patients with NSCLC display a tolerogenic phenotype, with more marked immunosuppression in the setting of adenocarcinoma and high tumor PD-L1 expression.

Keywords: non-small cell lung cancer, immunophenotyping, Tumor draining lymph node

MA 10.11 HYPERPROGRESSIVE DISEASE (HPD) IS FREQUENT IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) TREATED WITH ANTI PD1/PD-L1 AGENTS (IO)

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Background: Using Tumor Growth Rate (TGR), HPD was identified in 9% of 131 advanced cancer pts, treated with IO in a single institution (Champiat et al. 2017). In this study, we explored HPD in a large, multicenter cohort of advanced NSCLC pts treated with IO. **Method:** We performed a retrospective analysis of consecutive NSCLC pts treated with IO, in 8 institutions, between November 2012 and April 2017. Eligibility criteria required, for each patient: 2 CT scans performed before starting IO and one during IO, an interval between two CT scans ≥2 weeks or 3 months (m) and presence of target lesions. CT scans were centrally assessed according to RECIST 1.1 criteria. We calculated TGR before IO (TGR pre-IO) and during IO (TGR IO); patients were defined HPD if they had progression disease (PD) at first evaluation during IO and a ≥ 2-fold increase in the TGR IO compared to TGR pre-IO. Median overall survival (mOS) was estimated using Kaplan-Meier method for the total population and HPD pts. **Result:** Among 419 eligible pts, 86 were excluded for inadequate intervals between CT scans. Among 333 evaluable pts, 63% were male, 46% ≥65 years, 43% smokers; 12% had PS ≥ 2, 65% adenocarcinoma, 45% ≥3 metastatic sites, 22% KRAS mutation, 4% EGFR mutation, 1% ALK rearrangement; 21% had PD-L1 positive status, 10% negative, 69% unknown, >90% received single agent PD-1 inhibitor in ≥ 2 line. Response rate (RR) to IO was 18%, median follow up was 12 m [10-14]. 33% of pts had TGR IO ≥1 (not regressing tumors), 25% had TGR IO ≥ 2-fold TGR pre-IO and 54 pts (16%) had HPD. 15 pts (4%) had confirmed pseudoprogression, 3 were initially qualified as HPD. Compared to not-HPD, HPD pts had more frequently ≥ 3 metastatic sites at baseline (59% vs 43% p=0,02) and more new lung lesions during IO (34% vs 17% p=0,007). PD-L1 negative status was more common among HPD pts but the association was borderline significant (53% vs 28% p=0,05). Age, clinical, molecular characteristics, RR to treatment before IO, baseline tumor burden, liver or brain new lesions during IO were not different according to HPD status. mOS was 13 m [10-17] in the total population, 5 m [3-8] in HPD pts. **Conclusion:** HPD occurred in 16% of advanced NSCLC pts treated with IO and was associated with plurimetastatic disease and appearance of new lung lesions. Further work is needed to characterize HPD prognostic value.

Keywords: Hyperprogressive disease, advanced NSCLC, anti PD1/PD-L1 agents

MA 11.01 LIQUID BIOPSIES FOR MONITORING BRAF MUTATION (V600E) IN ANDVANCED BRAF (V600E) NON-SMALL CELL LUNG CANCER (NSCLC)

L. Mezquita[1], C. Jovelet[2], M. Ngocamus[3], E. Auclin[4], J. Remon[1], E. Green[5], V. Plagnol[5], C. Morris[5], A. Gazzah[3], C. Caramella[6], J. Adam[7], L. Lacroix[2], L. Friboulet[8], J. Soria[9], B. Besse[1], D. Planchard[10]

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Background: Circulating tumor DNA (ctDNA) has been shown beneficial in monitoring EGFR mutations in blood, especially for the detection of resistance mutations, like T790M in NSCLC patients. However, the role of BRAF (V600E) ctDNA for monitoring the patient's response has not been studied yet. The aim of this study was to determine the clinical relevance of BRAF (V600E) ctDNA for monitoring the response to BRAF inhibitors in a prospective cohort of advanced NSCLC BRAF (V600E) patients. **Method:** We prospectively enrolled advanced NSCLC patients with BRAF

(V600E) treated with BRAF +/- MEK inhibitors in our institution. A blood sample was collected at different time points, including at baseline, during treatment and at progressive disease. ctDNA BRAF analysis was performed using the Inivata InVision platform (enhanced tagged-amplicon next-generation sequencing (eTAM-Seq). **Result:** Between June 2016 and June 2017, 14 patients have been included. Eight patients (57%) were females, 9 (64%) non-smokers, with a median age of 63 years (35-70). All the patients had adenocarcinoma and BRAF (V600E) mutation in tissue analysis. Thirteen patients (93%) had stage IV at diagnosis, 7 patients (50%) with bone, 6 (43%) pleural and 4 (29%) lung metastasis. The median of lines of treatment received was 2 (1-4). Thirteen patients (93%) received BRAF + MEK inhibitor and 1 patient (14%) BRAF inhibitor, with an objective response rate of 64% (1 complete, 8 partial response) and disease control rate of 86%. BRAF mutation detection was tested under treatment in 12 patients (86%). Longitudinal analysis was performed from the serial sampling in 6 patients to date: 4 patients (67%) were ctDNA positive for BRAF (V600E) at time of progression, with a range of allelic frequency of 0.11-6.16%. BRAF mutation was not detectable in patients with objective response (2/6, 33%) at time of sample collection(s). Additional BRAF (V600E) NSCLC patient samples are being analyzed. **Conclusion:** Liquid biopsy for monitoring BRAF (V600E) using ctDNA appears to be feasible and useful in advanced NSCLC patients. Updated longitudinal results for the complete patient cohort will be presented at the meeting.

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MA 11.02 CIRCULATING TUMOUR DNA IN EARLY STAGE NSCLC: HIGH SENSITIVITY ANALYSIS IN LOW BURDEN DISEASE. LUCID STUDY UPDATE

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Background: To improve treatment selection and outcomes for patients with early stage non-small cell lung cancer (NSCLC) the development of an effective biomarker to diagnose and characterise the tumour and to detect residual disease after curative-intent treatment is crucial. Circulating tumour DNA (ctDNA) is a promising means to detect and track tumours non-invasively, as the genomic alterations in plasma are representative of the tumour's clonal populations and their levels correlate with the burden of disease. Furthermore, ctDNA has shown promise for detecting minimal residual disease after treatment in several cancer types. This could help in the selection of patients that, after surgery or radical radiotherapy, will benefit from subsequent treatment. Nonetheless, more sensitive techniques are needed to enable the detection and study of ctDNA at very low concentrations in settings such as these. **Method:** The LUCID study (early stages of non-small cell LUng cancer - CIrculating tumour DNA) was designed to prospectively collect plasma samples from patients with early-stage NSCLC before and after treatment with surgery or radiotherapy (±chemotherapy), and during a minimum follow up of 3 years after diagnosis, in order to explore the clinical utility of ctDNA. For high sensitivity detection of ctDNA, TAilored Panel Sequencing (TAPAS) was developed: exome sequencing of tumour tissue enables the creation of patient-specific panels to analyse in parallel, large numbers of mutations with high sequencing depth. Plasma samples are being analysed using this approach to assess the levels of ctDNA at diagnosis and after radical treatment. **Result:** 100 patients were recruited to the study. Longitudinal plasma sample collection and analysis are on-going. Preliminary analysis of the tumour tissue and pre-surgical plasma samples from 19 surgical patients show that most patients with early-stage NSCLC have detectable ctDNA. Analysis of additional samples will be presented. **Conclusion:** Preliminary data from LUCID suggest that the methods we have developed have high sensitivity and will allow detection of ctDNA at rates higher than previously reported. These methods will enable the study of ctDNA in early-stage cancers. We are also exploring the utility of these techniques for detection of minimal residual disease after radical treatment, as a potential tool to guide adjuvant or subsequent post-radiotherapy treatment.

Keywords: Circulating tumour DNA, early stage NSCLC, biomarker

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MA 11.03 GEFITINIB AS FIRST-LINE TREATMENT OF PLASMA CTDNA EGFR MUTATION-POSITIVE NSCLC DETECTED BY DDPCR: BENEFIT STUDY (CTONG1405)

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Background: EGFR mutations in plasma circulating free tumor-derived DNA (ctDNA) as a predictor of EGFR TKI efficacy in patients with NSCLC requires validation in prospective studies. The large, prospective Phase II, single-arm, multicenter BENEFIT study (CTONG1405; NCT02282267) validated the efficacy of first-line gefitinib in EGFR mutation-positive NSCLC detected in plasma ctDNA using droplet digital PCR (ddPCR). **Method:** Patients with stage IV lung adenocarcinoma and plasma ctDNA EGFR-sensitizing mutations (exon 19 del or exon 21 L858R; by ddPCR) received first-line gefitinib (250 mg once-daily) until progressive disease (PD). Blood samples were collected every 8 weeks for dynamic EGFR analysis until PD. Primary endpoint was ORR. Secondary endpoints included PFS, DCR (Week 8), and analysis of baseline ctDNA samples by next-generation sequencing (NGS). **Result:** From December 2014-January 2016, 426 patients from 15 Chinese centers were screened: 391 had matched tissue and blood samples; 188 had ctDNA EGFR mutation-positive NSCLC and received gefitinib; and 183 had ≥1 post-baseline tumor assessment and plasma samples every 8 weeks until PD. At data cutoff (January 31, 2017), 152 patients had progressed. ORR was 72.1% (95% CI 65.0%,78.5%); DCR (Week 8) was 92.3% (95% CI 87.5%,95.8%); and median PFS was 9.5 months (95% CI 9.07,11.04). PFS was significantly shorter in the subgroup with baseline ctDNA de novo T790M mutations (5.0%, n=9) versus the EGFR-sensitizing mutations subgroup (5.6 vs 9.6 months, HR=2.60; 95% CI 1.32,5.12, p=0.004). In patients with Week 8 on-treatment plasma samples (n=167), the subgroup who showed EGFR mutation clearance in ctDNA by ddPCR (88%, 147/167) had longer PFS compared with those who did not (11.0 vs 2.1 months, HR=7.28; 95% CI 4.35,12.18, p<0.0001). The median time to emergence of acquired T790M mutation in plasma was 7.6 months. The T790M-positive rate increased from Week 24 (15.7%) to Week 48 (32.6%), with a corresponding increase in PD rate (24.7% at Week 24, 56.9% at Week 48). Among 180 patients with baseline NGS data, 21 (11.7%) harbored aberrations in additional oncogenic drivers (MET, ERBB2, KRAS, BRAF, RET, or ROS1) and tumor suppressors (TP53, RB1, and PTEN). This subgroup had worse PFS versus those with EGFR-sensitizing mutations alone (3.9 vs 13.0 months, HR=2.83; 95% CI 1.65,4.87, p=0.00016). **Conclusion:** The BENEFIT study prospectively demonstrated that ctDNA-based EGFR mutation detection can be used to select patients for treatment with first-line gefitinib. Dynamic alterations in EGFR mutations could be used to predict efficacy and disease progression, ahead of radiological results.

Keywords: ctDNA, gefitinib, EGFR

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MA 11.05 TARGETED DNA- AND RNA-BASED NEXT-GENERATION SEQUENCING FOR IDENTIFYING MET EXON 14 ALTERATIONS IN PULMONARY SARCOMATOID CARCINOMA

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Background: Highly diverse somatic splice site alteration at MET exon 14 (METex14) result in exon skipping, which is supposed to be a therapeutic target in NSCLC. Here we report detection of METex14 alterations using targeted DNA- and RNA-based Next-Generation Sequencing (NGS) in pulmonary sarcomatoid carcinoma (PSC) with a high frequency of METex14 skipping. **Method:** Tumor specimens were collected from 77 Chinese PSC patients. DNA and RNA were subject to targeted NGS, allowing the detection of somatic splice site alterations and intragenic METex14 skipping respectively. Then, somatic mutations (mutation allele frequency ≥2%) that lead to METex14 skipping were recognized, and Fisher's exact test was used to examine the association between METex14 skipping and clinical characteristics or other mutations. Two-sided P-values <0.05 were considered statistically significant. Moreover, RT-PCR and Sanger sequencing was also performed on the METex14-positive specimens. **Result:** We have detected genetic aberrations in 77 FFPE samples. For RNA-based NGS, METex14 skipping was identified in 16 (20.78%) of 77 patient cases. And 15 (93.75%) METex14-positive patients were detected somatic mutations by DNA-based NGS, including 12 (80%) cases with splice donor site mutations, 1 (6.67%) cases with splice acceptor site alterations, 1 (6.67%) case with a novel deletion (chr7: 116411868 - 116411883) at MET intron 13 region and 1 (6.67%) case with a novel deletion (chr7: 116412027 - 116412042) at MET exon14 region. In this study, 6 somatic mutations which induce METex14 skipping were firstly discovered. So far, RT-PCR and Sanger sequencing were performed on 3 specimens, including 1 sample with conflicting RNA- and DNA-based NGS results and 2 samples with unreported somatic deletions. According to the results of RT-PCR and Sanger, the unmatched sample was false negative on the basis of DNA-based NGS result. Interestingly, METex14 skipping was mutually exclusive with other recognized genomic alterations (such as mutations in KRAS, BRAF, EGFR, NRAS and PIK3CA), while no significant difference was found between METex14 skipping and single driver gene. **Conclusion:** Mutational events of MET leading to exon 14 skipping are frequent occurred in Chinese PSC patients. DNA-based NGS could discover new somatic mutations which results in METex14 skipping. However, RNA-based NGS could provide more accurate results than DNA-based NGS. METex14 skipping was mutually exclusive with other drivers, thus strongly highlighting its potential oncogenic role.

Keywords: DNA- and RNA-based Next-Generation Sequencing, Pulmonary sarcomatoid carcinoma, METex14 skipping

MA 11.06 RETROSPECTIVE ANALYSIS OF NSCLC TESTING IN LOW TUMOR CONTENT SAMPLES: SINGLE-GENE TESTS, NGS, & THE ONCOMINE™ DX TARGET TEST

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Background: Clinical practice guidelines recommend genetic testing for advanced non-small cell lung cancer (aNSCLC) to guide 1st-line treatment. Small biopsies and low-tumor-content samples pose challenges to testing and reporting on an increasing number of relevant biomarkers. This study compared clinical aNSCLC biomarker testing to investigational use of the Oncomine™ Dx Target Test for different sample types. **Method:** A retrospective analysis was conducted using lung tissue testing data from a large, US-based commercial laboratory that offered single-gene tests (EGFR therascreen, ALK Vysis, BRAF cobas, and laboratory developed tests [LDT] for ROS1, HER2, BRAF, KRAS, MET, RET, and FGFR1) and a 173-gene next-generation sequencing (NGS) LDT panel (Illumina NextSeq 500). Clinical test orders received September 2015 – October 2016 were evaluated. This laboratory also conducted investigational testing on the Oncomine™ Dx Target Test (Ion Torrent PGM Dx) using archival tissue. Testing success rates and slide consumption were evaluated for core needle biopsies (CNBs; overall and by tumor content), fine needle aspirations (FNAs), and surgical resections. **Result:** Clinical testing orders were received on 1,029 CNBs, 144 FNAs, and 181 surgical resections. Among CNBs, 934 had tumor content data: 214 were 1-24% tumor; 720 were ≥25% tumor. Altogether, 3,571 single-gene tests and 198 NGS LDT panels were ordered. The Oncomine™ Dx Target Test was conducted on 169 archival samples: 69 CNBs (41 were 1-24% tumor; 28 were ≥25% tumor); 13 FNAs; 87 surgical resections.

Sample characteristics	Single-gene tests per clinical sample (N)*							173-gene NGS LDT	Oncomine™ Dx Target Test
	1	2	3	4	5	6	7	(N)	(N)
N samples	1,295	1,039	633	191	114	98	28	198	169
% samples able to successfully generate results for at least X tests, when ordered†									
CNB‡	89.2% (988)	85.3% (788)	76.2% (495)	77.9% (154)	70.8% (96)	61.9% (84)	58.3% (24)	N/A§	75.4% (69)
• 1-24% tumor	95.7% (209)	87.1% (170)	70.0% (110)	70.8% (24)	62.5% (16)	60.0% (15)	N/A (4)		70.7% (41)
• ≥25% tumor	98.2% (685)	91.8% (570)	82.9% (362)	85.8% (120)	76.3% (76)	66.2% (65)	61.1% (18)		82.1% (28)
FNA	79.3% (140)	72.4% (116)	75.0% (60)	40.0% (10)	N/A (4)	N/A (4)	N/A (1)		69.2% (13)
Surgical resection	100% (167)	98.5% (135)	91.0% (78)	88.9% (27)	64.3% (14)	50.0% (10)	N/A (3)		98.9% (87)
Total number of slides used to initiate exactly X tests									
CNB‡	2.6 (165)	4.1 (268)	5.5 (324)	8.7 (56)	8.5 (11)	11.8 (55)	16.8 (16)	16.5 (24)	1.0¶
• 1-24% tumor	2.7 (39)	4.8 (60)	5.9 (83)	9.5 (8)	9.0 (1)	12.3 (11)	18.3 (3)	18.7 (3)	
• ≥25% tumor	2.6 (118)	3.9 (208)	5.4 (241)	8.7 (47)	8.4 (10)	11.7 (44)	16.5 (13)	16.1 (21)	
FNA	2.4 (21)	4.3 (41)	6.1 (42)	9.8 (5)	N/A (0)	11.5 (2)	18.0 (1)	14.0 (2)	
Surgical resection	1.8 (32)	4.5 (57)	5.4 (51)	9.5 (13)	11.0 (4)	16.3 (7)	14.0 (2)	8.2 (13)	

*Excludes clinical samples on which the NGS LDT panel had been initiated. † Success rates were not evaluated if N<10. ‡ While all samples had tumor content >0%, exact percentages were missing for 94 CNBs, 28 FNAs, and 1 surgical resection. § Success rates not evaluated; nearly all NGS LDT panels were ordered on samples that also initiated single-gene tests, and tissue depletion prevented initiation of most of the ordered NGS LDT panels. ¶ All tests were conducted using 1 slide according to protocol.

Conclusion: Among lung tissue samples submitted for clinical testing, 13.4% were surgical resections, 10.6% FNAs, and 76% CNBs. The Oncomine™ Dx Target Test had higher testing success rates using fewer slides than single-gene testing for ≥5 biomarkers on CNBs, ≥4 on FNAs, and ≥2 on surgical resections. These preliminary results suggest the Oncomine™ Dx Target Test may facilitate multiple-biomarker testing for more aNSCLC patients to support therapy decisions as more gene targets are identified.

Keywords: next-generation sequencing, single-gene testing, real-world evidence

MA 11.07 EXOSOMES-TRANSMITTED MICRORNAS PROMOTE EGFR-TKIS RESISTANCE IN NSCLC BY ACTIVATING PI3K/AKT SIGNALING PATHWAY

X. Liu[1], T. Jiang[1], X. Li[2], J. Li[1], L. Zhang[1], S. Zhao[1], Y. Jia[1], J. Shi[1], C. Zhao[2], M. Qiao[1], F. Zhou[1], J. Zhao[3], C. Zhou[1]

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Background: Acquired epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) resistance is a major factor contributing to targeted therapy failure in EGFR mutant non-small cell lung cancer (NSCLC), among which T790M mutation accounts for 50-60%. Emerging evidence has shown that as mediators between cells, exosomes shed by drug resistant cancer cells have the ability to horizontally transfer drug resistant phenotype to drug sensitive cells, which has been described as an important mechanism of dissemination of drug resistance. However, whether exosomes derived from EGFR-TKIs resistant NSCLC cells harboring T790M mutation could transfer resistance to sensitive cells has not been understood and the potential mechanism also remains unknown. **Method:** Exosomes were isolated from supernatants of T790M mutant NSCLC cell line (H1975) and characterized by transmission electron microscopy, nanosight and western blot. Their potential roles in mediating gefitinib resistance in sensitive cell line (PC9) were investigated in vitro and in vivo. Cell viability and the effects of exosomes on downstream signaling pathways were analyzed by CCK-8 assays and western blot. The roles of exosomes in regulating gefitinib resistance in vivo were assessed by subcutaneous transplantation tumor model in athymic nude mice. Exosomes miRNA sequencing and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) were used for exploring the underlying mechanism. **Result:** Exosomes isolated from conditioned medium of NSCLC cell lines were cup-shaped membranous vesicles with a diameter of 30-100 nm and expressed the exosomal marker CD63. Exosomes derived from H1975 could transmit gefitinib resistance to PC9 ($P<0.01$) in vitro while exosomes released from PC9 cell don't have this effect. Treatment of PC9 with H1975-derived exosomes and the inhibitor of exosomes production (GW4869) could restore gefitinib response. In vivo, the tumor volume of xenograft model of PC9 cells treated with gefitinib plus H1975-derived exosomes was significantly larger than those mice treated with gefitinib alone ($P<0.05$). Furthermore, H1975 xenografts could disseminate gefitinib resistance to PC9 xenografts in the same mice. This difference disappeared by the addition of GW4869. Mechanistically, intercellular transfer of microRNAs (miR-522-3p and miR-454-3p) by exosomes disseminated gefitinib resistance through activating PI3K/AKT and MEK/ERK signaling pathways **Conclusion:** Our findings demonstrate that EGFR-TKIs resistant cells could disseminate drug resistance to sensitive cells by intercellular transfer of exosome-transmitted microRNAs and then activating PI3K/AKT and MEK/ERK signaling pathways, which reveals a novel mechanism of acquired resistance to EGFR-TKIs in NSCLC.

Keywords: non-small cell lung cancer, exosomes, EGFR-TKIs

MA 11.09 REAL WORLD DATA OF REBIOPSY, MUTATION STATUS, AND ITS ASSOCIATION WITH PLASMA GENOTYPING AFTER EGFR TKI FAILURE IN NSCLC

M.H. Hong[1], B.C. Ahn[1], H.R. Kim[1], S.J. Heo[2], J.H. Kim[1], I.Y. Bang[1], R. Kim[1], H.W. Jung[1], H.J. Cho[1], H. Kim[1], H. Kim[1], B.C. Cho[1]

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Background: After the introduction of third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in non-small cell lung cancer (NSCLC), the second tumor biopsy and EGFR mutation test to confirm T790M status is an established standard practice. But second biopsy is invasive, cost and time-consuming and occasionally impossible. We aimed to investigate the success rate of tissue rebiopsy and incidence of T790M mutation in tissue and plasma at the time of progression with earlier-generation EGFR TKIs in real world setting. Also, we studied the association between the efficacy of osimertinib and the status of tissue and/or plasma T790M mutation. **Method:** We analyzed patients who were screened and enrolled into ASTRIS trial in Yonsei Cancer Center (NCT02474355). Key inclusions were advanced/metastatic NSCLC with tissue and/or plasma T790M mutation and prior EGFR-TKI therapy. Tissue and plasma EGFR mutation tests were performed using PNAClamp™ and PANAMutyper™, respectively. **Result:** We screened 193 patients with NSCLC harboring EGFR-activating mutation who experienced disease progression upon earlier-generation EGFR TKIs during study period. The second biopsy including tissue and/or cytology was performed only in 60.1% of the patients (116/193) and the success rate was 86.2% (100/116). The reasons for not trying a biopsy were as follow: inaccessibility (n=25), poor PS (n=8), previously reported plasma T790M+ (n=8), and patients' refusal (n=4). The parenchymal lung tissue (n=61) was most commonly targeted lesion and bronchoscopy was the most frequently used method (n=35). Six patients underwent video-assisted thoracoscopic surgery. Tumor T790M mutation was reported in only 25.9% of patients (50/193). Of 193 patients, 88 patients were enrolled into ASTRIS trial and 43 patients were registered based on the plasma test only. With a median follow-up of 25.1 weeks, the objective response rate (ORR), median progression-free survival (PFS), and duration of the response (DoR) were 44.3%, 32.7 weeks, and 27.0 weeks, respectively. Median overall survival (OS) was not reached. The ORR, median PFS and DoR of tumor T790M+ (n=45) vs. plasma T790M+ (n=54) were 57.8% vs. 35.2%, 45.0 vs. 20.4 weeks, and 26.3 vs. 25.9 weeks, respectively. **Conclusion:** With the increasing importance of tissue rebiopsy after EGFR-TKI failure, there is a growing interest to overcome the challenge of subsequent biopsy. Even though relatively lower ORR and shorter PFS in patients with plasma T790M+ compared with tissue T790M+, the plasma EGFR genotyping may be good alternative to the tissue biopsy in consideration of long DoR when treated with osimertinib and low yield rate of tissue T790M testing.

Keywords: T790M, plasma, osimertinib

MA 11.10 EGFR TKI TREATMENT INDUCES ACTIVE DEAMINATION OF 5-METHYLCYTOSINE AND LEADS TO ACQUIRED T790M RESISTANT MUTATION

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Background: Epidermal growth factor receptor (EGFR) activation mutations occur in 10-50% of lung adenocarcinoma patients of Caucasian ethnicity and in 50% of Asian descent. Currently, EGFR tyrosine kinase inhibitors (TKIs) are first line therapy for stage IV non-small cell lung cancer (NSCLC) patients with EGFR mutations. Despite initial significant response to TKIs, most tumors develop resistance. The main mechanism of resistance detected in 50-60% of cases is a cytosine to thymine (C>T) single nucleotide transition mutation at position 2369. This leads to a threonine to methionine amino acid change at position 790 (i.e. T790M). Interestingly, a similar mechanism of C>T mutation is seen in imatinib treated CML and GIST tumors. Our data suggests that the C>T mutation is an acquired event secondary to 5-methylcytosine deamination with Activation Induced Cytosine Deamination enzyme (AICDA). **Method:** PC9 is a lung adenocarcinoma cell line known to have an EGFR del19 activation mutation and can acquire T790M mutation from T790M-negative clone. We utilized droplet digital PCR (ddPCR) to detect T790M mutations. In addition, qPCR was used to assess the expression of AICDA and NFκB pathway before and after TKI exposure. **Result:** Sub clones of PC9 cell line with no evidence of T790M mutation by ddPCR at baseline, were treated with EGFR TKI. After serially increasing the treatment dose, T790M mutation was detected by ddPCR associated with a significant increase in AICDA expression. Furthermore, using a UDG assay, we show that AICDA recognizes a CAC motif and can deaminate cytosine at position 2369. By mass spectrometry we established that 2369 cytosine is methylated. Deamination of 5-methylcytosine leads to thymine directly rather than uracil, explaining the C>T mutation. In addition, using ChIP assay and pharmacological inhibition we confirmed that NFκB binds AICDA promoter and induces its expression. Similarly, using a mouse xenograft model, EGFR TKI increases the expression of NFκB and AICDA; this is abrogated by concurrent use of an IKKα inhibitor. Knocking down AICDA by shRNA, decreases the rate of T790M development in PC9 cell lines after TKI exposure. Assessing AICDA expression in patients at baseline (n=4) and upon T790M mutation progression (n=4), there was a significant 20-fold increase in its expression. **Conclusion:** Our data suggest that upon exposure to EGFR TKI, AICDA is overexpressed through an NFκB dependent pathway, causing the deamination of 5-methylcytosine to thymine, manifesting as T790M mutation and leading to TKI resistance. This indicates that T790M is acquired and its development could be targeted.

Keywords: AICDA, EGFR, NSCLC

MA 11.11 ITALIAN NIVOLUMAB EXPANDED ACCESS PROGRAM IN NON-SQUAMOUS NSCLC PATIENTS: RESULTS IN NEVER SMOKERS AND EGFR POSITIVE PATIENTS

M. Garassino[1], E. Cortesi[2], F. Grossi[3], R. Chiari[4], H. Soto Parra[5], S. Cascinu[6], F. Cognetti[7], D. Turci[8], L. Blasi[9], C. Bengala[10], E. Mini[11], E. Baldini[12], T. Gamucci[13], G. Ceresoli[14], P. Antonelli[15], E. Vasile[16], C. Pinto[17], D. Galetta[18], M. Macerelli[19], F. De Marinis[20]

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Background: Nivolumab is the first checkpoint inhibitor approved for the treatment of non-Squamous non small cell lung cancer (non-Sq-NSCLC). Although smoking habits are considered a relevant risk factor related to the onset of lung cancer,

previous studies showed that current and former smokers patients (pts) treated with nivolumab may have a greater advantage in terms of clinical benefit than never smokers and EGFR mutated. Nevertheless, to date, no definitive conclusion may be drawn and no data are available from a real world setting. Here we report the data from Italian expanded access program (EAP) in the never smoker pts and EGFR mutated pts. **Method:** Nivolumab was provided upon physicians' request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months. Pts included in the analysis received ≥1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events. **Result:** Overall, of 1588 patients with non-Sq-NSCLC, smoking history was available for 1430 pts and 305 (21%) were never smokers and, among 1455 pts evaluable for EGFR mutation, 102 (7%) were positive. In the never smoker group, EGFR status was available for 287 pts, with 51 (18%) who harbored an activating EGFR mutation. Among never smokers, with a median follow-up (FU) of 7.0 months (0.1-20.3) and a median of 7 doses (1-38), the best objective response rate (BORR), the disease control rate (DCR) and the median overall survival (OS) were 9%, 42% and 10.0 months (8.1-11.9), respectively. Among all EGFR positive pts, with a median FU of 5.5 months (0.1-21.2) and a median of 6 doses (1-40), the BORR, DCR and median OS were 9%, 30% and 8.3 months (2.2-14.4), respectively. In the never smoker group, EGFR positive pts had 2% ORR, 26% DCR and 5.6 months (3.4-7.8) of median OS. However, it should be considered that these pts had poorer prognostic factors (ECOG performance status, brain metastasis) at baseline. **Conclusion:** These preliminary results represent the first real-life data regarding the efficacy of nivolumab in special subpopulations, including never smokers and EGFR positive pts. These results warrants further studies to evaluate the possible therapeutic options in these pts, also taking into account available alternatives and safety profile.

Keywords: non-sq NSCLC, never smokers, EGFR

MA 12 CIRCUMVENTING EGFR RESISTANCE
TUESDAY, OCTOBER 17, 2017 - 11:00-12:30

MA 12.01 A PHASE IB STUDY OF THE COMBINATION OF AFATINIB AND RUXOLITINIB IN EGFR MUTANT NSCLC PROGRESSED ON EGFR-TKI: AN UPDATED ANALYSIS

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Background: T790M mutation of EGFR exon 20 is observed in approximately 50% of the non-small cell lung cancer (NSCLC) patients progressed on EGFR tyrosine kinase inhibitors (TKIs). Based on a preclinical study demonstrating that pharmacologic JAK1 inhibition increased the anti-tumor activity of afatinib in T790M-positive NSCLC cell lines, we conducted a phase Ib study to evaluate the safety and efficacy of the combination of afatinib and ruxolitinib, a selective JAK inhibitor, in NSCLC patients who had progressed on EGFR-TKIs. **Method:** We used the classical 3+3 design for dose-escalation cohort (DAC). Patients with histologically diagnosed, EGFR mutant stage IV NSCLC and documented disease progression on EGFR-TKIs were considered eligible. Afatinib was administered alone once daily from day 1 through day 8 (run-in period), then ruxolitinib was orally administered twice daily concomitantly with afatinib until progression. The primary endpoint was to determine RP2D and DLT. If DLT was not observed in 9 patients at the cohort of the highest level, we planned to decide RP2D and enroll 6 additional patients in the dose-expansion cohort (DEC). **Result:** As of June 14, 2017, 21 patients (12 with exon19 deletion, 9 with exon21 L858R) were enrolled in DAC, 8 of which had T790M mutations. All patients were previously treated with erlotinib (n=6) or gefitinib (n=15), and previously received a median of 2 (range, 1-4) lines of chemotherapy. Because no DLT was observed in the 9 patients at the highest dose level (afatinib 50 mg once daily plus ruxolitinib 25 mg twice daily), 6 patients with T790M mutation were enrolled in the DEC. Frequent AEs included paronychia (G1 in 11 cases, G2 in 2 cases), diarrhea (G1 in 14 cases, G2 in 2 cases, and G3 in 2 cases), acneiform rash (G1 in 13 cases), and oral mucositis (G1 in 7 cases, G2 in 3 cases). SAEs were reported in 6 patients, which were not related to the investigational products. Partial responses were observed in 7 patients (25.9%) with disease control rate (CR+PR+SD) of 96.3%. Median PFS was 5.7 months (95% CI, 4.2-7.2) and 3 patients remain on study. **Conclusion:** The combination of afatinib with ruxolitinib was well tolerated with clinical benefit of disease control in NSCLC with acquired resistance to EGFR-TKIs (NCT02145637).

Keywords: EGFR T790M, Ruxolitinib, afatinib

MA 12 CIRCUMVENTING EGFR RESISTANCE
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MA 12.02 PHASE I/II STUDY OF S49076, A MET/AXL/FGFR INHIBITOR, COMBINED WITH GEFITINIB IN NSCLC PATIENTS PROGRESSING ON EGFR TKI

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Background: S49076 is a potent ATP-competitive TKI that targets MET, AXL and FGFR1/2/3 at clinically relevant doses. Preclinical data showed that combination of S49076 with 1st generation EGFR-TKI can overcome acquired resistance to EGFR inhibition in a NSCLC EGFR-mutated MET-amplified cell model. Here we report interim phase I data from NSCLC patients treated with S49076 in combination with gefitinib to overcome acquired non-EGFR-T790M-mediated resistance to EGFR TKI (1st/2nd generation). **Method:** This is a phase I dose-finding study of S49076 combination with a standard dose of gefitinib using a modified Bayesian Continual Reassessment Method with S49076 doses of 500 and 600mg. Both agents are administered orally once daily. The primary objective is to determine the safety profile of the combination and the recommended phase 2 dose (RP2D) based on safety assessments. Patients are selected according to tumor status; they carried an activating-EGFR mutation without secondary T790M mutation and with at least one of the following dysregulations: MET IHC3+, MET FISH 2+/3+, or AXL IHC 2+/3+. **Result:** In June 2017, molecular screening was performed in 48 EGFR/T790M-negative tumor samples to assess MET and AXL dysregulation. 17/48 met the molecular eligibility criteria: 12/17 with MET overexpression/amplification; 4/17 with both MET overexpression/amplification and AXL overexpression; and 1/17 with AXL overexpression. As regards S49076 dose levels, 4 patients were included at 500 mg and 4 at 600 mg. Five patients discontinued treatment: 4 disease progression and 1 consent withdrawal. The most frequent related AEs (≥2 patients) were asthenia (n=5), diarrhea, nausea and paronychia (n=4 each), ASAT/ALAT increase, anemia, and yellow skin (n=3 each), peripheral edema, stomatitis, blood creatinine increase, vomiting, hypoalbuminemia, and decreased appetite (n=2 each); most were grade 1-2. A DLT occurred in 1 patient at 600mg (grade 3 stomatitis). The other severe related AEs included grade 3 ALAT increase, asthenia, and neutrophil count decrease. Concomitant intake of gefitinib did not appear to modify the S49076 PK profile as compared to previous data. The best overall response rate were partial response (PR, 1/8), stable disease (SD, 6/8), and progressive disease (1/8), including 3 patients with PR/SD ≥6 months. **Conclusion:** According to preliminary data, the frequency of MET and AXL dysregulations is consistent with the literature. Combination of S49076 and gefitinib is well tolerated and safety data are consistent with the overall safety profile of each drug. The phase II part of this study will start once the RP2D is defined to evaluate the anti-tumour activity of the combination.

Keywords: EGFR tyrosine kinase inhibitor, MET / AXL inhibitor, Resistance

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MA 12.03 KINASE FUSIONS AS RECURRENT MECHANISMS OF ACQUIRED RESISTANCE IN EGFR-MUTATED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Resistance invariably develops in EGFR-mutated NSCLC treated with EGFR tyrosine kinase inhibitors (TKI). In approximately 50% of cases, resistance is mediated by the EGFR T790M mutation; however, multiple other mechanisms of resistance have also been described, including case reports of acquired kinase fusions (PMIDs: 26187428, 28089157). **Method:** Hybrid-capture based genomic profiling (FoundationOne® or FoundationACT™) was performed prospectively on DNA isolated from tissue-based FFPE samples or blood-based circulating tumor (ctDNA) samples from NSCLC patients. **Result:** From a dataset of 3,014 unique EGFR-mutated (exon 19 deletion, L858R, G719X, L861Q, or S768I) TKI naïve or relapsed NSCLCs we identified 28 (0.9%) cases with co-occurring likely activating kinase rearrangements (BRAF [12], FGFR3 [5], RET [5], ALK [4], NTRK1 [1], EGFR [1]), including 24 confirmed fusions. Treatment histories were available for 21/28 cases, and prior evidence of EGFR mutation and treatment with an EGFR TKI was evident in 21/21 (100%) cases. In 25/28 cases no other known mechanisms of acquired resistance co-occurred with the primary EGFR mutation and the kinase fusion. The 3 cases with co-occurring known resistance mechanisms (T790M or MET amplification) were those with BRAF rearrangements for which no fusion partner was identified. Additionally, our dataset included 10 paired pre- and post-EGFR TKI treatment samples where the latter sample showed an acquired kinase fusion (4 FGFR3-TACC3, 2 EML4-ALK, 2 CCDC6-RET, 1 AGK-BRAF, 1 TPM3-NTRK1) in addition to the primary EGFR alteration. Notably, in 3/10 paired cases (2 FGFR3 and 1 BRAF) the fusion was acquired in the setting of dropout of an existing T790M mutation. **Conclusion:** Acquired kinase fusions are rare yet recurrent mechanisms of acquired resistance in EGFR-driven NSCLCs, and may be enriched in the setting of resistance to T790M-specific inhibitors. Genomic profiling capable of detecting all classes of genomic alterations, including base substitutions, indels, copy number alterations, and fusions, is warranted at the time of progression on EGFR TKIs, and often provides rationale for treatment in such cases.

Keywords: EGFR, Acquired resistance, kinase fusion

MA 12.05 GENOMIC PROFILING OF EGFR T790M MUTATED NON-SMALL CELL LUNG CANCER TO EVALUATE THE MECHANISMS OF RESISTANCE TO OSIMERTINIB

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Background: The T790M mutation in the epidermal growth factor receptor (EGFR) gene altering the kinase domain is the most common mechanism of resistance to first or second-generation EGFR tyrosine kinase inhibitors (TKIs). Osimertinib is currently approved for treatment of metastatic EGFR T790M mutation positive non-small cell lung cancer (NSCLC). However, resistance to osimertinib is an emerging issue. Evaluation of the genomic profiles of patients with EGFR T790M mutated NSCLC treated with osimertinib is necessary to gain an understanding of the potential resistance mechanisms. **Method:** Between January 2014 and June 2017, we retrospectively reviewed DNA profiling data from blood and/or tissue (FoundationONE/ACT, Guardant 360, TruSight panel and/or Pyrosequencing) from patients with advanced NSCLC to identify those with an EGFR T790M mutation. For patients harboring the EGFR T790M mutation, electronic health records were reviewed to identify the clinical variables , outcomes and genotyping at the time of progression on osimertinib. Survival analysis was done using the Kaplan-Meier method (SPSS version 23). **Result:** We identified a total of 433 NSCLC patients who underwent genotypic profiling; EGFR T790M mutation was present in 29 (6.7%) patients. All patients received EGFR-TKIs prior to testing. Patient demographics included: Caucasian (76%), female (76%), adenocarcinoma (100%), never-smokers (52%) with a median age of 65 years and 3 median prior lines of treatment. At the time of identification of the T790M mutations, 27 (93%) patients retained their EGFR exon 19 deletion or exon 21 mutations and 24 (82%) patients received osimertinib. The median overall survival was 4.9 ± 3 months in patients not on osimertinib, and was not reachable in patients on osimertinib in the current follow up period. 7 of the 24 patients had repeat genotyping at the time of progression on osimertinib which revealed presence of acquired secondary mutations including EGFR C797S (43%, N=3), EGFR C797G (14%, N=1), amplifications in EGFR (43%, N=3), ERBB2 (HER2, 28%, N=2) and cell cycle genes (CD-K4, CCND1, CCND2, 28%, N=2), MAPK/ERK pathway alteration (KRAS amplification and Q61R mutation, 28%, N=2), PI3K/AKT/mTOR pathway alteration (ATK3 and PIK3C2B amplification, 14%, N=1) and RET fusion (NCOA4-RET, 14%, N=1). **Conclusion:** There is limited data regarding the mechanisms of resistance to osimertinib. In addition to the acquired mutations in C797S, our study identified several potential pathways for developing resistance to osimertinib including emergence of acquired amplification in EGFR and ERBB2, as well as MAP Kinase and PI3K/AKT pathway aberrations. Updated data will be presented at the meeting.

Keywords: T790M, osimertinib, resistance

MA 12.06 USING POPULATION DYNAMICS MATHEMATICAL MODELING TO OPTIMIZE AN INTERMITTENT DOSING REGIMEN FOR OSIMERTINIB IN EGFR-MUTANT NSCLC

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Background: Acquired resistance to therapy occurs with both first- and newer-generation epidermal growth factor receptor (EGFR) inhibitors. One strategy to delay the emergence of resistance is to use the most active/least toxic inhibitor and replace the traditional daily dosing with a biologically-rational dosing approach. Osimertinib is a covalent mutation-specific EGFR tyrosine kinase inhibitor (TKI) with activity against common EGFR plus EGFR-T790M mutations and less activity against the wild-type receptor. This drug is poised to become a 1st line EGFR TKI for treatment-naïve EGFR mutated lung adenocarcinomas. Therefore, it is an ideal candidate to devise rationale dosing schemes to maximize its efficacy and minimize tumor adaptation. **Method:** We explored pulse dosing of osimertinib, to delay the emergence of acquired resistance. We applied population dynamics mathematical modeling to this question, using key parameters ("birth rate" and "death rate"), established through cellular assays. These parameters are presumed to be dose-dependent. First, we experimentally determined the "birth-rates" of PC9 lung cancer cells, PC9 cells bearing the T790M resistance mutation, and PC9 cells that were resistant to osimertinib, with increasing concentrations of osimertinib (0 - 10μM, total of eight doses at half log intervals) using cell viability assays (MTS assay). Next, we determined cellular "death-rates" using annexin V/propidium iodide (PI) fluorescence-activated cell sorting (FACS). We then applied those parameters to our population dynamics model and simulated various treatment conditions with different dosing strategies, to identify the most effective regimens at delaying or preventing the emergence of resistance to osimertinib. **Result:** Using our mathematical model, we predicted that high-dose weekly treatment of osimertinib with a low maintenance dose led to minimal cell proliferation in comparison to daily dosing. Following this in silico prediction of the superiority of pulse dose treatment, we experimentally compared the frequency of emergence of resistance with different treatment dosing regimens, using a long-term cell culture system. Indeed, weekly administration of 5uM osimertinib to PC9 cells, followed by a maintenance dose of 0.25uM, suppressed the emergence of resistance for up to 5-7 weeks in culture. **Conclusion:** We have established a population dynamics mathematical model to predict optimal dosing regimens for osimertinib in treatment-naïve EGFR mutated lung cancers. The model was experimentally validated using a long-term culture system. Future validation in additional preclinical models (cell lines, xenografts and genetically engineered mice) can lead to rationale development of pulse-maintenance clinical trials of osimertinib and eventually establish a novel paradigm for clinical use of EGFR TKIs.

Keywords: EGFR resistance pulse-dose

MA 12.07 ADJUSTED INDIRECT COMPARISON OF OSIMERTINIB TO CHEMOTHERAPY IN NSCLC PATIENTS WITH EGFRM T790M WHO PROGRESSED AFTER EGFR-TKI

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Background: Osimertinib was granted conditional marketing authorization from the EMA and accelerated approval by the FDA based on single-arm trial (SAT) data. Subsequent full FDA approval was supported by the RCT AURA3 (NCT02151981) and based on superior progression-free survival (PFS) of osimertinib versus platinum-based doublet chemotherapy (PDC) for patients with epidermal growth factor receptor (EGFRm) T790M-positive non-small-cell lung cancer (NSCLC). Accelerated and conditional approval coupled with a large treatment effect led to increased treatment switching post-progression from the control arm to the intervention arm in the RCT as clinicians and patients demanded the new treatment. This will confound analysis of overall survival (OS) benefit in the RCT. Adjusted indirect comparison from other sources can offer a robust analysis of OS without confounding owing to treatment switching and difference in subsequent therapies post-progression. **Method:** Recent SAT data (data cut-off, 1 November 2016) for osimertinib were provided by the AURA (NCT01802632) and AURA2 (NCT02094261) studies (N=405). Data for PDC were provided for a subgroup of the control arm of an RCT, IMPRESS (NCT01544179), which comprised patients with centrally confirmed EGFRm T790M-positive NSCLC whose prior treatment with an EGFRm TKI had failed and were subsequently treated with PDC (N=61). A propensity score (PS) approach was used to adjust for differences in baseline demographics and disease characteristics. Baseline characteristics of both groups were compared using statistical tests. **Result:** Following estimation of PS for each patient and adjustment for heterogeneity across the groups by matching, 288 patients from the osimertinib group and 53 patients from the PDC group were retained for analysis. Osimertinib demonstrated a statistically significant improvement in median PFS of 10.9 months versus 5.3 months for PDC (HR 0.28, 95% CI 0.19 to 0.41, P<0.0001), which was consistent with the gain in PFS from the RCT AURA3 (10.1 months versus 4.4 months; HR 0.30, 95% CI 0.23 to 0.41, P<0.001), and a statistically significant improvement in OS (HR 0.41, 95% CI 0.27 to 0.62, P<0.0001). Median OS for osimertinib was not reached and was 14.1 months for PDC. **Conclusion:** The indirect comparison estimated a statistically significant improvement in PFS and OS with osimertinib compared with PDC. The PFS benefit was consistent with that of the confirmatory RCT. The combined evidence from RCT data and indirect comparisons described may bridge the potential gap and confounding in evidence for OS produced by subsequent treatments after first progression in the RCT.

Keywords: adjusted indirect comparison, NSCLC, osimertinib

MA 12.09 EGFR T790M CO-EXIST WITH SENSITIVE MUTATION IN THE SAME CELL GROUP IN LUNG ADENOCARCINOMA PATIENTS

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Background: EGFR TKI therapy has improved lung adenocarcinoma patients' prognosis tremendously, but almost all of the patients inevitably develop acquired resistance, and EGFR T790M mutation is the major contributors. T790M restores the EGFR tyrosine kinase domain affinity to ATP, and therefore gefitinib is displaced from the binding pocket, and the 'driving' signal for proliferation is switched on again. Previous work has shown that after TKI therapy, lung adenocarcinoma patients kept the sensitive mutation and acquired resistance mutation simultaneously by sequencing methods or in vitro cell line experiments. Whether the two different

type mutations are in the same cell group or in two different cell groups is unknown. None of them has observed what was happening in the tumor cells after TKI therapy. **Method:** RNA in situ hybridization methods was employed to examined EGFR T790M and L858R mutation in lung adenocarcinoma cancer tissues which was obtained before and after TKI therapy. EGFR expression was examined by immunohistochemistry. EGFR mutation were detected by ARMS PCR methods. **Result:** Twenty five patients were enrolled in this study which were divided into 3 groups. **Group 1**: 5 patients who had concurrent primary T790M and sensitive EGFR mutation. **Group 2**: 14 patients who acquired T790M mutation after receiving TKI therapy. Among them, 6 patients had biopsy tissues before and after TKI therapy. 8 patients only own tissues after TKI therapy. **Group 3**: 6 patients who had sensitive EGFR mutation and received TKI therapy, but re-biopsy tissues didn't had EGFR T790M. We found that the results of RNA ISH and ARMS PCR methods was identical in the majority of the examined tissues. Only one repeated biopsy tissue didn't identify EGFR T790M after TKI therapy by PCR in group 3, while the RNA ISH method detected T790M in this tissue which contain only 150 tumor cells. In the serial cut slides, we observed that T790M and L858R mutations were in the same cell group, not only in the primary resistance cases, but also in the acquired resistance cases. For the two cases which had tissues available after receiving third generation TKI therapy, we observed that T790M disappeared in the repeated biopsy specimen, leaving the sensitive mutation which existed from the beginning. **Conclusion:** In the primary and acquired resistance tissues, EGFR sensitive mutation and T790M co-exist in the same cell groups. EGFR sensitive mutation is a trunk and drive mutation, while T790M is a passenger mutation during the treatment process by TKI therapy.

Keywords: EGFR, T790M, L858R

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MA 12.10 CLINICAL UTILITY OF PLASMA EGFR T790M MUTATION DETECTION IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS ACCORDING TO RECIST CRITERIA

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Background: Circulating tumor DNA (ctDNA) has emerged as a specific and sensitive blood based biomarker for detection of several mutations in non–small cell lung cancer (NSCLC). Other clinical applications for ctDNA include molecular assessment of patients at diagnosis and serial (real-time) monitoring of biomarker status or the development of resistance mutations. **Method:** Eighty patients with advanced NSCLC who either (Group 1) had a new diagnosis or (Group 2) had developed acquired resistance to an EGFR kinase inhibitor were analyzed with highly sensitive Biocept, Inc. TargetSelector™ Real Time PCR based plasma assays genotyping for the detection of EGFR mutations L858R, Del19 and T790M. In addition, group 1 was analyzed for KRAS, BRAF, ROS1 and ALK and circulating tumor cells (CTCs) before and after TKI treatment. **Result:** Our results showed concordance rates of EGFR, KRAS and ALK mutations for up to 90% between the tissue and blood samples in newly diagnosed patients (Group 1). Paired analysis of mutations status monitoring in this group (P= 0.016) showed that the pattern of mutant ctDNA and CTCs changed in response to systemic therapy in 83% of the cases (Partial response or disease progression; R2=0.808). Plasma ctDNA analysis of multiple mutations showed that 40% of patients had at least one more mutation besides the one detected in tissue biopsy; 28% of EGFR tissue positive patients also had a KRAS mutation. In addition, 75% of KRAS positive patients had a BRAF mutation. These results demonstrate that plasma ctDNA analysis may even detect mutations missed by standard tissue genotyping due to tissue heterogeneity. Plasma EGFR T790M mutation was analyzed in patients with clinical progression to TKI inhibitors. Considering the RECIST criteria, 58% of progressive disease, 10% of stable disease and 16% of partial response patients were positive for T790M. According to metastatic disease type (locoregional, oligometastatic, polimetastatic), the T790M mutation was found on 64.3% of polimetastatic patients, 30.8% of oligometastatic patients and 17.6% of loco-regional patients. **Conclusion:** TargetSelector™ ctDNA assay is capable of rapidly detecting EGFR, KRAS and ALK mutations and is highly concordant with mutations present in tumor tissue with the robustness needed for real world testing to identify patients who progress on first line TKI therapy as well as for real-time monitoring of patients' clinical status. Our findings highlight the importance of the RECIST criteria to define the progressive disease and determine the right moment to test for T790M mutation regardless the metastatic disease type.

Keywords: ctDNA, NSCLC, TKI resistance

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MA 12.11 THE ALTERATION OF T790M PREVALENCE BETWEEN 19 DELETIONS AND L858R IN NSCLC AFTER EGFR-TKIS THERAPY, A META-ANALYSIS

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Background: Pre-treatment EGFR T790M mutation is more likely to coexist with L858R mutation than with exon 19 deletions (19del) in NSCLC. However, EGFR-TKIs might alter this status. We sought to compare the prevalence of T790M upon acquired resistance to EGFR-TKIs between 19del and L858R by assembling all existed data. **Method:** Electronic databases were comprehensively searched for eligible studies. The primary endpoint was the odds ratio (OR) of T790M mutation in NSCLC co-existing with L858R mutation and 19del upon resistance to first-generation EGFR-TKIs. A random effects model was used. Stratified analysis was performed based on study type (retrospective and prospective), race (Asians and Caucasians) and sample type (tissue and plasma). **Result:** A total of 25 studies involving 1,770 patients were included. The overall T790M existent rate was 45.25%. Post-resistance T790M was more frequent in 19del than in L858R mutated patients (53% vs. 36%; OR 1.87; p=0.00). All outcomes of subgroup and overall analyses were similar. In contrast, we re-analyzed the previous meta-analysis, finding that the pooled rate of pretreatment T790M was 14% and 22% in 19del and L858R respectively (OR 0.59; p<0.01). The increase of T790M rate was 2.79-fold in 19del and only 0.63-fold in L858R in the course of EGFR-TKIs therapy. **Conclusion:** Opposite to the situation of de novo T790M, it was observed that T790M was more frequent in exon 19del than in L858R among EGFR-TKI resistant acquired patients. The difference in T790M alteration between 19del and L858R encourages development of specific resistance mechanism detection or treatment strategies.

Keywords: 19del, T790M, L858R

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 13.01 CLINICAL AND PATHOLOGICAL VARIABLES INFLUENCING NONINVASIVE DETECTION OF EARLY STAGE LUNG CANCER USING CIRCULATING TUMOR DNA

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Background: Analysis of circulating tumor DNA (ctDNA) represents a potential strategy for the early detection of lung cancer. Despite significant interest, few studies have evaluated ctDNA levels in early stage lung cancer patients and the feasibility of ctDNA-based screening remains unclear. **Method:** We applied lung cancer-focused Cancer Personalized Profiling by deep Sequencing (CAPP-Seq) to assess ctDNA levels in 55 localized lung cancer patients treated with curative intent (stage I: n=22, stage II: n=7, stage III: n=26) and 50 healthy controls. Histological subtypes included: adenocarcinoma (n=30), squamous cell carcinoma (n=19), NSCLC NOS (n=4), and small cell lung cancer (n=2). Sensitivity and specificity of ctDNA detection were evaluated in all patients and in a subset of NSCLC patients with node negative (N0) stage I-II disease. Additionally, for patients with stage I adenocarcinoma in whom ctDNA was not detectable using the standard population-based CAPP-Seq approach, we designed personalized CAPP-Seq assays covering a median of 320 mutations/patient based on tumor exome sequencing from the respective patients. **Result:** We detected ctDNA in the pre-treatment plasma of 43/55 (78%) patients at a median allele fraction (AF) of 0.48% (range: 0.004%-26.1%). ROC analysis revealed an area under curve of 0.91, with sensitivity and specificity of 78% and 98%, respectively. Among patients with non-adenocarcinoma histologies, 92% (23/25) had detectable ctDNA (median AF: 0.90%), compared to 67% of patients with adenocarcinoma (20/30; median AF: 0.23%; P=0.046). However, tumor volumes were significantly smaller in adenocarcinomas (P=0.01) and in multivariate analysis ctDNA detection was significantly associated with tumor volume (P=0.01) but not histological subtype (P=0.16). In N0 stage I-II NSCLC patients (n=22), ctDNA was detected in 64% of patients (7/14 adeno vs 7/8 non-adeno) with a specificity of 98% and median AF of 0.022% (median AF of 0.018% vs 0.030% in adeno vs non-adeno patients, respectively). Using personalized CAPP-Seq assays, we detected ctDNA in 3/4 patients with stage I adenocarcinoma in whom ctDNA was not detected using our standard lung-cancer focused CAPP-Seq assay. In these 3 patients, tumor volumes ranged from 11.6-14.7 mL and the ctDNA AF ranged from 0.0014%-0.003%. Taken together, we detected ctDNA in 17/22 (77%) N0 stage I-II tumors. **Conclusion:** These data suggest tumor volume is a stronger determinant of ctDNA levels than histology in localized lung cancers. Additionally, our findings suggest that the majority of localized

lung cancers shed ctDNA and that ultra-sensitive assays will be required for early detection of lung cancer using ctDNA

Keywords: ctDNA, Screening, Early Detection

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 13.02 COMPREHENSIVE GENETIC ANALYSIS RELATED TO PD-L1 EXPRESSION IN EARLY-STAGE LUNG SQUAMOUS CELL CARCINOMA

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Background: Recently, anti PD-1/PD-L1 immunotherapies have yielded promising outcomes in advanced squamous NSCLC. Several studies have suggested that tumor PD-L1 protein expression status might correlate with outcome and response to treatment. The aim of this study is to identify mRNA gene signatures and microRNAs associated with tumor PD-L1 expression in early-stage lung squamous cell carcinoma (SCC). **Method:** Early stage (I-II) SCC resected patient tumors were collected from 6 cancer centers as part of the SPECS II program. Gene expression profiling was performed on the specimens. PD-L1 protein expression was evaluated by immunohistochemistry on SCC FFPE tissue using the Dako 22C3 PD-L1 antibody. The tumor proportion score (TPS) for PD-L1 protein expression was compared with comprehensive clinicopathological, mRNA and miRNA data. **Result:** The prevalence of PD-L1 expression in this cohort of 255 Stage I-II SCC patients was 46.7% with a TPS cutoff of ≥ 1%, and 9.8% with a cutoff of ≥ 50%. Among 202 cases with available clinical and expression data, no significant association was observed between PD-L1 expression and clinical outcome. We identified a 12-gene signature from mRNA microarray using the Minimax Concave Penalty (MCP) regression method with an AUC of 0.92 at ≥ 5% TPS cutoff. A subset of 138 miRNAs was shown to be significantly differentially expressed between PD-L1 positive and PD-L1 negative groups at false discovery rate (FDR) of 0.05 with TPS cutoffs of ≥ 1%, ≥ 5% and ≥ 10%. No miRNAs were found to be significantly differentially expressed between the groups using a TPS cutoff of ≥ 50%. Gene Set Enrichment Analysis (GSEA) identified two pathways with gene sets that were significantly enriched (FDR < 0.05) in the PD-L1 negative group. No significant association was found between tumor mutation burden and PD-L1 expression level. **Conclusion:** PD-L1 expression prevalence is lower in early-stage lung SCC than in advanced NSCLC. No significant association was found between PD-L1 expression and prognosis in this cohort. Both mRNA gene signatures and miRNAs were identified to be predictive of PD-L1 expression. Through GSEA, two distinct gene sets were identified with expression correlated to PD-L1, one comprising genes related to ovary and another related to collagens and extracellular matrix (ECM). No significant association was found between tumor mutation burden and PD-L1 expression level. Following validation, these predictive signatures could be used to select patients with positive PD-L1 expression who may benefit from immunotherapy.

Keywords: PD-L1, gene signatures, early stage lung squamous cell carcinoma

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
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MA 13.03 QUANTITATIVE SPATIAL PROFILING OF PD-1/PD-L1 INTERACTION PREDICTS RESPONSE TO ADJUVANT CHEMOTHERAPY NON–SMALL-CELL LUNG CANCER

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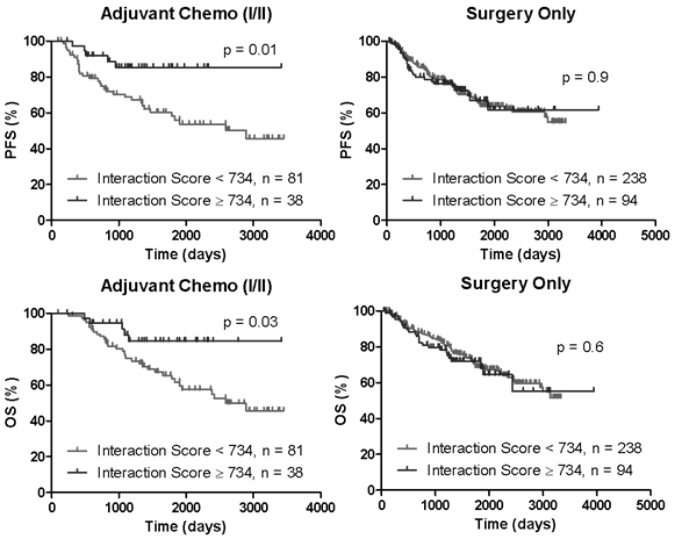
Background: Adjuvant chemotherapy (ACT) for ES-NSCLC has a modest improvement in survival but it is often associated with serious adverse effects. Thus, identifying subgroups of ES-NSCLC patients who may benefit from ACT is of high clinical relevance. We evaluated the prognostic and predictive role of quantitative spatial profiling of PD-1/PD-L1 interaction in the tumor cells of ES-NSCLC patients. **Method:** 451 whole tissue sections of formalin-fixed, paraffin embedded surgical resection specimens from ES-NSCLC patients with/without ACT were tested with a multiplexed fluorescence immunohistochemistry assay to detect PD-1, PD-L1, cytokeratin and DAPI labeling. Fluorescence Images were acquired on the Perkin Elmer Vectra platform and analyzed with AQUA® algorithms to determine the percent positivity of each biomarker as well as the co-localization of PD-1 and PD-L1 (the Interaction Score). **Result:** High PD-1/PD-L1 Interaction Scores correlated with improved progression-free and overall survival for ES-NSCLC patients receiving ACT after surgery (p = 0.01) whereas no difference in survival was observed for patients who received surgery alone (p = 0.9) (Figure 1). Interestingly, the levels of PD-1 or PD-L1 alone did not demonstrate any difference in survival for surgery + ACT or surgery alone patient populations.



Conclusion: PD-1/PD-L1 Interaction Score is predictive of benefit from ACT in patients with ES-NSCLC. Future studies will determine if this tool can be used to select patients that may be spared chemotherapy without compromising outcome.

Keywords: Biomarkers, early stage non-small cell lung cancer, adjuvant chemotherapy

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
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MA 13.04 ADJUVANT SYSTEMIC THERAPY IN PATIENTS WITH EARLY-STAGE NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH STEREOTACTIC BODY RADIATION THERAPY

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Background: Stereotactic body radiation therapy (SBRT) is currently the standard of care for inoperable patients with early stage non-small cell lung cancer (NSCLC). Despite this, ≈20% will relapse at 2 years. While adjuvant chemotherapy is recommended for surgically resected patients with early stage NSCLC (IB-IIIA), data on the role of adjuvant systemic therapy following SBRT for early stage NSCLC are sparse. The goal of this study was to evaluate the role of adjuvant chemotherapy following SBRT in early-stage, inoperable NSCLC. **Method:** Adults diagnosed with early-stage (clinical stage I and II) between the years of 2004 and 2013 were identified from the National Cancer Database (NCDB). Variables abstracted included: age, gender, clinical stage, race, comorbidity, insurance status, treating facility, treatment received and survival. Chi-square tests were used to compare clinical characteristics by therapy type. Kaplan-Meier, Cox regression, and propensity score analyses were employed for survival analyses. **Result:** Data from 12,414 patients with early-stage NSCLC were analyzed. Of these, 75.6% and 25.4% had clinical stage I and II disease, respectively. A total of 9,164 (73.6%) patients received SBRT alone and 3,268 (26.4%) had SBRT followed by chemotherapy. Among patients with clinical stage I, 83.5% received SBRT alone and 16.5% received SBRT followed by chemotherapy. Among those with clinical stage II, 43% received SBRT alone while 57% received SBRT followed by systemic therapy. On multivariate analysis, increasing age, male gender and stage II disease were associated with worse overall survival (OS). There was evidence of a clinical stage by treatment interaction (p <0.001). When treatment effect was analyzed by stage after adjusting for age and gender, patients with stage I treated with SBRT alone had a better median OS, 26.2 months compared to 22.4 months in the combined arm (HR=0.78; p<0.001; CI: 0.73-0.83). In contrast, among patients with stage II NSCLC, median OS was 15 months in the SBRT compared to 20.2 months in the combined group (HR=1.3; p<0.001; CI: 1.22-1.44). **Conclusion:** SBRT should be the sole modality treatment for patients with inoperable stage I NSCLC. However, patients with stage II disease appear to benefit from adjuvant chemotherapy. Randomized trials are needed in this area to answer this question conclusively.

Keywords: non-small cell lung cancer (NSCLC), stereotactic body radiation therapy (SBRT), adjuvant chemotherapy

MA 13.06 NEW RISK FACTORS FOR OVERALL SURVIVAL AFTER SBRT IN EARLY STAGE NSCLC: A ROLE OF RT PLAN OPTIMIZATION

F. Kong[1], Y. Liu[2], H. Zhang[1], H. Yao[1], A. Cerra-Franco[1], K. Shiue[1], D. Vile[1], W. Wang[1], M. Langer[1], G. Watson[1], G. Bartlett[1], K. Diab[3], T. Birdas[4], T. Lautenschlaeger[1], J. Jin[1]

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Background: Stereotactic body radiation therapy (SBRT) provides over 90% local tumor control, is a treatment of choice in patients with early stage medically inoperable non-small cell lung cancer (NSCLC). However, long-term overall survival after SBRT remain suboptimal, with 5-year rates rendering less than 50%, which cannot be fully explained by comorbidity, distant tumor progression or commonly known toxicities. We hypothesize that doses of radiation to normal lung and heart contribute to poor survival in these patients. **Method:** Patients with T1-T2 NSCLC received more than 100 Gy BED and with retrievable RT plan were eligible. The primary endpoint was overall survival, calculated from the start of SBRT. Clinical factors included age, gender, race, tobacco history, respiratory and cardiovascular comorbidity, tumor lobar location, histology, T stage, gross tumor volume (GTV), planning target volume (PTV), and prescription dose. Heart and lung were contoured consistently by one radiation oncologist according to the RTOG atlas. Dosimetric factors of the total lung were computed with biocorrection of fractionation effect. **Result:** A total of 280 patients with T1-3N0 met criteria. The median follow-up were 47 months. The median survival time was 33 months (95% CI: 25-42 months). The 2-year, 3-year and 5-year survival rates were 63%, 53% and 45%, respectively. Univariate analysis demonstrated that age (HR=1.02, p=0.04), gender (HR=0.75 for female, p=0.07), tumor T stage (HR=1.3 for T2, 2.5 for T3, using T1 as the reference, p=0.10), GTV (HR=1.01, p<0.001), PTV (HR=1.01, p<0.001), mean lung dose (HR=1.2, p<0.001), V5 (HR=1.02, p=0.03), V10 (HR=1.03, p=0.01), V20 (HR=1.1, p<0.001) of total lung and mean heart dose (HR=1.001, p=0.029) were associated with survival probability. The median mean lung and heart doses were 4.1Gy (range 0.8-11.2) and 0.99 Gy (range 0.3-9.7), respectively. Presence of radiation pneumonitis was not significant (p>0.1). Multivariate analysis was not performed as the dosimetric factors were correlated with each other. Among the risk factors, lung dosimetric factors were most significant. Increase in dose or volume of lung was significantly associated with poorer overall survival. A 1 Gy increase in mean lung dose corresponded to a 12 % increase in the risk of death, or 5% reduction in 5-year survival. **Conclusion:** This study demonstrated at the first time that doses to lung and heart are significant for overall survival after SBRT, while radiation pneumonitis was not. This suggests that the suboptimal survival after SBRT may be improved with plan optimization. This data also challenges the current practice of toxicity based normal tissue dose tolerance policy.

Keywords: Heart Doses, SBRT, Mean Lung

MA 13.07 A RANDOMIZED TRIAL OF SABR VS CONVENTIONAL RADIOTHERAPY FOR INOPERABLE STAGE I NON-SMALL CELL LUNG CANCER: TROG 09.02 (CHISEL)

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Background: Although stereotactic ablative body radiotherapy (SABR) is now well established as a treatment for stage I non-small cell lung cancer (NSCLC), there is limited evidence that it is as or more effective than conventional fully fractionated radiotherapy (CRT). We conducted a randomized trial to determine if SABR results in longer time to local failure than CRT. **Method:** This was a multicentre trial of the Trans-Tasman Radiation Oncology Group (TROG) and Australasian Lung Cancer Trials Group, registration number NCT01014130. Patients were eligible if they had biopsy proven stage I (T1- T2a N0M0) NSCLC based on PET and were medically inoperable or refused surgery. Patients had to be performance status ECOG 0 or 1, and the tumor had to be at least 2 cm or more from the bifurcation of the lobar bronchus. Patients were randomized 2:1 to SABR (54 Gy in 3 fractions, or 48 Gy in 4 fractions, depending on proximity to the chest wall, to the isodose covering the PTV) or to CRT (66 Gy in 33 fractions or 50 Gy in 20 fractions). The primary objective was to compare time to local failure between arms. Assuming that the rate of local failure at 2 years would be 10% in patients randomized to SABR versus 30% in patients randomized to CRT, 100 patients were required. All living patients were followed for a minimum of 2 years. Analysis was based on the intention to treat principle. Funding: In Australia: Grant #1060822 was awarded through Cancer Australia. In New Zealand, The Cancer Society of New Zealand and the Genesis Oncology Trust. **Result:** Between 12/09 and 6/15, 101 patients were enrolled. There were 56 males and 45 females with a median age of 74 years (range 55-89), ECOG performance status – 28 were 0, 71 were 1 and 1 was 2. TNM stage was T1N0M0 in 71 and T2aN0M0 in 30. Sixty six patients were randomized to SABR and 35 patients to CRT. Patients randomized to SABR had superior freedom from local failure (HR = 0.29, 95% CI 0.130, 0.662, P=0.002) and longer overall survival (HR = 0.51, 95% CI 0.51, 0.911, P=0.020). Worst toxicities by arm were: CRT grade 3, 2 patients; SABR grade 4, 1 patient and grade 3, 9 patients. **Conclusion:** In patients with inoperable stage I NSCLC, compared with CRT, SABR resulted in superior freedom from local failure and was associated with an improvement in overall survival.

Keywords: phase III randomized trial, Stereotactic ablative body radiotherapy, stage I non-small cell lung cancer

MA 13.08 LONG TERM FOLLOW-UP ON NRG ONCOLOGY RTOG 0915 (NCCTG N0927): A RANDOMIZED PHASE II STUDY OF 2 SBRT SCHEDULES FOR LUNG CANCER

G. Videtic[1], R. Paulus[2], A. Singh[3], J. Chang[4], W. Parker[5], K. Olivier[6], R. Timmerman[7], R. Komaki[8], J. Urbanic[9], K. Stephans[1], S. Yom[10], C. Robinson[11], C. Belani[12], P. Iyengar[13], M. Ajlouni[14], D. Gopaul[15], S. Lele[3], R. Mcgarry[16], H. Choy[17], J. Bradley[18]

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Background: NRG Oncology RTOG 0915/NCCTG N0927 was a randomized lung stereotactic body radiotherapy (SBRT) trial of 34 Gy in 1 fraction (arm 1) versus 48 Gy in 4 fractions (arm 2) designed to select the better of the 2 regimens by comparing them at 1 year (yr): first by rates of pre-specified protocol-specified adverse events (psAEs), then by primary tumor control for each arm. 34 Gy emerged as the least toxic yet equally efficacious regimen. Herein, we update those results with long-term follow-up. **Method:** This phase II North American multicenter study of patients aged 18 yrs or older with medically inoperable non-small cell lung cancer with biopsy-proven peripheral (≥2 cm from the central bronchial tree) T1 or T2, N0 (clinically node negative by positron emission tomography), M0 tumors was designed to detect 1-yr psAEs rates >17% as primary endpoint. Primary tumor failure (PTF) (either infield or marginal failure) and local failure (either infield, marginal, or involved lobe failure) [with death without failure considered as a competing event]; overall survival (OS); disease-free survival (DFS) and progression-free survival (PFS) were secondary endpoints, but the study was not designed for statistical comparisons of these outcomes. The study opened in September 2009 and closed in March 2011. Updated data were analyzed through November 14, 2016. **Result:** Ninety four patients were accrued, with 86 eligible for analysis: 41 in arm 1 and 45 in arm 2, after 8 cases were excluded. Median follow-up time was 3.8 yrs for all patients, and 5.1 yrs for those alive at analysis. The grade 3 and higher treatment-related toxicity profile was unchanged since previous report, with specifically no new high grade chest wall or grade 5 events. Four of 48 Gy patients had subsequent grade 3 changes in spirometry since meeting the primary endpoint. Medians (in yrs) for 34 Gy and 48 Gy were: 4.1 vs. 4.0 for OS, and 2.6 vs. 2.8 for DFS, respectively. Five-yr outcomes as % (95% CI) for 34 Gy and 48 Gy were: PTF rate of 7.9 (2.0, 19.5) vs. 6.8 (1.7, 16.9); OS of 28.8 (15.4, 43.8) vs. 40.2 (24.9, 55.0); PFS of 19.1 (8.5, 33.0) vs. 31.8 (18.6, 45.9); and second primary rate of 15.5 (6.1, 28.9) vs. 13.3 (5.3, 25.1), respectively. Distant failure as the sole failure or a component of first failure was numerically higher in the 34 Gy arm (7 (46.7%)), but in the 48 Gy arm, rate of second primary development was higher (7 (43.8%)). Approximately 1/3 of patients' causes of death was unknown, and another 1/3 was related to causes other than cancer or treatment. **Conclusion:** No excess in late-appearing toxicity was seen in either arm. Primary tumor control rates at 5 yrs were similar by arm. Median survival times of 4 yrs for each arm suggest similar efficacy pending any larger studies appropriately powered to detect survival differences.

Keywords: SBRT dose/fractionation, medically inoperable early stage lung cancer, randomized phase II

MA 13.09 TOXICITY AND SECOND PRIMARY LUNG CANCERS IN LATE SURVIVORS FOLLOWING LUNG SBRT

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Background: There is a paucity of data on the long-term outcomes following lung SBRT. This impacts our understanding of late toxicity, relapse patterns and rates of second lung cancers. We report our multi-institutional outcomes of those who survived ≥5 years from lung SBRT treatment. **Method:** 1192 patients were treated

for primary non-small cell lung cancer, T1/2N0 from 5 international institutions. For those who survived ≥5 years from lung SBRT treatment details of patient factors, treatment and outcome factors were extracted from the multi-institutional database. All events were calculated from the end of radiotherapy. Local (LR), regional (RR), and distant metastases (DM) and toxicity events after 5 years are reported. New cases of metachronous lung cancers after 5 years are reported. Univariable analyses was performed to determine factors associated with survival ≥5 years. **Result:** Of 1192 patients there were 182 (14%) ≥5 year survivors. Only 52 (8%) survived ≥ 7 years and 2 (0.2%) ≥10 years. Those surviving ≥5 years were younger (74.3 vs 71.5 years; p<0.01) and had better FEV1 (55% vs 65%; p<0.01) than those that did not survive 5 years. The Charleston Comorbidity Score was 1.4 (0-12) vs 2.1 (0-7) (p<0.001) in those who survived < vs ≥5 years. Those who survived <5 years had a trend to larger tumors (2.4cm vs 2.3 cm; p=0.07). Of the 182 patients 23 (13%) were operable, 67 (37%) were <70 years old at treatment, 115 (63%) were ECOG 0-1 and 156 (86%) had peripheral tumor location at time of initial diagnosis. 84 (46.2%) were T1a, 60 (33%) T1b, 33 (18.1%) T2a and 5 (2.7%) T2b. After 5 years there were 13 new events of grade ≥ 2 toxicity. These toxicities were 4 grade 2 fatigue, 1 grade 2 rib fracture, 7 grade 2 chronic myositis and 1 patient with grade 2 chronic myositis and fatigue. In this 182 patient cohort, after 5 years, there were 3 local recurrences, 2 regional failures and 5 distant failures. After 5 years follow-up there were 22 (12%) new primary lung tumors in the 182 patients (and 20 had a subsequent lung SBRT treatment). **Conclusion:** Late survivors after SBRT require dedicated follow-up as they remain at risk for second lung cancer, tumor recurrence and toxicity. Second cancers in these late survivors can be considered for SBRT treatments.

Keywords: SBRT, survivorship, second primary tumors

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
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MA 13.11 CLINICAL SIGNIFICANCE OF LOBAR AND SEGMENTAL LYMPH NODE METASTASIS IN CT1N0M0 LUNG ADENOCARCINOMA

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Background: The regularity of intrapulmonary lobar and segmental lymph node (LSN) metastasis in cT1N0M0 stage lung adenocarcinoma remains unclear. Thus, segmentectomy with uncertain LSNs metastatic status remains a potential oncological risk. We aimed to facilitate more accurate determination of N staging and identification of more suitable cases for segmentectomy. **Method:** A prospective study was performed from March 2014 to March 2016. A total of 156 patients diagnosed with cT1N0M0 stage lung adenocarcinoma received lobectomy and mediastinal lymph node dissection. The intrapulmonary LSNs were dissected and classified as adjacent LSNs or isolated LSNs. The metastatic status of the LSNs together with the TNM stage were analyzed. A comparison of the metastatic probability of isolated LSNs was carried out considering imaging features, serum carcinoembryonic (CEA) levels, pathological subtypes, size of the lesions, and metastatic status of adjacent LSNs. **Result:** Among the 156 cases enrolled, 129 were confirmed as pN0, 21 as pN1, 5 as pN1+N2, and 1 as skip pN2. When the LSNs had not been dissected, the false negative rate for N staging was 5.1% (7/136). Patients with a pure ground-glass-nodule had a lower isolated LSN metastasis rate (p = 0.027). Non-lepidic predominant invasive adenocarcinoma (p = 0.003), the cT1c group (p = 0.020), and those with adjacent LSN metastasis (p < 0.001) were detected with a higher isolated LSN metastasis rate. No significant difference in isolated LSN metastasis rate was found between groups with different serum CEA levels (p = 0.121). **Conclusion:** Dissection of intrapulmonary LSNs reduces the false negative rate of lymph node metastasis. Partial solid or solid lung adenocarcinoma, non-lepidic predominant invasive adenocarcinoma, and cT1c lung adenocarcinoma might not be suitable for segmentectomy. The lymph node sampling area during segmentectomy should include adjacent LSNs of the target segment. When metastasis to the adjacent LSNs is confirmed by fast frozen pathology, segmentectomy would not be suitable.

Keywords: segmentectomy, lung adenocarcinoma, lymph node

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
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MA 13.12 WEDGE RESECTION AND SEGMENTECTOMY ARE ASSOCIATED WITH COMPARABLE OUTCOMES FOR PATIENTS WITH LESS THAN 2CM NON-SMALL CELL LUNG CANCER

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Background: Sublobar resection is widespread for selected patients with small sized non-small cell lung cancer (NSCLC). Segmentectomy has been considered superior to wedge resection, however well-balanced comparative studies are lacking. We compared oncologic outcomes between wedge resection and segmentectomy for patients with less than 2cm of NSCLC according to parenchymal safety margin **Method:** A retrospective review of a prospective database was performed (2003-2015), excluding patients with poor lung function (FEV_1 or DLCO <50%), neoadjuvant therapy, previous lobar resection for primary lung cancer, and multiple primary other cancer. Demographic, clinical, and pathological data were reviewed. Overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method and differences compared using log-rank test. Lymph nodes (LN) were evaluated preoperatively by PET/CT and EBUS-FNA if chest CT showed more than 1cm of LN short diameter **Result:** Two hundred nighty-six patients met our selection criteria, including wedge resection (W) in 188 and segmentectomy (S) in 108. There was no difference in smoking history, comorbidity, pulmonary reserve, cell type, and postoperative complication rate. All enrolled patients had clinically negative LN and 3 patients (1 in W, 2 in S) had pathologically node positive LN. The segmentectomy had more likely to have larger tumor (1.26 vs 1.36, p=0.045), more total nodes resected (1 vs 6, p<0.001), more distance of safety margin (median 0.5 vs 1.5, p<0.001). There was no statistical difference in OS (p=0.897), CSS (p=0.844), and RFS (p=0.763) between two groups. Patients were stratified by safety margin into ≤ 5mm in 118 (w101 vs s17), 5~10mm in 65 (w48 vs s17), 11~15mm in 45 (w23 vs s22), 16~20mm in 23 (w9 vs s14), and >20mm in 45 (w7 vs s38). Recurrence was developed in 8 (7%, w5 vs s3), 2 (3%, w2 vs s0), 1 (2%, s1), 0 (0%), 1 (2%, s1) of each safety margin. There was no significant difference of RFS between wedge resection and segmentectomy in each safety margin **Conclusion:** Wedge resection and segmentectomy showed comparable oncologic outcomes for carefully staged less than 2cm NSCLC patients. After thorough preoperative LN evaluation, wedge resection of sufficient safety margin is good surgical option

Keywords: sublobar resection, safety margin, NSCLC

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
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MA 13.13 SPREAD THROUGH AIR SPACES IS A PROGNOSTIC FACTOR IN WEDGE RESECTION OF NON-SMALL CELL LUNG CANCER

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Background: Spread through air spaces (STAS), defined as "micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma" (Travis WD, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 2015), has been recognized as a pattern of tumor invasiveness. Because complete lymph node dissection and sufficient surgical margin lengths are difficult to obtain, wedge resection is associated with worse surgical outcomes than those of lobectomy. Because of the insufficient margin length associated with wedge resection, we speculated that STAS has a prognostic impact in wedge resection cases compared with segmentectomy cases. The aim of this study was to clarify the prognostic impact of STAS in patients with non-small cell lung cancer (NSCLC) who underwent wedge resection. **Method:** This was a retrospective study using our prospectively collected institutional database, established in May 2004. From May 2004 to May 2017, 1071 patients with NSCLC underwent complete resection. After excluding patients with pure ground glass opacity or multiple lung cancers and those who underwent lobectomy or preoperative therapy, we evaluated 196 patients with clinical stage IA cancer who underwent segmentectomy or wedge resection. TNM staging was performed according to the seventh edition. We assessed the prognostic impact of STAS on stage IA lung cancer cases who underwent wedge resection compared with segmentectomy. **Result:** Segmentectomy was performed in 110 patients and wedge resection in 86. The wedge resection cases were older (p<0.001) and had a higher CEA level (p=0.023). The frequencies of STAS were 14.5% and 18.6% in the segmentectomy and wedge resection cases, respectively (p=0.447). STAS was a significant prognostic factor for overall survival in the wedge resection cases on univariate (p=0.003) and multivariate (p=0.013) analyses, but it was not significant in the segmentectomy cases (p=0.597). STAS was a significant prognostic factor for disease-free survival in the wedge resection cases on univariate (p<0.001) and multivariate (p<0.001) analyses, but this was not the case in the segmentectomy cases (p=0.108). STAS was a significant prognostic factor for the recurrence-free rate in the wedge resection cases on univariate (p<0.001) and multivariate (p<0.001) analyses, but it was not significant in the segmentectomy cases (p=0.205). **Conclusion:** STAS is a prognosticator of poor survival outcomes in NSCLC patients who underwent wedge resection, but not in those who underwent segmentectomy. We speculate that NSCLC with STAS tends to have invasive characteristics, and wedge resection is not sufficient to improve survival outcomes in such patients.

Keywords: Spread Through Air Spaces, lung cancer, wedge resection

MA 13 NEW INSIGHTS OF DIAGNOSIS AND UPDATE OF TREATMENT
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MA 13.14 SURGICAL OUTCOMES AND SURVIVAL ANALYSIS FOLLOWING SECOND PULMONARY RESECTION FOR NON-SMALL CELL LUNG CANCER

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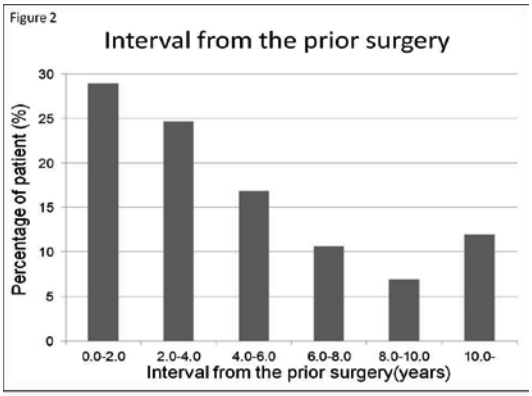
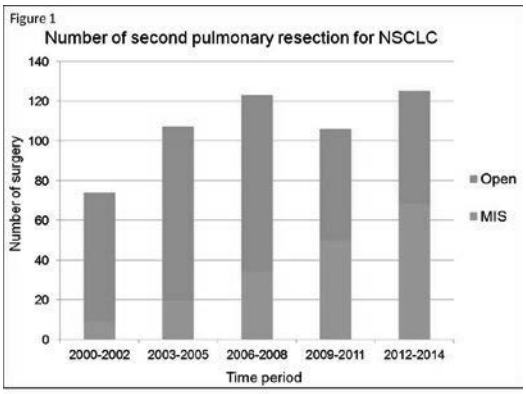
Background: The early detection and improved survival of resected non-small cell

lung cancer (NSCLC) may increase the number of patients who eventually undergo subsequent pulmonary resection. We investigated the surgical outcomes and survival of patients following second and third pulmonary resections for NSCLC. **Method:** Patients who underwent second or third pulmonary resections without induction therapy for synchronous or metachronous NSCLC (511 patients, 535 procedures, 2000-2014) were included in the analysis. **Result:** Among 535 operations, 361 (67%) were sublobar resection and 103 (19%) were performed by minimally invasive approach, with the proportion of minimally-invasive procedures increasing in recent years (Fig. 1). The majority of re-resections were performed within 4 years of the previous resection (Fig. 2). Risk regression analysis demonstrated that predicted postoperative (ppo) FEV1 ($p<0.001$) and same side operation ($p=0.002$) were independent risk factors for severe complications (CTCAE grade ≧ 3; N=45). Multivariable Cox regression analysis revealed that age at subsequent surgery, male sex, ppoDLCO, interval from prior surgery, and tumor stage were independently associated with overall survival. **Conclusion:** In this large cohort of pulmonary re-resections for NSCLC, predicted postoperative pulmonary function tests were indictive of major complications and overall survival.





Keywords: second primary lung cancer, surgery, complication, prognosis

MA 14 DIAGNOSTIC RADIOLOGY, STAGING AND SCREENING FOR LUNG CANCER I
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 14.01 INFLUENCE OF EARLY LUNG CANCER SCREENING PROGRAMME ON TREATED PATIENTS' PROFILE AND ACTIVITY OF THORACIC SURGERY DEPARTMENT

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Background: The objective of the study was to compare the program of early detection of lung cancer by low-dose computed tomography scan with other groups of lung cancer patients who live in the area where such a program is carried out. The study was based on the materials of one thoracic surgery clinic and the screening was carried out on the inhabitants of one district city. The objective of the study was implemented by analyzing selected factors that impact the activities of surgery ward. The study was retrospective. **Method:** The patients were divided into three groups. Group 1a - 52 patients operated due to primary lung cancer which were detected during the screening. Group 1b - 87 patients operated for primary lung cancer during the screening, but who did not participate in the screening program. Group 2 - 103 patients operated before the commencement of the screening. The analysis involved among others the factors described in the table below. For the statistics we utilised Statistica PL 2010 program. Non parametric Mann-Whitney U-test was used for not normally distributed data. Parametric t-Student test was used for normally distributed data and $p<0.05$ was considered significant. **Result:**

Significant differences among the groups						
		Group	Group	Group	Statistics	Statistics
	unit	**1a**	1b	2	p 1a/1b	p 1a/2
Patiens	n	**52**	87	103	-	-
Adenocarcinoma	%	**58**	34	38	0.01	0.03
G2 grading	%	**44**	28	24	0.03	0.02
Tumour volume	cm^3	**8**	21	20	0.004	0.01
T1 factor	%	**54**	28	34	0.004	0.02
IA stage	%	**50**	24	32	0.003	0.02
Right side	%	**73**	63	59	ns	0.05
Lobectomy	%	**75**	53	56	0.02	0.04
Operation time	min	**129**	114	112	0.02	0.007

Conclusion: In the screening 1a group adenocarcinoma was detected more frequently, as a smaller tumour, at an earlier stage, with the prevalent G2 factor and located mainly on the right side. In the group 1a lobectomy was performed more frequently, than the other groups. The duration of surgery of 1a group was longer than the other groups due to more often intraoperative assessment use. There were no differences according to postoperative complications and deaths among all groups. Our screening program detectes lung cancer at earlier stage and offers faster definitive surgical treatment, probably improving 5 year survival, what is being evaluated now.

Keywords: lung cancer screening, Low dose computed tomography, Thoracic Surgery

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MA 14.02 SIMULATION OF THE FOUR ROUNDS OF NELSON LUNG CANCER SCREENING TRIAGE ALGORITHM

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Background: Imaging screening programs are designed for specific eligibility criteria and technologies. Effectiveness of these programs is precisely known only after monitoring large populations over a long period. Ensuring generalizability of screening programs is required when targeting a population which is different from the original one tested or when modifying involved technologies. The NELSON screening program is a lung cancer triage process featuring four rounds of variable intervals (1, 2 and 2.5 years). Each screening round classifies the nodule's malignancy according to the nodule's volume, growth and volume doubling time, using CT. The aim of our study was to assess by simulation the influence of variable precision of measurement on the robustness of NELSON's diagnostic algorithm. **Method:** We simulated 10^6 nodules using a Chi^2 distribution for nodule size [3mm; 20mm], an inverse Chi^2 distribution of growing. 2.1% of nodules were malignant (true positive). We tested several distributions of measurement error using a zero-mean Gaussian distribution and a standard deviation (SD) ranging [0%; 20%]. We reported positive and negative predictive values (PPV, NPV) at each round. **Result:** After round 4, we found that NPV decreased with increasing measurement error from 100% to 99.89%, PPV decreased from 100% to 29.6%.

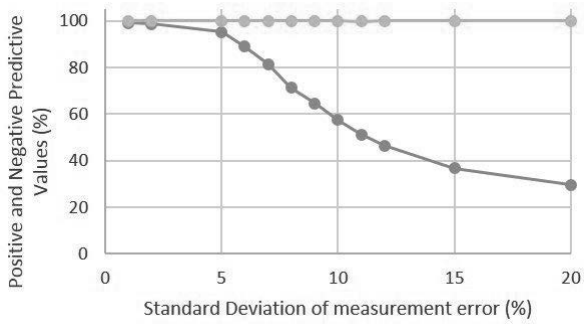

Figure 1: Detection performances of NELSON's triage algorithm depending on measurement error. As shown in this graph, an increase of SD leads to a decrease of PPV (gray curve) and has almost no impact on NPV (yellow curve). **Conclusion:** Increasing measurement error of nodules significantly degrades the positive predictive value of NELSON's diagnostic algorithm in identifying malignant pulmonary nodules, whereas the negative predictive value remained stable. We confirmed the efficacy of the successive rounds when measurement error is larger than 5%; however, the algorithm could be improved for larger measurement errors. Simulations could help us to assess better strategies lung in screening studies.

Keywords: simulation, nelson algorithm, Screening

MA 14.03 LUNG CANCER RISK SCORE ANALYSIS USING PLASMA MICRORNA PROFILES

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Background: There is a need for more accurate and minimally invasive methods to screen high risk populations and diagnose lung cancer during its asymptomatic early stages. microRNAs (miRNAs) are small, non-coding strands of RNA that are shown to lead to carcinogenesis when dysregulated. miRNAs, expressed in a tissue specific manner, are stable and detectable in small quantities, thus are promising candidates for biomarkers. Through the use of previous miRNA profiling done in our group, we aim to validate this panel in a large sample size of non-small cell lung cancers (NSCLC) using miRNAs 21, 155, 210, and 223 in blood plasma to determine if this miRNA panel is able to differentiate lung cancer cases from controls. **Method:** A nested case-control study of 64 patients with stage I/II NSCLC and 110 healthy controls with similar age, gender, and smoking history was performed. Plasma was provided by Conservant Bio, Lung Cancer Biospecimen Resource Network, and Alberta's Tomorrow Project. miRNA was isolated using the Qiagen miRNeasy serum/plasma kit. miR-21, 155, 210, and 223 were quantified via RT-PCR using C. elegans miR-39 as a spiked-in endogenous control. Binary logistic regression (SPSS version 15) was performed to develop a combined risk score of the patients' risk of having lung cancer. Receiver operating curve (ROC) analysis was used to determine risk category cut-off values based on the sensitivity and specificity. Plasma samples were taken 4-7 months post resection and also analyzed and compared to pre-operative samples and controls. **Result:** The cases and controls showed similar age ranges (mean=61.97, SD=7.76; mean=61.38, SD=7.95) respectively. Smoking history was higher in the cases (mean=51.5, SD=29.46) than controls (mean=30.98, SD=10.84). The combined score was dichotomized at -0.4169 into high and low risk categories (sensitivity=81%, specificity=41%, AUC=72.3%), the cases pre-operative samples compared to healthy controls was significantly different (odds ratio=3, p-value=0.003, 95% C.I.=[1.440,6.249]). For the cases post-operative samples compared to healthy controls, the combined score was dichotomized at -0.3255 (sensitivity=77%, specificity=41%, AUC=67%), also showing a significant difference (odds ratio=2.3, p-value=0.023, 95% C.I.=[1.120,4.621]). There is no significant difference in the combined risk score when comparing the pre-operative and post-operative NSCLC samples. **Conclusion:** Through binary logistic regression miRNA profiling has the potential to assist in screening the high-risk population for lung cancer. Used in conjunction with radiologic screening, this approach could allow early detection and treatment of disease while sparing patients unnecessary investigations and biopsies.

Keywords: miRNA, Biomarkers, Screening

MA 14.04 THERAPEUTIC RESPONSE ASSESSMENT OF NSCLC PATIENTS TREATED WITH APATINIB: A RADIOMICS APPROACH BASED ON CT TEXTURE FEATURES

L. Peng[1], Z. Hong[1], Y. Wang[1], X. Ye[1], X. Li[2], P. Pang[2], F. Chen[1], Q. Zhao[1]

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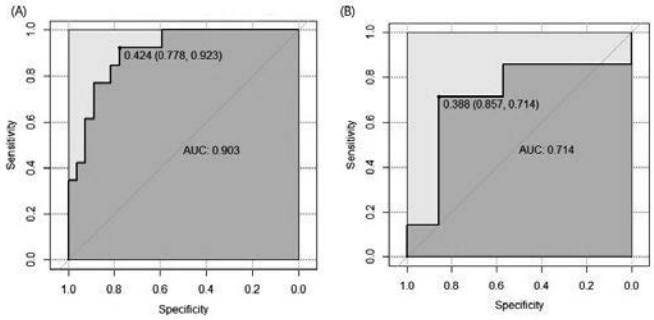
Background: Apatinib is a novel small molecular drug targeting vascular endothelial growth factor receptor-2 (VEGFR-2), which is currently being studied in multiple tumor types. The purpose of this study was to assess the treatment response in non-small cell lung cancer (NSCLC) patients enrolled in a clinical trial of apatinib according to the response evaluation criteria in solid tumors (RECIST) using non-contrast-enhanced computed tomography (CT) texture-based radiomics approach. **Method:** A total of 19 NSCLC patients from our single center participated in the currently undergoing multi-center phase III ANSWER study of apatinib (NCT 02332512). Patients were categorized as responders (CR and PR) and non-responders (SD and PD) according to RECIST criteria. Radiomic texture features were extracted from target lesions in post-therapy CT of NSCLC. Lasso regression was used to establish a model to discriminate between responders and non-responders. The performance of the model was assessed with ROC in both internal and independent validation cohorts. **Result:** Altogether, 108 CT scans were performed. Among them, 75 scans were randomly selected as internal validation group (70%), while the remaining 33 scans (30%) were identified as an independent validation group. Three hundred and eighty-four CT texture parameters were extracted and 21 out of 384 CT texture were finally selected for the model. The area under the curve (AUC) of ROC was 0.903 in the internal validation group, and that of the independent validation group was 0.714.



Conclusion: A radiomic discriminate model was built based on post-therapy CT texture features, which demonstrated a good performance in assessing the therapeutic response in NSCLC patients treated with apatinib.

Keywords: Apatinib, Radiomics, CT texture

MA 14.06 POPULATION BASED COHORT STUDY TO EVALUATE LUNG CANCER SCREENING USING LOW DOSE CT IN HITACHI CITY

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Background: In 1998, low-dose CT screening for lung cancer was introduced in Hitachi City, Japan. Based on time trend analysis, a significant reduction in lung cancer mortality was observed 4–8 years after introduction of CT screening. **Method:** To evaluate the effectiveness of lung cancer screening, we conducted a cohort study for CT screening participants and X-ray screening participants among Hitachi residents. Citizens aged 50 to 75 who underwent CT screening from 1998-2006 were defined as the CT group, and those who underwent X-ray screening during the same period, but did not receive CT screening throughout the follow-up period were defined as the X-ray group. We investigated lung cancer mortality and all-cause mortality of both groups from the first lung cancer screening of the subject to the end of 2012 using residence registry, the regional cancer registry, and national death statistics. **Result:** From the CT group (17,935 cases, 9,790 men and 8,145 women), 273 cases of lung cancer (1.5%), 72 cases of lung cancer death (0.4%), and 885 cases of all-cause mortality (4.9%) were observed. On the other hand, 164 cases (1.1%) of lung cancer, 80 cases (0.5%) of lung cancer death, and 1,188 cases (7.6%) of all-cause mortality were observed in the X-ray group (15,548 cases, 6,526 men and 9,022 women). The hazard ratios of the CT group to the X-ray group adjusted for sex, age, and smoking history were 0.49 for lung cancer mortality and 0.57 for all-cause mortality. **Conclusion:** Low dose CT screening participants exhibited a 51% reduction in lung cancer mortality during the observation period compared with the X-ray group. Although all-cause mortality also decreased by 43% in the CT group, the decrease in proportion of lung cancer deaths was greater.

Keywords: low-dose CT screening, cohort study, lung cancer mortality

MA 14.07 RANDOMIZED LUNG CANCER SCREENING WITH LOW-DOSE CT IN CHINA: A SPECIFIC RISK-BASED SCREENING FOR CHINESE POPULATION

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Shanghai Chest Hospital, Shanghai/CN

Background: The purpose of the present study was to investigate whether low-dose computed tomography (LDCT) screening is capable of enhancing the detection rate of early-stage lung cancer and reducing lung cancer mortality rate in China, thus determining the appropriate duration of screening and identifying additional risk factors for lung cancers in Chinese population. **Method:** A randomized lung cancer screening study was performed with participants aged 45 to 70 years old who had at least one high-risk factor as follows: 1) a history of cigarette smoking ≥20 pack-years; former smokers who had quit within the past 15 years; 2) cancer history in immediate family members; 3) personal cancer history; 4) professional exposure to carcinogens (asbestos, dust or radiation); 5) long history of passive smoking; or 6) long-term exposure to cooking oil fumes. Participants were randomly assigned to a screening group with alternating years of LDCT screening (R1, R2) or a control group with biennial questionnaire inquiries. **Result:** A total of 6657 eligible participants were enrolled, 3145 participants were assigned to the control group and 3512 were assigned to the baseline LDCT screening (R1) group. 1516 participants (43.2%)

underwent the second round of LDCT screening (R2) in the alternate year. At R1 and R2 rounds, 19.6% and 24.0% participants showed non-calcified nodules ≥4 mm on LDCT images. Among these, lung cancer was diagnosed in 44 participants (1.3%) at R1, 12 (0.8%) at R2, and 10 (0.3%) in the control group through either biopsy or cytologic analysis. The proportions of early-stage (0 to I) lung cancer were 97.7% at R1, 91.7% at R2 and 20% in the control group, respectively. At R1, the sensitivity of LDCT for lung cancer screening was 97.7%, the specificity was 76.8%, the positive predictive value was 5.1%, and the negative predictive value (NPV) was 99.9%; at R2, both the sensitivity and the negative predictive value increased to 100%. Two cases of lung cancer-specific deaths occurred in the control group, but no death occurred in the LDCT group. **Conclusion:** Compared to usual care, the two biennial screenings with LDCT led to a 77.7% increase at R1 and 71.7% at R2 in detecting early-stage lung cancer and a 20% decrease in lung cancer mortality. Biennial screening may be at least as efficient as annual screening in terms of detecting rate, sensitivity and NPV. This study provides insights about the non-smoking related risk factors of lung cancer in the Chinese population.

Keywords: low-dose CT, lung cancer, Early-stage detection

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MA 14.08 HEMATOLOGY/ONCOLOGY PROVIDERS' PRACTICES AND ATTITUDES OF LUNG CANCER SCREENING AND TOBACCO CESSATION AT AN ACADEMIC MEDICAL CENTER AND VA

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Background: Advances in cancer screening and therapeutics have led to an estimated 15.5 million US cancer survivors. A history of cancer is a known risk factor for lung cancer. Lung cancer screening (LCS) with low-dose CT (LDCT) and smoking cessation in high-risk populations are recommended standard-of-care practices for cancer survivors, yet knowledge and practice of these interventions is low among PCPs. Hematologists and oncologists commonly provide cancer survivorship care, and yet their practices of and attitudes toward LCS are unknown. Based on prior data, we hypothesized that very few providers (<25%) would report performing LDCT screening while most (>75%) would report providing tobacco cessation services in the last year, and that knowledge of LCS guidelines would be associated with LDCT screening. **Method:** We electronically surveyed all Hematology/Oncology providers (n = 104) at a large academic institution in the Mid-South and its affiliated VA from February to May 2017. The survey queried: LCS/tobacco cessation practices (LDCT screening as primary outcome), perceived cancer screening/tobacco cessation effectiveness, knowledge of USPSTF LCS guideline recommendations and CMS coverage, perceived barriers to LDCT screening, and interest in future provider/patient LCS education and reminder tools. Data were summarized using counts, proportions, means, and medians. We used logistic regression to evaluate the association of LCS guideline knowledge (primary predictor) with reported LDCT screening. **Result:** The overall survey response rate was 73%. Few providers (38%) reported performing LDCT screening in the past year, while almost all providers (95%) reported providing tobacco cessation services. In unadjusted analysis, providers who knew at least three LCS guideline components were more likely to perform LDCT screening (OR 5.96, CI 2.03-17.49; P = 0.001). Only 55% of providers knew at least three LCS guideline components. More providers rated Pap-smear (75%), colonoscopy (71%), smoking cessation (68%), and mammography (39%) as very effective at reducing cancer-specific mortality compared to LDCT (24%). Major perceived barriers included: lack of patient awareness (74%) and patient financial cost (51%). More VA providers (37%) rated lack of a multi-disciplinary screening program as a major screening barrier compared to academic providers (7%) (P = 0.002). Majority of providers (≥ 56%) reported interest in future provider/patient LCS education and reminders. **Conclusion:** LDCT screening is currently an uncommon practice among Hematology/Oncology providers. Future interventions aimed at the provider, patient, and health system levels are needed to ensure standard-of-care LCS practices in the cancer survivor population. Provider level interventions should incorporate education on screening/tobacco cessation effectiveness and screening guideline recommendations.

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MA 14.09 IMPACT OF LUNG CANCER PERCEIVED RISK, SCREENING ELIGIBILITY AND WORRY ON LDCT SCREENING PREFERENCE - CHALLENGES FOR ENGAGING PATIENTS AT HIGH RISK

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Background: Lung cancer screening is only effective at reducing lung cancer deaths when the highest risk individuals are screened and followed. An individual's risk of lung cancer, and therefore their screening eligibility, has not been shown to correlate with their perceived risk or intention to participate in screening. While previous studies have suggested many at-risk individuals are supportive of screening, no validated risk perception questionnaire has been used to compare perceived risk and worry with screening preference between eligible and ineligible individuals. **Method:** Participants were current or former smokers aged 55 to 80 years old who presented for medical outpatient specialist appointments at three Australian hospitals. The survey included 1) demographics and previous cancer screening participation 2) objective lung cancer risk measured by PLCOm2012 lung cancer risk prediction model 3) perceived lung cancer risk and worry about lung cancer measured by the questionnaire developed by Park et al and validated in sub-set of National Lung Screening Trial (NLST) participants and 4) preference for screening measured by a five point Likert scale. Eligibility for screening was PLCOm2012 risk >1.5%. Ordinal logistic regression identified factors associated with screening preference. **Result:** 760 people 55-80 years old participated, of which 306 were ever-smokers. The participation rate was 26.9%. 23 did not complete either sufficient smoking details for PLCOm2012 risk or screening preference leaving 283 responses. Mean±SD age was 66.3±6.5, 60.4% (171/283) were male, median (IQR) PLCOm2012 risk was 1.28% (0.44-3.11) and 45.6% (129/283) were eligible for screening. Overall screening preference was high; 72.1% (204/283) either agreed or strongly agreed to having screening if offered. Objective lung cancer risk (PLCOm2012) was weakly correlated with both perceived lung cancer risk (r=0.28, p<0.0001) and worry (r=0.21, p<0.001). In univariate analysis, worry (OR 1.37, 95% CI [1.18-1.60], p<0.001), perceived risk (OR 1.10, 95% CI[1.04-1.16], p=0.002) and PLCOm2012 risk (OR 1.06, 95% CI[1.01-1.12], p=0.02) were associated with higher screening preference, but not associated with higher screening eligibility (OR 1.50, 95%CI[0.97-2.30], p=0.06). Age, gender, smoking status, family history of lung cancer and previous screening practice were not associated with screening preference. Only worry remained significantly associated with screening preference (adj-OR 1.33, [95%CI 1.10-1.60], p=0.003) with multivariate analysis. **Conclusion:** Worry about lung cancer appears to be a more important driver for screening preference than eligibility status. This presents a unique challenge when trying to engage with eligible individuals while minimizing screening demand from the ineligible majority.

Keywords: Lung cancer risk perception, LDCT screening

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MA 14.11 MALIGNANCY RISK PREDICTION OF PULMONARY NODULE IN LUNG CANCER SCREENING – DIAMETER OR VOLUMETRIC MEASUREMENT

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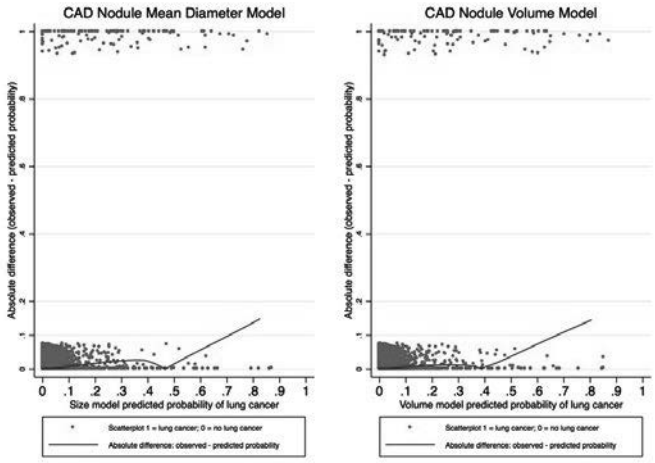
Background: Nodule size is an important parameter to determine malignancy risk. Semi-automated size measurements have the potential to replace manual measurements due to their higher accuracy and reproducibility, and less inter/intra-user variation. However, controversy exists regarding the relative accuracy of 2D diameter versus 3D volumetric measurement to predict malignancy risk. The objective of this study is to compare nodule malignancy prediction models based on 2D mean diameter versus volumetric measurement, both generated by a CAD Software. **Method:** We analyzed baseline LDCT reconstructed using high spatial frequency algorithm from 1746 participants (47% women, 53% men, age: 62.5 ± 5.8 yrs) in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan), who had ≥1 non-calcified nodules ≥3mm in diameter. CAD software (CIRRUS Lung Screening, Radboud University Medical Center, Nijmegen, the Netherlands) performed an automatic nodule segmentation, which could be optimised manually, measurement of mean diameter and volume was generated. Malignant or benign nodule status was confirmed by pathology or prolonged follow-up (median follow-up 5.5 years). Logistic regression models predicting cancer were prepared with one including mean diameter and the other including volume. The discrimination, the ability to classify cancer versus benign nodules correctly, was evaluated by the area under the receiver operator characteristic cure (AUC). The calibration - do predicted probabilities match observed probabilities, was assessed using Spiegelhalter's z-test and graphically by plotting the observed and predicted mean probabilities of cancer by deciles of model risk. **Result:** There were in total 5878 nodules, including 119 cancers in 115 individuals. Both models gave similar predictive performances. AUC was 0.947 (95% CI 0.922-0.964) in the mean diameter model and 0.946 (95% CI 0.921-0.966) in the volumetric model (p=0.83). The calibrations were similar between the two models (figure).



Conclusion: The predictive performances of nodule malignancy prediction models using mean 2D nodule diameter and 3D volumetric data were indistinguishable.

Keywords: Early Detection, lung cancer, computed tomography

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MA 14.12 DETECTING EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION STATUS IN PATIENTS WITH LUNG ADENOCARCINOMA USING RADIOMICS AND RANDOM FOREST

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Background: We tried a radiomics approach to build a random forest classifier for recognition of epidermal growth factor receptor (EGFR) mutation status in Chinese patients with lung adenocarcinomas using quantitative image features extracted from non-enhanced computed tomography (CT) images **Method:** From October 2008 to December 2015, 355 patients diagnosed with lung adenocarcinomas were included in this retrospective study. They all have complete clinical, pathological, and EGFR mutation status information, and their CT images were scanned before any invasive operation. Tumors with ground glass component or diameter smaller than 2 cm were not included. Their pathological phenotypes and EGFR mutation status were gained from surgical resections. Region of tumors on CT images were segmented semi-automatically first then manually modified by experienced clinicians. 440 quantitative image features were extracted from CT images and fall into four groups: first order statistics, shape and size based features, textural features, and wavelet features. Random forest was used to build the classification model which takes all the features into consideration and make an overall probability of mutation based on the vote of decision trees. The random forest classifier was validated using an independent set and its performance was evaluated using area under curve (AUC) values of the receiver operating characteristic **Result:** 355 patients diagnosed with lung adenocarcinoma were enrolled in this study (170 male, 185 female; 54 smokers, 301 non-smokers). The patients all received surgery based treatment and their tumor stage varied from I to IV. EGFR mutations (mainly 19del and 21L858R) were found in 187/285(65.6%) and 48/70(68.6%) patients in training and validation sets respectively. The random forest model showed an AUC of 0.781 (95% confidence interval: 0.668-0.894, p<0.001) in the validation set. The sensitivity and specificity are 60.4% and 90.9% at best diagnostic decision point. These results were highest among published results of only using images to detect EGFR. **Conclusion:** The random forest classifier based on CT images showed potential ability to identify EGFR mutations in patients with lung adenocarcinomas and could be improved in future works.

Keywords: Radiomic, Random Forest, EGFR

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MA 14.13 NODULE SIZE ISN'T EVERYTHING: IMAGING FEATURES OTHER THAN SIZE CONTRIBUTE TO AI BASED RISK STRATIFICATION OF SOLID NODULES

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Background: Previously proposed risk models for the malignancy of Indeterminate Pulmonary Nodules (IPNs) detected on Computed Tomography (CT) typically incorporate a mixture of clinical factors, such as age and smoking history, and radiological factors such as nodule size and location. Of the latter, size is considered one of the most significant. Artificial Intelligence based risk stratification software has been previously proposed that uses Texture Analysis with Machine Learning to predict IPN malignancy and has been shown to achieve high classification performance. While it is assumed that such techniques can capture image texture patterns that separate benignity from malignancy, such methods also intrinsically measure nodule size. The contribution of texture to classifier performance beyond size has not been studied and we seek to quantify this. We show, for the first time, the relative contributions of texture and size on the performance of Artificial Intelligence risk stratification of solid nodules. **Method:** Two datasets were created from the US National Lung Screening Trial (NLST). The first (A), comprising 640 solid nodules, was built to remove size as a discriminatory factor between benign and malignant; all malignant solid nodules between 4 and 20 mm diameter were selected, and for each, a benign solid nodule was selected that most closely matched it in diameter. Any malignant nodule for which an equivalently sized benign could not be found within 0.8 mm was rejected. Sizes were measured using automated volumetric segmentation. The second dataset (B), also comprising 640 subjects, included all malignant nodules in A but benign nodules were randomly selected following the empirical size distribution of the whole NLST dataset. Therefore, nodule size cannot be a discriminative factor in A but would be in B. Two nodule stratification algorithms were developed using Texture Analysis combined with Machine Learning (Support Vector Regression) integrating 20 variables including 3D Haralick, Gabor and Shape features, from A and B respectively using five-fold cross validation and the performance compared measuring Area-Under-the-Curve (AUC). **Result:** The average AUC for the algorithm trained on dataset A was 0.70 whereas using size alone on the same dataset gave an AUC of 0.50. The AUC was 0.91 for the algorithm trained on B. **Conclusion:** On this data, Texture Analysis with Machine Learning contributes 0.20 AUC points to classfication performance. Artificial Intelligence based risk classification can identify radiological features that are predictive of solid nodule malignancy that are independent of nodule size.

Keywords: Artificial Intelligence, Risk stratification, solid nodules

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MA 14.14 THE FIRST 100 DAYS: EARLY FINDINGS FROM THE LUNG CANCER SCREENING PILOT FOR PEOPLE AT HIGH RISK IN ONTARIO, CANADA

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Background: An estimated 330,000 people in the province of Ontario are at high risk of developing lung cancer and eligible for screening with low-dose computed tomography (LDCT). On June 1 2017 Cancer Care Ontario launched the Lung Cancer Screening Pilot for People at High Risk with the purpose of informing the design and implementation of a province-wide organized screening program. Organized screening is available at 3 hospitals, and provider and public recruitment strategies are being implemented to engage the target population in regional catchment areas. Key aspects of pilot design include eligibility based on the $PLCO_{M2012noRace}$ risk prediction model, navigation support, informed participation, embedded smoking cessation services, radiology quality assurance, LDCT findings categorized in accordance with Lung-RADS™, provision of same-visit screening results and seamless transition to a Diagnostic Assessment Program (DAP) for assessment of findings suspicious for lung cancer. Data collected for 3,000 participants over a 2-year period will inform a comprehensive evaluation of the pilot. **Method:** Indicators were selected to assess impacts of early recruitment efforts and outcomes of key screening processes related to eligibility assessment, the LDCT scan and smoking cessation. Data were collected by the pilot sites and submitted to Cancer Care Ontario. Participant feedback on the screening experience was collected by survey. Data were collected in June and July 2017; data from August 2017 will be available for presentation. **Result:** The majority (87%) of the 862 people recruited into the pilot were provider-referred. Of the 472 people who completed a risk assessment, 71% were found to be eligible for screening ($PLCO_{M2012noRace}$ 6-year risk ≥2.0%). Baseline LDCT scans were conducted for 156 participants; approximately 8% of these participants were referred to a DAP for further assessment. Uptake of smoking cessation services by current smokers was high (data to be included in presentation). Feedback surveys were received from 78 of 156 participants screened. Overall experience with the screening visit was rated as 'excellent' by 91% of respondents, and 70% indicated a preference to receive results during the same visit as the LDCT. **Conclusion:** Provider-led recruitment supports the identification of screen-eligible individuals. Implementation of navigator-guided organized screening, following a detailed screening pathway that features provision of same-visit results, has contributed to high participant satisfaction to date. To our knowledge, this pilot involves the most detailed organized screening pathway and comprehensive evaluation plan developed to date. Learnings from this pilot will be highly relevant to jurisdictions around the world that are adopting screening.

Keywords: lung cancer screening, Evaluation, pilot

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MA 15.01 LUNGBEAM: A PROSPECTIVE MULTICENTER TRIAL TO MONITOR EGFR MUTATIONS USING BEAMING TECHNOLOGY IN STAGE IV NSCLC PATIENTS

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Background: Liquid biopsy is a promising approach to improve the management of NSCLC patients, offering a minimally-invasive alternative to tumor tissue testing and enabling timely monitoring of patients on-therapy. The goal of the present study was to evaluate the performance of the OncoBEAM EGFR plasma vs EGFR tissue testing across 19 Spanish hospitals and to examine the timing of T790M mutation emergence in patients during first-line EGFR TKI therapy with respect to radiological progression. **Method:** Blood samples from 112 therapy-naïve advanced NSCLC patients were collected at baseline and throughout EGFR TKI therapy. Results from OncoBEAM EGFR mutation were performed by Sysmex in Hamburg, Germany and then compared to those obtained by the initial EGFR tissue testing obtained at the referring hospital. In addition, the time at which T790M was first detected was compared to the date of progression determined by radiological imaging. **Result:** 112 stage IV NSCLC patients (p) were enrolled between Nov 2016 and May 2017. Clinical characteristics: median age 65 y. , 81 female. Smoking pattern: never 70 p (62,5%), former 33 p (29.4%) and active 9 (8%). M1a 28 p (25%), M1b only brain 10 p (8.9%), only bone 17 p (15%). Baseline tissue samples: Exon 19 deletion 74 p (66%) , L858R 38 p (34%). Initial positive percent agreement (PPA) in 69 out of 112 p was 52/69 or 75.4%. Interestingly, the agreement between plasma and tissue EGFR mutation results for patients diagnosed at M0 was 56%, versus 81% with patients diagnosed at M1. In addition, the average number of days between tissue biopsy and blood collection for concordant cases was 128 days, versus 358 days for discordant cases. Currently, the tissue EGFR mutation status of all discordant cases is being re-examined using BEAMing. Preliminary results from serial T790M plasma analyses revealed cases where detection by OncoBEAM was observed several weeks prior to documented progression by imaging. More mature results will be available at the time of the meeting **Conclusion:** Overall, these initial results show high PPA of plasma and tissue EGFR mutation status at baseline. Moreover, early detection of T790M in blood may assist in anticipating resistance to first-line EGFR TKI therapy.

Keywords: EGFR, Liquid biopsy, Beaming, Monitoring EGFR,

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MA 15.02 PLASMA CFDNA NEXT GENERATION SEQUENCING IN NON-SMALL CELL LUNG CANCER: CLINICAL OUTCOMES AND COMPARISON TO TISSUE

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Background: Next-generation sequencing (NGS) of cell-free DNA (cfDNA) in plasma can be an alternative or complement to tissue biopsy for genomic analysis of non-small cell lung cancer (NSCLC), particularly for identifying driver and resistance alterations. We presented preliminary data in 67 patients comparing NGS in plasma vs. tissue (Santos et al. JTO; 11:10, S199-200) and found EGFR mutation agreement of 68% between plasma and tissue. We now present an expanded patient cohort with more extensive concordance analysis, longer follow-up, and clinical outcomes. **Method:** We analyzed data from advanced (stage III/IV) NSCLC patients seen at three cancer centers in Florida (US; Memorial Cancer Institute, Florida Hospital Cancer Center, Mount Sinai Cancer Center) that had alterations detected on Guardant360 (G360) testing through January 2017. G360 is a plasma cfDNA NGS assay that detects single nucleotide variations, amplifications, fusions, and indels in targeted genes using massively parallel digital sequencing; panel composition expanded from 54 to 73 genes over the course of the cohort. NGS performed on solid tumor biopsies from each subject were reviewed for comparison where available but may not have been collected contemporaneously to the plasma samples. Treatment information and clinical outcomes were collected for those patients with actionable mutations per NCCN guidelines (v3.2017). **Result:** A total of 190 G360 test results on 171 unique patients were identified (some patients underwent serial testing at multiple clinical timepoints, e.g. progression). Forty percent of patients were male; the median age was 65 (32-94). Excluding variants of uncertain significance, patients were most likely to have cfDNA alterations in TP53 (44%), EGFR (21%), KRAS (19%), BRAF (8%), and MET (8%). Forty-seven patients (28%) had at least one actionable mutation identified on G360, including SNVs, indels, fusions, and amplifications. Preliminary clinical outcomes data include durable (≥10 months) partial responses on targeted therapy based on multiple plasma-detected alterations in EGFR and BRAF V600E; complete analysis will be presented at the meeting. **Conclusion:** Liquid biopsy plays an important role in genomic analysis of NSCLC, offering reliable information to guide therapeutic decision-making. Results in our cohort include a noteworthy proportion of patients with highly actionable mutations, like EGFR drivers and targetable resistance mutations, and G360 offers an alternative to tissue biopsy in these patients.

Keywords: next generation sequencing, liquid biopsies, cfDNA

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MA 15.03 DISTRIBUTION OF CIRCULATING TUMOR DNA IN LUNG CANCER: ANALYSIS OF PRIMARY LESION, PULMONARY VEIN, BONE MARROW AND PRIPHERAL BLOOD

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Background: Circulating tumor DNA (ctDNA), extracted from plasma, is a non-invasive surrogate biomarker. However, the distribution of ctDNA in the body still remains to be elucidated. In this study, resected lung tumors, with simultaneous blood and bone marrow samples, were analyzed to elucidate the distribution of ctDNA. **Method:** Rib bone marrow, pulmonary venous blood (Pul.V) and peripheral blood (Peri.B) were obtained from 30 patients. The liquid samples were divided into cell pellets and supernatant by centrifugation; a total of 212 DNA samples were subjected to massively parallel sequencing. **Result:** ctDNA was detected in 5 patients. Given that the frequency of mutations in the primary tumor was considered to be 100%, those in the other specimens were as follows; Pul.V plasma 20%, Peri.B plasma 11%, and the other samples 0%. Furthermore, ctDNA reflected the predominant mutations in the primary lesion. Clinically, the presence of ctDNA was associated with significantly poorer survival. **Conclusion:** These results suggest ctDNA "spill over" into an immediate outflow tract (Pul.V), and from there is disseminated to the entire body. Thus, it can be inferred that ctDNA reflects the cancer progression and could function as a prognostic marker.

Keywords: Circulating Tumor DNA, next-generation sequencing, distribution

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MA 15.04 DETECTION OF ALK REARRANGEMENTS IN NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS BY LIQUID BIOPSY

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Background: The ALK rearrangement (ALK+) is an important actionable genetic aberration of NSCLC, which is associated with high sensitivity to targeted agents such as crizotinib and alectinib. Currently, ALK+ is mainly detected by fluorescent in situ hybridization (FISH) or immunohistochemistry that strictly require the availability of tumor sample, however, in NSCLC, tumor tissue are not always valid or sufficient for testing and non-invasive analyzing methods are urgently needed. Recent years, next generation sequencing (NGS) based liquid biopsy has emerged as a useful complementary technique for the analysis of cancer genetic profile, in the present study, we aimed to evaluate the performance of liquid biopsy for the detection of ALK rearrangements in NSCLC. **Method:** From January 2016 to May 2017, paired tumor and cell-free plasma samples were collected form 360 histologically proven NSCLC patients. The presence of ALK+ was detected by fluorescent in situ hybridization (FISH) in tumor samples and by a NGS based liquid biopsy technology that targeted 96 genes, including ALK, in plasma samples. Genomic alterations in cancer-associated somatic variants are analyzed by massively parallel sequencing. The FISH results were set as golden-standard for the presence of ALK+. The specificity and sensitivity of liquid biopsy for the detection of ALK+ were evaluated. **Result:** ALK+ were detected in 28/360 (7.8%) of the tumor samples and 25/360 (6.9%) of the plasma samples. All the 25 ALK+ plasma samples were also ALK+ in their corresponding tumor samples. Liquid biopsy failed to detect ALK+ in 3 samples that were positive in tumor sample. Thus, the specificity and sensitivity of liquid biopsy for detection of ALK+ in plasma were 100% and 89.3%, respectively. **Conclusion:** NGS based liquid biopsy technology is a promising, non-invasive method for the detection of ALK rearrangement that may benefit NSCLC patients who have difficult to obtain tumor samples or need continuous monitor of ALK status.

Keywords: liquid biopsy, ALK

MA 15.06 ERBB RECEPTOR FEEDBACK INHIBITOR-1 ALTERATIONS IN NON-SMALL CELL LUNG CANCER

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Background: ERBB Receptor Feedback Inhibitor-1 (ERRFI-1) encodes MIG6, which is a negative regulator of EGFR and ERBB2 signaling. Loss of function alterations at ERRFI-1 would be expected to promote oncogenesis, but the role of ERRFI-1 alterations in conferring sensitivity to targeted therapies remains to be fully investigated. **Method:** We reviewed 19,347 cases of NSCLC in the Foundation Medicine data base for ERRFI-1alterations that had been previously assayed by hybrid-capture based genomic DNA profiling of FFPE tissue specimens. Two patients, so identified, had been treated with EGFR pathway antagonist therapies and their outcomes are reported herein. **Result:** ERRFI-1 truncating mutations were identified in 0.62 % (120/ 19,347) of all screened NSCLC specimens. ERRFI-1 alterations were seen in all NSCLC histologic subtypes examined at similar frequencies: adenocarcinoma (0.7%), squamous carcinoma (0.3%), large cell carcinomas (0.8%), adenosquamous (0.6%), sarcomatoid (0.6%), and not otherwise specified (0.6%). Co-existing alterations included: P53 (59%), KRAS (19%), EGFR exon 19 del (9.2%), EGFR L858R (3.3%), EGFR T790M (3.3%), EGFR amp (6.7%), ERBB2 mut (7.5%), and ERBB2 amp (3.3%). Two female patients with ERRFI-1 mutations who were wildtype for known NSCLC driver mutations and targeted therapy naive, achieved RECIST criteria partial responses after treatment with single agent EGFR TKI therapies. Following subsequent disease progression, one of these patients also achieved a secondary response to single agent EGFR directed monoclonal antibody therapy. To our knowledge, these are the first two reported patient outcomes for targeted therapies in ERRFI-1 altered NSCLC. **Conclusion:** The index cases presented here suggest that NSCLC patients with genetic lesions in ERRFI-1 may respond to both anti-EGFR TKIs and monoclonal antibodies. However, co-occurrence between ERFFI-1 mutations and alterations in known NSCLC drivers such as EGFR exon 19 del and L858R may also indicate that in some contexts, ERRFI-1 alterations may provide a mechanism for acquired resistance to targeted therapies as well. Further investigation including assessment of ERRFI-1 loss of heterozygosity, ERRFI-1 VUSs , and clinical evaluation of additional cases including response and resistance to targeted therapy will be performed to more fully delineate the role of ERRFI-1 in NSCLC.

Keywords: EGFR, ERBB2, ERRFI-1

MA 15.07 CONSISTENCY ANALYSIS OF MUTATIONS IN TUMOR TISSUE AND CIRCULATING CELL-FREE DNA IN LUNG CANCER PATIENTS THROUGH NEXT GENERATION SEQUENCING

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Background: Remarkable advances for clinical diagnosis and treatment in cancers including lung cancer involve cell-free circulating tumor DNA (ctDNA) detection through next generation sequencing. However, before the sensitivity and specificity of ctDNA detection can be widely recognized, the consistency of mutations in tumor tissue and ctDNA should be evaluated. The urgency of this consistency is extremely obvious in lung cancer to which great attention has been paid to in liquid biopsy field. **Method:** Averagely 10 ml preoperative blood samples were collected from 30 patients containing pulmonary space occupying pathological changes by traditional clinic diagnosis. cfDNA from plasma, genomic DNA from white blood cells, and genomic DNA from solid tumor of above patients were extracted and constructed as libraries for each sample before subjected to sequencing by a panel contains 50 cancer-associated genes covering 1654 hotspots by custom probe hybridization capture with average depth >40000, 7000, or 6300 folds respectively. **Result:** Detection limit for mutant allele frequency in our study was 0.1%. The sequencing results were analyzed by bioinformatic expertise based on our previous studies on the baseline mutation profiling of circulating cell-free DNA and the clinicopathological data of these patients. Among all the 27 lung cancer patients, 80 percent were predicted as positive by ctDNA sequencing when the standard was defined as at least one of the hotspot mutations detected in the blood (ctDNA) was also detected in tumor tissue. Pneumonia and pulmonary tuberculosis were detected as negative according to the above standard. When evaluating all hotspots, 949 of 1265 (75 percent) mutations detected in tumor tissue were also detected in patients' blood. When evaluating all genetic variations, including those present at high levels in tumor tissue (clonal, driver genes in the panel) as well as those at low levels (subclonal, passenger genes in the panel), 327 of 583 (56 percent) detected in tumor tissue were also detected in patients' blood. Mutations detected only in blood (ctDNA and genomic DNA in white blood cells) but not in tumor tissue are not well understood yet. **Conclusion:** We demonstrated the importance of sequencing both circulating cell-free DNA and genomic DNA in tumor tissue for ctDNA detection in lung cancer. We also determined and confirmed the consistency of ctDNA and tumor tissue through NGS according to the criteria explored in our studies. Our strategy can initially distinguish the lung cancer from other space occupying lesions of lung. Our work shows that the consistency will be benefited from the optimization in sensitivity and specificity in ctDNA detection.

Keywords: next generation sequencing, Circulating Tumor DNA, lung cancer

MA 15.08 SAFETY AND EFFICACY OF OSIMERTINIB IN TREATING AN EGFR-MUTANT LUNG CANCER PATIENT WITH A GERMLINE EGFR T790M MUTATION

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Background: Limited and conflicting data are available for the safety and clinical efficacy of EGFR TKIs, especially third-generation TKI osimertinib, in the rare (<0.1%) subset of NSCLC patients carrying a germline EGFR T790M mutation. We here report a patient with concurrent somatic EGFR L858R and germline EGFR T790M mutations detected by liquid biopsy and tumor genomic profiling assay. **Method:** A 67-year-old male, life-long never smoker was initially found to have bilateral, small lung nodules incidentally on a CT scan during the workup for a kidney stone. His family history suggests a hereditary predisposition to lung cancer given there were three other individuals (including two never smokers) across three generations with a history of lung cancer. The patient underwent annual surveillance chest CT scans over a two-year period before a biopsy-proven stage IA lung adenocarcinoma was found, which was treated with stereotactic body radiation. Unfortunately, this patient developed local tumor recurrence in the lung and wide spread bony metastases in less than one year. To determine the effect of EGFR TKIs on normal blood cells, we established a permanent Epstein-Barr Virus (EBV)-transformed lymphoblastoid cell line from the patient's peripheral blood mononuclear cells (PBMCs) and determined the in vitro cytotoxicity of the cell line to first, second, and third generation EGFR TKIs. Serial tumor genomic profiling of plasma ctDNA by the Guardant360 assay was obtained each time clinical treatment was changed for this patient. **Result:** We found neither EGFR nor AKT expression in the PBMCs and the EBV-transformed lymphoblastoid cell line established from this patient. The EBV-transformed lymphoblastoid cells were resistant to all first, second and third generation EGFR TKIs tested. This patient achieved rapid clinical response to osimertinib after progression on radiation, chemotherapy, and afatinib. Serial genotyping of plasma ctDNA showed the alteration of EGFR L858R level correlated with tumor response while the mutant allelic frequency of EGFR T790M remained at ~50%. A heterozygous EGFR T790M germline mutation was confirmed by genetic testing. **Conclusion:** To our knowledge, this is the first combined in vitro and clinical data supporting the safety and efficacy of osimertinib in patients with the germline EGFR T790M mutation. Further mechanistic studies are needed to understand the tumorigenesis and clinical management for lung cancer patients and carriers with a germline EGFR T790M mutation.

Keywords: osimertinib, lung cancer, Germline EGFR T790M

MA 15.09 CIRCUMFERENTIAL DISTRIBUTION AND DISTANCE FROM MAIN TUMOR OF TUMOR SPREAD THROUGH AIR SPACES (STAS) ARE PROGNOSTIC

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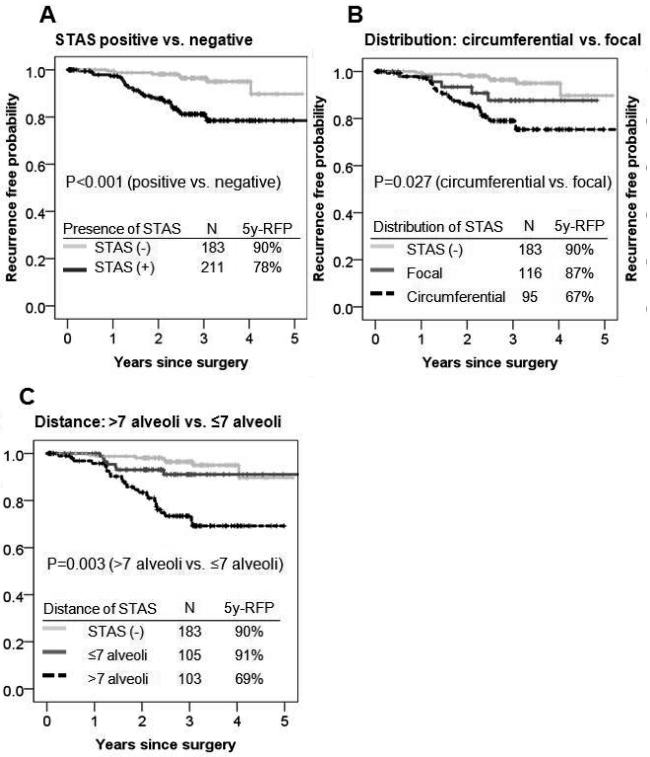
Background: The prognostic impact of the presence of tumor spread through air spaces (STAS) has been reported in lung adenocarcinoma (ADC). The aim of this study is to investigate the prognostic impact of the distribution, distance from the primary tumor, and quantification of STAS. **Method:** A cohort of 394 patients with pathologic stage I lung ADC (2012-2014) were investigated. The distribution of STAS around the tumor was classified into focal or circumferential. The distance of STAS was evaluated by counting the number of air spaces between the farthest STAS and the tumor edge. STAS was quantified by counting the number of STAS areas in the three most STAS- dense 20x high power fields (HPFs). The recurrence free probability (RFP) was analyzed by the Kaplan-Meier method with a log-rank test. **Result:** STAS was present in 211 (54%) cases. The presence of STAS was associated with a higher risk of recurrence (5-y RFP in STAS-positive vs. STAS-negative; 78% vs 90%, p<0.001, Fig 1A). Circumferential STAS was associated with a

higher risk of recurrence than focal STAS (5-y RFP in circumferential vs. focal; 67% vs 87%, p=0.027, Fig 1B). A longer distance of STAS was associated with a higher risk of recurrence (5-y RFP >7 alveoli vs.≤7 alveoli, 69% vs. 91%, p=0.003, Fig 1C). Quantification of STAS was not prognostic (5-y RFP in >3/HPFs vs. ≤3/HPFs, 75% vs. 88 %, p=0.15).



Conclusion: Beyond just the presence of STAS, the distribution and distance of STAS can further stratify the risk of recurrence in stage I lung ADC.

Keywords: Spread Through Air Spaces, lung adenocarcinoma, recurrence

MA 15 LUNG CANCER BIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 15.11 CCNE1, PTGS2, TGFA AND WISP2 PREDICT BENEFIT FROM BEVACIZUMAB AND CHEMOTHERAPY IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (SAKK19/09)

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Background: Bevacizumab (Bev; Avastin®) is a monoclonal antibody against the vascular endothelial growth factor. No predictive biomarkers for the use of Bev have been established so far. We aimed identifying genes predictive for progression-free survival (PFS) and overall survival (OS) of patients treated in the trial SAKK19/09 (NCT01116219). **Method:** SAKK19/09 was a non-randomized phase II trial with two sequential cohorts including patients with non-squamous NSCLC and EGFR wild-type. In Cohort 1, 77 patients were treated with cisplatin (C) 75mg/m^2, pemetrexed (Pem) 500mg/m^2 and Bev 7.5mg/kg, followed by Bev+Pem maintenance. Cohort 2 included 52 patients treated with C+Pem followed by Pem maintenance. RNA was isolated from baseline tumor tissue sections and processed for gene expression analysis by Nanostring. Using the Nanostring nCounter® System (Nanostring Technologies) gene expression of 201 genes, including 6 housekeeping genes was measured using a custom-designed codeset. For each gene, a Cox regression was performed with normalized gene expressions, treatment and the interaction for PFS and OS. No adjustment for multiple testing was done. **Result:**

Gene	Accession	HR (95% confidence interval)		p-value of interaction
		Cohort 1	Cohort 2	
Potential predictive markers for PFS				
AURKB	NM_004217	1.09 (0.84-1.42)	0.78 (0.61-0.99)	0.0481
CCNE1	NM_001238	1.09 (0.87-1.36)	0.73 (0.53-1.02)	0.0312
CDKN2B	NM_004936.3	0.80 (0.67-0.95)	1.10 (0.85-1.43)	0.0375
MMP2	NM_004530.2	0.81 (0.67-0.97)	1.10 (0.91-1.34)	0.0258
PTGS2 (COX-2)	NM_000963.1	1.29 (1.06-1.58)	0.90 (0.78-1.04)	0.00352
TGFA	NM_003236.2	1.13 (0.94-1.37)	0.74 (0.53-1.03)	0.0452
WISP2	NM_003881.2	0.82 (0.69-0.98)	1.24 (1.02-1.51)	0.0015
Potential predictive markers for OS				
CCNE1	NM_001238	1.08 (0.86-1.36)	0.71 (0.49-1.02)	0.0324
PTGS2 (COX-2)	NM_000963.1	1.35 (1.10-1.65)	0.81 (0.69-0.95)	<0.0001
TGFA	NM_003236.2	1.17 (0.96-1.43)	0.55 (0.33-0.91)	0.00352
WISP2	NM_003881.2	0.87 (0.73-1.03)	1.14 (0.92-1.42)	0.0314

We analyzed 99 patient samples (61 in Cohort 1; 38 in Cohort 2) with 201 genes at baseline. We found 7 genes potentially predictive for PFS (AURKB, CCNE1, CDKN2B, MMP2, PTGS2, TGFA, WISP2), 4 of which were also potentially predictive for OS (CCNE1, PTGS2, TGFA and WISP2) (Table 1). **Conclusion:** We identified several potentially predictive genes for Bev activity in combination with chemotherapy. Several of these (AURKB, CCNE1, CDKN2B, TGFA) have previously been shown to play an important role in cell cycle regulation and cell proliferation supporting the hypothesis that Bev supports chemotherapy activity. Notably, also a gene involved in inflammation (PTGS2) was significantly predictive for outcome. Further work is ongoing to explore changes in gene expression using tumor rebiopsies at progression.

Keywords: Predictive biomarker, bevacizumab

MA 15 LUNG CANCER BIOLOGY II
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MA 15.12 EXPANDING THE LUNG SMALL RNA TRANSCRIPTOME: DISCOVERY OF UNANNOTATED MICRORNAS WITH ROLES IN DEVELOPMENT AND TUMOURIGENESIS

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Background: MicroRNAs (miRNAs) are key regulators of gene expression. They participate in many biological and pathological processes, from organ development to malignant transformation. Their functions are widely conserved, involving post-transcriptional silencing of gene expression. Over 2500 mature miRNA sequences have been identified in humans; however, recent studies have showed that the number of annotated miRNAs represent only a fraction of the total pool of existing miRNAs, suggesting that there are still many potentially undiscovered biologically relevant miRNAs encoded by the human genome. Here, we perform a comprehensive study to identify novel miRNA sequences expressed in non-malignant lung tissues, as well as samples from developmental stages and pathological conditions. **Method:** A total of 422 samples were included in this analysis. First, 209 non-malignant samples from two cohorts (BCCA, n=118 and TCGA, n=91) were analyzed using our customized small RNA sequence analysis pipeline. Sequence reads were aligned to the hg38 build of the human genome (STAR algorithm) and novel miRNAs were predicted using mirDeep2. The results were compared to miRNA databases and further filtered by abundance and for miRNA-compatible structure. The same procedure was applied to matched tumours (n=209) and samples derived from fetal lungs (n=4). The biological relevance of the novel sequences was investigated by assessing their expression in tumours and fetal samples, together with gene target prediction and tissue-specific protein-protein interaction (PPI) network analyses using IID. **Result:** Our study discovered the expression of 294 novel miRNA sequences in lung tissue, significantly expanding the current human lung miRNA transcriptome.

These novel miRNAs showed similar nucleotide composition and genomic distribution compared to known miRNAs, providing additional evidence of their miRNA-compatible nature. Interestingly, a subset of these miRNAs were also found to be expressed in tumour and fetal samples, indicating that they might play important roles in organ development and tumourigenesis. Likewise, target prediction analysis revealed that these novel miRNAs are involved in key cellular processes including cell proliferation, migration and survival, as well as pathways known to be deregulated in cancer, as comprehensively analyzed using pathDIP. **Conclusion:** Our study has significantly expanded the lung small RNA transcriptome, and provided evidence that the novel miRNAs are involved in molecular networks relevant to lung biology and pathology. These results also highlight their specific roles in developmental regulation and malignant transformation, suggesting their role as biological regulators and implicating their potential as therapeutic targets.

Keywords: lung cancer, novel microRNAs, development

MA 15 LUNG CANCER BIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 15.13 THE TRANSFER OF EXOGENOUS UCHL-1 VIA MESENCHYMAL LUNG CANCER EXOSOMES TO MEDIATE PHENOTYPIC ALTERATIONS OF RECIPIENTS

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Background: Cancer-derived exosomes are micro-vesicles released by tumor cells and are believed to be involved in intercellular signaling and communication. Recent evidence suggests exosomes help tumor cells invade neighboring tissues and prime metastatic sites for disease spread. Non-small cell lung cancer (NSCLC) is a highly metastatic disease and little is known about how tumor-derived exosomes may influence migration or invasion of lung cancer cells and prime metastatic niches. **Method:** Exosomes were recovered by a sequential centrifugation schema. Exosomes isolated from lung cancer cell line H1299, A549, H1993, and H2073, and non-malignant, immortalized human bronchial epithelial cell (HBEC) 3KT and 30KT were characterized. We examined the effects of cancer-derived exosomes on HBECs, oncogenically progressed HBECs (HBEC sh-p53+KRAS^{v12}; HBEC3KTRL53) in vitro and their influence on metastasis in murine models. Mass spectrometry was performed to identify candidate proteins carried in tumor exosomes that induce phenotypic changes in recipient cells. **Result:** Cancer-derived exosomes but not HBEC-derived exosomes confer invasiveness and increased motility on recipient cells (HBEC3KT, HBEC3KTRL53) in wound healing and Boyden chamber assays. Mesenchymal NSCLC exosomes induce mesenchymal-like phenotypic changes (loss of EPCAM expression and upregulated EMT-transcriptional factors) in HBEC3KT in FACS and qRT-PCR analyses. Cancer-derived exosomes but not HBEC3KT exosomes enhance the lung endothelial permeability, promote lung metastasis, and recruit myeloid-derived suppressor cells in vivo. Mass spectrometry shows that H1299 exosomes contains a wide variety of deubiquitinating enzymes (DUBs) compared to HBEC3KT exosomes, and UCHL-1 (Ubiquitin carboxy-terminal hydrolase L1) is the most highly expressed DUB in H1299 exosomes. UCHL-1 expression is upregulated in mesenchymal NSCLC cells/exosomes, and HBEC3KT cells treated with mesenchymal NSCLC exosomes in vitro, and activated in metastatic sites after cancer-derived exosome treatment in vivo. UCHL-1 knockdown suppresses metastasis induced by cancer-derived exosomes. Exosomes derived from UCHL-1-knockdown H1299 show a decreased effect of the induction of migration, invasiveness, and epithelial/mesenchymal phenotypic changes on recipient cells. **Conclusion:** Mesenchymal NSCLCs-derived exosomes compared to HBECs-derived exosomes induced an increased migratory/invasive phenotype with lung vascular leakiness, metastatic niche formation, and higher xenograft tumor take rates. UHCL-1 was overexpressed only in mesenchymal NSCLCs/exosomes. UCHL-1 knockdown suppressed metastasis, and its exosomes also showed a decreased effect of the induction of tumor progression. These results suggest that understanding and targeting UCHL-1 likely as a key factor of mesenchymal NSCLC-derived exosome behavior could lead to novel therapeutic strategies.

Keywords: UCHL-1, Exosome, EMT

MA 15 LUNG CANCER BIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 15.14 LONG NON-CODING RNA DISRUPTION IN LUNG ADENOCARCINOMA REVEALS NOVEL MECHANISMS OF METASTASIS

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Background: Identifying the drivers of metastasis will yield new molecular targets for prognostics and therapeutics. Long non-coding RNAs (lncRNAs) are known to regulate gene transcription through their influence on the expression of nearby (cis) and distant (trans) genes. Emerging evidence suggests that lncRNAs are involved in key cellular processes, presenting an opportunity for large-scale identification of lncRNA genes critical to lung cancer progression. Here we investigate the contribution of this class of non-coding RNA to lung adenocarcinoma (LUAD) metastasis. **Method:** Stage T1 and T2 tumours with (N≥1 and/or M≥1) and without (N=0 and M=0) metastasis were examined for expression comparisons. Sequencing data from 265 non-metastatic and 130 metastatic tumours obtained from The Cancer Genome Atlas were used as our discovery cohort. Results were validated in 20 non-metastatic and 10 metastatic tumour samples microdissected to 90% purity and sequenced using the Illumina Hi-Seq platform. Normalized sequence read count comparisons were performed (Mann Whitney U-Test, FDR-BH $p<0.05$) to identify lncRNAs significantly deregulated in metastatic samples. LncRNAs over- and under-expressed in metastatic LUAD were compared to nearby protein-coding-target genes to identify putative mechanisms of regulation in cis. **Result:** We discovered 150 lncRNAs to be significantly differentially expressed between metastatic and non-metastatic tumours, including lncRNAs with previously described oncogenic roles in lung cancer, such as Lung Cancer Associated Transcript 1 and H19. As individual lncRNAs can positively or negatively regulate target-gene expression, it is noteworthy that we identified potential protein-coding-target genes that display both concordant and discordant expression patterns with specific lncRNAs. For example, we discovered the upregulation of linc00942 in metastatic LUAD (FDR-BH $p=0.001$) and the concordant overexpression of its corresponding protein-coding-target gene, ELKS/RAB6-Interacting/CAST Family Member 1 (ERC1) (FDR-BH $p=0.02$). Further, metastatic LUAD samples stratified by linc00942 expression also display corresponding elevation of ERC1 ($p=0.0002$), which holds true in the validation cohort. ERC1 (an upstream member of the NF-κB signaling pathway) is implicated in cell migration and focal adhesion, and displays deregulated expression in a number of cancer types. Thus, overexpression of linc00942 may act as a novel positive cis-regulator of ERC1, promoting metastasis. **Conclusion:** This work has led to the discovery of a large number of lncRNA genes deregulated in metastatic LUAD, suggesting that altered lncRNA expression contributes functionally to malignant progression. Understanding cis- or trans-mediated mechanisms of gene deregulation enacted by metastasis-associated lncRNAs will present novel opportunities for diagnosis and treatment.

Keywords: metastasis, epigenetics, non-coding RNAs

MA 16 MEDIASTINAL, TRACHEAL AND ESOPHAGEAL TUMOR: MULTIMODALITY APPROACHES
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 16.01 CHARACTERIZATION OF AUTOANTIBODY RESPONSES IN THYMOMA WITH MYASTHENIA GRAVIS BY SINGLE-CELL SEQUENCING OF B-CELLS

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Background: Thymomas are frequently associated with paraneoplastic autoimmune syndromes, with the most common being Myasthenia Gravis (MG). MG is characterized by autoantibodies against muscle antigens, most frequently the acetylcholine receptor (AChR). Patients with thymoma also present with autoantibodies against striational muscle proteins (STR-Abs), such as the sarcomeric protein titin and the ryanodine receptor. These autoantibodies have been primarily regarded as diagnostic or prognostic markers, but little is known about their pathological mechanisms. Comprehensive mechanistic studies have been hindered by the lack of patient-derived monoclonal antibodies (mAbs). Such mAbs could help to define immunogenic epitopes in known or novel autoantigens, and would be useful for deciphering pathological mechanisms in vitro or in animal models. **Method:** We studied mAbs derived from a patient with thymoma and MG, with the patient's written informed consent and under a Stanford IRB approved protocol. The patient had Masaoka-Koga stage II type B2 thymoma, with multiple recurrences over a period of 8 years. The patient's MG symptoms included fatigable muscle weakness, the presence of anti-AChR antibodies, and high titer STR-Abs. The patient also had myositis with muscle-related symptoms worsening after thymectomy. We sequenced the repertoire of the patient's plasmablasts, which are antibody-producing cells derived from the activated B-cell clones, using a barcode-based method for sequencing single-cell immunoglobulin genes developed in our lab. We then expressed 26 mAbs from clonally expanded families of antibodies from two different timepoints that are six months apart. The first timepoint was two years post-Rituximab, coinciding with a tumor recurrence and slow progression of muscle weakness. The second timepoint was a month after radiotherapy when the patient was admitted with severe muscle weakness and pain. Treatment included plasmapheresis/IVIG and Rituximab, with limited improvement over the weeks following hospitalization. The patient was on steroids at both timepoints. Anti-Titin serum antibody titers increased by 60% between these two timepoints. **Result:** Two of the mAbs that were expressed reacted with the main immunogenic region of titin in ELISA, and one of the clones was present at both of the timepoints investigated. These clones were detected despite B-cell depletion by treatment with Rituximab. **Conclusion:** Our results suggest that (i) sequencing single-cell immunoglobulins is a powerful technique for isolating and functionally characterizing mAbs against autoantigens in thymoma and that (ii) persisting or recurring autoreactive clones in patients with thymoma, such as anti-titin clones, may be associated with refractory paraneoplastic syndromes despite use of immunosuppressive therapies.

Keywords: Paraneoplastic syndromes, Autoimmunity, Thymoma

MA 16.02 DIFFERENT PATTERN AND PROGNOSTIC ROLE OF PD-L1, IDO, AND FOXP3 TREG EXPRESSION IN THYMOMA AND THYMIC CARCINOMA

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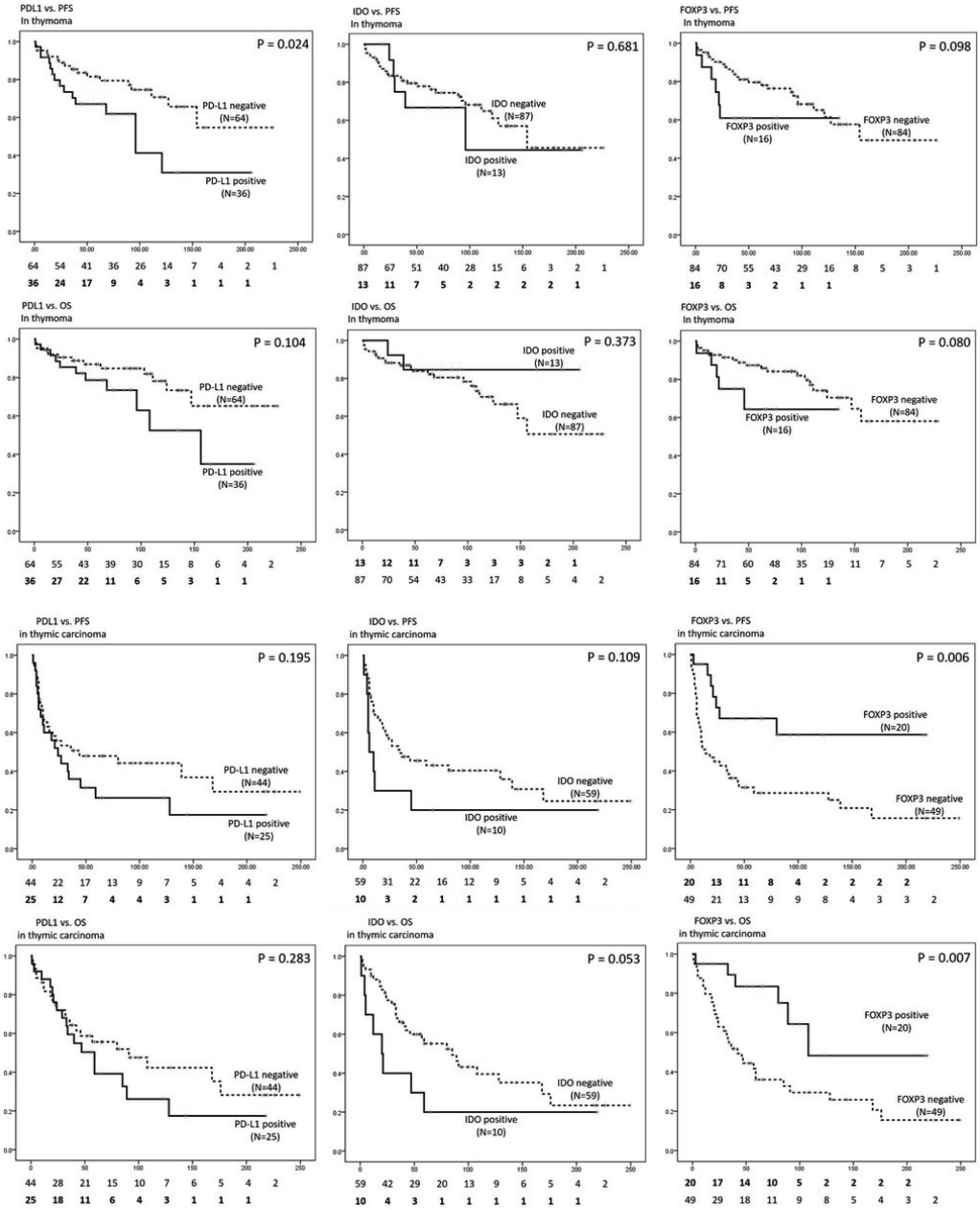
Background: The immune checkpoint ligand programmed cell death 1 ligand (PD-L1) is expressed in various tumors, and the expression of indoleamine 2,3-dioxygenase (IDO) and Foxp3 Tregs are associated with tumor-induced tolerance and reported to be responsible for worse survival. Their prognostic role in thymoma and thymic carcinoma, however, has not been investigated. **Method:** A tissue microarray comprised of 100 surgically treated thymomas and 69 surgically treated thymic carcinomas was evaluated. PD-L1, IDO, and Foxp3 Treg staining was scored based on intensity as follows: 0 = none, 1 = equivocal/uninterpretable, 2 = weak, and 3 = intermediate-strong. The PD-L1, IDO, and Foxp3 Treg expression score was calculated using a semiquantitive method by multiplying the intensity [0-3] by the staining area [0-100%]. Those cases with all cores scoring three and 2 in more than 50% in the staining area were categorized as PD-L1, IDO, and Foxp3 Treg high expression and the remaining as low expression. Clinical information was also collected on age, sex, Masaoka staging, tumor histology, surgical radicality, and locoregional invasion. Statistical associations were evaluated using χ^2 test and Fisher's exact test. Progression-free survival and overall survival curves were established by the Kaplan-Meier method and compared using a log-rank test. **Result:** Thirty-six (36%) thymoma and 25 (36%) thymic carcinoma cases revealed high expression of PD-L1. PD-L1 expression in thymoma is significantly associated with Masaoka staging ($p<0.001$), tumor histology ($p<0.001$). Although there was a trend toward worse progression-free and overall survival in thymoma and thymic carcinoma with high-expression of PD-L1, only the progression-free survival in thymoma was significantly worse ($p=0.024$). High expression of IDO was detected in 13 (13%) thymoma and 10 (14%) thymic carcinoma cases, whereas Foxp3 Treg was detected in 16 thymoma (16%) and 20 (29%) thymic carcinoma cases. The expressions of IDO and Foxp3 Treg were significantly associated with tumor histology in thymoma ($p=0.002$ and 0.016, respectively), but not in thymic carcinoma. Thymic carcinoma with high expression of IDO had a trend toward worse progression-free and overall survival trend ($p=0.109$ and 0.053, respectively). High expression of Foxp3 Treg, however, was significantly associated with better progression-free survival ($p=0.006$) and overall survival ($p=0.007$) in thymic carcinoma. **Conclusion:** This is the largest-scale study to evaluate PD-L1 expression in thymic epithelial tumors. Although high expression of PD-L1 might be associated with worse prognosis in thymoma and thymic carcinoma, further investigation into PD-L1, IDO, and Foxp3 Treg should be conducted to benefit anti-PD-L1 immunotherapy for thymic epithelial tumor.

Keywords: IDO, thymic epithelial tumor, PD-L1



MA 16.03 HEALTH UTILITY SCORES IN PATIENTS WITH THYMIC MALIGNANCIES TREATED WITH MULTIMODALITY THERAPY

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Background: The management of patients with locally advanced thymic malignancies remains controversial. Various combinations of surgical resection, chemotherapy and radiation are currently used. Given the generally favorable prognosis, treatment related toxicities and quality of life (QOL) could inform therapeutic options. For economic analyses, QOL can be measured as health utilities. This study describes health utility scores (HUS) in patients with locally advanced thymic malignancies, while determining the impact of multimodality regimens on HUS. **Method:** In a cross-sectional study (2014-2017), patients with Masaoka stage II-IVa thymic malignancies seen at a comprehensive cancer centre completed various self-reported questionnaires at routine medical visits. HUS as measured by the EuroQol-5-Dimensions (EQ-5D) with visual analogue scale (VAS) and self-reported Eastern Cooperative Oncology Group (ECOG) performance status were compared in patients treated with trimodality versus uni- or bimodality regimens. Patient-reported Edmonton Symptom Assessment Scale (ESAS) scores were also collected to explore symptom burden. Regression analysis was used to compare groups; multivariable analysis investigating potential confounders was also conducted. **Result:** From 2014 to 2017, 72 patients were included in the study; 43 (59.7%) were male with a median age of 58 years, 65 (90.3%) had thymoma while 7 (9.7%) had thymic carcinomas and median time since diagnosis was 50.5 months (range: 3-266). Compared to patients treated with uni/bimodality regimens (n=48), those treated with trimodality (n=24) had higher stage of disease at diagnosis and were more likely to have received multiple lines of chemotherapy. Median HUS and VAS did not differ between groups (trimodality vs uni/bimodality: HUS=0.77 vs 0.80, p=0.26; and VAS=80 vs 75, p=0.79, respectively). The distribution of patient-reported ECOG at assessment was also similar (p=1.00). ESAS scores for pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath were neither statistically nor clinically different by number of modalities of therapy. Subset analyses of individuals who were 1+ year since diagnosis affirmed these findings. **Conclusion:** Patients with stage II-IVa thymic malignancies report favorable HUS, VAS and self-reported ECOG with minimal symptom burden. Trimodality therapy appears similarly tolerable when compared to uni- and bimodality regimens in this population.

Keywords: Thymic malignancies, health utility scores, multimodality therapy

MA 16.04 PHASE II TRIAL OF S-1 TREATMENT AS PALLIATIVE-INTENT CHEMOTHERAPY FOR PREVIOUSLY TREATED ADVANCED THYMIC CARCINOMA

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Background: Thymic carcinoma (TC) is a rare cancer with minimal evidence of survival with palliative-intent chemotherapy. Sunitinib and everolimus monotherapies have been proposed as active molecular-targeted approaches based on phase II (Ph II) trials, and S-1, an oral fluoropyrimidine, has been described in the NCCN guideline as an active cytotoxic agent for refractory TC based on a case series. Therefore, we conducted a Ph II trial to study the result of S-1 treatment in patients with refractory TC. **Method:** In this Ph II study performed at three cancer centers in Tokyo, we aimed to enroll 26 TC patients previously treated with platinum-based chemotherapy. The patients received S-1 orally twice daily at a dose of 40–60 mg/m2 for 4 weeks, followed by 2 weeks off until progressive disease or unacceptable toxicities. S-1 was used off-label. The primary end-point was determining the objective response rate, and secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicities. **Result:** Twenty-six patients (10 males) were recruited between November 2013 and May 2016. The median age was 63 (27–74) years. Among the 26 patients, 23 had squamous cell carcinoma histology and 10 had an ECOG performance status of 0. Additionally, one patient showed complete response and seven patients showed partial responses, resulting in a 30.8% response rate (95% confidence interval [CI], 16.5–50.0) and a 65.4% disease control rate (95% CI, 46.2–80.6). After a median follow-up of 13.4 months, the median PFS was 4.3 months (95% CI, 2.3–7.6 months) and median OS was 23.4 months (95% CI, 12.8–not reached). Treatment-related adverse events (AEs) of grade ≥3 included neutropenia (12%), skin rash (8%), elevated ALT, decreased WBC count, and fatigue (4%). No treatment-related death was observed. However, treatment was discontinued in three patients (12%) because of AEs. **Conclusion:** S-1 for refractory TC confirmed clinical activity with good tolerability. Clinical trial identification: UMIN000010736

Keywords: chemotherapy, Thymic carcinoma, S-1

MA 16.06 MINIMALLY INVASIVE THORACOSCOPIC THYMECTOMY FOR EARLY-STAGE THYMOMAS: MODIFIED SUBXIPHOID APPROACH VERSUS UNILATERAL APPROACH

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Background: Conventionally, minimally invasive thymectomy for early-stage thymoma was performed via unilateral thoracoscopic approach. However it is sometimes criticized for bad exposure of anterior mediastinum which may be disadvantagous for the surgery. Recently, we attempted a modified subxiphoid thoracoscopic approach with novel sternal-elevating technique to reach better surgical exposure and less trauma. **Method:** From January 2015 to December 2016, a total of 83 consecutive patients with early-stage thymomas without myasthenia gravis were enrolled. Between them, 36 patients were performed thoracoscopic thymectomy via subxiphoid approach (Group S) . Three subxiphoid incisions (12mm*1, 5mm*2) with the aid of artificial CO_2 pneumothorax (8cmH_2O) were used. Additionally, we used the sternum-elevating device (Rul-tractor, USA) through the 3rd intercostal incision (5mm*1) beside the sternum. And the other 47 cases underwent conventional thymectomy via unilateral 3-port thoracoscopic approach (Group UL). The perioperative outcome of two groups were compared. **Result:** The two groups were comparable on patients' demographics. Conversion to open surgery occurred in 1 case (due to bleeding) in Group UL. Compared with Group UL, the patients in Group S had much shorter surgical duration [(63.5±10.7)min vs (87.7±13.1)min, p=0.000], much less pain scores (2.3±1.0 vs 3.1±1.30, p=0.002) and earlier pleural drainage removal [(1.6±0.6)d vs (2.3±0.9)d, p=0.000]. The complications were similar (5.6% vs 6.4%, p=0.758). No significant difference was found on the other outcomes between the two groups, including blood loss and postoperative hospital stay. **Conclusion:** This study suggests that the modified subxiphoid thoracoscopic approach seems to be more effective for thymectomy for early-stage thymomas. This novel approach could improve surgical exposure, accelerate the operative progress and result in less trauma and pain. It could be a promising refinement for future thymic surgery.

Keywords: Thymic malignancies, Minimally invasive thymectomy, subxiphoid thoracoscopic approach

MA 16.07 APPROPRIATE TIME TO ADJUVANT RADIOTHERAPY FOR THYMOMA WITH MG AFTER EXTENDED THYMECTOMY

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Background: The co-existence of MG and thymoma makes the surgical treatment more complicated and adjuvant radiation more controversial. The aim of this article is to investigate whether patients with MG and thymoma should receive mediastinal radiation therapy and when after extended thymectomy. **Method:** Between 2003 and 2014, 181 patients with MG and thymoma underwent extended thymectomy. According to application of radiation therapy, these patients were divided into 2 groups: Group 1 (n=157), patients having mediastinal radiation therapy after surgery; Group 2, without adjuvant radiation therapy (n = 24). Group 1 was subdivided into 3 subgroups: 1-month subgroup(n = 98); 2-month subgroup(n = 7): and 3-month subgroup(n = 52). **Result:** There were no intraoperative deaths and no inoperable cases. 172 patients underwent extended thymectomy by video-assisted thoracoscopic surgery, and 9 undergoing the trans-sternal approach due to thymoma invading great vessels. There was no significant difference in the aspects, such as length of surgery, Operative complications, and ICU stay, between 1-month subgroup, 3-month subgroup and Group 2. The proportions of type A, AB, B1, B2, B3, and thymic carcinoma were 0.6%, 18.2%, 26.5%, 33.7%,21.0%, and 0%, respectively. There were no radiation-related deaths. 159 patients were followed for 15 months to 12 years. Postoperative myasthenic crisis occurred in 40 cases. There was a significant difference in occurrence of postoperative myasthenic crisis between 1-month subgroup and Group 2 (P=0.031). The rates of reaching CSR were 32.6% in 1-month subgroup, 25% in 3-month subgroup, and 22.7% in Group 2, respectively. Overall survival rates of 1-month subgroup, 3-month subgroup, and Group 2 were 88.8%, 83.3%, and 77.3%, respectively. Among 14 recurrences, 11 cases happened in pleural cavity; 2 recurrences in lung; and one patient having metastasis to liver. There was no lymph node metastasis detected. Kaplan-Meier survival curves demonstrate that within 7 years after surgery, there is no significant difference in aspects of overall survival and disease-free survival between 1-month subgroup, 3-month subgroup and Group 2; over 8 years after surgery, disease-free survival rates in 1-month subgroup, 3-month subgroup and Group 2 were 79.4%, 70.6% and 55.3%, respectively. **Conclusion:** Adjuvant radiation within one month after extended thymectomy may be helpful in controlling postoperative MG, such as decreasing possibility of postoperative myasthenic crisis, and raising cumulative probabilities of reaching CSR. Whether it might have influence in prognosis of thymoma with MG needs to be further investigated in the future. In recurrences of thymoma patients with MG, no lymph node metastasis was detected

Keywords: Thymoma, Myasthenia gravis, Adjuvant Radiation

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MA 16.08 SURGERY FOR PLEURAL DISSEMINATION OF THYMOMA; A 20-YEAR EXPERIENCE

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Background: Surgical management of pleural dissemination of thymoma has been recommended in some reports, while reports on the long- term results of pleural dissemination resection are few. The aim of this study was to assess mid- and long-term results of surgical resection of pleural dissemination of thymoma. **Method:** We retrospectively analyzed data from patients with synchronous or metachronous pleural dissemination and primary thymoma who underwent surgical resection between 1996 and 2016 in our hospital. **Result:** During the study period, 38 patients underwent resection of pleural dissemination of thymoma. The synchronous group consisted of 21 patients with a median age of 50.2 years (range: 28—75 years) at the time of resection. The metachronous group consisted of 17 patients with a median age of 46.7 years (range: 30—65 years) at the time of resection of pleural dissemination. The median follow-up was 72.7 months (range: 3—248 months). In the synchronous group, 19 patients were in stage IVa and 2 patients were in stage IVb. The histological type of thymoma was type B1 in 3 patients, type B2 in 9 patients, typeB3 in 9 patients. In the metachronous group, Masaoka stage of the primary thymoma was as follows; 3 patients were in stage I, 5 patients were in stage II, 7 patients were in stage III and 2 patients were in stage IVb. The histological types of the resected dissemination nodule were type AB in 1 patient, type B1 in 1 patient, type B2 in 5 patients, and typeB3 in 10 patients. A macroscopic complete resection of pleural dissemination was achieved in 30 patients (79%) of all the patients. No perioperative deaths occured. Postoperative complications occurred in 5 patients (13.2%). During the observation period, 5 patients died (relation to the tumor in 4) in the synchronous group and 1 patient died (unrelated to the tumor) in the metachronous group. The 5- and 10-year overall survival rates of all the patients were 87.6% and 69.2%, respectively. Of all the patients, 14 received repeated resection of the pleural disseminated nodule. The 5- and 10-year overall survival rates from the first resection of pleural dissemination were 76.6% and 46.0% in the non-repeat resection group and 100% and 88.9% in the repeat resection group, respectively. **Conclusion:** Surgery for pleural dissemination of thymoma was safely performed and provides favorable prognosis. Repeat resection for pleural dissemination could be effective in achieving a prolonged survival.

Keywords: dissemination, Surgery, Thymoma

MA 16 MEDIASTINAL, TRACHEAL AND ESOPHAGEAL TUMOR: MULTIMODALITY APPROACHES
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MA 16.10 TREATMENT OUTCOMES OF PRIMARY MALIGNANT GERM CELL TUMORS OF THE MEDIASTINUM

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Background: Primary mediastinal malignant germ cell tumors (GCT) are rare neoplasms with various histopathological findings and contain complicated clinical characteristics. Chemotherapy plays an important role in the treatment and there are some cases where a good prognosis is expected with multimodal treatment including surgical resection, pre- and postoperative chemoradiotherapy. **Method:** The medical records of 27 patients who were treated in our institution between 1988 and 2014 were retrospectively reviewed. We investigated the clinical characteristics and the outcomes of treatment. **Result:** All patients were male with a mean age of 30.7 years (range, 16-53 years), including 17 cases of seminoma (SGCT group) and 10 cases of non-seminoma (NSGCT group). Twenty-three patients underwent surgery and the remaining four patients received chemotherapy and/or radiotherapy without surgery. Of the 23 patients who underwent surgery, 17 cases received preoperative chemotherapy and 15 cases were treated with postoperative chemo/radiotherapy. In six patients, surgery was performed without preoperative chemotherapy due to the suspicious of thymoma, and was followed by postoperative chemo/radiotherapy. Among 24 patients whose serum tumor marker levels were measured before the treatment, 15 patients showed elevated serum tumor marker levels [five (35.7%) in SGCT group and 10 (100.0%) in NSGCT group]. Furthermore, among 20 patients whose serum tumor marker levels were measured before surgery, four patients showed elevated serum tumor marker levels [one (9.1%) in SGCT group and three (33.3%) in NSGCT group]. The median follow-up period after the treatment was 68 months (range, 4-316 months). The 5-year and 10-year survival rate was 88% and 88% in SGCT group, respectively, and 60% and 45% in NSGCT group, respectively (p=0.031). Although there was no relationship between the serum tumor marker levels before the treatment and the prognosis, the patients without elevated tumor marker levels revealed better prognosis than those with elevated one (p=0.014). **Conclusion:** The treatment for mediastinal malignant GCT in our institution was feasible with favorable outcomes. Although malignant GCT has poor prognosis especially in NSGCT group, chemotherapy which normalizes serum tumor marker levels can improve its prognosis.

Keywords: germ cell tumor, mediastinum

MA 16 MEDIASTINAL, TRACHEAL AND ESOPHAGEAL TUMOR: MULTIMODALITY APPROACHES
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MA 16.11 ALTERATIONS OF NOTCH PATHWAY AMONG PATIENTS WITH ADENOID CYSTIC CARCINOMA OF THE TRACHEA AND ITS IMPACT ON SURVIVAL

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Background: Adenoid cystic carcinoma (ACC) of the trachea represents less than 1% of all respiratory tract cancers and lacks well-characterized molecular markers. There is no standard of care treatment for patients with recurrent and/or metastatic disease. The aim of this study is to identify and characterize novel, activating mutations in Notch receptors in ACC of the trachea and to determine response to Notch inhibitor Brontictuzumab. **Method:** Patients with ACC of the trachea at four institutions from 2011 through 2016 were identified. Target exome sequencing or analysis of hotspot mutations in cancer-related genes was performed by next-generation sequencing. Luciferase reporter assays were performed to confirm target gene expression in vitro. Patient-derived xenograft (PDX) models were sequenced, and Notch-mutant models were treated with Brontictuzumab. Gene-expression and functional analyses were performed to study the mechanism of activation through mutation and inhibition by Brontictuzumab. **Result:** We showed that gain-of-function mutations of the Notch-1 gene in the PEST domain occurred in 10/62 tumors, leading to stabilization of the intracellular cleaved formed of Notch-1 (ICN1). Notch-1 mutations were associated with increased Notch-1 activation and its target gene HES-1. Mutations in Notch-2 (3/62), Notch-4 (3/62), Jagged-1 (2/62), FBXW-7 (4/62), and SPEN (1/62) were also identified in 13 (21.0%) patients. We observed a strong inverse correlation of mRNA levels between FBXW-7 and HES-1. Notch-1 mutations were associated with solid subtype (P = 0.02), advanced stage at diagnosis (P = 0.01), metastasis (P = 0.002), shorter relapse-free survival (RFS) (P = 0.008) and shorter overall survival (OS) (P = 0.006) compared with Notch-1 wild-type tumors. Notch-1 mutations were not an independent prognostic factor in the presence of histologic subtype and tumor stage. We demonstrated that Notch inhibition by Brontictuzumab reduced tumor cell proliferation and tumor formation in ACC patient-derived xenograft model harboring Notch-1 mutation. **Conclusion:** These data suggest that activated Notch pathway may be important to pathogenesis of ACC of the trachea and reveal Notch-1 as a target for therapeutic intervention in this subset of patients.

Keywords: adenoid cystic carcinoma, Notch pathway, tracheal tumor

MA 16 MEDIASTINAL, TRACHEAL AND ESOPHAGEAL TUMOR: MULTIMODALITY APPROACHES
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MA 16.12 PROLONGED SURVIVAL AFTER PULMONARY METASTASECTOMY FOR TESTICULAR GERM-CELL TUMORS IN A SINGLE INSTITUTION

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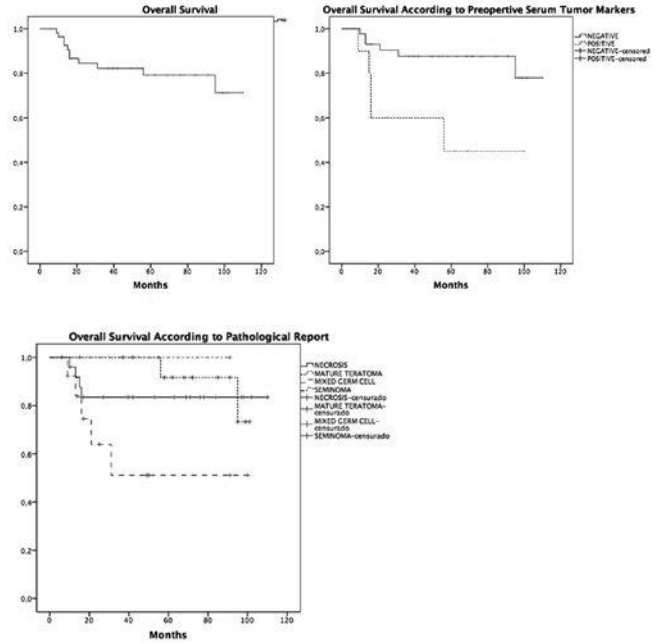
Background: Testicular Germ-cell tumors are a common cancer in adults younger than 30 years-old. Extensive dissemination and high senitivity to chemotherapy are their principal characteristics. Chemotherapy is the standard of care, with an 80% probability of complete biochemical response with first line chemotherapy. Surgical resection of residual lesions after chemotherapy is indicated in some cases to rule out the presence of mature teratoma or viable tumor. **Method:** Retrospective chart review of patients with metastastic testicular Germ-cell tumors treated with chemotherapy and pulmonary metastasectomy from January 2006 to December 2014. **Result:** We found 56 cases with complete data for revision. Mean age was 25 years (16-48) Patients with lung metastases at diagnosis were 83.9%. All patients were treated with chemotherapy after initial orchiectomy. Preoperative serum tumor markers were negative in 44 patients (78%) Thoracotomy was performed in 48 cases (85.7%) and minimally invasive surgery in 8 cases (14.3%) Pulmonary wedge resection was performed in 52 patients (92.8%) and a lobectomy was required in 4 patients (7.2%) A R0 resection was achieved in 98.3%. Necrosis was reported in 25 cases (44.6%), mature teratoma in 17 (30.4%), viable germ-cell tumor in 13 patients (23.2%) and 1 case with seminoma (1.8%) All patients with viable tumor were offered postoperative chemotherapy. Median follow-up was 53.2 months (6-110). Median Overall Survival has not reached. Factors associated with improved survival were negative preoperative serum tumor markers and abscense of viable germ-cell tumor on resected specimens.



Conclusion: Removal of residual lesions after chemotherapy serves a double purpose, as an adjuvant treatment to chemotherapy allowing for "local" control of metastases and it also provides information about response to chemotherapy, with implications on prognosis and guiding postoperative treatment. In our cohort we demonstrate that despite a high proportion of viable tumors on surgical specimen, multi-modality treatment including lung metastasectomy is associated with prolonged survival

Keywords: lung metastasectomy, germ-cell tumors, pulmonary metastasectomy

MA 16 MEDIASTINAL, TRACHEAL AND ESOPHAGEAL TUMOR: MULTIMODALITY APPROACHES
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MA 16.13 PD-L1 EXPRESSION IS A PROGNOSTIC FACTOR IN PATIENTS WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA TREATED WITH POSTOPERATIVE ADJUVANT RADIOTHERAPY

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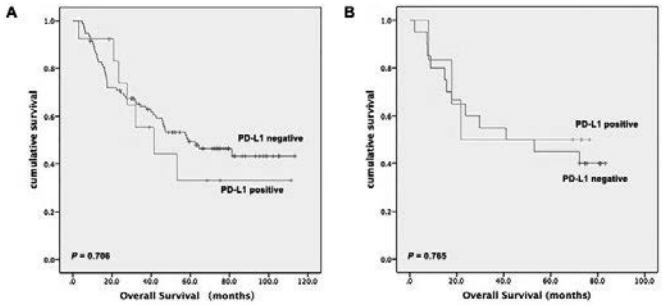
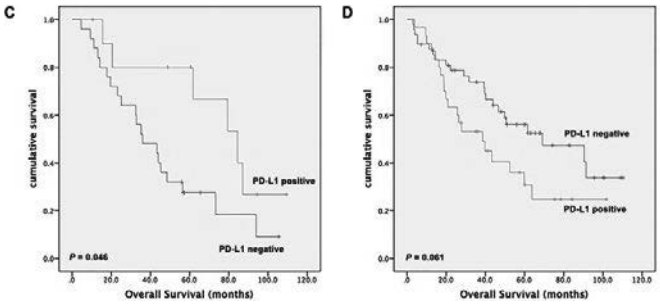
Background: Programmed death-ligand 1 (PD-L1), is reported to serve as an indicator of prognosis in many malignant tumors. The aim of this study was to determine whether PD-L1 expression status in tumor cell can predict patient's prognosis in esophageal squamous cell carcinoma (ESCC). **Method:** 246 paraffin-embedded tissue samples were detected PD-L1 expression by immunohistochemistry from ESCC patients after surgery. And we statistically analyzed the association between expression of PD-L1 and clinicopathological factors and outcomes of survival. **Result:** The rate of positive PD-L1 expression was 24.4% (60/246) . Multivariate analysis indicated positive PD-L1 expression was associated with advanced TNM stage (P=0.009). The median of overall survival (OS) for patients with positive PD-L1 expression was similar to those with negative PD-L1 expression (Median OS, 52.4 vs. 56.4 months, P=0.466). However, in the subgroup analysis, the results indicated that the prognosis of patients with positive PD-L1 expression treated with adjuvant radiotherapy was significantly better than those with negative PD-L1 expression (Median OS, 84.4 vs. 36.0 months, P=0.046), while the OS of positive PD-L1 expression patients treated with adjuvant chemotherapy was poorer than those with negative PD-L1 expression although without significant statistical differences (Median OS, 21.8 months vs. 41.0 months, P=0.765) (Figure 1). Multivariate Cox regression hazards analysis revealed PD-L1 expression statue was not an independent prognostic factor (P=0.804) for entire cohort.





Subgroup analysis for OS in ESCC based upon PD-L1 expression. (A) Subgroup of surgery alone; (B) Subgroup of surgery plus adjuvant chemotherapy; (C) Subgroup of surgery plus adjuvant radiotherapy; (D) Subgroup of surgery plus adjuvant chemoradiotherapy. **Conclusion:** Positive PD-L1 expression was likely to be more associated with malignant biological behavior of ESCC. PD-L1 expression was not a prognostic factor of OS for entire cohort, however, it is a prognostic factor in patients treated with postoperative adjuvant radiotherapy.

Keywords: ESCC, PD-L1, Prognosis

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MA 16.14 C-MET IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA: AN INDEPENDENT PROGNOSTIC FACTOR AND POTENTIAL THERAPEUTIC TARGET

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Background: c-Met is reported to serve as a poor prognostic factor in many malignant tumors. Previous studies have suggested the involvement of c-Met in esophageal squamous cell carcinoma (ESCC), but the correlation between c-Met status and clinical outcome remains unclear. Furthermore, the identification of a novel molecular therapeutic target might potentially help improve the clinical outcome of ESCC patients. **Method:** The expression of c-Met was immunohistochemically assessed in 180 surgically obtained tissue specimens. The correlation between c-Met expression and patients' clinicopathological features, including survival, was evaluated. We also investigated changes in cell functions and protein expression of c-Met and its downstream signaling pathway components under treatments with c-Met inhibitor in ESCC cell line. **Result:** There was no significantly correlated between c-Met expression and patients' clinicopathological features. However, there was a significant difference in OS (median: 41.9 vs. 56.7 months; p= 0.001) between the high c-Met and low/negative c-Met expressing groups. In subgroup of patients with adjuvant radiotherapy, high expression of c-Met was correlated with poor disease prognosis (p= 0.002), while there was no significant correlation in patients with adjuvant chemotherapy. In addition, multivariate analysis identified the high expression of c-Met as an independent prognostic factor. Treatment with c-Met inhibitor significantly inhibited the growth of an ESCC cell line with high c-Met mRNA expression. Moreover, c-Met and its downstream signaling inactivation was also detected after treatment with c-Met inhibitor. **Conclusion:** The results of our study identified c-Met expression as an independent prognostic factor in ESCC and demonstrated that c-Met could be a potential molecular therapeutic target for the treatment of ESCC with high c-Met expression.

Keywords: c-Met, Esophageal squamous cell carcinoma, Molecular targeted therapy

MA 17 LOCALLY ADVANCED NSCLC
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 17.01 SKIP N2, AN INDEPENDENT PROGNOSTIC FACTOR OF SURVIVAL: ANALYSIS OF A FAVOURABLE N2 SUBGROUP

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Background: To date the nodal status is considered one of the most important indicators of prognosis for resectable NSCLC. The latest edition of lung TNM does not include any changes to N descriptors, but several changing proposals are under evaluation: IASLC proposed a subclassification of pN1-N2 based on the number of nodal station involved (pN1a, pN1b; pN2a1, pN2a2, pN2b). The number of positive lymph nodes and the lymph node ratio were also proposed as prognostic indicators of resected NSCLC. The aim of this study was to compare overall survival (OS) and Disease Free Interval (DFI) of pN2a1 ("skip" metastasis) to pN1b and pN2a2-pN2b. **Method:** A retrospectively analysis of 155 patients who underwent a complete resection and a systematic lymph node dissection for T1/T2 N1-N2 NSCLC (VII TNM edition) between 2006 and 2010 was conducted. Patients who underwent induction

therapies or extended resections were excluded. All patients were restaged with the new IASLC proposal. OS, DFI and risk factors of pN1b, pN2a and pN2b patients were analysed. **Result:** An overall mean number of 16 (DS 8,4) lymph nodes were resected: 7,18 (DS 4,2) from the hilum and 8,72 (DS 5,9) from the mediastinum. After restaging all cases with new IASLC proposal we observed: 48 (30,9%) pN1b, 26 (16,8%) pN2a1, 63 (40,7%) pN2a2 and 18 (11,6%) pN2b. With a median follow up of 93 months, the median overall survival of the entire cohort was 27 months. pN2a1 had a significant better overall survival when compared with the other three groups (p=0,042). 1, 3 and 5-year survival for pN1b, pN2a1, pN2a2 and pN2b were 75%, 90%, 81% and 71%; 46%, 53%, 37% and 24%; 24%, 45%, 26% and 19% respectively. A number of more than 5 positive lymph nodes and a lymph node ratio >50% were independent prognostic factors of a worse survival (p=0,004 and p=0,035). **Conclusion:** Our data supports the new IASLC proposal for the revision of N descriptors. Patients with skip lymph node metastasis (pN2a1) have a significant better prognosis compared both to other pN2 groups and to pN1b. Moreover, we confirmed the important prognostic value of the number of the involved lymph node, which should be considered as well in the next edition of the lung cancer staging system.

Keywords: NSCLC, pN2, Surgery

MA 17 LOCALLY ADVANCED NSCLC
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MA 17.02 CLINICAL IMPACT OF THE TUMOR IMMUNE MICROENVIRONMENT AND IMMUNOSCORE IN COMPLETELY RESECTED STAGE IIIA(N2) NON-SMALL CELL LUNG CANCER

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Background: Completely resected stage IIIA(N2) non-small cell lung cancer (NSCLC) patients are considered to be a heterogeneous population. The heterogeneity applies to tumor cells but to the microenvironment as well. Mounting evidence suggests that tumor infiltrating lymphocytes (TILs) are of clinical importance. Hence, we aimed to evaluate the role of the immune microenvironment as an immunoscore in a uniform cohort of patients with completely resected stage IIIA(N2) NSCLC. **Method:** All patients with pathologic stage IIIA(N2) NSCLC who underwent complete resection in our hospital from 2005 to 2012 were retrospectively reviewed. Tissue microarrays were constructed by the surgical pathology specimens from primary lung tumors. For each specimen, we selected two cores from the tumor center (CT) and two cores from invasive margin (IM) region. Densities of immune cell subpopulations (CD3+, CD45RO+, and CD8+ TILs) were evaluated using immunohistochemistry with image analysis workstation (Vectra 3.0). Immunoscore is based on the numeration of two lymphocyte populations: CD45RO+ memory lymphocytes and CD8+ cytotoxic cells, quantified within the CT and IM. The immunoscore (I) provides a score ranging from I0 when low densities of both cell types are found in both regions, to I4 when high densities are found in both regions. The results were correlated with tumor recurrence and patient survival. **Result:** Of the eligible 357 patients, 288 patients with well-established lung tumor samples were obtained and included in the analysis. The median follow-up duration was 54.9 months (range, 23.9-132 months) for the living patients. The 5-year distant metastasis-free survival (DMFS) and overall survival (OS) rates were 26% and 34%, respectively. In univariate analyses, densities of CD3+ cells were associated with neither OS nor DMFS, whereas CD45RO+ cells in IM were prognostic for DMFS (P=0.02) and OS (P=0.05). Combining CD45RO and CD8+ TILs (CT plus IM), the immunoscore(I) significantly increased the prognostic impact. Of the 288 patients, there were 68 (24%) with I0, 64 (22%) I1, 58 (20%) I2, 48 (17%) I3, and 50 (17%) I4. Five-year DMFS and OS rates were 17% and 28% for the group with low immune score (N=190, I0-2), compared with 42% and 45% for the group with high immune score (N=98, I3-4), respectively (DMFS P<0.001; OS P=0.001). Multivariate analyses showed that the immunoscore had independent effects on DMFS (P<0.001) and OS (P<0.001). **Conclusion:** The immunoscore in NSCLC may provide powerful prognostic information, including the prediction of DMFS and OS, and thus facilitate clinical decision making regarding systemic therapy in patients with completely resected stage IIIA(N2) NSCLC.

Keywords: stage IIIA(N2) non-small cell lung cancer, immunoscore, tumor microenvironment

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MA 17.03 PROGNOSTIC VALUE OF THE NEW IASLC/ATS/ERS LUNG ADENOCARCINOMA CLASSIFICATION IN COMPLETELY RESECTED STAGE IIIA(N2) NSCLC

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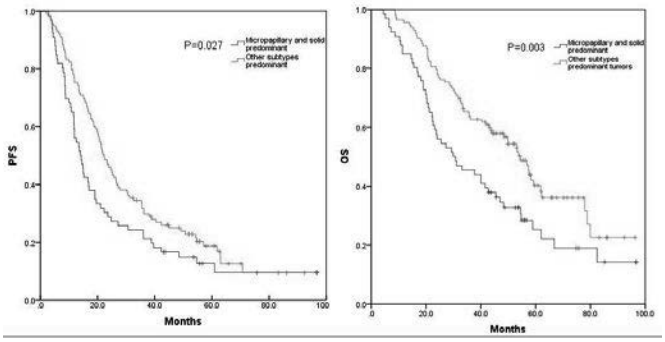
Background: Completely resected stage IIIA(N2) non-small cell lung cancer (NSCLC) patients are a heterogeneous population, with 5-year survival rates ranging from 10% to 30%. The aim of this study was to investigate the relationship between the predominant subtype according to the new IASLC/ATS/ERS pathologic classification and prognosis in completely resected stage IIIA(N2) lung adenocarcinoma. **Method:** The medical records of 179 consecutive patients with completely resected stage IIIA(N2) NSCLC were reviewed between January 2005 and July 2012. According to the new pathologic classification, each tumor was reviewed using the comprehensive histological subtyping while recording the percentage in 5% increments for each histological component. Adenocarcinoma was divided into lepidic predominant, papillary predominant, acinar predominant, micropapillary predominant and solid-predominant. The predominant pattern was defined as the pattern with the largest percentage. To compare progression-free survival (PFS) and overall survival (OS) time between difference subtypes in lung adenocarcinomas, log-rank test was used for univariate analysis, and cox regression was used for multivariate analysis. **Result:** The median follow-up time was 42.7 months (range, 4.4–96.7months). The median PFS and OS time was 19.6 and 45.5 months, respectively. The 5-year PFS and OS rates were 16.4% and 34.6%, respectively. Patients with micropapillary and solid predominant tumors had poorer PFS (p=0.027) and OS (p=0.003) as compared to those with other subtypes predominant tumors. Micropapillary and solid predominant tumors were also significantly associated with an increased risk of locoregional recurrence (P=0.025), while not significantly associated with distant metastasis (P=0.21) than other subtypes predominant tumors. Multivariate analysis revealed that the new classification, chemotherapy, clinical N stage and LN ratio were independent prognostic factors for OS.



Conclusion: In patients with completely resected stage IIIA(N2) NSCLC, the predominant subtype according to new IASLC/ATS/ERS classification was an independent prognostic factor. It is valuable of screening out high risk patients to receive postoperative adjuvant therapy.

Keywords: IASLC/ATS/ERS classification, Prognosis, non-small cell lung cancer

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MA 17.04 INITIAL SURGERY IN PATIENTS WITH CLINICAL N2 NON-SMALL CELL LUNG CANCER: A MULTI-INSTITUTION RETROSPECTIVE STUDY

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Background: There is no large scale study of the initial surgery for patients with cN2 disease who received positron emission tomography (PET). We investigated the outcomes of initial surgery for patients with cN2 disease who had received PET, by conducting a multi-institutional retrospective study. **Method:** Clinical data for 143 patients who had cN2 disease and underwent initial surgery at 12 Japanese institutions in Thoracic Surgery Study Group of Osaka University (TSSGO) between January 2006 and December 2013 were collected. After reviewing all the data for eligibility, completeness, and consistency, 8 cases were excluded. The remaining 135 cases were feasible for analysis. Among these patients, 98 received PET and were analyzed. **Result:** The median follow-up was 56.5 months (2-110 months). The median age was 67 (35-80) years. There were 71 males and 27 females. The histology was adenocarcinoma (n=66), non-adenocarcinoma (n=33). The tumor location was the right upper lobe and left upper segment (n=66, 67.3%), and the others (n=32, 32.6%). Of 98 patients, 85 (86.7%) had clinical single N2 disease and 80 (81.6%) had no mode of spread lesion and 90 (91.8%) underwent lobectomy. The 5-year relapse free survival (RFS) rate and the 5-year overall survival (OS) rate for patients with cN2 were 34.6% and 46.6%. There were 24 patients (24.9%) with cN2pN0,1 and 74 patients (75.5%) with pN2. Of 74 patients with cN2pN2 disease, 42 (59.5%) had pathological single N2 disease and 40 (54.0%) underwent adjuvant chemotherapy. The 5-year RFS for the patients with cN2 in the cN2pN0,1 and cN2pN2 groups were 62.2% and 26.0%, respectively (p=0.0025). The 5-year OS for the patients with cN2 in the cN2pN0,1 and cN2pN2 groups were 74.8% and 40.0%, respectively (p=0.029). Moreover, we provided the following 3 criteria: primary tumor in right upper lobe or left upper segment, N2 disease with regional mode of spread, and patients who did not undergo pneumonectomy. 60 patients who fulfilled all of these

criteria were regarded as specific group. The 5-year OS for the patients with cN2 in the specific group and non-specific group was 55.8% and 32.0%, respectively (p=0.024). **Conclusion:** Among patients with cN2 disease, those with pN2 disease were more in number in our study than in previous reports. Our patients with cN2pN2 had better survival compared with those in previous reports. In particularly, patients with clinical N2 disease in specific group have a favorable prognosis. An initial surgery may be considered as a treatment option for these patients.

Keywords: clinical N2 disease, initial surgery, Positron emission tomography

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MA 17.06 SAFETY DATA FROM RANDOMIZED PHASE II STUDY OF CDDP+S-1 VS CDDP+PEM COMBINED WITH TRT FOR LOCALLY ADVANCED NON-SQUAMOUS NSCLC

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Background: Both cisplatin (CDDP)+S-1 and CDDP+pemetrexed (PEM) can be given at full systemic doses with thoracic radiotherapy (TRT) in locally advanced non-small cell lung cancer (NSCLC), and CDDP+PEM is one of the standard chemotherapy regimens in patients with advanced non-squamous (non-sq) NSCLC. This multicenter, randomized, open-label, phase II study (SPECTRA) compared the efficacy and safety of the two above-mentioned promising regimens combined with TRT in patients with unresectable locally advanced non-sq NSCLC. **Method:** Patients were randomly assigned to receive CDDP+S-1 (CDDP 60mg/m2, d1, and S-1 80mg/m2, d1-14, q4w, up to 4 cycles) or CDDP+PEM (CDDP 75mg/m2, d1, and PEM 500mg/m2, d1, q3w, up to 4 cycles) combined with TRT 60Gy in 30 fractions. The primary endpoint was 2-year progression-free survival (PFS) rate. If the 2-year PFS rate is assumed to be 25% in the inferior therapy group and 15% higher in the superior therapy group of this study, the sample size needed for selection of the optimum treatment group at a probability of approximately 95% will be 51 cases/group with the Simon's selection design. The sample size was set at 100 patients. **Result:** Between Jan 2013 and Oct 2016, 102 patients were enrolled in this study from 9 institutions in Japan. All 102 patients were eligible and assessable, of whom 52 were assigned to CDDP+S-1 and 50 to CDDP+PEM. Baseline characteristics were similar (CDDP+S-1/CDDP+PEM): median age (range) 64.5 (39-73)/63.5 (32-74) years; women, n=17 (33%)/n=17 (34%); stage IIIB, n=21 (40%)/n=20 (40%); ECOG PS of 1, n=14 (27%)/n=14 (28%); never smoker, n=12 (23%)/n=12 (24%); and adenocarcinoma, n=47(90%)/n=45(90%). Completion rate of TRT (60Gy) and chemotherapy (4 cycles) was 92%/98% and 73%/86%, respectively. Response rate was 60%/64%. Grade 3 or higher toxicities included febrile neutropenia (12%/2%), anorexia (8%/16%), diarrhea (8%/0%), esophagitis (6%/8%), pneumonia (4%/4%), neutropenia (38%/52%), anemia (8%/12%), thrombocytopenia (4%/6%), and hyponatremia (12%/12%). Grade 1 radiation pneumonitis was observed in 8 (15%)/2 (4%) patients on the basis of the data collected 30 days or less after the discontinuation of protocol treatment. No treatment-related death was observed. The data on PFS and overall survival are immature. **Conclusion:** Response rate was similar between the two arms. Toxicities were tolerable and manageable in both arms; however febrile neutropenia was more frequently observed in the CDDP+S-1 arm. We will present the updated safety data of this study at the conference. Survival data will be analyzed in late 2018.

Keywords: Locally advanced non-squamous NSCLC, CDDP+S-1, CDDP+pemetrexed

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MA 17.07 VELIPARIB IN COMBINATION WITH PACLITAXEL/CARBOPLATIN (P/C)-BASED CHEMORADIOTHERAPY (CRT) IN PATIENTS WITH STAGE III NSCLC

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Background: CRT is a standard for patients with Stage III non-small cell lung cancer (NSCLC). Veliparib (V) is a potent, orally bioavailable PARP1/2 inhibitor that can delay DNA repair following chemotherapy or radiation induced damage. A phase 2 study indicated favorable efficacy of V vs placebo when added to P/C in advanced NSCLC (Ramalingam et al. Clin Cancer Res. 2016). Based on these results, a phase 1/2 trial was initiated to study the safety and efficacy of V/P/C-based CRT in the treatment of Stage III NSCLC. **Method:** Patients without prior NSCLC therapy suitable for definitive CRT received V plus C AUC 2 + P 45 mg/m^2 weekly + 60 Gy over 6-9 weeks. V was escalated from 60 mg BID to a maximum planned dose based on prior studies of 240 mg BID via 3+3 design with over-enrollment allowed followed by consolidation therapy of V 120 mg BID + C AUC 6 + P 200 mg/m^2 for up to two 21-day cycles. **Result:** Thirty-nine patients (median age 66; 14 male) have been enrolled to date into dosing cohorts at 60 mg (7), 80 mg (9), 120 mg (7), 200 mg (8), and a maximum planned dose of 240 mg (8). Median tumor volume at screening was 81 cc (16-555 cc). PK of V was dose proportional. CRT or V required dose reduction for 0 or 1 patient, respectively. Four (10%) patients discontinued study during CRT. No DLTs were observed and an MTD has not been identified. The most common any-grade AEs were esophagitis (23), nausea (22), fatigue (20), neutropenia (19), and thrombocytopenia (19). 27 SAEs occurred including 12 SAEs with reasonable attribution to V but outside the DLT window including G3/4 febrile neutropenia (2), G3 dehydration (1), G3 vomiting (1), G3 esophagitis (1), G3 radiation esophagitis (1), G3 esophageal stricture (1), G3 intractable N/V (1), G3 aspiration pneumonia (1), G3 radiation pneumonitis (1), G4 sepsis (1), and G5 sepsis during consolidation (1). Of 29 patients evaluable for tumor assessment, best response was CR (2), PR (22), SD (3), and PD (2). **Conclusion:** V/P/C-based CRT followed by V/P/C consolidation therapy is a tolerable regimen for the treatment of Stage III NSCLC. The RPTD for V during CRT is 240mg BID. A randomized placebo-controlled phase 2 extension of this study is planned. Clinical trial information: NCT02412371

Keywords: Chemoradiotherapy, veliparib, non-small cell lung cancer

MA 17 LOCALLY ADVANCED NSCLC
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 17.08 THE VALIDITY OF TNM CLASSIFICATION AFTER INDUCTION TREATMENT IN PATIENTS WITH NSCLC: PULMONARY RESECTION WITH OR WITHOUT INDUCTION TREATMENT

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Background: Pathological staging (pTNM) after lung resection provides the most reliable data for staging non-small cell lung cancer (NSCLC) and predicting long-term survival. However, the survival rate of patients who undergo direct surgical treatment (pTNM) may differ from those who undergo lung resection after induction treatment due to locally advanced lung cancer (ypTNM). In this study we aim to compare the survival rate of pTNM versus ypTNM. **Method:** In this study, we retrospectively reviewed the prospectively recorded data of the patients undergoing surgery (segmentectomy or more) for NSCLC between 2006 and 2016. The patients were staged according to the 8th edition of TNM staging and divided into two groups. Group 1: patients who underwent direct surgical resection (n:450), Group 2: patients who received induction treatment before surgical resection for locally advanced NSCLC (n:345). We compared the survival rates and additional factors that affected the survival rates. **Result:** Postoperative histopathological investigation revealed ypT0N0 in 66 patients (complete response, group 2), stage 1 in 310 patients (group 1 n=211, group 2 n= 99) stage 2 in 223 patients (group 1 n=133, group 2 n= 90), stage 3 in 177 patients (group 1 n=100, group 2 n= 77), stage 4 in 19 patients (group 1 n=6, group 2 n= 13). Five year survival rate in all patients was 59,4% (group 1= 64,6%, group 2= 52,7%, p=0,001). Five year survival rate was 69,7% for complete response group. For patients with stage 1 disease survival rates were 81,9% for group 1 and 63,5% for group 2 (p=0,001). Patients with stage 2 had 5 year survival rates of 55,9% for group 1 and 45,9% for group 2 (p=0,11). Patients staged 3 and 4 had 5 year survival rates of 44,8% for group 1 and 34,4% for group 2 (p=0,10). **Conclusion:** This study revealed that survival rates varied between the patients who underwent direct surgery (pTNM) and the patients who underwent induction treatment before lung resection for locally advanced NSCLC. We recommend that the IASLC should examine the ypTNM stage in more detail in order to achieve more accurate results.

Keywords: TNM, Staging, Neoadjuvant treatment

MA 17 LOCALLY ADVANCED NSCLC
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MA 17.10 TOXICITY RESULTS FROM THE RANDOMIZED PHASE III NVALT-11 STUDY OF PROPHYLACTIC CRANIAL IRRADIATION VS. OBSERVATION IN STAGE III NSCLC

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Background: NVALT-11 randomized trial showed that PCI reduced the proportion of stage III NSCLC patients with symptomatic BM from 28 % to 5 % (Groen ASCO 2017). Here, we report on the toxicity. **Method:** We randomized between PCI or observation in radically treated stage III NSCLC. Primary endpoint: incidence of symptomatic brain metastases; secondary endpoints: OS, toxicity and quality of life. **Result:** Between 2009 and 2015 a total of 195 pts were registered, 175 were randomized, 87 received PCI and 88 pts were in the observation arm. Median follow up: 48.5 months (95% CI, 39-54). Neurological adverse events (AE) of all grades that occurred more frequently in the PCI vs. the observation arm: cognitive disturbance (18 vs. 2 pt; $p< 10^{-4}$) and memory impairment (25 vs. 7 pt; $p<10^{-3}$). No significant difference in G3-4 cognitive disturbance and memory impairment. Non-neurological AE of all grades that were more frequent in the PCI arm: alopecia (36 vs. 5 pt; $p<10^{-6}$), fatigue (55 vs. 29 patients; $p<10^{-4}$), nausea (30 vs. 15 patients; p=0.01), anorexia (6 vs. 0 patients; p=0.01) and dysphagia (11 vs. 2 pt; p=0.01). Of the G3-4 AE, only fatigue was significantly more present in the PCI arm (13 vs. 2 pt, $p < 0.01$). Scored as treatment-related, neurological toxicities of all grades that occurred more frequently in the PCI vs. the observation arm: cognitive disturbance (7 vs. 0 pt; p=0.01), dizziness (7 vs. 0 pt; p=0.01) and memory impairment (14 vs. 0 pt; $p<10^{-4}$). No significant differences in G3-4 toxicities, with only one patient reporting severe cognitive disturbance in the PCI group. Scored as treatment-related, non-neurological toxicities of all grades that were more frequent in the PCI arm: alopecia (26 vs. 1 pt; $p<10^{-6}$), fatigue (19 vs. 2 patients; $p<10^{-4}$), nausea (16 vs. 0 patients; $p<10^{-5}$), headache (19 vs. 1 pt; $p<10^{-5}$), rash (8 vs. 0 pt; p<0.01) and vomiting (9 vs. 0 pt; p<0.01). No significant differences in G3-4 toxicities, with 3 patients reporting severe fatigue, 2 nausea and 1 vomiting, all in the PCI group. Overall QoL was worse in the PCI arm 3 months post-treatment, but was similar to observation thereafter. **Conclusion:** PCI related symptoms were mainly grade 1-2 memory and cognitive disturbances and fatigue. G3-4 toxicities were very rare. QoL was only temporarily affected by PCI. The side effects of PCI should be balanced against deteriorating BM symptoms and the lack of OS benefit (Groen ASCO 2017).

Keywords: PCI, Phase III trial, non-small cell lung cancer

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MA 17.11 PREDICTION OF RESPONSE TO TRIMODALITY THERAPY USING CT-DERIVED RADIOMIC FEATURES IN STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

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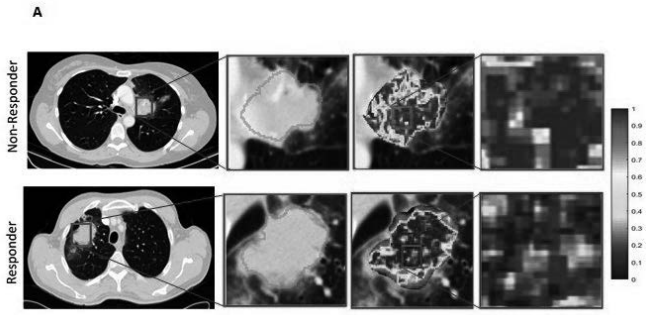
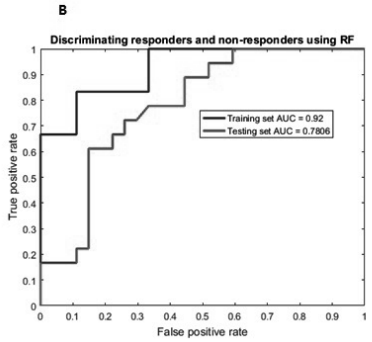
Background: There are no clinically validated biomarkers to identify patients with locally advanced NSCLC who benefit from trimodality therapy (TMT) (i.e. neoadjuvant chemoradiation (NAT) followed by surgery). In this study, we evaluate radiomic (i.e. computer extracted imaging) features of tumor phenotype as potential predictors of pathological response. **Method:** 123 patients with stage III NSCLC who received TMT were selected for this study. Of these, 33 patients including those with distant metastasis at presentation and those without baseline pre-NAT CT scans were excluded. Lung tumors were retrospectively contoured on 3D SLICER software by an expert reader. A total of 1542 radiomic features (textural and shape) were extracted from intra and peritumoral region using the MATLAB® 2016a platform (Mathworks, Natick, MA). A random forest (RF) machine classifier was trained with the most predictive features identified on the training set (n=45) and then validated on an independent test set (n=45). The primary endpoint of our study was pathological response defined as the percentage of the residual viable tumor. **Result:** 90 patients with NSCLC were included for analysis with a median age of 64 years (38–88), and 54.4 % men. Tumor histology was predominantly adenocarcinoma (71.1%), stage IIIA (94.4%), with positive N2 nodes (91.1%). Pathological response was achieved in 36 (40%) patients; labeled responders (R) and the rest 54 (60%) were labeled non-responders (NR). No statistically significant difference was found in clinical characteristics. We identified five radiomic features (intratumoral and peritumoral textural patterns) predictive of pathological response (Area under Receiver Operating Characteristic (ROC) Curve = 0.7806, RF classifier).





A) Higher textural entropy values observed for non responders compared to responders, in turn reflecting more disordered tumor microarchitecture in non-responders. B) ROC curve for discriminating responders and non-responders using RF classifier.

Conclusion: Texture features extracted from within and around the lung tumor on CT images were predictive of pathological response to NAT. Additional validation of these quantitative image-based biomarkers is warranted for accurate early identification of responders who could be potentially spared surgery.

Keywords: radiomics, non-small cell lung cancer, chemoradiation

MA 17 LOCALLY ADVANCED NSCLC
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MA 17.12 COMPARISON OF EORTC, PERCIST, PETERMAC & DEAUVILLE PET RESPONSE CRITERIA AFTER RADICAL CHEMORT IN NON-SMALL-CELL LUNG CANCER

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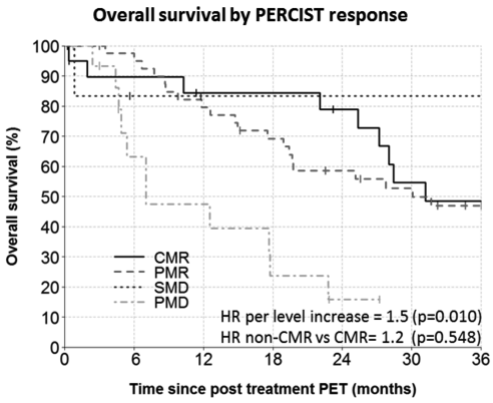
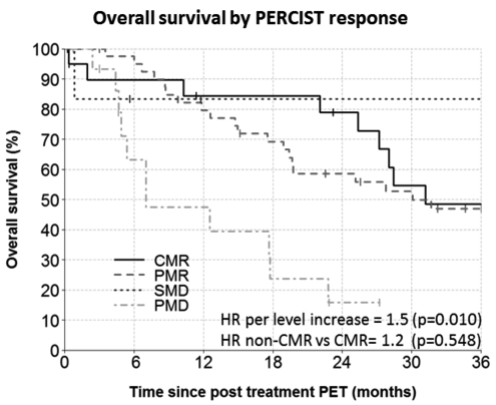
Background: Response criteria for 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) for thoracic malignancies include European Organization for Research and Treatment of Cancer (EORTC) criteria, Positron Emission tomography Response Criteria In Solid Tumors 1.0 (PERCIST), PeterMac Metabolic Visual Criteria and Deauville Criteria. It is unknown which criteria have the highest prognostic value in NSCLC. **Method:** Between 2004 and 2016, three NSCLC prospective trials included patients treated with radical radiotherapy (RT) or chemoRT with baseline and post-treatment FDG-PET imaging. For each patient, the four FDG-PET response criteria were reported retrospectively and blinded to outcome. Responses to therapy were categorized as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD) or progressive metabolic disease (PMD) and correlated with subsequent survival using Cox proportional hazard models, c-statistic, r^2 and Akaike information criterion (AIC). **Result:** Eighty-seven NSCLC patients underwent FDG-PET before and after radical RT (n=7) or chemoRT (n=80). Follow-up FDG-PET scans were performed at a median of 89 days (range 47-123 days) after RT. After a median follow-up of 49 months, median survival after PET response imaging was 28 months. Both qualitative response criteria (PeterMac and Deauville) showed perfect agreement (kappa = 1.0). Both semiquantitative criteria (EORTC and PERCIST) showed almost perfect agreement (kappa = 0.96). All four response criteria showed statistically significant associations with overall survival. The PeterMac and the Deauville criteria showed stronger survival associations (AIC=357.9) compared to EORTC (AIC=362.3) and PERCIST (AIC=362.6). The two qualitative criteria also performed better in the distinction between CMR and non-CMR (HR = 1.9, CI 1.0-3.4, p=0.047) versus EORTC (HR=1.2, CI 0.6-2.3, p=0.566) and PERCIST (HR 1.2, CI 0.6-2.3, p=0.548). Only 1, 4 and 6 patients had SMD in respectively PeterMac/Deauville, EORTC and PERCIST.





Conclusion: The visual PeterMac and Deauville criteria showed stronger predictive capacity than EORTC and PERCIST criteria, especially for distinguishing CMR from non-CMR.

Keywords: chemoradiation, Locally advanced NSCLC, FDG-PET response

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MA 17.13 IMPACT OF HISTOLOGIC SUBTYPE OF LOCALLY ADVANCED LUNG ADENOCARCINOMA ON OUTCOMES AFTER DEFINITIVE CHEMORADIATION

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Background: Micropapillary and solid subtypes of lung adenocarcinoma have significantly worse outcomes and survival after surgical resection for early-stage disease. These subtypes have recently been shown to have higher locoregional and metastatic progression after definitive stereotactic radiation therapy (SBRT) as well. However, the potential impact of histologic subtype on locally advanced disease treated with definitive concurrent or sequential chemoradiation (CRT) has not been previously explored. We sought to identify high-risk subtype patients treated with CRT, and compare their outcomes with those not known to have high-risk histologic subtypes. **Method:** We identified 249 consecutive patients with stage IIIA-B lung adenocarcinoma who had undergone CRT at our institution from 2008 to 2015. All patients had pathology reviewed by pathologists at our institution with subspecialty expertise in thoracic pathology. Twenty-five patients had elements of micropapillary and/or solid subtype on core biopsy, according to the 2015 World Health Organization classification. The remaining 224 patients were considered non-high-risk (8 patients had core biopsy with no high-risk subtypes identified; 216 patients either did not undergo core biopsy or did not have subtyping performed). Local, nodal, regional, and distant failure were estimated using cumulative incidence (CI) curves and compared using the log-rank test. Time to each event was measured from the date of diagnosis until the event of interest or the last follow-up visit. **Result:** With median followup of 19.7 months, there was a trend towards greater 2-year CI of local failure in the high-risk vs. non-high-risk group (40.7% vs. 26.7% p=0.060). The 2-year CI of nodal, regional, and distant failure in high-risk versus non-high-risk groups was 30.9% vs. 32.6% (p=0.576), 24.7% vs. 20.1% (p=0.468), and 63.9% vs. 59.8% (p=0.272), respectively, though statistical power was limited due to the small number of known high-risk patients. **Conclusion:** Though only a limited proportion of patients had demonstrated high-risk subtypes in this cohort, there was a trend towards earlier local failure in locally advanced adenocarcinoma patients treated with definitive concurrent or sequential chemoradiation, similar to what has been observed for early-stage tumors treated with SBRT. Hence, high-risk histologic subtype may be a prognostic factor for early treatment failure in locally advanced adenocarcinoma patients treated with CRT. We suggest that core biopsies, which are required for histologic subtyping, should be obtained more often in these patients, to allow for further study of the hypothesis that histologic subtype predicts outcomes after definitive chemoradiation.

Keywords: histologic subtype, chemoradiation

MA 17 LOCALLY ADVANCED NSCLC
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MA 17.14 PHASE I TRIAL EVALUATING MEK INHIBITOR SELUMETINIB WITH CONCOMITANT THORACIC RADIOTHERAPY IN NON-SMALL-CELL LUNG CANCER

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Background: The RAS/RAF/MEK/ERK signalling pathway has a pivotal role in cancer proliferation and modulating response to treatment. Selumetinib, an inhibitor of MEK, has been shown to enhance the effect of radiotherapy (RT) in preclinical studies. **Method:** Single-arm, single-centre, open-label phase I trial. Patients with stage III non-small cell lung cancer (NSCLC) not suitable for concurrent chemo-radiotherapy or stage IV with dominant thoracic symptoms. Patients were recruited to a dose-finding stage (based on the Fibonacci 3+3 design; maximum number =18) followed by the recruitment of an expanded cohort (n=15). Oral Selumetinib (AZD6244, ARRY-142886) was administered at a starting dose of 50mg twice daily commencing 7 days prior to RT, then in combination with thoracic RT for 6-6.5 weeks (60-66Gy in 30-33 fractions). The primary objective was to determine the recommended Phase II dose. **Result:** From 06/10-02/15, 21patients enrolled. Median age 63 years (range 50-73). M:F ratio 12(57%):9(43%). ECOG PS 0:1, 7(33%):14(67%). Stage III 16(76%):IV 5(24%). Mean GTV 64cm^3 (range 0.8–223.7). In the dose-finding stage, 2 out of 6 patients experienced dose-limiting toxicities (DLT) but only one DLT (G3 diarrhoea) was attributable to treatment. Despite meeting criteria for escalation, trial management group elected to treat patients on the expanded cohort (n=15) at the starting dose. All 21 patients completed RT as planned and received induction chemotherapy. Compliance rate of Selumetinib was >80%. Common adverse events are listed-see table. There were 2 survivors (24 & 26months) at analysis. The median survival was 9.7 months and 2-year survival was 24%. The main cause of disease progression was distant metastases in 16/21 (76%). **Conclusion:** The combination of thoracic RT and Selumetinib is feasible and associated with an acceptable toxicity profile. However our efficacy results, based on 21 patients, suggest that this combination should not be pursued in a subsequent phase II trial.

Acute Toxicity (CTCAE v4.0) (during treatment and including up to 3 months post treatment)		
Toxicity	**Grade**	**N = 21 (%)**
Acneiform rash	0 1 2 3	4 (19.04%) 7 (33.33%) 9 (42.86%) 1 (4.76%)
AST[1] increased	0 1 3	17 (80.95%) 3 (14.29%) 1 (4.76%)**
Diarrhoea	0 1 2 3	5 (23.81%) 13 (61.90%) 2 (9.52%) 1 (4.76%)*
GGT[2] increased	0 1 2 3	16 (76.19%) 2 (9.52%) 2 (9.52%) 1 (4.76%)
Haemoptysis	0 1	19 (90.48%) 2 (9.52%)
Maculo-papular rash	0 1 3	16 (76.19%) 4 (19.05%) 1 (4.76%)
Mucositis	0 1 2	18 (85.71%) 2 (9.52%) 1 (4.76%)
Nausea	0 1 2	11 (52.38%) 9 (42.86%) 1 (4.76%)
Radiation dermatitis	0 1 2 3	8 (38.10%) 7 (33.33%) 5 (23.81%) 1 (4.76%)
Radiation oesophagitis	0 1 2 3	3 (14.29%) 2 (9.52%) 15 (71.43%) 1 (4.76%)
Radiation pneumonitis	0 1 2	15 (71.43%) 0 6 (28.57%)
Late Toxicity (follow up from 3+ months onwards)		
Toxicity	**Grade**	**N = 21 (%)**
Pneumonitis	0 1 2	16 2 (9.52%) 3 (14.29%)
Pulmonary fibrosis	0 1	19 2 (9.52%)
Radiation oesophagitis	0 2	19 (90.48%) 2 (9.52%)
* patient stopped drug on day 49 **patient stopped drug on day 29 abbreviations: 1) AST, Aspartate aminotransferase 2) GGT; Gamma-glutamyltransferase		

Keywords: MEK inhibitor, Radiotherapy, phase i

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
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MA 18.01 DRIVING IMPROVEMENTS IN CANCER CARE ONTARIO'S SMOKING CESSATION INITIATIVE FOR CANCER PATIENTS IN ONTARIO, CANADA

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Background: Substantial evidence exists that quitting smoking after a cancer diagnosis can result in improved treatment efficacy and safety, decreased risk of recurrence and second primary cancers, and lower mortality. Based on this evidence,

Cancer Care Ontario (CCO) implemented a smoking cessation program for new ambulatory cancer patients in Ontario's 14 Regional Cancer Centres (RCCs) in 2014. Implementation is monitored centrally by CCO using performance indicators and monthly discussions with regional champions. Significant variation in implementation processes and performance metrics amongst RCCs highlighted a need for quality improvements. **Method:** Funding received from the Canadian Partnership Against Cancer enabled CCO to undertake a series of initiatives to enhance provider and patient education and to standardize processes. Based on program learnings and emerging evidence, the program model was revised from 5As (Ask, Advise, Assess, Assist, Arrange) to 3As (Ask, Advise, Act), and site-specific recommendations were provided to support consistency in implementation. Patient-facing materials, an on-line learning module, scripts and videos were developed to educate healthcare providers and patients on the health benefits of smoking cessation in order to improve rates of screening and referrals to cessation services. Importantly, two performance indicators have been included on CCO's Regional Scorecard, which measures performance against targets and determines an RCC's overall performance ranking within the province. **Result:** Performance on the Tobacco Use Screening indicator (proportion of new cancer patients screened for tobacco use) was 42.0% across Ontario in April 2015 when first included on the Scorecard. By March 2017, performance had improved to 62.7%, with significant improvements seen among the lowest-performing RCCs. The Accepted a Cessation Referral indicator (proportion of tobacco users who accepted referral to cessation services) improved only modestly from 19.7% in Q1 of 2016/17 to 23.4% in Q4. This indicator will be added to the Regional Scorecard starting in 2017/18. Both indicators are discussed at the quarterly performance reviews with the Regional Vice-Presidents responsible for cancer services. In 2016/17, lung cancer patients accounted for the largest percentage of current users of tobacco by tumour site (21.9%); in addition, almost a quarter of all patients accepting a referral (24.3%) were lung cancer patients. **Conclusion:** The CCO performance Scorecard is a strong driver of quality improvement. CCO is encouraged by regional enthusiasm to adopt the refined 3As model, and anticipates further improvements in the performance metrics, especially in the number of tobacco users who accept referral to cessation services.

Keywords: smoking cessation, implementation, performance indicators

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
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MA 18.02 OUTCOMES OF INTEGRATING SMOKING CESSATION COUNSELING IN A LUNG SCREENING PROGRAM

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Background: The National Lung Screening Trial demonstrated that lung screening reduces lung cancer mortality. In our lung screening program, the incidence of lung cancer is a small percentage (2.3% (10/440)). A more common, treatable, and potentially overlooked condition in this population is nicotine addiction (70.2% smoking (309/440) in our program). It has been widely postulated that lung cancer screening provides a "teachable moment" for smoking cessation. Smoking cessation counseling has been integrated in our lung cancer screening program since 2014. The goal is to report outcomes of integrating smoking cessation in the lung screening program. **Method:** In our lung screening program, all scheduling is done by a single coordinator who is both a Nurse Practitioner and a Certified Tobacco Treatment Specialist (CTTS). A call to schedule the scan is done and initial basic tobacco cessation intervention is integrated into every call. Further follow up as in depth face-to-face counseling is offered at the point of the scan, by the coordinator or other CTTS. Tobacco cessation follow up may be further integrated into telephone calls to give patients screening results. Patients noted to be smoking at the time of the screen (n=103) were surveyed by telephone by a researcher to determine whether they had quit smoking, reduced, or made no changes. Further chart review yielded 107 additional patients unable to be reached by the researcher, but data regarding smoking was available from medical records. **Result:** Of the patients able to be contacted by telephone, 11.7% (12/103) quit smoking, 53.4% (55/103) had reduced the amount they were smoking, and 35.0% (36/103) had made no changes. Additional chart review yielded 107 patients screened and 14.0% (15/107) had documented cessation at least one year after screening. **Conclusion:** Integration of tobacco cessation counseling into our lung screening program led to an overall quit rate of 12.9% (27/210) and of those interviewed, 60.4% (55/91) of those who did not quit, reduced the amount that they smoked. While this may sound modest, this population is heavily addicted, and unaided cessation has poor success rates, often cited as less than 4%. This supports integration of cessation counseling as a potential model for improving smoking cessation in the lung screening population. Further work with integrating pharmacotherapy and more frequent regular follow up may yield even higher success rates.

Keywords: Smoking Cessation, Tobacco Control, Screening

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MA 18.03 ROLE OF ELECTRONIC CIGARETTES IN LUNG CANCER PREVENTION AMONG SMOKERS

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Background: Although the best way for smokers to avoid the health risks associated with smoking is to quit smoking altogether, for those who do continue to smoke the application of a harm reduction strategy could result in substantial reductions in mortality and morbidity. One such approach for continuing smokers would be to promote the substitution of alternative, less toxic means of delivering nicotine, assuming that these were proven to be less hazardous than tobacco smoking and did not cause any additional health risks. Electronic cigarettes, commonly called "e-cigarettes", represent a new stage in which nicotine is delivered in a method that simulates smoking but without involving a tobacco combustion process. **Method:** We measured levels of selected carcinogens and toxicants in aerosol generated from ecigarettes. Using in vitro systems, we studied toxicological effects of e-cigarette aerosol on bronchial epithelial cells. In a longitudinal within-subjects observational study, we assessed exposure to nicotine and selected carcinogens in cigarette smokers who switched to e-cigarettes. In a cross-sectional study, we compared exposure to nicotine and carcinogens among smokers of combustible cigarettes only, e-cigarette user, former smokers with long-term nicotine replacement therapy (NRT) use, and dual users of both combustible cigarettes and e-cigarettes. **Result:** Nicotine solutions used in e-cigarettes vary with respect to concentrations of toxicants. We identified a number of toxicants in e-cigarettes; however the levels of these toxicants were orders of magnitude lower than those found in cigarette smoke. In vitro studies showed that cell viability and metabolic activity were more adversely affected by conventional cigarettes than e-cigarettes. In longitudinal observational study of smokers, we found that after switching from tobacco to e-cigarettes nicotine exposure is unchanged while exposure to toxicants is substantially reduced. Long-term e-cigarette use, but not dual use of e-cigarettes with combustible cigarettes, is associated with substantially reduced exposure levels to carcinogens relative to smoking combustible cigarettes. **Conclusion:** Although it cannot be said that currently marketed e-cigarettes are safe, e-cigarette aerosol is likely to be much less toxic than cigarette smoke. The devices likely pose less direct hazard to the individual smoker than tobacco cigarettes and might help smokers quit smoking or reduce harm by smoking fewer cigarettes. The use of e-cigarettes as a harm reduction strategy among cigarette smokers who are unable to quit, warrants further studies. Further research is needed to evaluate long term effects of switching, including the health effects of continued use of e-cigarettes.

Keywords: smoking, electronic cigarettes, prevention

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
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MA 18.04 CHANGES IN SMOKING BEHAVIOUR IN THE EARLY CANCER DETECTION TEST LUNG CANCER SCOTLAND (ECLS) STUDY

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Background: Lung cancer screening might be a 'teachable moment' for smoking cessation or conversely could provide a 'license to smoke'. Such effects should be considered in the overall benefits and harms of screening. Existing evidence of the impact of screening on smoking is mixed. **Method:** A randomised controlled trial of a blood autoantibody test (EarlyCDT-Lung) for the early detection of lung cancer was conducted in 12,210 smokers and ex-smokers in Scotland, UK. The test allowed risk stratification for targeting of a chest X-ray and repeat CT scans. Sub-samples of positive test (n = 321), negative test (n = 361) and control (n = 350) participants completed questionnaires before screening, after receipt of blood test results and at 3, 6 and 12 months post-screening. They self-reported smoking point prevalence, attempts to quit, number of cigarettes smoked per day and the Heaviness of Smoking Index. Multi-level regression analyses, adjusted for confounders, explored differences in smoking over time between screened and control arms and between positive test, negative test and control groups. **Result:** Preliminary results show no statistically significant differences in smoking prevalence between the screened and control arms over time. There was a reduction in smoking prevalence of borderline statistical significance in the positive test group versus controls across all time points (OR 0.46, 95% CI 0.21-1.03). This difference reduced when assuming non-responding smokers were still smoking (OR 0.73, 95% CI 0.38-1.42). Significantly more smokers in the positive test group had recently attempted to stop smoking at 3 months compared to controls (OR 2.29, 95% CI 1.04-5.04). Positive test group smokers were significantly less likely to report smoking 20 or more cigarettes a day than controls across all time points (OR 0.32, 95% CI 0.14-0.69). Negative test group smokers were more likely to score moderate/high/very high on the Heaviness of Smoking Index compared to controls at 6 months. This difference was statistically significant before adjusting for confounders but the adjusted model was no longer significant (OR 2.51, 95% CI 0.90-6.97). **Conclusion:** There was no effect of lung cancer screening on smoking prevalence. The findings indicate a positive test result can be a teachable moment for smoking cessation. They also highlight the short term risk of heavier smoking after a negative test result. This is an important area for further research to ensure

negative lung cancer screening test results do not inadvertently promote continued and heavier smoking.

Keywords: heaviness of smoking, lung cancer screening, Smoking Cessation

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
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MA 18.06 CLINICAL PROGNOSTIC MODEL FOR OLDER PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The median age at diagnosis of lung cancer is 70 years. Older patients are often not prescribed standard therapy. Due to multiple competing causes of death, older patients often do not demonstrate a benefit in overall survival (OS). It is important to know which older patients would actually be candidates for aggressive therapy based on their prognosis, and to develop a simple prognostic model that can help clinicians determine individual prognosis. **Method:** Data on patients enrolled on 38 NCI-sponsored cooperative group clinical trials of advanced non-small cell lung cancer (NSCLC) from 1991 to 2011 were analyzed. Multivariable Cox PH model was built with a stepwise procedure with all potential predictors: age, sex, race, ethnicity (Hispanic or non-Hispanic), performance status, initial stage, BMI, and weight loss in the past 3/6 months. We derived a prognostic score using the estimated Cox PH regression coefficient in the training set. To assess the performance of our prognostic model, we calculated the area under receiver operating characteristic (ROC) curve of 1- and 2-year survival in the testing set. **Result:** The final analysis included 1454 NSCLC patients ≥70 years of age. These patients were randomly divided into a training set (n=962) and a testing set (n=492). The prognostic risk score was calculated as: 3 (if male) + 3 (if PS=1) + 8 (if PS=2) + 11 (if initial stage=IV) + 4 (if weight loss). Patients were classified into three prognostic groups by tertiles: good (0-6), intermediate (7-14) and poor (≥15). The median OS in the three groups in the testing set were: 14.6 months (95% CI, 12.2-18.5); 12.2 months (95% CI, 10.7-14.4) and 7.0 months (95% CI, 5.6-8.9), respectively. Despite its simplicity, the present model had area under the 1-year and 2-year ROCs (0.63 and 0.68, respectively) that were higher than existing models. **Conclusion:** Male gender, poor performance status, distant metastases and weight loss immediately prior to diagnosis predict for poor OS in older patients with advanced NSCLC. This study proposes a simple prognostic model for older adults with advanced NSCLC based on basic clinical characteristics that are part of the routine evaluation process for every patient with NSCLC.

Keywords: older patients, prognostic model, Advanced Non-Small Cell Lung Cancer

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MA 18.07 DISPARITY IN PROGNOSTIC FACTORS AFTER PULMONARY RESECTION IN NON-SMALL CELL LUNG CANCER BETWEEN ASIAN AND WHITE PATIENTS

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Background: Overall survival and in-hospital mortality in resectable non-small cell lung cancer (NSCLC) patients varies with race. Asian patients have a better overall survival compared with White and Black patients, however, the prognostic factors contributing to these differences are still under studied. The aim of this study was to identify race-specific prognostic factors of overall mortality and in-hospital mortality in resectable NSCLC patients. **Method:** Using the Surveillance, Epidemiology, and End Results Registry linked to Medicare claims between 1991-2010, 35,461 NSCLC patients who underwent pulmonary resection were extracted. Factors associated with in-hospital mortality and overall mortality stratified by Asian and White were analyzed by multivariable logistic regression analysis and multivariable cox regression analysis, respectively. **Result:** Factors associated with in-hospital mortality in Asian patients were age ≥ 80 years (adjusted odd ratios (OR_{adj})=5.8, 95% Confidence interval (CI)=1.59-21.23), stage III disease (OR_{adj}=3.93, 95%CI=1.55-9.96), lower lobe lesion (OR_{adj}=3.52, 95%CI=1.54-8.02), pneumonectomy (OR_{adj}=11.12, 95%CI=2.61-47.34), postoperative pulmonary complication (OR_{adj}=5.39, 95%CI=2.51-11.56), postoperative infections (OR_{adj}=28.19, (95%CI=10.62-74.83), and intraoperative complication (OR_{adj}=10.87, 95%CI=2.64-44.79). In White patients factors associated with in-hospital mortality were old age, male gender, higher comorbidity index, advanced stage, non-teaching hospital, lower hospital volume, pneumonectomy, preoperative radiotherapy, postoperative and intraoperative complications. Factors associated with overall mortality in Asian patients were age ≥ 80 years (HR_{adj}=1.63, 95%CI=1.23-2.16), higher Elixhauser comorbidity index (HR_{adj}=1.02, 95%CI=1.01-1.04), lower median income, stage (HR_{adj}(95%CI) =1.89(1.41-2.54) for stage II, 2.19(1.69-2.83) for stage III, and 3.85(2.59-5.73) for stage IV versus stage I), non-teaching hospital, and receiving radiotherapy (HR_{adj}=1.76,95%CI=1.35-2.30). In White patients, factors associated with overall mortality included old age, male gender, single status, higher comorbidity index and score, lower median income, higher stage, non-squamous cell carcinoma, higher tumor differentiation, location of tumor, lower hospital volume, pneumonectomy, no mediastinal lymph node dissection, and receiving chemotherapy or radiotherapy. **Conclusion:** Race specific differences in number and type of prognostic factors for in-hospital and overall mortality point at biological differences in the tumor as well as differences in treatment.

Keywords: Race-specific, In-hospital mortality, overall mortality

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 18.08 ASSESSMENT OF BASELINE SYMPTOM BURDEN IN TREATMENT-NAÏVE PATIENTS WITH LUNG CANCER

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Background: While most cancer therapies are associated with toxicities, a major component of cancer treatment is to reduce cancer-related symptoms and impairment of function. Assessing how well this goal is achieved is dependent on accurate assessments of baseline symptoms prior to initiation of therapy. The objectives of this study were to describe the symptom burden of treatment-naïve lung cancer patients and to examine demographic and disease factors that correlate with symptom severity. **Method:** Symptom data from 460 treatment-naïve patients with lung cancer were obtained using the validated MD Anderson Symptom Inventory via a 0-10 numeric rating scale. Descriptive statistics were used to summarize patient demographic and clinical characteristics. Differences in symptom severity, symptom interference and quality of life by disease stage and histology were examined using either t-test or ANOVA. Multiple linear regression analysis was performed using age, gender, tumor stage and histology to determine significant predictors of pain and shortness of breath. **Result:** The most severe symptoms were fatigue, disturbed sleep, distress, pain, shortness of breath, sadness and drowsiness. About 62% of patients had at least one moderate to severe (rated 5 or greater) symptom, while 48% had at least one severe (rated 7 or greater) symptom. Disturbed sleep, distress, shortness of breath, sadness, and drowsiness were reported to be severe by at least 16% of the patients. As expected, patients with advanced stage had significantly more severe symptoms. Patients with small-cell carcinoma reported the most severe pain and shortness of breath. Multiple linear regression analysis showed that stage was a significant predictor of pain severity while controlling for histology, age and gender. Patients with advanced stage had a pain level that was 1.2 higher than patients with early stage disease (95% CI= 0.5 – 1.8, $p<0.001$. For shortness of breath, both histology and stage were significant predictors of severe levels while controlling for age and gender. Patients with advanced stage had a shortness of breath level that was 0.9 higher than patients with early stage disease (95% CI= 0.4 – 1.6, $p<0.001$). Patients with small cell carcinoma had a shortness of breath level that was 1.5 higher than those with adenocarcinoma (95% CI= 0.35 – 2.6, $p<0.01$). **Conclusion:** In conclusion, as much as 62% of treatment-naïve patients with lung cancer reported at least one moderate-to-severe symptoms prior to initiation of cancer therapy. This high burden suggests that symptoms should be assessed routinely and tracked in parallel with cancer treatment.

Keywords: assessment, symptoms, treatment-naive

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 18.09 ENROLLMENT OF MINORITIES, THE ELDERLY, AND WOMEN IN LUNG CANCER CLINICAL TRIALS

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Background: Despite multiple efforts led by the National Cancer Institute (NCI) specific patient populations remained underrepresented in cancer clinical trials (CT). Therefore, we determined the representation of minorities, the elderly, and women in lung cancer CT in the past 16 years. **Method:** Clinicaltrials.gov was queried on December 31st, 2016 for all completed therapeutic lung cancer trials from 2000 to 2016. Trials with recruitment outside of the U.S. were excluded. Enrollment fraction (EF) was defined as the number of enrollees divided by the 2013 SEER cancer prevalence. Geographic location was classified within the 5 major U.S. regions: Northeast, Southeast, Midwest, Northwest and Southwest. **Result:** Out of 320 CT, only 88 trials (27.5%) reported race/ethnicity comprising 11, 723 enrollees. Industry sponsored 65% of the trials. Non-Hispanic whites (NHW) were more likely to be enrolled in CT (EF 2.8%) than African Americans (AA) (EF 1.5%, $p<0.001$) and Hispanics (EF 2.1% $p<0.03$). Asian patients were well represented (EF 9.2 %). Distribution by race and sex is described on Table 1. Only 44 (50%) trials divided participants by age (<65 or ≥65 years). The representation of trial participants was heavily skewed towards the younger age group. Median age was 62 years and

8,440 (72%) participants were <65 years of age (p<0.001). Industry sponsored trials were less likely to enroll Hispanic patients than NCI sponsored trials (1.1% vs. 3.8%). African Americans were less likely to be recruited in first line trials compared to NHW (11% vs. 36%, p<0.0001). Underrepresentation of minorities was not affected by recruitment site geographic location. **Conclusion:** NHW were more likely to be enrolled in clinical trials than African American and Hispanics, independent of the recruitment site geographic location. Collaboration between investigators, NCI, industry, and the community is necessary to ensure broad access of unrepresented populations to clinical trials.

Race/Ethnicity	2000-2016 Trial Participants n/%	Enrollment Fraction %	2013 Lung Cancer Prevalence %
Non-Hispanic White	9,350 (79.8)	2.8	82.7
African American	638 (5.4)	1.5	10.6
Hispanic	314 (2.7)	2.1	3.6
Asian/PI	1083 (9.2)	8.7	3.1
Native American	75 (0.6)	N/A	N/A
Other	263 (2.2)		
Sex			
Female	4,571 (39)	2.0	55.2
Male	7,152 (61)	3.8	44.8

Keywords: Minorities, disparities, clinical trials

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 18.11 HIGH INCIDENCE OF LUNG CANCER IN EARLY STAGE TCC PATIENTS

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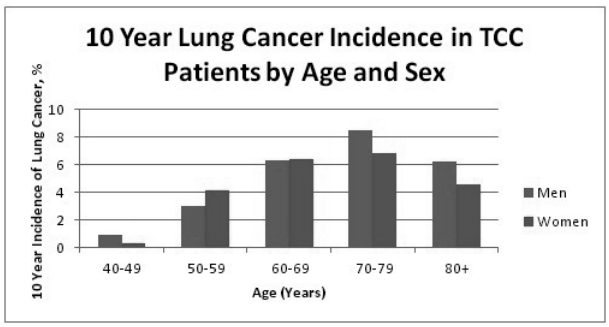
Background: In recent years, clinical studies on screening for lung cancer have demonstrated an initial lung cancer detection rate of 0.8-2.2%, with a total of 2.4-4.7% in 34-78 months of follow up. The National Lung Screening Trial (NLST), which compared screening by LDCT to annual chest X-ray, showed a 20% decrease in mortality in the screened population. Transitional cell carcinoma of the bladder (TCC) has a high survival rate, and has similar risk factors to lung cancer. Thus, TCC patients may stand to benefit from lung cancer screening. **Method:** The SEER (Statistics, Epidemiology and End Results) database was used to determine the incidence, Person-years at risk and the average time to diagnosis of lung cancer in patients with localized TCC of the bladder (American Joint Committee on cancer, 6th ed., stages 0-1) in years 2000-2013. Cumulative Incidence rates were calculated and stratified by age, sex and county level smoking data. **Result:** Based on 88,564 patients with localized TCC (F:M ratio 1:3.3), the 5 year incidence of lung cancer was 3.16%, and 10 year incidence was 5.85%. among patients over 40 from counties with a high percentage of smokers, the 5 year incidence of lung cancer was 3.46%, and 10 year incidence was 6.64%. The median time until diagnosis of lung cancer was 3.89 years for men and 3.16 years for women for ages 60-79, the age group with the highest incidence.



Conclusion: Incidence of lung cancer is high in localized TCC patients and comparable to results seen in the high risk groups currently being screened. Early stage TCC patients may therefore stand to gain from lung cancer screening, and should be considered as potential screening candidates.

Keywords: lung cancer, TCC, Screening

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 18.12 QUALITY OF DATA INFORMING EPIDEMIOLOGICAL STUDIES IN PATIENTS WITH LUNG CANCER

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Background: Epidemiological studies commonly use data from clinical (i.e. medical records) and administrative (i.e. claims data) datasets for the purposes of exploratory analyses, as well as clinical and quality reporting, benchmarking, risk adjustment, and machine learning. Validity is contingent on accurate and detailed reporting of data, demanding robust methodological validation. **Method:** Single centre retrospective comparative study assessing completeness and agreement (kappa-statistic (κ)) of data reporting for key prognostic variables across three independent data sources, among patients with lung cancer. The study population was formed by random selection of patients from an Australian single centre prospective study. Prospectively collected research study-data (SD) was extracted, and then compared to data extracted from individual patient medical records (MR) as well as International Classification of Diseases (ICD) coding from administrative data (AD). **Result:** The study population included 10% of patients from an Australian lung cancer cohort (n=111/1090), and represented the overall cohort in terms of patient demographics and disease characteristics. Prognostic data for stage, comorbidities, smoking history, performance status, and weight loss at diagnosis, was reported for >96% of patients in SD. Comparatively, AD did not report any prognostic data for 42% (47/111) of patients treated in ambulatory settings, and indeed when reported was grossly inaccurate. By way of examples, according to AD, 23% of patients had ≥1 comorbidity versus 68% by MR and 64% by SD; 38% had positive smoking history versus 78% by MR and 81% by SD; 2% had respiratory comorbidity versus 28% by MR and 37% by SD. Similar patterns were observed for other comorbid conditions. Complete TNM staging was captured in only 45% of MR at the time of first treatment, although with good concordance with SD (κ=0.9, 95%CI 0.7, 1.0). Equally when factors were documented in MR they were reasonably concordant with SD: smoking status (completeness 96.4%, κ=0.9, 95%CI 0.8, 1.0), performance status (completeness 82.0%, κ=0.5, 95%CI 0.4, 0.7) and weight loss (completeness 71.1%, κ=0.3, 95%CI 0.1, 0.5). **Conclusion:** Poor capture of factors (either omission or inaccuracy) limit the potential contribution of both MR and AD for use in clinical, epidemiological, and machine learning research – particularly when being utilised to derive diagnostic, prognostic and classification systems. Use of this data for purposes other than intended may misinform estimates of comorbidity disease burden and fail to appropriately adjust for competing mortality risks in models that inform outcomes reporting and ensuing policy decisions.

Keywords: data quality, epidemiology, administrative data

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 18.13 MUTATION PROFILE OF EGFR GENE IN CHINESE PATIENTS WITH NON-SMALL-CELL LUNG CANCER (NSCLC): AN ANALYSIS OF 2,666 CASES

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Background: Mutations of epidermal growth factor receptor (EGFR) gene have been proved as the strongest predictor of response to EGFR-tyrosine kinase inhibitor (TKI) treatment in NSCLC. Currently, 7 most common somatic mutations of EGFR have been reported, among which, L858R and exon 19 deletion theoretically confer sensitivity to EGFR TKIs, other primary EGFR mutations may confer resistance. The EGFR mutation profile showed significant geographical differences (about 35% in East-Asia and 10% in Caucasian population) but very limit data have been reported from China. In addition, we carried liquid biopsy and next generation DNA sequencing analysis on 180 samples from NSCLC patients. We hereby reported the mutation profile EGFR gene in a large scale, real world cohort of 2,666 Chinese NSCLC patients. **Method:** From January 2016 to June 2017, 7 primary EGFR mutations (L858R, Exon 19 del, G719X, L861Q, Exon 20 ins, S768I and T790M) were assayed in tumor tissue (paraffin-embedded or fresh) of 2,666 Chinese patients with NSCLC by a commercial TaqMan PCR kit (Human EGFR Gene Mutations Detection Kit (ACCB)). For liquid biopsy analysis, cell-free DNA is extracted from plasma, a panel of 96-targeted genes was assayed, and genomic alterations in cancer-associated somatic variants are analyzed by massively parallel sequencing. **Result:** Among the 2,666, 1,601(45.9%) were female and 1,447(54.1%) were male, 2,446 (91.7%) had adenocarcinoma (ADC) and 220(8.3%) had squamous carcinoma (SC).The median age of patients was 63 yr (range 17yr-91yr). The detailed EGFR mutation profile was shown in Table 1, the overall incidence of EGFR mutation was 1,319(49.5%). Compare to female patients, male patients showed significant lower rate of EGFR mutation (67.2% vs. 34.6%, p<0.01). More than 50% of patients with ADC showed EGFR mutation while the rate was only 10% in patients with SC. Exon 19 del and L858R, 2 markers for potential better response of TKI, account for the vast majority of all the EGFR mutations.

We found the mutation profiles from samples analyzed by NGS is similar to those analyzed by PCR method. **Conclusion:** In Chinese NSCLC female patients with lung adenocarcinoma, exon 19 del and L858R represented more than 90% of the total EGFR mutations, thus, for those whose EGFR status was unable to be determined, direct TKI treatment many has an odd of 60% to benefit the patients. About 5% of SC patients also showed exon 19 del and L858R mutation which means they could be subjects for TKI treatment.

Keywords: L858R and exon 19 deletion, TKI treatment

MA 18 GLOBAL TOBACCO CONTROL AND EPIDEMIOLOGY II
TUESDAY, OCTOBER 17, 2017 - 15:45-17:30

MA 18.14 NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT AND SURVIVAL IN SCANDINAVIA: THE SCAN-LEAF STUDY

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Background: As the lung cancer treatment landscape evolves, it is important to understand changes in care and outcomes of patients with NSCLC. SCAN-LEAF objectives include describing NSCLC disease, treatments and health outcomes in Scandinavia (Denmark, Norway and Sweden). The present analyses examined treatment proportions and temporal trends in overall survival, drawing on national registry data. **Method:** NSCLC patients diagnosed 2005-2013 (follow-up until 2014) were included in the present analyses of this retrospective longitudinal cohort study. Patient characteristics and treatment described included demographics, disease stage at initial diagnosis [resectable: I-IIIA; locally advanced: IIIA-B (radiation therapy within 3 months); advanced: IIIB (no radiation therapy within 3 months)-IV], histology, non-drug treatment (surgery and radiation: present analyses include Norway and Sweden 2008-2014 only), and survival. Overall survival (OS) (%+95% CI) was calculated 1, 3, and 5 years post-diagnosis, by stage, and by diagnosis year. 66,012 NSCLC patients were diagnosed during 2005-2013 in Scandinavia (53.6% male, mean age 68.9 years); diagnosis stage: resectable (26%), locally advanced (15%), advanced (59%). In Norway and Sweden, surgery was performed on 58.5%, 9.9% and 1.9% of patients at resectable, locally advanced and advanced stage, respectively; radiation therapy in 28.0%, 58.0% and 30.4%, respectively. 1-yr OS gradually and significantly improved by calendar year of diagnosis for all disease stages. At 3 and 5 years post-diagnosis, OS was positively and significantly associated with calendar year of diagnosis for patients with resectable and locally advanced, but not advanced disease (Table 1). **Conclusion:** These analyses showed modest improvements in survival for patients with earlier stage disease over time. However, the majority of patients were diagnosed with advanced stage disease for which no improvement in temporal trends of survival was found, beyond one year post-diagnosis. This suggests an unmet need for effective treatments still remains, particularly for patients with advanced disease.

Keywords: survival, advanced disease, NSCLC

Result:

Table 1. Proportion NSCLC patients from Denmark, Norway and Sweden diagnosed during 2005-2013 who survived 1, 3 and 5 years after diagnosis, by stage and calendar year of diagnosis.

Stage at diagnosis & Calendar year of diagnosis	% survived 1-, 3- and 5-years after NSCLC diagnosis		
	1-year	3-year	5-year
Resectable disease			
Overall	81.0% (80.4%, 81.6%)	56.8% (55.9%, 57.7%)	43.5% (42.5%, 44.6%)
2005	74.7% (72.5%, 77.0%)	51.0% (48.5%, 53.6%)	40.0% (37.4%, 42.5%)
2006	77.0% (74.8%, 79.2%)	53.3% (50.7%, 55.9%)	42.3% (39.7%, 44.8%)
2007	78.6% (76.6%, 80.7%)	55.0% (52.5%, 57.5%)	43.5% (41.1%, 46.0%)
2008	80.6% (78.6%, 82.5%)	56.4% (53.9%, 58.8%)	44.2% (41.7%, 46.7%)
2009	79.7% (77.7%, 81.7%)	57.4% (55.0%, 59.8%)	45.8% (43.3%, 48.2%)
2010	81.4% (79.6%, 83.2%)	59.1% (56.8%, 61.4%)	
2011	83.1% (81.4%, 84.7%)	61.2% (59.0%, 63.4%)	
2012	85.5% (84.0%, 87.0%)		
2013	84.2% (82.7%, 85.8%)		
p-value trend	<0.0001	<0.0001	0.0008
Locally advanced disease			
Overall	52.0% (51.0%, 53.0%)	18.4% (17.5%, 19.3%)	10.8% (9.9%, 11.6%)
2005	45.7% (42.4%, 49.0%)	13.9% (11.6%, 16.2%)	7.8% (6.1%, 9.6%)
2006	45.7% (42.3%, 49.1%)	15.4% (12.9%, 17.8%)	10.7% (8.6%, 12.9%)
2007	51.5% (48.2%, 54.7%)	18.6% (16.0%, 21.1%)	11.0% (9.0%, 13.1%)
2008	50.0% (46.7%, 53.3%)	17.0% (14.5%, 19.4%)	10.3% (8.3%, 12.3%)
2009	50.9% (47.8%, 54.0%)	19.8% (17.4%, 22.3%)	12.9% (10.8%, 15.0%)
2010	51.1% (48.1%, 54.1%)	18.9% (16.5%, 21.2%)	
2011	55.9% (53.1%, 58.7%)	21.2% (18.9%, 23.5%)	
2012	57.0% (54.2%, 59.9%)		
2013	56.1% (53.2%, 59.0%)		
p-value trend	<0.0001	<0.0001	0.0021
Advanced disease			
Overall	26.2% (25.7%, 26.6%)	6.3% (6.0%, 6.6%)	3.4% (3.2%, 3.7%)
2005	24.4% (23.1%, 25.8%)	6.3% (5.5%, 7.0%)	3.5% (2.9%, 4.1%)
2006	24.2% (22.8%, 25.5%)	6.1% (5.4%, 6.9%)	3.4% (2.8%, 4.0%)
2007	25.7% (24.4%, 27.0%)	5.9% (5.2%, 6.6%)	3.1% (2.6%, 3.7%)
2008	25.0% (23.7%, 26.3%)	6.0% (5.3%, 6.7%)	3.3% (2.8%, 3.9%)
2009	26.5% (25.0%, 28.0%)	6.9% (6.0%, 7.8%)	3.9% (3.2%, 4.5%)
2010	26.3% (24.9%, 27.7%)	7.0% (6.2%, 7.8%)	
2011	27.4% (26.1%, 28.8%)	6.2% (5.4%, 6.9%)	
2012	28.1% (26.7%, 29.5%)		
2013	27.9% (26.6%, 29.3%)		
p-value trend	<0.0001	0.2480	0.5359

MA 19 MESOTHELIOMA: BENCH TO BEDSIDE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MA 19.01 A PHASE II STUDY OF NIVOLUMAB: A MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY IN MALIGNANT PLEURAL MESOTHELIOMA (MERIT)

Y. Goto[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 limited treatment options beyond progression after platinum-based combination with pemetrexed chemotherapy. Nivolumab (anti-PD-1, ONO-4538, BMS-936558), a humanized monoclonal antibody, PD-1 immune-checkpoint inhibitor, has demonstrated antitumor activity and a manageable safety profile in several advanced malignancies. Here, we report the preliminary results of a phase II study to evaluate the efficacy and safety of Nivolumab in previously treated Japanese MPM patients (pts): ONO-4538-41/JapicCTI-No.163247. **Method:** This open-label study enrolled advanced or metastatic MPM pts previously treated with up to two regimens of chemotherapy including platinum-based combination therapy with pemetrexed. Enrollment criteria also included histologically-confirmed, unresectable MPM without prior surgery, measurable disease 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. The primary endpoint was the 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, progression-free survival (PFS), and overall survival (OS). **Result:** From July to October 2016, 34 pts were enrolled in 15 centers. 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%. Median follow-up was 6.7 months. Independent review committee-assessed 6-month ORR was 29.4% (n=10, 95%CI: 16.8-46.2) and objective responses were observed across tissue types, epithelioid 7/27 (25.9%), sarcomatoid 2/3 (66.7%), biphasic 1/4 (25.0%). 13 pts (38.2%) had stable disease, resulting in a 6-month DCR of 67.6%. Median PFS was 6.1 months (95%IC: 2.9-NR). Median OS has not been reached. 6-month PFS and OS rates are 50.9% (95%CI: 32.7-66.5) and 85.3% (95%IC: 68.2-93.6). 23 (67.6%) pts experienced drug-related adverse event (DRAE), and 7 (20.6%) experienced grade 3/4 DRAEs. 2 pts required dose discontinuation because of pneumonitis (Grade2 and 3). **Conclusion:** Single-agent Nivolumab has significant activity in 2nd/3rd line MPM pts and met the primary endpoint, suggesting that Nivolumab has a potential to be a new therapeutic option for MPM.

Keywords: malignant pleural mesothelioma, Nivolumab, PD-1

MA 19 MESOTHELIOMA: BENCH TO BEDSIDE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MA 19.02 TREMELIMUMAB PLUS DURVALUMAB IN FIRST- OR SECOND-LINE MESOTHELIOMA PATIENTS: FINAL ANALYSIS OF THE NIBIT-MESO-1 STUDY

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Background: The anti-CTLA-4 tremelimumab as monotherapy showed initial signs of activity in second-line malignant mesothelioma (MM) patients (Calabrò et al., Lancet Oncol, 2013; Calabrò et al., Lancet Respir Med, 2015), though it failed to improve the overall survival (OS) of second or third line mesothelioma patients compared to placebo in the DETERMINE study (Maio et al., Lancet Oncol, in press). These results and the efficacy of targeting the PD-1/PD-L1 axis in a variety of tumor types, prompted the NIBIT-MESO-1 study aimed at investigating the activity and safety of tremelimumab combined with the anti-PD-L1 durvalumab in MM patients. Here, we report conclusive efficacy and safety analysis from the fully-enrolled NIBIT-MESO-1 study. **Method:** The NIBIT-MESO-1 is a phase II, open-label, single Center study. Forty MM patients received tremelimumab at 1 mg/Kg i.v. every 4 weeks (Q4W) for 4 doses, and durvalumab at 20 mg/Kg i.v. Q4W for 13 doses. Primary objective is immune-related (ir)-objective response rate; secondary are ir-disease control rate, ir-progression free survival, OS, and safety. Tumor assessment per ir-modified RECIST or ir-RECIST 1.1 for pleural or peritoneal MM, respectively, was performed at baseline and q12 weeks. Adverse events (AEs) were recorded according to CTC v4.0. **Result:** From October 2015 to October 2016, 40 MM patients (38 pleural and 2 peritoneal), median age 64 years (range 41-80), ECOG performance status 0 (n = 19) or 1 (n = 21) were enrolled in the study. MM histology was epithelioid (n = 32), biphasic (n = 5), sarcomatoid (n = 2) or undefined (n = 1). As of April 2017, 12 first or 28 second-line MM patients received a median of 6 doses of therapy (range = 1-13). Ten ir-objective responses (9 confirmed) were observed (25%), and 25 patients reached an ir-disease control rate (62.5%). The median OS was not reached with a median follow-up of 9.5 months (inter-quartile range: 6.2-12.5 months). Thirty patients (75%) experienced any grade irAEs: grade 1-2 irAEs were observed in 67.5% and grade 3-4 irAEs in 17.5%. AEs were generally manageable and reversible per protocol guidelines. **Conclusion:** These data suggest that the combination of tremelimumab and durvalumab is active, with a good safety profile in MM patients, and warrant further exploration. Clinical trial information: .

Keywords: Immunotherapy, Mesothelioma, Immune checkpoint blockade

MA 19 MESOTHELIOMA: BENCH TO BEDSIDE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MA 19.03 NINTEDANIB + PEMETREXED/CISPLATIN IN MALIGNANT PLEURAL MESOTHELIOMA (MPM): PHASE II BIOMARKER DATA FROM THE LUMEMESO STUDY

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Background: Nintedanib is a triple angiokinase inhibitor. LUME-Meso (NCT01907100) is a randomised, Phase II/III study of ≤6 cycles of nintedanib+pemetrexed/cisplatin versus placebo+pemetrexed/cisplatin, followed by nintedanib or placebo maintenance, in chemo-naïve patients with MPM. In Phase II results, nintedanib+pemetrexed/cisplatin improved progression-free survival (PFS) versus control (hazard ratio [HR]=0.54; p=0.010), with a trend for prolonged overall survival (OS; HR=0.77; p=0.319). Benefit was most pronounced in patients with epithelioid tumours. Since no pharmacodynamic/predictive biomarkers are validated for anti-angiogenic therapies, exploratory analyses were conducted to investigate potential associations of plasma-derived angiogenic factors and genomic markers with treatment outcome in the LUME-Meso Phase II epithelioid population. **Method:** Blood samples were collected at baseline and, for patients receiving maintenance, at monotherapy Cycle 3 (C3mono) and end of monotherapy (EoTmono). Analyses focused on 58 angiogenic factors (Human AngiogenesisMAP® panel, Myriad RBM) and single-nucleotide polymorphisms (SNPs) in genes implicated in mesothelioma and/or associated with response to anti-angiogenic therapies in other tumour types (VEGFR1, VEGFR3 and mesothelin). Associations of biomarkers with treatment effect were evaluated by Cox regression and tested for interaction with false discovery rate (FDR) adjustment. Adjusted mean changes in angiogenic factor levels were compared between arms by ANCOVA. Analyses were exploratory, limited by small sample size, and considered hypothesis generating. **Result:** Of 77 patients with epithelioid tumours, angiogenic factor and genomic data were available for 71 and 67 patients, respectively. PFS/OS benefit of nintedanib appeared potentially more pronounced in patients with baseline plasma endoglin level below the median. There were possible weak associations between major homozygous genotypes for two VEGFR3 SNPs (rs307821 G/G and rs307826 A/A), and OS benefit and between VEGFR1 SNP rs9582036 A/A genotype and PFS benefit. Biomarker treatment associations were limited by small subgroup size, especially for low-frequency SNPs, and interaction tests were not significant after FDR adjustment. Regarding pharmacodynamic effects, adjusted mean change in interleukin-8 levels with nintedanib was greater from baseline to C3mono and lower from C3mono until EoTmono, compared with placebo. Nintedanib showed lower adjusted mean changes versus placebo for VEGFR2 from baseline to C3mono, and for VEGFR2 and VEGFR3 from baseline to EoTmono. **Conclusion:** These analyses represent the first biomarker results for nintedanib-treated MPM. While there seemed to be signals for greater PFS and OS improvement in patients with low plasma endoglin and major homozygous VEGFR1/3 genotypes, no biomarkers showed clear significant association with treatment benefit. These findings warrant further evaluation in the Phase III study.

Keywords: nintedanib, Biomarkers, malignant pleural mesothelioma

MA 19.05 PEGYLATED ARGININE DEIMINASE POTENTIATES PD-1/PD-L1 IMMUNE CHECKPOINT BLOCKADE IN MALIGNANT MESOTHELIOMA

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Background: Malignant pleural mesothelioma is a difficult to treat asbestos-driven cancer that is on the increase globally. The urea cycle and tumor suppressor enzyme argininosuccinate synthetase 1 (ASS1), involved in arginine synthesis, is downregulated in half of mesotheliomas which are then sensitive to arginine deprivation therapy. Trials of the arginine depletor pegylated arginine deiminase, ADI-PEG20, have confirmed single-agent and combination safety and efficacy in patients with mesothelioma. Here, we explored the immunometabolic consequences of ASS1 loss in mesothelioma uncovering a role for combining ADI-PEG20 with PD1/PD-L1 checkpoint blockade. **Method:** Three ASS1-negative and one ASS1-positive MPM cell lines were assessed for PD-L1 expression by real-time quantitative PCR, western blot and FACS analysis. Cell lines were manipulated for ASS1 overexpression (endogenous and genetic) and siRNA followed by gene expression analysis. Cell lines were cultured with and without ADI-PEG20 and assessed for PD-L1 expression and cytokine production by ELISA. An immunocompetent murine tumor model of ASS1 loss mimicking aggressive mesothelioma was treated with PBS control, ADI-PEG20, anti-PD-1 antibody, and ADI-PEG20 plus anti-PD-1 antibody. Tumors were harvested and analysed for immune cell subsets by FACS. Finally, human mesothelioma biopsies from trials of ADI-PEG20 were analyzed for ASS1 and PD-L1 and immune cell subsets. **Result:** PDL1 protein was absent in the three ASS1 negative MPM cell lines but was present in the ASS1 positive cell line. Transfection of ASS1 in the ASS1 negative MPM cell lines led to an increase in PD-L1 expression, which was reversible following ASS1 knockdown. Induction of PD-L1 expression by forced ASS1 overexpression was accompanied by an increase in interferon type I signaling. Similar results were obtained in a mesothelioma cell line developing resistance to ADI-PEG20 under long-term culture. Next, ADI-PEG20 treatment triggered release of interferon-alpha/beta which induced PD-L1 expression by 24hrs in the ASS1-negative MPM cell lines before declining by 48hrs. Analysis of MPM biopsies of patients progressing on ADI-PEG20 revealed upregulation of ASS1 and a concomitant increase in tumoral PD-L1 and CD3 positive T cells. ADI-PEG20 synergized with PD-1 blockade in the immunocompetent murine tumor model that was refractory to PD-1 inhibition. **Conclusion:** ASS1 and ADI-PEG20 modulate PDL1 expression via type I interferon signaling in malignant mesothelioma cell lines. Arginine deprivation with ADI-PEG20 combined with PD-1 blockade is synergistic and warrants further exploration in the clinic. A phase 1 trial of ADI-PEG20 combined with PD1 blockade is planned in patients with ASS1-negative cancers, including malignant mesothelioma.

Keywords: mesothelioma, ADI-PEG20, immunotherapy

MA 19.06 MULTIPLE MECHANISMS CONTRIBUTE TO DOWNREGULATION OF TUMOUR SUPPRESSOR MICRORNAS IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a disease with an almost invariably fatal diagnosis with limited therapeutic options. Characteristic patterns of deregulated microRNA expression have been demonstrated in MPM, and many downregulated microRNAs have been shown to have tumour suppressor activity. However, apart from silencing of miR-34b/c by promoter hypermethylation and co-deletion of miR-31 with the CDKN2A locus, the mechanisms responsible for downregulation of other tumour suppressor miRNAs such as miR-16 are yet to be elucidated. **Method:** Tumour samples (n=60) were from MPM patients undergoing extrapleural pneumonectomy, and samples of pleura (n=23) collected from patients undergoing cardiac surgery were used as normal controls. MPM cells lines were obtained from the ATCC. Expression levels of mature microRNAs in MPM tumour samples and cell lines, and pri-miRs and miRNA host genes in cell lines, were determined by RT-qPCR. Copy number variation (CNV) was analysed by droplet digital PCR (ddPCR), and methylation was inferred by miRNA expression following decitabine treatment. MYC was analysed by Western blot, and expression modulated by siRNAs. **Result:** Analysis of microRNA expression in tumour samples revealed a consistent and significant downregulation of miR-15a (4-fold, $P<0.01$), 15b (10-fold, $P<0.01$), 16 (22-fold, $P<0.05$), 34a (1.6-fold, $P<0.05$), 34b (1.8-fold, $P<0.01$), 34c (2.3-fold, $P<0.0001$) and 193a (3.1-fold, $P<0.001$) compared with normal pleura. Copy number variation analysis showed evidence of heterozygous loss for miR-193a (4 of 5 cell lines) and miR-15a/16-1 (2 of 5), but no change in miR-15b/16-2. Treating cell lines with the demethylating agent decitabine resulted in dramatic upregulation only in the case of miR-34c. RNAi-mediated knockdown of c-MYC led to upregulation of miR-15b and 16, and to a lesser extent miR-15a, as well as a consistent increase in the miR-15b/16-2 host gene SMC4 and the miR-15a/16-1 host gene DLEU2. Analysing the expression of these microRNAs in the tumour samples revealed a strong correlation between miR-15b and 16 ($R^2=0.793$) and miR-34b and 34c ($R^2=0.753$), but not between others. **Conclusion:** Our data suggest that a combination of deletion, hypermethylation and transcriptional regulation contribute to the downregulation of miR-15a/b, 16, 34a/b/c and 193a. In MPM, unlike other cancers, the downregulation of miR-15a/16-1, miR-15b/16-2 appears to be due to transcriptional changes rather than deletion or promoter hypermethylation. MYC appears to contribute to miR-16 downregulation primarily via control of SMC4 and the miR-15b/16-2 locus, suggesting that the transcriptional control of miR-16 expression by c-Myc contributes to the malignant phenotype of MPM.

Keywords: MYC, microRNA, Mesothelioma

MA 19.07 DOES LOSS OF SMAD7 LEAD TO INCREASED AGGRESSIVENESS OF MALIGNANT PLEURAL MESOTHELIOMA?

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Background: Malignant pleural mesothelioma (MPM) is characterized by aggressive growth, limited therapeutic options and rapid recurrence following treatment. A better understanding of biological factors underlying MPM aggressiveness offers the chance to improve therapeutic strategies. Growth factors of the TGF-beta superfamily including TGF-beta itself, activins and BMPs have been repeatedly linked to MPM growth. In the current study, we focus on the role of Smad7, a key intracellular antagonist of TGF-beta and activin signaling, in MPM. **Method:** A panel of 17 human MPM cell lines was screened for tumorigenicity in SCID mice. Comparative genomic hybridization and whole genome gene expression arrays were used for identification of genes correlating with tumorigenicity. Immunoblotting and qPCR were used to detect Smad7 expression levels in cell lines. For ectopic overexpression of Smad7 in MPM cells, a retroviral expression system was used. Various in vitro assays, immunoblotting and reporter gene assays were employed to characterize the effect of Smad7 overexpression on MPM cell proliferation, migration, signal transduction and drug response. **Result:** When human MPM cell lines were dichotomized into tumorigenic ones and non-tumorigenic ones based on their ability to form tumors in SCID mice, loss of Smad7 was one of the most conspicuous associations with tumorigenicity identified in CGH arrays. The tumorigenic group also showed a reduced Smad7 transcript expression in gene expression microarrays. Based on these data we screened a larger panel of MPM cell lines for Smad7 mRNA and protein expression and identified cell lines with high, medium and low Smad7 expression. We generated a retroviral expression construct and established an isogenic subline overexpressing Smad7 from the MPM cell line VMC33 that shows low endogenous Smad7 expression. Compared to parental VMC33 cells or VMC33-RFP cells, which overexpress red fluorescent protein and were used as control, VMC33-Smad7 cells showed a reduced growth rate and diminished clone forming capacity in vitro. VMC33-Smad7 also showed reduced cell migration, but no difference in invasion could be detected. Since Smad7 was described as antagonist of TGF-beta, we tested its effect on TGF-beta signaling with a reporter gene assay and indeed found a blunted response to TGF-b in Smad7 overexpressing cells. With respect to sensitivity against kinase inhibitors targeting TGF-beta receptors, VMC33-Smad7 showed a decreased response to galunisertib and SB-431542 compared to VMC33-RFP. **Conclusion:** Taken together, these data suggest that Smad7 may have a growth limiting function in MPM, possibly by antagonizing growth-promoting TGF-beta and/or activin signals.

Keywords: TGF-beta, Smad7, mesothelioma cell models

MA 19.09 THE ROLE OF NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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Background: The treatment of localized malignant pleural mesothelioma (MPM) involves multimodality therapy, however, there is no standard of care with respect to operative procedure and timing of chemotherapy. We analyzed data from a single institution to identify whether the use of pemetrexed-platinum neoadjuvant chemotherapy impacts survival. **Method:** Patients with histologically-proven MPM who had surgery from 1996 to 2016 were identified. Follow-up was complete for a median of 24 months. Survival was calculated from time of diagnosis to last follow up or death. Univariate and multivariate Cox proportional hazards were used. **Result:** From

1996 to 2016 we identified 376 patients. Mean age was 66+/-8 years and 54 (14%) were female. There was no difference in survival for pleurectomy/decortication or extrapleural pneumonectomy. Neoadjuvant chemotherapy significantly improved survival compared to surgery followed by chemotherapy (table 1). Multivariate analysis was significantly associated for increased survival for epithelioid histology, T-status, node positivity, and neoadjuvant chemotherapy (table 2).

Table 1. Univariate Analysis

Variable	(n)	Median survival (mo.)	P value
Gender	Male (322) Female (54)	13.6 17.2	P=0.043
Histology	Epithelial (252) Mixed (91) Sarcomatoid (26)	18.3 12.1 6.5	P<0.0001
T stage	T 1-2 (33) T 3-4 (343)	42.6 14.3	P=0.0002
N status	N 0 (129) N 1-2 (113)	23.1 11.3	P<0.0001
Neoadjuvant chemotherapy	Yes (153) No (223)	19.8 11.3	P<0.0001

Table 2. Cox Proportional Hazards Model

Covariate	Hazard Ratio	95% CI	p-value
Histology (ref: Epithelioid) Biphasic Sarcomatoid	ref 1.66 4.24	[ref] [1.17-2.36] [1.77-10.1]	ref 0.005 0.001
T-status 3-4 vs 1-2	3.07	[1.32-7.15]	0.009
Node-positivity	1.93	[1.40-2.66]	<0.001
Neoadjuvant chemotherapy	0.65	[0.47-0.91]	0.011

Cox proportional hazards model including histology, t-status, n-status, and neoadjuvant chemotherapy C-index: 0.69 **Conclusion:** Our results suggest that neoadjuvant chemotherapy increases survival and likely enhances the complete resection rate. These data are being evaluated in a multi-institutional cohort of five major mesothelioma programs in North America to improve guidelines for mesothelioma therapy.

Keywords: neoadjuvantchemotherapy, Mesothelioma, outcomes

MA 19 MESOTHELIOMA: BENCH TO BEDSIDE
WEDNESDAY, OCTOBER 18, 2017 - 11:00-12:30

MA 19.10 COMPARATIVE VALUE OF MR AND CT FOR TUMOR VOLUMETRIC AND CLINICAL STAGING OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Tumor volumetrics is currently being explored as a means of enhancing the accuracy of clinical staging of malignant pleural mesothelioma (MPM). In a recent multicenter study (JTO 2016, 11(8):1335-1344) evaluating feasibility of volume estimation using CT (VolCT), clinical staging by CT was poorly correlated between readers and underestimated pathological stage, but correlation of VolCT estimates between two experienced readers was high (rho = 0.82). MR has been found superior to CT in evaluating certain staging parameters, and may enhance volumetrics based on improved contrast. Here we evaluate the relative performance and reproducibility of MR for volumetrics (VolMR) and clinical staging of MPM in a single institution cohort. **Method:** Patients with MPM who underwent surgical resection between 2009 and 2014 with preoperative CT and MR imaging were studied. MR images were acquired using a uniform clinical protocol. VolMR was performed independently by two observers, one an experienced radiologist and one fellow. Vitrea (Vital Images) software was used for volumetric calculations and estimates were compared using Spearman correlation. Clinical staging accuracy (AJCC 7th edition criteria; versus pathological stage) and interobserver variability were also evaluated. VolMR and VolCT were performed for all cases by the experienced radiologist and qualitatively compared. **Result:** The study cohort comprised 139 patients, 113 (81%) men, median age 68 (30-82), with 74 (53%) epithelioid subtype tumors. Pathological stage was I: 14 (10%); II: 16 (12%); III: 75 (54%); IV: 34 (24%). Clinical staging by MR was concordant between reviewers for 86 (62%) cases, and with pathological stage for 65 (47%) and 63 (45%) respectively. VolMR was significantly correlated both between reviewers (rho = 0.99) and with VolCT (rho = 0.68). VolMR tended to result in higher volume estimates (median 633, IQR 365-885 cc) than VolCT (median 239, IQR 75-597 cc). **Conclusion:** VolMR was found to be feasible and reproducible, independent of observer experience. Clinical AJCC staging by MR was found to compare favorably to staging by CT in terms of both interobserver variablilty and prediction of pathological stage. Although MR is not yet universally available and has the disadvantages of higher cost, requirement for optimization and longer scan times, it may neverthheless offer improved accuracy and reproducibility of clinical staging and volumetric analysis. Further evaluation in larger multi-institutional cohorts is warranted.

Keywords: Volumetric , MR volume , clinical staging

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MA 20.01 FIDUCIAL MARKER PLACEMENT USING ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY IN THE PROSPECTIVE, MULTICENTER NAVIGATE STUDY

M. Bowling[1], E. Folch[2], S. Khandhar[3], J. Kazakov[4], W. Krimsky[5], G. Lemense[6], P. Linden[7], B. Murillo[8], M. Nead[9], C. Teba[4], C. Towe[7], C. Anciano[1]

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Background: Fiducial markers guide stereotactic body radiotherapy (SBRT) and can be used to localize lesions for surgical resection in the management of lung cancer. We report the safety, accuracy and common practice patterns of fiducial placement guided by electromagnetic navigation bronchoscopy (ENB). **Method:** NAVIGATE (www.clinicaltrials.gov, NCT02410837) is a prospective, multicenter, global, single-arm, observational cohort study of ENB using the superDimension™ navigation system (Medtronic, Minneapolis). This abstract presents the patient demographics, procedural characteristics, and 1-month outcomes in the subset of NAVIGATE subjects from the United States cohort who had fiducial markers placed. Continued enrollment in Europe and 2-year follow-up are ongoing. Study sponsored and funded by Medtronic. **Result:** 258 subjects from 21 United States centers (29 operators) received fiducial markers during their ENB procedure. Most subjects received between 1 and 5 fiducial markers (mean 2.2±1.7). General anesthesia was used in 69.4%. Real-time confirmation by radial endobronchial ultrasound (r-EBUS) was used in 34.5% of ENB procedures. The median ENB procedure time (first locatable guide [LG] / extended working channel [EWC] entry to last LG/EWC exit) was 31.0 minutes. Among the 258 subjects undergoing ENB-guided fiducial marker placement, 213 subjects also had lung lesion biopsy. Based on subjective operator assessment, 99.2% of fiducial markers were accurately placed. Follow-up imaging an average of 4.7 days post-procedure showed that 94.3% (232/246) of markers were still in place. The ENB-related pneumothorax rate was 5.0% (13/258) overall and 3.1% were Grade ≥2 based on the Common Terminology Criteria for Adverse Events scale (i.e., requiring chest tube placement or hospitalization). The ENB-related Grade ≥2 bronchopulmonary hemorrhage and Grade ≥4 respiratory failures rates were 0.0% and 1.6%, respectively. Among the 39 subjects undergoing fiducial placement alone with no biopsy, there was 1 respiratory failure and no pneumothoraces or bronchopulmonary hemorrhages. **Conclusion:** We report the largest series to date of fiducial marker placement by ENB guidance. Our data suggest that ENB-guided fiducial marker placement is versatile and accurate, with low complication rates. Practice variations in number and type of fiducial placed between operators were noted in our data. We did not identify the type of radiotherapy system used at each institution or how many fiducial markers were useful during the therapy. In addition, not all SBRT systems require fiducial marker placement, and some fiducial markers were placed for surgical localization. Further investigation should explore these practice patterns to further hone the usefulness and accuracy of placement of fiducial markers for SBRT and surgical localization.

Keywords: Fiducial, Electromagnetic Navigation Bronchoscopy, Stereotactic body radiation therapy

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MA 20.02 PLEURAL DYE MARKING OF LUNG NODULES BY ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY IN THE PROSPECTIVE, MULTICENTER NAVIGATE STUDY

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Background: Pleural dye marking guided by electromagnetic navigation bronchoscopy (ENB) has been useful in identifying small peripheral lesions for sublobar resection in the management of non-small cell lung cancer and indeterminate lung nodules. We report the use of this procedure among the participants of the NAVIGATE study. **Method:** NAVIGATE (www.clinicaltrials.gov, NCT02410837) is a prospective, multicenter, global, single-arm, observational cohort study of ENB using the superDimension™ navigation system (Medtronic, Minneapolis). Enrollment of up to 1,500 subjects is planned at 37 sites in the United States and Europe.

European enrollment and 2-year follow-up are in progress. This abstract presents a prespecified 1-month interim analysis of NAVIGATE subjects from the United States cohort who underwent ENB-guided pleural dye marking. Study sponsored and funded by Medtronic. **Result:** From April 2015 to August 2016 at 29 clinical sites, 1218 subjects were enrolled in the NAVIGATE United States cohort. In 7 clinical centers (7/29), 23 subjects (24 lesions) underwent pleural dye marking in preparation for surgical resection. Ten subjects underwent dye marking alone while 13 had dye marking concurrent with lung lesion biopsy and/or fiducial placement. The median nodule size was 10 mm (range 4-22) and 83.3% (20/24) were less than 20 mm in diameter. Most lesions (95.5%; 21/22) were located in the peripheral third of the lung. The median distance of the target lesion from the visceral pleura was 3.0 mm. The median total bronchoscopic procedure time was 22.0 minutes and the median ENB procedure time (first locatable guide [LG] / extended working channel [EWC] entry to last LG/EWC exit) was 11.5 minutes (range 4-38). Dye marking was considered accurate for surgical resection in 91.3% of the cases and the median time of dye marking to surgical resection was 0.5 hours (range 0.3-24). Seventy five percent of the lesions were malignant (18/24) and 50% were adenocarcinoma. **Conclusion:** Our data demonstrates that pleural dye marking with ENB guidance is useful for locating small peripheral lesions for surgical resection without adding significant additional time to the procedure. An interesting finding in our report is the underutilization of this procedure in the NAVIGATE cohort (23/1218). Given that sublobar and lung parenchymal sparing resections for non-small cell lung cancer are becoming more common, it is unclear why surgeons are not more frequently utilizing pleural dye marking. Further investigation concerning physician behavior and practice patterns in the use of lung sparing surgery needs to be explored.

Keywords: Electromagnetic Navigation Bronchoscopy, lung cancer, pleural dye marking

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.03 SAFETY OF ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY IN PATIENTS WITH COPD: RESULTS FROM THE NAVIGATE STUDY

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Background: Electromagnetic navigation bronchoscopy (ENB) is used to access lung lesions or lymph nodes for biopsy and/or to guide fiducial or dye marking for stereotactic radiation or surgical localization. CT-guided lung biopsy can be complicated by pneumothorax, particularly in patients with emphysema. We examined the safety of ENB in patients with COPD and/or poor lung function. **Method:** NAVIGATE (www.clinicaltrials.gov, NCT02410837) is a prospective, multicenter, global, single-arm, observational study of ENB using the superDimension™ system (Medtronic, Minneapolis). This NAVIGATE substudy analyzes the 1-month follow-up of the first 1,000 subjects enrolled in the United States and Europe. Subjects were determined to have COPD by medical history. Pulmonary function test results (PFTs) were collected if available. Procedure-related pneumothorax, bronchopulmonary hemorrhage, respiratory failure, and composite complications were prospectively captured. Study sponsored and funded by Medtronic. **Result:** 1,000 subjects were enrolled at 29 clinical sites, including 448 with COPD and 541 without COPD (COPD data missing in 11). One-month follow-up was completed in 933 subjects (93.3%). Subjects with COPD tended to be older, male, and have history of tobacco exposure, asthma, and recent pneumonia. Nodule size, location, and procedure time were similar between groups. There was no statistically significant difference in the procedure-related composite complication rate between groups (7.4% with COPD, 7.8% without COPD, 9.1% in subjects missing COPD data, P=0.81). CTCAE Grade ≥2 pneumothorax was not different between groups (2.7%, 3.7%, 0.0%, respectively, P=0.63). Severity of FEV1 or DLCO impairment was not associated with increased composite procedure-related complications (ppFEV1 P=0.66, ppDLCO P=0.37).

Adverse Events Related to the ENB Index Procedure or Devices (1 Month Follow-up)*

	Subjects with COPD (n=448)	Subjects without COPD (n=541)	Subjects with Missing COPD Status (n=11)	*P* Value
Composite Complication Rate	7.4 (33/448) [34]	7.8 (42/541) [44]	9.1% (1/11) [1]	0.81
Death (Procedure-Related)	0.0 (0/448)	0.2 (1/541) †	0.0% (0/11)	>0.99
Pneumothorax (All Grades)	4.0 (18/448)	5.5 (30/541)	9.1% (1/11)	0.28
CTCAE Grade ≥2	2.7 (12/448)	3.7 (20/541)	0.0% (0/11)	0.63
Bronchopulmonary Hemorrhage (All Grades)	2.5 (11/448)	2.2 (12/541)	0.0% (0/11)	0.87
CTCAE Grade ≥2	0.4% (2/448)	1.5% (8/541)	0.0% (0/11)	0.22
Respiratory Failure, Grade ≥4	1.1 (5/448)	0.2 (1/541) †	0.0% (0/11)	0.16

Data are presented as % (n/N subjects) [n events]. There were 3 subjects with 2 events each.
* Other than common or expected observations associated with anesthesia (e.g., transient nausea, emesis, constipation)
† Grade 5 hypoxic respiratory failure 9 days after the ENB index procedure, deemed related to complications of general anesthesia, in a patient with multiple comorbidities, including cirrhosis, hepatocellular carcinoma, small cell carcinoma, and ovarian cancer. As of the 1-month follow-up, no other deaths were considered related to the ENB device or associated tools by either the clinical investigator or the independent medical monitor.
Acronyms: COPD: chronic obstructive pulmonary disease; CTCAE: Common Terminology Criteria for Adverse Events; ENB: electromagnetic navigational bronchoscopy.

Conclusion: Patients with a clinical diagnosis of COPD or with poor PFTs can undergo ENB without an increase in complication rates. Because the risk of pneumothorax is not elevated, in patients undergoing ENB in this analysis, ENB may be the preferred method to biopsy peripheral lung lesions in patients with COPD and/or poor PFTs.

Keywords: prospective clinical study, Chronic obstructive pulmonary disease, respiratory safety

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.04 INTELIGENT BIOPSY DEVICE FOR SPN DIAGNOSIS

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Background: Solitary pulmonary nodules are increasingly encountered in current medicine. There are interesting new technologies available for this difficult diagnostics category of pulmonary pathologies like endobronchial navigation techniques and transparietal CT guided biopsy. In order to increase diagnostic yield of those techniques precise biopsy instruments are needed. **Method:** We utilise new instrument based on near infrared diagnostics. This simple needle sheath can be used during routine bronchoscopy examination and enables simultaneous spectral measurement and obtaining of histology tissue samples in situ at the same time. This intelligent sheath with standard needle can be used both during fluoroscopy navigation and EBUS guided navigation to confirm correct biopsy instrument position during the sampling itself. According to our results diagnostic yield of navigation method is significantly increased using such device. Instrument itself consists of elastic tubing while along the length of tube on opposite sides of cross section perimeter there are two segments fixed with 6 optic microfibers covered with insulation as NIR spectroscopic probe. Core consists of the channel for of standard biopsy needle introduction. Instrument itself is introduced to the area of interest through the working channel of the bronchoscope. **Result:** We performed 40 consecutive examinations of SPN (diameter 1-3cm) using intelligent needle during navigational bronchoscopic procedure executing fluoroscopy and radial EBUS. Correct placement of biopsy instrument confirmed by NIR spectroscopy was possible in 32 cases. In all these cases positive cytology specimen containing diagnostic material was obtained. **Conclusion:** Intelligent NIR based biopsy needle appears to be good adjunct in the diagnosis of SPNs. More extensive studies are needed to prove diagnostic potency of this device.

Keywords: NIR spectroscopy, standard needle, solitary pulmonary nodule

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.06 DISCERNING LUNG CANCER CELL PATTERNS WITH CONFOCAL ENDOMICROSCOPY

M. Diez-Ferrer[1], B. Torrejon[2], N. Baixeras[3], E. Minchole[1], R.M. Ortiz[1], N. Cubero[1], R. Lopez-Lisbona[1], J. Dorca[1], A. Rosell[1]

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Background: Probe-based confocal endomicroscopy (pCLE) allows confocal microscopy of lung tissue in vivo but limited evidence is available. The objective was to discriminate pCLE patterns of lung cancer in vivo. **Method:** Fluorescence properties of methylene blue (MB) were examined ex vivo in confocal microscope. Next, 15 regions of the central airways were studied in vivo with pCLE and a representative image chosen for analysis with ImageJ software. Biopsy was performed for final diagnosis. **Result:** Ex vivo study showed no differences between 1% and 2% MB concentrations and rapid extinction of fluorescence after 10 minutes of MB application (figure). In vivo study included samples of bronchial mucosa (n = 6), inflammation (n = 3) and tumor (n = 6). pCLE image evaluation (table) showed inflammation and tumor nuclei were bigger (except SCLC) and occupied a greater area. Fluorescence of tumor nuclei was more intense. Non fluorescent area was inferior for both inflammation and tumor samples. Number of nuclei could not discriminate between normal and tumor.

Figure. Ex vivo study of MB fluorescence. MB concentrations 1% (A1) and 2% (A2). MB1% extinction after dye application (B1) and 10 minutes after application (B2).

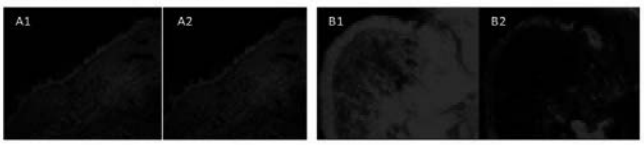

Table. Imaging features evaluated in pCLE frames

	Area occupied by nuclei (μm²)	Intensity of nuclei (UA)	Mean size of nuclei (μm²)	Non-fluorescent area (μm²)	Number of nuclei (μm²)
Bronchial epithelium (mean(SD))	97,769 (9,451)	126 (9)	107 (10)	67,100 (12,567)	937(84)
Inflammation (mean(SD))	117,381 (22,166)	122 (27)	127 (15)	35,124 (32,630)	933(225)
B cell lymphoma	138,354	145	185	49,269	746
Adenocarcinoma	155,033	198	177	5,225	875
Squamous cell carcinoma	102,805	145	155	54,301	663
Small cell lung cancer	107,201	157	63	11,257	1,687
Non-small cell lung cancer	113,173	187	122	32,359	926
Hamartoma	120,188	145	114	25,438	1,058

Conclusion: 1. MB fluorescence is unaffected by stain concentration 2. There is exponential extinction of MB over time 3. Lung cancer cell pattern distinction in vivo is feasible Funded by Fundació MaratóTV3, SEPAR and FUCAP

Keywords: in vivo diagnosis, bronchoscopy, lung cancer

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.07 ENDOBRONCHIAL ULTRASOUND ELASTOGRAPHY: MEDIASTINAL STAGING IN NON-SMALL CELL LUNG CANCER AND TECHNICAL FACTORS

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Background: Endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) is the standard of care for diagnosis and mediastinal staging of non-small cell lung cancer (NSCLC). Studies suggest that elastography, an ultrasonic measure of tissue elasticity, may identify malignant lymph nodes (LNs) with sufficient accuracy to guide which LNs need sampling at EBUS and reduce the time and complexity of staging procedures. This study aims to confirm these findings while also describing technical factors that affect elastographic measurements. **Method:** All patients undergoing EBUS TBNA to investigate possible NSCLC were prospectively recruited. Elastographic analysis was performed prior to TBNA of LNs and later correlated with pathology from EBUS TBNA and/or surgical specimens. All LNs were classified qualitatively according to elastographic colour pattern: predominantly blue, predominantly green and mixed. Strain ratios (SR) were calculated to give quantitative measures of elasticity. Measures were compared to PET and sub-group analyses according to LN FDG avidity were performed. Finally the influence of various technical factors (probe pressure, Region of interest selection, and frame average function) were assessed. **Result:** There were 82 LNs from 50 patients who underwent EBUS elastography with the final diagnosis being malignant in 29(35%) and non-malignant in 57(69%). PET was available for 58 LNs. Diagnostic indices relating to elastographic features and effects of various technical factors are shown in Table 1.

Table 1 Diagnostic indices for elastographic identification of malignant LNs (A) and Effects of technical factors (B)

A. Variable	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Elastography All	88%	47%	42%	90%
Elastography PET Positive	90%	64%	66%	90%
Elastography PET negative	63%	88%	70%	85%
Strain Ratio All	Pending	Pending	Pending	Pending
Strain Ratio PET positive	Pending	Pending	Pending	Pending
Strain Ratio PET negative	Pending	Pending	Pending	Pending
Sonographic features	81%	60%	54%	84%
PET All	82%	51%	52%	81%
B. Variation in technique	**Difference**	**p value**		
Probe Pressure - colour map	Pending	Pending		
Probe pressure - strain ratio	Pending	Pending		
ROI pressure	Pending	Pending		
ROI Placement	Pending	Pending		
Frame average - colour map	Pending	Pending		

Conclusion: EBUS elastography can identify malignant LNs with equivalent power to sonography and FDG PET and may have a role in selecting which PET-negative nodes require sampling in staging procedures. It is highly dependent on technique which must be standardised to ensure accuracy of results. Please note: Data acquisition is still underway and planned to continue for a further 2 months. Analysis shall be complete by the time of the conference.

Keywords: Staging, NSCLCa, Elastography

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.08 CLASSIFICATION OF CONFOCAL ENDOMICROSCOPY PATTERNS FOR DIAGNOSIS OF LUNG CANCER

R.M. Ortiz Comino[1], D. Gil[2], E. Minchole[1], M. Diez-Ferrer[1], N. Cubero[1], R. Lopez-Lisbona[1], C. Sanchez[2], O. Ramos[2], A. Esteban[2], J. Dorca[1], A. Rosell[1]

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Background: Solitary pulmonary nodules diagnosis and management is so challenging that nNew endoscopic techniques are being introduced to reduce uncertainty in peripheral pulmonary lesions (PPL) diagnosis and management. increase its diagnostic yield. Probe-based confocal laser endomicroscopy (pCLE) is a technique that can microscopically image the lung tissue in vivo during flexible bronchoscopy, though it can be difficult for pulmonologists to distinguish cellular patterns in a monochrome vision under respiratory and cardiac movements. . The goal of this work is to explore explore if Computed-Aided Diagnoses (CAD) tools can obtain a reliable diagnoses with pCLE in lung cancer. **Method:** A pilot study using 2 different methods for pCLE pattern analysis was performed:, one based on visual analysis by 3 experts and the other one based on computeron computerized analysis of visual patterns called Graphcom. Twelve 12 pCLE videos (obtainedobtained using mMethylene blue dye (1%) and Alveloflex-Cellvizio 660nm miniprobe) were selected from patients with endobronchial lesionsperipheral SPNs (6 with lung adenocarcinoma cancer and 6 with inflammatory disease) during rigid bronchoscopy under general anesthesia. Afterwards, Vvideo sequences from pCLE were visually explored by one of the authors to select between 10 and 15 framesimages that presented a clear cellular pattern, without artifacts. . These images were shown to 3 observers who were familiar with confocal images but ignored the final histopathological diagnosis for a blind visual labellinglabeling. Images were also computationally analyzed using methods from social networks community analysis in a graph representation of pCLE images based on visual features to potentially overlapping groups of images that share common visual properties. **Result:** Our preliminary results indicate that on average visual analysis with 3 independent experts can only achieve a 60.2% of accuracy and has large variability amongst observers, while the accuracy of the proposed unsupervised image pattern classification rai(GraphCom) sesrises to 83,4.4%. **Conclusion:** Visual inspection of CLE images from lung tissue fails to provide accurate diagnosis. CLE images contain enough visual information for in vivo detection of neoplastic cell patterns that could be discriminated using cComputation methods and graph structural analysis applied to deep-learning feature spaces can increase diagnostic accuracy of pCLE images against visual analysis (83.4% vs 60.2%). Future studies are needed to apply this method in a real time scenario during bronchoscopy for PPL diagnoses.

Keywords: bronchoscopy, Confocal endomicroscopy, Computer analysis

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.09 ACCURACY & UTILITY OF SYSTEMATIC MEDIASTINAL LN STAGING VIA EBUS-TBNA IN CN0/N1 NSCLC: SYSTEMATIC REVIEW & META-ANALYSIS

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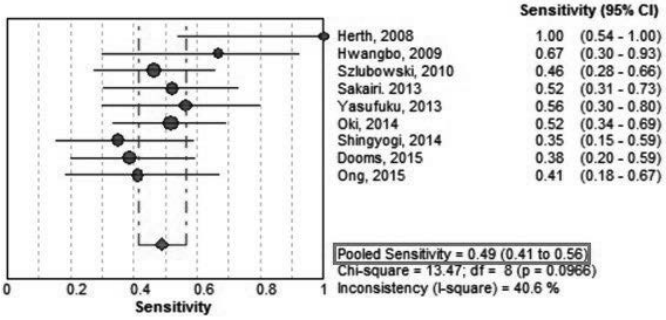
Background: Accurate mediastinal staging is crucial in potentially operable lung cancer to avoid non-therapeutic resection. Performance of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for staging of the radiologically normal mediastinum has been reported with inconsistent findings. We assessed the value of pre-operative systematic staging using EBUS-TBNA in cN0/N1 lung cancer. **Method:** For this systematic review and meta-analysis, we searched MEDLINE, PubMed, EMBASE, Cochrane databases from inception to October 2016. We included studies evaluating EBUS-TBNA for systematic mediastinal staging in cN0/N1 lung cancer. For each study, we extracted data on participant age and sex, radiological stage, EBUS-TBNA protocol, number and size of lymph nodes sampled, EBUS-TBNA stage, reference standard stage, and 2x2 tables. We evaluated the diagnostic accuracy of EBUS-TBNA for detection of occult mediastinal metastases. PROSPERO registration number CRD42017057020 **Result:** We identified 1,173 articles, of which nine (1,146 patients) were included in meta-analysis. Mean prevalence of N2/N3 disease was 15% (6-24%). EBUS-TBNA had a **pooled sensitivity 49%** (95%CI 41-57%) (see figure 1), pooled specificity 100% (95%CI 99-100%), and mean negative predictive value 91% (82-100%) for detection of unsuspected N2/N3 disease. Number Needed to Test to detect occult N2/N3 disease was **14** (95%CI 10.8-16.3), **NNT was reduced to 7** for studies which added endoscopic ultrasound to EBUS-TBNA.

Moderate inter-study heterogeneitywas observed (I^2 40.6%).



Conclusion: Pre-operative systematic staging by EBUS-TBNA of early lung cancer can reduce rates of non-therapeutic resection and decrease incidence of post-operative upstaging. Sensitivity for detection of radiologically occult mediastinal metastases appears lower than for targeted sampling of pathologic lymph nodes. Verification of negative results by mediastinoscopy in selected cases remains of value.

Keywords: systematic staging, EUS-B-FNA, endosonography

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.11 CHRONIC OBSTRUCTIVE PULMONARY DISEASE PREVALENCE IN A LUNG CANCER SCREENING POPULATION

J. Goffin[1], G. Pond[1], A. Tremblay[2], M. Johnston[3], G. Goss[4], G. Nicholas[5], S. Martel[6], R. Bhatia[7], G. Liu[8], H. Roberts[9], M. Tammemägi[10], S. Atkar-Khattra[11], M. Tsao[12], S. Lam[13], S. Puksa[1]

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Background: Chronic obstructive pulmonary disease (COPD) and lung cancer are associated through tobacco use. COPD is underdiagnosed in both the primary care and lung cancer populations. Diagnosis of COPD should lead to improved care and quality of life. Screening programs could provide an opportunity to capture undiagnosed COPD. We analyzed the Pan-Canadian Early Detection of Lung Cancer Study (PanCan Study) to evaluate the prevalence of COPD in a screening population. **Method:** The PanCan Study was a single arm lung cancer screening trial which recruited individuals to low dose CT scan, autofluorescence bronchoscopy, and biomarker screening. Eligible individuals were 50-75 years of age, had smoked within 15 years, and had a minimum six-year risk of lung cancer ≥ 2% based on a risk prediction model derived from PLCO study data, which included COPD as a risk factor. Consenting subjects completed a questionnaire including background medical conditions, high-risk work exposures, and smoking history. Baseline spirometry was performed, and COPD was defined by GOLD criteria. For individuals not receiving post-bronchodilator spirometry, COPD was defined as 'probable' if GOLD criteria were met pre-bronchodilator and there was no prior diagnosis of asthma. Individuals with definite or probable COPD were defined as having COPD. **Result:** Of 2537 individuals recruited, 2514 had available spirometry data. Mean age was 62.3 years, 55.3% were male, median pack-years smoked was 50, 62.3% were active smokers, 45.1% had symptoms of dyspnea, 52.4% cough, and 37.5% wheeze. 35.2% had worked in a high-risk occupation. Overall, 1136 (45.2%) met spirometry criteria for COPD. Of 1987 individuals without a prior history of COPD, 41.9% met spirometry criteria for COPD, of which 53.7% had moderate to severe disease. Of 527 individuals (21%) reporting a diagnosis of COPD at baseline, 57.5% met spirometry criteria for COPD, 32.2% did not, and 10.3% had a prior diagnosis of asthma. In a multivariate model for risk of COPD, age (odds ratio $(OR)_{per\ year}$ 1.06), dyspnea (OR 1.42), being a current smoker (OR 1.43), and pack-years (log transformed OR 1.42) were significant (all p < 0.001) as were high-risk occupation (OR 1.24, p=0.013) and wheeze (OR 1.24, p = 0.024). **Conclusion:** A diagnosis of COPD by spirometry is common in a lung cancer screening trial population. Individuals with a pre-existing self-reported diagnosis of COPD often fail to meet spirometry criteria for their diagnosis. Testing a lung cancer screening population for COPD could significantly improve COPD diagnosis and treatment.

Keywords: copd, Screening, lung cancer

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.12 LONGITUDINAL EVALUATION OF PULMONARY FUNCTION IN PATIENTS WITH ADVANCED NSCLC TREATED WITH CONCURRENT CHEMO-RADIOTHERAPY

M. Arroyo Hernandez[1], L. Torre Bouscoulet[2], L. Bacon[3], F. Lozano-Ruiz[1], L. Gochicoa-Rangel[2], C. García-Sancho[1], E. Vergara[1], D. Martínez Briseño[2], A. Guzmán-Barragán[2], R. Fernández Plata[2], M. Blake Cerda[1], F. Maldonado[1], O. Arrieta[1]

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Background: Patients with locally advanced Non-small cell lung cancer (aNSCLC) receive standard treatment with concurrent chemo-radiotherapy (CCRT). Different studies have tried to identify the changes in lung function after radiation exposition due to the high risk of pulmonary toxicity. The aim of this work is to evaluate lung function with a broad spectrum of respiratory tests as an objective way of assessing lung injury in patients with locally aNSCLC treated with CCRT. **Method:** A prospective study was conducted from June 2013 to July 2015. Fifty-two patients with locally advanced and oligometastatic NSCLC were included. The candidates received treatment with CCRT at the Instituto Nacional de Cancerología (Mexico). Participants were evaluated at baseline, end of RT, week 6, 12, 24 and 48 post-RT through forced spirometry with bronchodilator, body plethysmography, carbon monoxide diffusing capacity (DLCO), arterial blood gases, impulse oscillometry, 6-minute walk test and exhaled fraction of NO (FeNO). The study was registered in clinicaltrials.gov (NCT01580579). **Result:** Before treatment, 34.7% patients presented airflow obstruction (post-BD FEV_1/FVC < 70%) which remained constant after RT (33.3%). For baseline results, the median of the % of the predictive value in FEV_1 post-BD was 97% (79-108), FVC 105% (90-116), TLC 101% (91-111) and DLCO 77% (55-103). At the end of CCRT, FEV_1 and FVC showed a significant reduction of 10% within week 12-48 (p=0.0004, p= 0.0005). TLC declined after week 6 post-RT, with a maximum drop of 15% at week 48 (p=0.0015). DLCO changes occurred from RT start to week 48, decreasing up to 20% at week 12 (p=0.0001). FeNO increased, exceeding 20% of its initial/baseline value with a peak at week 6 post-RT. Eighteen patients (34.7%) were hypoxemic (SO2 <90%) at the beginning of the trial, oxygen saturation had a statistically significant reduction at week 6 and week 48 (p<0.03, p<0.01). No significant differences were found in impulse oscillometry and 6-minute walk test. The results of the respiratory tests that decreased with the CCRT did not return to baseline at the end of follow-up. **Conclusion:** Regardless of pre-existing lung damage, the reduction in FEV_1, FVC, DLCO, TLC and SO2 may represent increased inflammation, tissue remodeling and modification in gas exchange, however further studies are required. The nadir of the lung function occurred at 12 weeks from CCRT initiation. Increased FeNO values may represent a non-invasive marker of airway inflammation that correlates with RT lung injury mechanisms.

Keywords: chemoradiation, Radiation pneumonitis, Pulmonary function tests

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
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MA 20.13 ETDNA: TUMOR-DERIVED DNA FROM PLEURAL EFFUSION SUPERNATANT AS A PROMISING SOURCE FOR NGS-BASED MUTATION PROFILING IN LUNG CANCER

L. Tong[1], N. Ding[1], J. Li[1], X. Wang[1], Y. Zhang[1], X. Xu[1], M. Ye[1], C. Li[1], H. Zhang[1], X. Zhu[1], Z. Zhu[1], J. Zhou[1], J. She[1], J. Zhou[1], Y.W. Shao[2], X. Zhang[3], H. Bao[3], S. Xu[3], X. Zhang[1], Q. Hong[1], C. Bai[1], J. Hu[1]

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Background: Mutation profiling of circulating tumor DNA (ctDNA) and pleural effusion sediment containing tumor cells (ETCs) were commonly applied in clinical practice. Several studies suggested that tumor-derived DNA from pleural effusion supernatant (etDNA) might be a better candidate for detecting gene alterations in lung cancer. However, little is known regarding the abundance and diversity of tumor DNA acquired among different types of liquid biopsy. **Method:** We performed targeted next generation sequencing (NGS)-based genetic profiling on tumor tissue, pleural effusion (etDNA & ETCs) and contemporaneous ctDNA from 63 lung cancer patients (58 adenocarcinoma, 2 adenosquamous carcinoma, 2 SCLC, 1 neuroendocrine carcinoma), among which 28 patients had paired tumor tissue samples. Genomic DNA from whole blood of each patient was used for germline control. Driver mutation and rearrangement profiling was validated using ARMS-PCR, FISH, or Ventana IHC assay in tumor tissue as golden standard. **Result:** We identified tumor-specific mutations in 98%, 89%, 86%, and 100% of patients in their etDNAs, ETCs, ctDNAs and tumor tissues, respectively (p<0.01). etDNAs showed a significantly higher tumor-specific mutation number per patient (Median: 5) compared to ETCs and plasma ctDNAs (Median of 3 for both), while the median number in tumor tissues is 4 per patient. The detection sensitivity for EGFR mutations in etDNAs is 95%, higher than that in ETCs and ctDNAs (89% and 63%, respectively). Two patients detected ALK fusion in tumor tissue were also positive in etDNA, only one patient was positive in ETCs and ctDNA, respectively. A total of 298 genetic alterations, including point mutations, indels, copy number variations (CNVs) and gene fusions, were identified in etDNAs from all the patients. However, only 74% and 57% of these alterations were detected in contemporaneous ETCs and ctDNA samples, with CNVs having the lowest detection

sensitivity as 49% and 11%, especially in lung cancer patients without extrathoracic metastasis, as none of the CNVs detected in etDNAs were captured in plasma ctDNAs of these patients. Furthermore, driver mutations and rearrangements in etDNA showed a strong correlation to targeted therapy efficacy. **Conclusion:** This study demonstrated that etDNA had significantly higher tumor-specific mutation detection rate and sensitivity compared to ETCs and ctDNA. etDNA from supernatant of pleural effusion is a promising source for genetic testing to guide treatment-decision making in lung cancer. This study is funded by Shanghai Science and Technology Program (15ZR1406400).

Keywords: pleural effusion, liquid biopsy, NGS

MA 20 RECENT ADVANCES IN PULMONOLOGY/ENDOSCOPY
WEDNESDAY, OCTOBER 18, 2017 - 14:30-16:15

MA 20.14 GENOTYPING OF LUNG CANCER USING CELL-FREE DNA (CFDNA) FROM CYTOLOGIC SUPERNATANT (CSN)

N. Guibert[1], H. Tsukada[2], D. Hwang[3], T. Bale[3], E. Chambers[1], B. Ulrich[4], C. Paweletz[5], L. Sholl[3], G. Oxnard[6]

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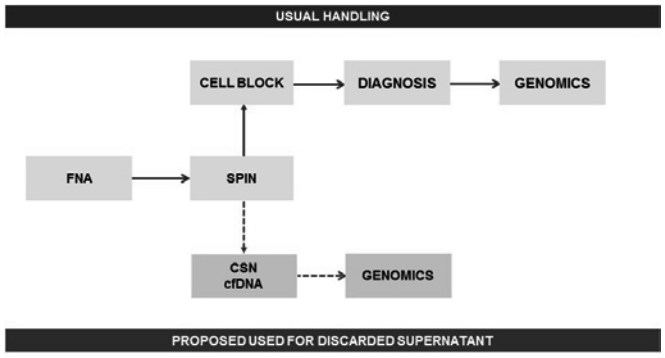
Background: Tumor genotyping is transforming lung cancer care but increasingly requires more tumor tissue. Advances in minimally invasive bronchoscopic techniques increase access to small lesions, but often result in smaller samples. With the advent of new cfDNA ("liquid biopsy") genotyping technologies, we hypothesized that CSN might increase the yield from small FNAs, facilitating cancer genotyping. **Method:** We studied patients with known or suspected lung cancer undergoing FNAs. CSN, which is usually discarded, was collected under IRB approval. cfDNA was extracted after a hard spin (1600 Gs) and tested by both ddPCR (EGFR, KRAS mutations) and targeted next-generation sequencing (NGS). **Result:** 14 patients with suspected or known lung cancer were studied at time of analysis (final diagnosis: 2 non-malignant, 9 adenocarcinomas, 1 small-cell carcinoma, 2 squamous cell carcinomas), including 12 EBUS-TBNAs and 2 CT-guided FNAs. Among 6 known KRAS and EGFR mutations, all could be detected with ddPCR of CSN, with allelic fraction (AF) ranging from 1%-46% (median 8.5%). No ddPCR false positives were seen across 9 cases. NGS analysis was piloted on 7 specimens; 5 failed due to insufficient residual DNA. In one specimen, an EGFR exon 19 deletion was detected at 6% AF (2% AF ddPCR). In the other, a BRAF V600E, PIK3CA E784D and TP53 V274F mutations were detected at 48% (46% AF ddPCR), 18% and 86% AF, respectively. **Conclusion:** Cytology supernatant, usually discarded, may be a rich source of fresh tumor DNA, increasing the yield from FNAs. This widely available biospecimen has potential for aiding resistance genotyping, reducing turnaround time of cancer genotyping, and possibly a future role in clarifying the malignant potential of non-diagnostic biopsies. Enrollment continues in order to optimize this biospecimen for NGS.



Keywords: cell-free DNA, Genotyping, EBUS-TBNA

POSTER SESSION 1 | MONDAY, OCTOBER 16, 2017

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-001 DEPTH OF TARGET LESION RESPONSE TO BRIGATINIB AND ITS ASSOCIATION WITH OUTCOMES IN PATIENTS WITH ALK+ NSCLC IN THE ALTA TRIAL

D.R. Camidge[1], M. Tiseo[2], M. Ahn[3], K. Reckamp[4], K. Hansen[5], S. Kim[6], R. Huber[7], H. West[8], H. Groen[9], M. Hochmair[10], N. Leighl[11], S. Gettinger[12], C. Langer[13], L. Paz-Ares[14], E. Smit[15], E. Kim[16], W. Reichmann[17], D. Kerstein[17], D. Kim[18]

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Background: Depth of target lesion response to crizotinib has been associated with overall survival (OS) (*J Clin Oncol* 2016;34:abstract 2590). ALTA (NCT02094573) is an ongoing randomized phase 2 trial of brigatinib, an ALK inhibitor, in crizotinib-refractory advanced ALK+ NSCLC patients. As the ALTA primary endpoint of confirmed objective response rate (cORR), a binary outcome, might not fully capture clinical benefit, we examined the association of maximum decrease in target lesions with progression-free survival (PFS) and OS. **Method:** Patients were randomized to receive brigatinib at 90 mg qd (arm A; n=112) or 180 mg qd with a 7-day lead-in at 90 mg (arm B; n=110). Arms were pooled in this analysis. Patients with any target lesion shrinkage were sorted into 4 groups based on greatest decrease from baseline per RECIST v1.1; outcomes in these groups were compared with outcomes in patients with no shrinkage. **Result:** As of February 21, 2017, cORR in arm A/B (ITT population) was 46%/55% per investigators. 201/222 patients had ≥1 evaluable response assessment with 18.4-month median follow-up. Median age of these patients was 53 years; 57% were female. Patients with target lesion shrinkage (vs none) had numerically longer PFS (hazard ratios [95% CIs]: 0.61 [0.30–1.22], 1%–25% shrinkage; 0.47 [0.24–0.91], 26%–50%; 0.54 [0.28–1.05], 51%–75%; 0.30 [0.15–0.63], 76%–100%) and numerically higher estimated 1-year OS (Table). In a multivariable analysis, 76%–100% shrinkage (vs none) was independently associated with longer PFS/OS (hazard ratios [95% CIs]: 0.37 [0.18–0.76]/0.35 [0.14–0.89]); arm B (vs A) was independently associated with longer PFS. **Conclusion:** In this exploratory post hoc analysis, brigatinib-treated patients with target lesion shrinkage, including those without confirmed partial response, had improved PFS/OS vs patients without shrinkage. Patients with the deepest response (76%–100% shrinkage) appeared to have the longest PFS and higher estimated 1-year OS.

Best Target Lesion Shrinkage	n (%)a	Median PFS,b,cMonths (95% CI)	Median OS,bMonths (95% CI)	1-year OS,b % (95% CI)
None	18 (9)	3.7 (1.9–11.0)	8.3 (4.7–NR)	48 (22–99)
1%–25%	40 (20)	9.3 (4.0–21.2)	NR (14.5–NR)	75 (58–99)
26%–50%	60 (30)	12.8 (9.2–15.7)	NR (NR–NR)	82 (70–99)
51%–75%	44 (22)	11.1 (7.4–18.2)	27.6 (20.2–NR)	77 (62–99)
76%–100%	39 (19)	19.5 (12.6–NR)	NR (22.3–NR)	92 (78–99)
NR, not reached [a]Evaluable patients [b]Kaplan-Meier estimate [c]Per investigator				

Keywords: ALK, brigatinib, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-002 TP53 MUTATIONS PREDICT FOR POOR SURVIVAL IN ALK REARRANGEMENT LUNG ADENOCARCINOMA PATIENTS TREATED WITH CRIZOTINIB

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Background: Advanced non-small-cell lung cancer patients who harbor anaplastic lymphoma kinase (ALK) rearrangement are sensitive to an ALK inhibitor (Crizotinib), but not all ALK-positive patients benefit equally from crizotinib treatment. We analyze the impact of TP53 mutations on response to crizotinib in patients with ALK rearrangement non-small cell lung cancer (NSCLC). **Method:** 66 ALK rearrangement NSCLC patients receiving crizotinib were analyzed. 21 cases were detected successfully by the next generation sequencing validation FFPE before crizotinib. TP53 mutations were evaluated in 8 patients in relation to disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). **Result:** TP53 mutations were observed in 2 (25.00%), 1 (12.50%), 1 (12.50%) and 4 (50.00%) patients in exons 5, 6, 7 and 8, respectively. The majority of patients were male (75.00%, 6/8), less than 60 years old (62.50%, 5/8) and never smokers (75.00%, 6/8). ORR and DCR for crizotinib in the entire case series were 61.90% and 71.43%, respectively. Statistically significant difference was observed in terms of PFS and OS between TP53 gene wild group and mutation group patients (P=0.038, P=0.021, respectively). **Conclusion:** TP53 mutations reduce responsiveness to crizotinib and worsen prognosis in ALK rearrangement NSCLC patients.

Keywords: TP53, ALK, crizotinib

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-003 PATIENTS HARBORING A NOVEL PIK3CA POINT MUTATION AFTER ACQUIRED RESISTANCE TO CRIZOTINIB IN ROS1 REARRANGEMENT ADENOCARCINOMA: A CASE REPORT

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Background: The c-ros oncogene 1 receptor tyrosine kinase (ROS1) rearrangement has been identified in 1%-2% of non-small cell lung cancer (NSCLC) cases, these patients would benefit from the inhibitor of anaplastic lymphoma kinase (ALK), crizotinib. But the resistance to crizotinib inevitably developed in the patients with ROS1 rearrangement NSCLC and shown a response to crizotinib initially. The mechanism of acquired resistance to crizotinib for the patients with ROS1 rearrangement NSCLC is not identified completely now. **Method:** A 66-year-old female diagnosed with adenocarcinoma, who shown EGFR wild and ALK negative detected by Polymerase Chain Reaction(PCR). According to the detection of ROS1 rearrangement by the next generation sequencing (NGS) in blood after the patient received chemotherapy twice (pemetrexed and carboplatin), the addition of bevacizumab to chemotherapy 4 times (pemetrexed, carboplatin and bevacizumab) and maintenance therapy 3 times (pemetrexed and bevacizumab), crizotinib was used. Disease progressed explosively 6 months later, although the patient shown a response to crizotinib initially. Then NGS was carried out on blood again, a novel point mutation (p.L531P)of the PIK3CA gene was detected. **Result:** This case was the second report for bypass activation conferred crizotinib resistance to the patient with ROS1 rearrangement NSCLC. And it also was the first report that confirmed mTOR signaling pathways activation would lead to acquired resistance to crizotinib in the clinical. And everolimus, the mTOR signaling pathway inhibitor, was used. However, the disease of the patient was too serious, and she still died of circulatory failure. In conclusion, progression-free survival was 5.0 months and overall survival was 16.0 months. **Conclusion:** Bypass activation is one of potential resistance mechanisms to ROS1 rearrangement NSCLC conferred crizotinib and regimen for mTOR signaling pathway inhibitor may be one of the treatment options.

Keywords: ros1 rearrangement, Acquired resistance, PIK3CA

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-004 HYPERTENSION WITH BRIGATINIB: EXPERIENCE IN ALTA, A RANDOMIZED PHASE 2 TRIAL IN CRIZOTINIB-REFRACTORY ALK+ NSCLC

D.R. Camidge[1], M. Ahn[2], K. Reckamp[3], H. West[4], R. Huber[5], C. Langer[6], L. Bazhenova[7], N. Leighl[8], W. Reichmann[9], D. Kerstein[9], D. Kim[10]

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Background: The next-generation ALK inhibitor brigatinib received accelerated approval in the United States in April 2017 for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant to crizotinib. Hypertension has been identified as an adverse event of interest with brigatinib treatment based on prior clinical data; here, we report incidence, management, and outcomes of hypertension in ALTA (NCT02094573). **Method:** In ALTA, 222 patients were randomized 1:1 to receive brigatinib at 90 mg qd (arm A; n=112 randomized, n=109 treated) or 180 mg qd with a 7-day lead-in at 90 mg (arm B; n=110 randomized and treated). A medical history of hypertension was allowed, but patients with significant, uncontrolled, or active cardiovascular disease were excluded. Blood

pressure (BP) was measured at screening, on days 1, 8, and 15 of the first 28-day cycle, and then every 4 weeks (starting on day 1 of cycle 2). **Result:** Median age was 50/57 years in treated patients in A/B; 22%/25% of treated patients in A/B had a history of hypertension at baseline. As of February 21, 2017, hypertension was reported as a treatment-emergent adverse event (TEAE; any grade) in 17%/27% of patients (A/B) and as a grade 3 TEAE in 6%/8%; no grade 4 hypertension was reported. Few patients had dose interruptions (1%/2%, A/B) or reductions (1%/1%) due to hypertension; no patients discontinued brigatinib due to hypertension. Among patients with hypertension, median time to onset of first hypertension TEAE was 5.8 months/2.1 months in A/B. Among patients with baseline systolic BP <120 mmHg (n=50/n=48, A/B), 20%/42% had a maximum shift to 140–159 mmHg postbaseline (6%/10%, <120 mmHg to ≥160 mmHg); among patients with baseline diastolic BP <80 mmHg (n=68/n=72, A/B), 29%/35% had a maximum shift to 90–99 mmHg postbaseline (10%/8%, <80 mmHg to ≥100 mmHg). Among patients with hypertension TEAEs (n=19/n=30, A/B), 84%/80% started a new antihypertensive medication during the study. Among patients with hypertension TEAEs and no medical history of hypertension (n=11/n=20, A/B), 73%/70% started a new antihypertensive medication during the study. Cardiovascular events in patients with hypertension TEAEs included: angina pectoris in 1 patient without a medical history of hypertension and, in patients with a medical history of hypertension, hypertensive retinopathy (n=1), intermittent claudication (n=1), and peripheral artery stenosis (n=1). **Conclusion:** Hypertension was observed frequently with brigatinib, and appeared dose-related, but was managed with antihypertensive therapy and rarely led to dose modification or discontinuation.

Keywords: ALK, brigatinib, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-005 OVERALL SURVIVAL (OS) AFTER DISEASE PROGRESSION (PD) ON BRIGATINIB IN PATIENTS WITH CRIZOTINIB-REFRACTORY ALK+ NSCLC IN ALTA

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Background: Brigatinib, a next-generation ALK inhibitor, has been associated with a median progression-free survival of approximately 16 months in ALTA, a randomized phase 2 trial (NCT02094573) investigating 2 brigatinib regimens in patients with crizotinib-refractory, advanced ALK+ NSCLC. This post hoc analysis explores the clinical benefit of continuing brigatinib beyond PD in ALTA. **Method:** Patients were randomized to arm A (brigatinib 90 mg qd; n=112) or B (brigatinib 180 mg qd with 7-day lead-in at 90 mg; n=110). Patients in arm A were permitted to escalate to 180 mg qd after RECIST PD. 107 patients who had PD on brigatinib, did not have PD as their best response, and survived ≥21 days post-PD were analyzed here. **Result:** As of February 21, 2017, 84 patients continued and 23 discontinued brigatinib treatment post-PD. Estimated 1-year OS after first PD and OS hazard ratios (HRs; unadjusted and adjusted) are shown in the table. Unadjusted HRs indicated significantly longer OS in patients who continued brigatinib vs those who did not (HR: 0.32 [95% CI, 0.17–0.62]), particularly those who continued at 180 mg. Patients who were more heavily pretreated, had longer duration of brigatinib therapy before PD, did not progress due to new lesions, had confirmed objective response, and had better ECOG performance status at PD were more likely to continue brigatinib post-PD. Adjusted HRs indicated numerically longer OS in patients who continued brigatinib (HR: 0.53 [95% CI, 0.26–1.08]). Number of prior regimens (2 vs ≥3), shorter time to investigator-assessed PD, PD due to new lesions only, and ECOG performance status at PD (≥2 vs 0) were independently associated with worse OS (P<0.05). **Conclusion:** Survival was better among patients who continued vs discontinued brigatinib after PD. Continuing brigatinib, especially at 180 mg, could be one of many factors associated with longer OS after PD in these patients.

Patients With PD on Brigatinib (n=107)	n	1-Year OS Post-PD,a% (95% CI)	Unadjusted HR (95% CI)	Adjusted HRb (95% CI)
Continued brigatinib	84	66(53–99)	0.32(0.17–0.62)	0.53(0.26–1.08)
At 90 mg qd (arm A without escalation)	23	62(38–99)	0.49(0.22–1.11)	0.61(0.25–1.46)
At 180 mg qd	61	68 (51–99)	0.26(0.13–0.54)	0.48(0.21–1.06)
Arm A with escalation	23	70(44–99)	0.29(0.12–0.72)	0.51(0.19–1.33)
Arm B	38	66(44–99)	0.25(0.11–0.57)	0.45(0.18–1.16)
Did not continue brigatinib 23 31(13–100) Reference				

[a]Kaplan-Meier estimate from time of first PD [b]Adjusted for duration of prior crizotinib exposure, number of prior treatment regimens (1, 2, or ≥3), time to investigator-assessed PD, PD due to new lesions only (yes/no), and ECOG performance status at PD (0, 1, or ≥2)

Keywords: ALK, brigatinib, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-006 EFFECT OF EML-ALK FUSION VARIANT AND FUSION ABUNDANCE ON THE EFFICACY OF CRIZOTINIB IN NON-SMALL CELL LUNG CANCER

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Background: EML4-ALK fusion gene is a molecular subtype of non-small cell lung cancer (NSCLC), which is carcinogenic both in vitro and in vivo. Most of the EML4-ALK-positive NSCLC patients have effectively sensitivity with an ALK tyrosine kinase inhibitor (TKI), such as crizotinib. However, the treatment outcomes and duration of response are heterogeneous. EML4-ALK has several variants. The effects of ALK fusion variants on the efficacy of crizotinib is still unclear, although many scientists are committed to this work. In addition, we also unknown the effects of ALK variants allele fraction (AF) on the efficacy of crizotinib. **Method:** Among 54 patients with advanced NSCLC were treated with crizotinib as the first-line or further-line ALK-TKI between 2013 and 2017, eventually, we identified 48 patients whose the tumor samples were detected by IHC(38), FISH(2), NGS(5),PCR(1) and ARMS(2). Through retrospective analysis, we assumed the efficacy of crizotinib on the basis of the PFS according to the ALK variants and its allele fraction. **Result:** Among the 29 ALK-positive patients, the most common ALK variants was variant 1 in 13 patients (44.9%), followed by variant 3 in 7 patients (24.1%), variants 2 in 2 patients (6.9%), other variants in 7 patients (24.1%). We divided all variants into two subgroups: V1/3 and V2/others. We found 35.4% of the samples test results between the next generation sequencing (NGS) and hospital immunohistochemical were not concordence. Further analysis found that patients who did not match that PFS were shorter (p=0.036). By the NGS, we observed from the figure that the variant 2/others group, the median PFS had a longer trend than V1/3 group, although not statistically significant (p>0.05. The level of AF was no correlated with PFS (P=0.346). **Conclusion:** The above results show that next-generation sequencing (NGS) can identify ALK variants and AF, therefore, NGS can be used as a supplement to a detection method. The type of EML4-ALK fusion variants may has a certain correlation with PFS in patients who oral crizotinib treatment. Since the sample size of this study is small, we have not yielded accurate results and found only these phenomena. We believe that in the near future, most NSCLC patients can be detected by NGS detection of gene mutations, especially EML4-ALK fusion gene, and according the different of the fusion gene variant type which can be estimated the efficacy of the ALK-TKIs, to provide the basis of individualized treatment options for NSCLC patients.

Keywords: Effect, EML-Alk fusion variant, fusion abundance, efficacy of Crizotinib, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-007 ALK TESTING TRENDS AND PATTERNS AMONG COMMUNITY PRACTICES IN THE UNITED STATES

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Background: The CAP/IASLC/AMP molecular testing guidelines recommend ALK testing on patients with lung adenocarcinoma, regardless of clinical characteristics. FISH is the recommended assay to detect ALK rearrangement, however other assays, such as NGS and IHC, are available. There have been limited published data to assess adherence to ALK testing guidelines using large real-world data sources. The objective of this study was to assess real-world ALK testing patterns among community practices in the United States. **Method:** The Flatiron database provides real-world clinical data collected from EHRs used by US cancer care providers. The Flatiron network comprises ~15% of US cancer patients and is geographically and demographically diverse. Patients with ≥2 visits within the Flatiron Network after Jan 1, 2011, >=18 years of age, and an stage IIIB/IV NSCLC diagnosis from 2011 through 2017 Q1 were included in this analysis. Logistic regression was used to identify patient characteristics associated with receiving ALK testing. **Result:** Of 29,903 patients identified from community-based clinics (mean age: 71.6, 52.2% male), ALK testing rates have steadily increased over time from 32.2% in 2011 to 61.0% in 2016 for all NSCLC patients, and 41.0% in 2011 to 74.0% in non-squamous patients. Patients that are younger, no history of smoking, women and living in the West region were more likely to be tested for ALK. Patients with Medicaid insurance, recurrent disease and squamous histology were less likely to be tested. The most common first assay to test for ALK was FISH (70%) followed by NGS (8%), PCR (4%) and IHC (1%). The median time from specimen receipt by lab to test result ranged from 6 days (FISH) to 11 days (NGS). Patients who had NGS testing were more likely to initiate chemotherapy prior to test result (34% of patients tested with NGS) than FISH (20%). 1235 patients had at least one FISH and another ALK test, with the percent agreement between FISH and other assays (NGS, PCR, IHC) ranging from 92% to 97%. **Conclusion:** Several patient characteristics predicted ALK testing indicating that some subgroups of patients may be under tested, according to guidelines. Consistent with guidelines, FISH was the most common assay and turnaround times from lab receipt to test result was under 2 weeks. There was a high agreement between FISH and NGS, indicating the potentially clinical utility of NGS, however NGS had also the longest turn around time and the highest proportion of patients initiating treatment prior to test results.

Keywords: ALK, biomarker testing

P1.01-008 REAL-WORLD PATIENT CHARACTERISTICS, TESTING AND TREATMENT PATTERNS OF ALK+ NSCLC

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Background: Based on clinical trials, ALK+ patients have been described as typically younger and never/former smokers, however patients enrolled in clinical trials may be different than those in the real-world. While the ALK positivity rate has been described as about 4% among all NSCLC patients, limited information is available on the positivity rates in patient subgroups. The objective of this study is to describe the real-world ALK positivity rates, patient characteristics and treatment patterns in ALK+ NSCLC patients. **Method:** The Flatiron database provides real-world clinical data collected from EHRs used by US cancer care providers. The Flatiron network comprises ~15% of US cancer patients and is geographically and demographically diverse. Patients with ≥2 visits within the Flatiron Network after Jan 1, 2011, ≥18 years of age, ≥1 ALK+ test result and an stage IIIB/IV NSCLC diagnosis from 2011 through 2017 Q1 were included in this analysis. Logistic regression was used to examine the association of ALK positivity and initiation of ALK inhibitor therapy based on patient characteristics. Survival model adjusting for censoring was used to estimate the time to ALK inhibitor order. **Result:** 599 out of 15,551 ALK tested patients were identified to have an ALK positive test result, for a positivity rate of 3.9%. The ALK positivity rate varied by age (<65: 6.3% vs. ≥65: 2.9%), smoking status (no history of smoking: 11.6% vs. history of smoking: 2.3%), and histology (non-squamous: 4.0% vs. squamous: 1.8%). Factors associated with ALK positivity included younger age, academic practice, male, non-squamous histology, and no history of smoking. 78% of patients with ALK+ disease had evidence of an order for an ALK inhibitor after NSCLC diagnosis. The median time from test result to ALK inhibitor order was 24 days, with 42% of patients without an order for an ALK inhibitor within 90 days. Among patients with an order for an ALK inhibitor, 23% received chemotherapy prior to their ALK test result and 20% received chemotherapy after their test result but before the first order of ALK inhibitor. Patients diagnosed after 2014 and patients who received chemotherapy prior to the ALK test result were more likely to have an order for an ALK inhibitor. **Conclusion:** The ALK positivity rate and patient characteristics in this real-world NSCLC population are consistent with clinical trials, with some subgroups having higher positivity rates. ALK inhibitors were the most frequently ordered treatment, however many patients had a delayed time to ordering the ALK inhibitor.

Keywords: treatment patterns, ALK, biomarker testing

P1.01-009 CLINICALLY PRIMARY AND SECONDARY RESISTANCE TO ALK INHIBITORS IN ALK-POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Crizotinib is a standard of care in anaplastic lymphoma kinase(ALK)-positive advanced non-small-cell lung cancers (NSCLC).Undoubtedly,the resistance to crizotinib is a current bottleneck.Hence,it is necessary to explore the resistance mechanisms to ALK inhibitors. **Method:** From October 2010 to May 2017,225 ALK-positive NSCLC patients treated with crizotinib were reviewed at the Guangdong General Hospital in China.The status of *ALK* rearrangement was assessed by Lysis ALK Break Apart fluorescence in situ hybridization,reverse transcription polymerase chain reaction,or Ventana ALK immunohistochemistry.Next generation sequencing(NGS) was used to test the tissue or plasma from patients with resistance to crizotinib. Primary resistance to crizotinib occurred when Progression-free survival was less than 3 months for the patients treated with crizotinib. **Result:** Among enrolled patients,72.4%(163/225) gained secondary resistance,and 8.9%(20/225) had primary resistance. Molecular mechanisms of clinically primary resistance were shown in Figure a.The variants of ALK fusion were different between primary and secondary resistance patients.There were more variants of ALK fusion appeared in the group with primary resistance except E6-A20 and E13-A20.Among secondary resistant patients,non-EML4 partners fusion,such as DMD-ALK fusion,YWHAQ&TAF1B-ALK fusion,GALNT14-ALK fusion and SLC19A3-CCL20-ALK fusion were found,which responsed to crizotinib treatment.Acquired ALK L1196M/G1269A mutations were found in both primary and secondary resistant patients,and while ALK I1171T mutation was only found in secondary resistantpatients.Wnt signaling pathway was activated significantly after the treatment of crizotinib according to Kyoto Encyclopedia of Genes and Genomes(KEGG) and GeneOntology(GO) analyses.Moreover, AMER1 aberrance was inclined to appear in the primary resistance patients, which was significant different between the two groups in KEGG and GO analyses.

Figure a Distribution of primary resistance to crizotinib

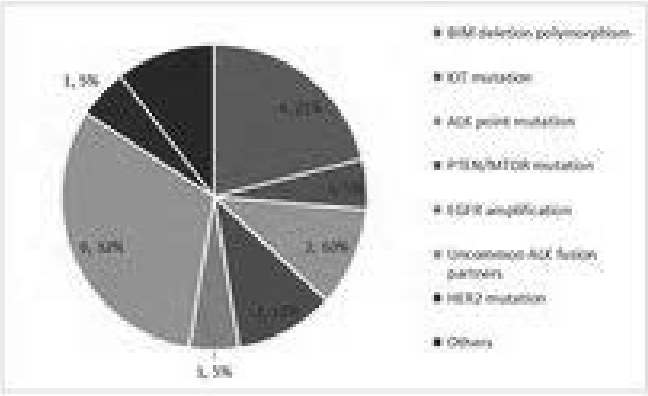


Figure b The variants of ALK fusion

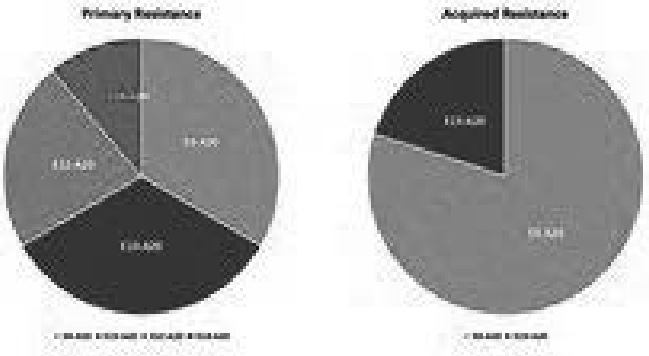
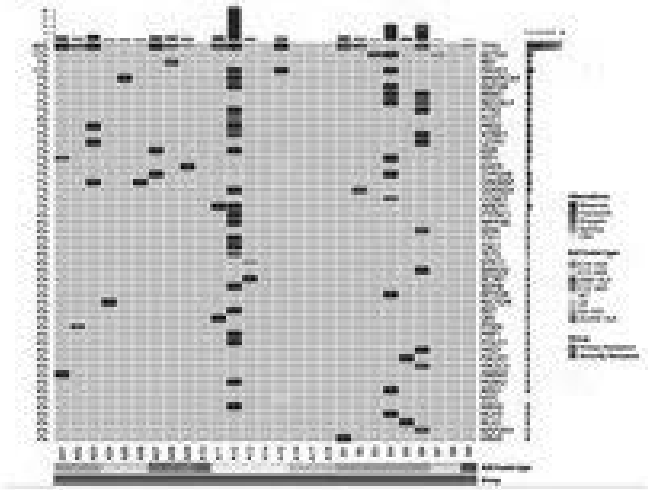


Figure c The mutational spectrum after resistance



Conclusion: ALK mutations could exist in both primary and secondary resistance to crizotinib in ALK-rearranged NSCLC. Response to crizotinib was also observed in ALK-rearranged NSCLC patients with non-EML4 partners. NGS may facilitate precision treatment for both primary and secondary resistant patients though they have a few differences in molecular mechanisms of resistance.

Keywords: Resistance to ALK inhibitors

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-010 CIRCULATING CELL-FREE DNA OF CEREBROSPINAL FLUID MAY FUNCTION AS LIQUID BIOPSY FOR LEPTOMENINGEAL METASTASES OF ALK REARRANGEMENT NSCLC

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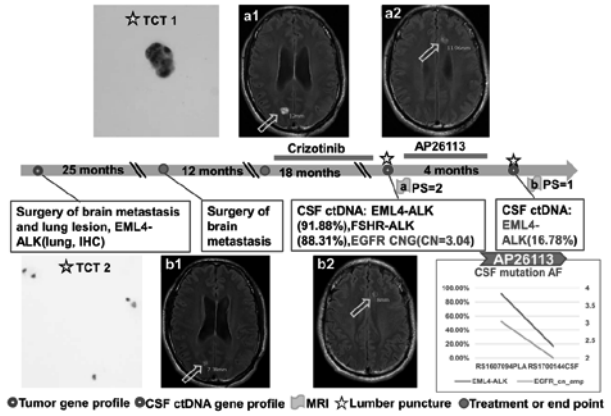
Background: Leptomeningeal metastases (LM) are more frequent in non-small cell lung cancer (NSCLC) patients with oncogenic drivers. Resistance mechanisms of LM with *ALK* rearrangement remained unclear due to limited access to leptomeningeal lesions. **Method:** Primary tumor, cerebrospinal fluid (CSF) and plasma in patients with suspected LM of NSCLC were tested by Next-Generation Sequencing. **Result:** In patents with *ALK* rearrangement, driver genes were detected in 66.7%, 50.0% and 28.6% patients of CSF cfDNA, CSF precipitates and plasma, respectively; and all of them had much higher allele fractions in CSF cfDNA than the other two media. The diagnosis criteria of LM were positive in brain MRI or CSF cytology, and driver genes were identified in CSF cfDNA of all patients with positive CSF cytology while in those CSF cytology negative all genes were negative. Resistance mutations including gatekeeper genes ALK G1202R and ALK G1269A were identified in CSF cfDNA but they were absent in their plasma. Moreover, tailor therapy based on CSF cfDNA obtained surprising outcomes, and genetic profiles of CSF cfDNA showed dynamic changes, suggesting the potential role of CSF for follow-up studies.



Conclusion: CSF cfDNA could reveal the driver and resistant genes of LM, and it may function as the media of liquid biopsy for LM in NSCLC with *ALK* rearrangement.

Keywords: ALK rearrangement, cell-free DNA, Leptomeningeal metastases

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-011 PATTERN OF CARE AND SURVIVAL OF ALK REARRANGED NON-SMALL CELL LUNG CANCER IN TWO AUSTRALIAN REFERRAL CENTRES

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Background: *ALK* rearranged non-small cell lung cancer (ALK+NSCLC) represents a unique sub-group of lung cancer. Multiple effective treatments have been investigated and reported with the optimal strategy to treat advanced disease evolving rapidly with new data. First, second and now third generation single agent ALK inhibitors (ALKi) achieve excellent objective response rates (ORR), superior to chemotherapy; however, drug resistance is inevitable and remains under ongoing evaluation. Further studies are underway incorporating combination treatments, particularly immunotherapy with ALKi. Overall survival data from clinical trials continues to mature, as few non-trial series have been reported. We report our overall survival (OS) experience in treating ALK+NSCLC in a real-world cohort. **Method:** All patients with advanced lung cancer and a diagnosis of ALK+ NSCLC treated until Jan 2017 in two tertiary referral centres in Sydney, Australia were pooled together for analysis. Baseline demographic, symptom, treatment and sequencing, ORR and central nervous system (CNS) ORR, survival, toxicity and cause of death data were collected. Data will be presented on updated survival via Kaplan-Meir plots with 95% confidence intervals and a swimmer plot of treatment sequencing and ORR via RECIST 1.1. **Result:** Between 18/2/2010 and 28/1/2017, 56 *ALK*-rearranged lung cancer patients were identified. Median age was 63 years, 41% were female; 62% never-smokers, 63% non-Asian and 66% managed on a clinical trial. At first data cut (March 31, 2017), 52% had died. Median OS in the whole cohort was 44.6 months (95%CI: 27.8-61.4mo). Two patients were not fit for active treatment; one did not receive CNS imaging. All current ALKi therapies, chemotherapy, brain directed therapy, treatment to oligo-progressive disease and combination ALKi/immunotherapy were represented. Sixty-one percent of patients received an ALKi first line with an ORR 87%; 85% of the 34 (61%) patients who received second line therapy received an ALKi, ORR 52%. Thirty-percent received at least two lines of ALKi; 44% who received only one line of ALKi remained on and are still responding at data cut-off. Median OS in the 59% of patients with CNS metastases was 44.6mo (95% CI 14.7-74.6 mo). **Conclusion:** Analysis of real world data from two ALK referral centres in Australia reveals an imposing survival, despite many patients being managed before next generation inhibitors were available in the early line setting. While CNS disease is common in ALK patients, with aggressive local therapy and evolving treatments, survival in this cohort was comparable to those without brain metastases.

Keywords: ALK, NSCLC, survival

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-012 CERITINIB IN ANAPLASTIC LYMPHOMA KINASE (ALK)+ NSCLC PATIENTS PRETREATED WITH ONLY CRIZOTINIB: ASCEND-1 SUBGROUP ANALYSIS

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Background: In phase 1 ASCEND-1 study (NCT01283516), ceritinib 750 mg/day (fasted) demonstrated durable whole-body and intracranial responses in both anaplastic lymphoma kinase inhibitor (ALKi)-naïve and ALKi-pretreated patients with *ALK*-rearranged non-small cell lung cancer (NSCLC). Here, we report the efficacy and safety of ceritinib in patients who were pretreated with crizotinib only from the ASCEND-1 study. **Method:** Patients with *ALK*+ NSCLC who were enrolled globally received ceritinib 750 mg/day (fasted). Efficacy and safety were evaluated in a subset of patients who had received prior crizotinib only (no other prior antineoplastic therapy). Data cut-off was May 03, 2016. **Result:** Overall, 246 patients with *ALK*+ NSCLC (83 ALKi-naïve and 163 ALKi-pretreated) received ≥1 dose of ceritinib, of whom, 26 had received prior crizotinib only. Among the 26 crizotinib-pretreated patients, 11 (42.3%) had baseline brain metastases, of which, 7 received prior radiotherapy, 6 (23.1%) had an ECOG performance status of 0, and 24 (92.3%) patients had stage IV disease. The median time from initial diagnosis to ceritinib

initiation was 10.5 months (range, 2.4-33.0). At data cut-off, the median duration of exposure (range) was 41.0 weeks (2.9-180.4). In the 26 crizotinib-pretreated patients, per investigator assessment, the overall response rate was 65.4% (95% confidence interval [CI]: 44.3, 82.8), and the disease control rate was 80.8% (95% CI: 60.6, 93.4) (Table). The most frequently reported grade 3/4 adverse events (AEs), regardless of study drug relationship, were ALT increased (30.8%), AST increased (15.4%), diarrhea (11.5%), nausea (7.7%), fatigue (7.7%), and blood alkaline phosphatase increased (7.7%). All 26 patients discontinued treatment due to disease progression (n=12), consent withdrawal (n=6), AEs (n=2), administrative problems (n=4), or death (n=2).

	Investigator Assessment N=26	**Blinded Independent Review Committee Assessment N=26**
Best overall response		
Complete response (CR), n (%)	1 (3.8%)	1 (3.8%)
Partial response (PR), n (%)	16 (61.5%)	15 (57.7%)
Stable disease (SD), n (%)	4 (15.4%)	5 (19.2%)
Progressive disease (PD), n (%)	2 (7.7%)	1 (3.8%)
Unknown, n (%)	3 (11.5%)	4 (15.4%)
Overall response rate (ORR), % [95% CI]	**65.4% [44.3-82.8]**	**61.5% [40.6-79.8]**
Disease control rate (DCR), % [95% CI]	**80.8% [60.6-93.4]**	**80.8% [60.6-93.4]**
Median time to response*, weeks [95% CI]	**6.1 [5.1-23.6]**	**6.4 [5.1-14.0]**
Median DOR, months [95% CI]**	**8.3 [4.2-11.2]**	**8.5 [3.0-13.6]**
Median PFS, months [95% CI]**	**8.5 [5.3-9.9]**	**8.2 [4.4-15.2]**

*Median value derived from summary statistics; **Median value estimated by Kaplan-Meier method. **Conclusion:** Ceritinib demonstrated durable efficacy in crizotinib-pretreated patients with *ALK*-rearranged NSCLC. Safety was consistent with the overall ASCEND-1 study population.

Keywords: Ceritinib, ALK, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-013 PATIENT-REPORTED OUTCOMES AND SAFETY FROM THE PHASE III ALUR STUDY OF ALECTINIB VS CHEMOTHERAPY IN PRE-TREATED ALK+ NSCLC

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Background: Alectinib demonstrated superior efficacy versus chemotherapy in *ALK*+ NSCLC after crizotinib failure (ALUR; NCT02604342). We present PROs and safety in the ITT population and in patients with baseline CNS disease (C-ITT). **Method:** Patients (n=107) with pre-treated *ALK*+ NSCLC (randomised 2:1) received alectinib (600mg BID) or chemotherapy (pemetrexed 500mg/m^2 or docetaxel 75mg/m^2 q3w) until PD/death/withdrawal. Primary endpoint: investigator-assessed PFS. Secondary endpoints: safety and PROs. Symptoms, functioning, and HRQoL were reported using questionnaires: EORTC QLQ-C30; lung module QLQ-LC13; BN-20 (3 items, CNS symptoms). Pre-specified endpoints included time-to-deterioration (TTD) in lung cancer symptoms, longitudinal analyses of mean score changes from baseline, proportion of patients with clinically meaningful change (≥10-point change from baseline) during treatment. **Result:** High compliance with assessment completion (alectinib 91.7%, chemotherapy 88.6% at baseline); compliance remained ≥70% with alectinib, and decreased with chemotherapy (64.3%, Week 6; ≤70% thereafter). Deterioration of patient-reported fatigue (median TTD 2.7 vs 1.4 months) and arm/shoulder pain (median TTD 8.1 vs 1.9 months) was delayed with alectinib versus chemotherapy. Median TTD in composite symptom endpoint (cough, dyspnoea, chest-pain) was similar between arms. Alectinib patients reported improvement in lung cancer symptoms from baseline (least square [LS] mean) during treatment: fatigue (-6.2), single-item dyspnoea (-6.0), multi-item dyspnoea scale (-2.3), coughing (-4.9), chest pain (-4.2), pain in other parts (-5.3). More patients reported improvement in baseline symptoms (nausea/vomiting, diarrhoea, peripheral neuropathy) with alectinib versus chemotherapy, except constipation. More alectinib patients reported improvements in cognitive function versus chemotherapy (ITT 19% vs 3%; C-ITT 24% vs 4%); average change from baseline in cognitive function favoured alectinib (LS means difference 10.0, 95% CI 2.2–17.7). Median treatment duration: 20.1 weeks alectinib (95% CI 0.4–8.2), 6 weeks chemotherapy (95% CI 1.9–47.1). For alectinib versus chemotherapy: AEs leading to discontinuation, 5.7% vs 8.8%; dose reductions, 4.3% vs 11.8%; dose interruptions due to AEs, 18.3% vs 8.8%. AEs: 77.1% alectinib (grade 3–5, 27.1%); 85.3% chemotherapy (grade 3–5, 41.2%); one fatal AE (chemotherapy); grade ≥3 AEs: 41.2% chemotherapy versus 27.1% alectinib. TEAEs occurring in ≥10% patients: constipation (alectinib 18.6%, all grade 1–2; chemotherapy 8.8% [grade ≥3 2.9%]), nausea (alectinib 1.4%, all grade 1–2; chemotherapy 17.6% [grade ≥3 2.9%]) and fatigue (alectinib 5.7%, all grade 1–2; chemotherapy 26.5% [grade ≥3 8.8%]). **Conclusion:** Alectinib improved HRQoL, functioning, and symptom burden versus chemotherapy (except constipation). Safety of alectinib compared favourably to chemotherapy. Alectinib patients (ITT and C-ITT populations) derived benefit versus chemotherapy.

Keywords: Alectinib, chemotherapy, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-014 FEASIBILITY OF LIQUID BIOPSY USING PLASMA AND PLATELETS FOR DETECTION OF ALK REARRANGEMENTS IN NON-SMALL CELL LUNG CANCER

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Background: Fluorescence in situ hybridization (FISH) using tissue biopsy specimen is the gold standard for detection and confirmation of ALK rearrangement in non-small cell lung cancers (NSCLC), but it is time-consuming and labor-dependent procedure. Liquid biopsy using reverse-transcriptase polymerase chain reaction (RT-PCR) is expected to overcome these limitations, and provide an easy accessibility and frequent assessment of biomarkers. The aim of this study is to investigate the feasibility of liquid biopsy using plasma and platelets for detection of ALK rearrangement. **Method:** FISH was performed in 664 patients between January 2015 and May 2017. We retrospectively analyzed the formalin-fixed paraffin-embedded (FFPE) tissue and blood sample to detect ALK rearrangement using multiplex RT-PCR from 30 advanced NSCLC patients who had available tissue specimen and agreed with venous sampling. Total RNA were extracted from FFPE cell blocks, plasma and platelets, respectively. Echinoderm microtubule-associated protein-like 4 (EML4)-ALK, the most common translocation, fusion RNA was detected using PANAqPCR™ EML4-ALK fusion gene detection kit. **Result:** Twenty-eight patients were FISH positive and two were negative. In a validation data compared with FISH, RT-PCR using FFPE tissue demonstrated 57.1% sensitivity and 69.2% accuracy. Liquid biopsy (plasma or platelets-positive) had higher sensitivity (96.4%) and accuracy (93.3%). Among the specimen of liquid biopsy, platelets showed slightly higher sensitivity and accuracy than plasma (82.1 and 83.3% vs 78.6 and 76.7%). Compared with FFPE tissue using RT-PCR, liquid biopsy showed 100% sensitivity, 20.0% specificity and 69.2% accuracy. Median proportion of positive cells in FISH was higher in subgroups of liquid biopsy with positive result (Plasma, 30.0 vs 15.0%; Platelets 30.0 vs 20.0%), but it was not statistically significant (p=0.062 and 0.104). In 18 patients with crizotinib treatment, platelets-positive subgroup showed a tendency of longer duration of treatment (7.2 vs 1.5 months) and higher response rate (57.1 vs 0.0 %), but the difference was not significant (p=0.071 and 0.100). However, platelets-positive subgroup showed significantly higher disease control rate than platelets-negative subgroup when they were treated with crizotinib (85.7 vs 25.0%, p=0.044). **Conclusion:** Plasma and platelets are a valuable source for liquid biopsy using RT-PCR technique in detection of ALK rearrangement, and they could play a supplementary role in diagnosis of ALK-positive NSCLC. Furthermore, platelets, especially, may be useful for predicting the treatment outcome of crizotinib.

Keywords: liquid biopsy, ALK, non-small cell lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-015 CRIZOTINIB IN ROS1 REARRANGED OR MET DEREGULATED NON-SMALL-CELL LUNG CANCER (NSCLC): FINAL RESULTS OF THE METROS TRIAL

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Background: Crizotinib is the standard of care in NSCLC with *ALK* rearrangement. Recent data showed that the drug is dramatically effective in patients with *ROS1* rearrangement (*ROS1*+), with promising activity also in individuals with *MET exon 14* mutations (*MET*^{Ex14}) or *MET* amplification (*MET*$^{FISH+}$). **Method:** The METROS is an Italian multicenter prospective phase II trial designed to assess the efficacy and safety of crizotinib in *ROS1*+ *or MET*^{Ex14} or *MET*$^{FISH+}$ advanced NSCLC patients who failed at least 1 standard chemotherapy regimen. The co-primary end-point was response rate (RR) in cohort A (ROS1+: centrally confirmed *ROS1* rearrangement) and cohort B (MET+: centrally confirmed *MET*$^{FISH+}$ defined as ratio MET/CEP7 >2.2 or locally confirmed *MET*^{Ex14}). Eligible patients received crizotinib at the standard dose of 250 mg BID orally. **Result:** At the data cut-off of April 30th, 2017, both cohorts completed accrual. Among 498 screened patients, 52 accounted for the intent-to-treat population (ITT) and received at least 1 dose of crizotinib. Among them, 26 resulted *ROS1*+, 16 *MET*$^{FISH+}$ and 10 *MET*^{Ex14}. Notably, 3 *MET*^{Ex14} cases had concurrent KRAS mutation and 1 had concurrent *MET* gene amplification. No concomitant driver event was detected in the *ROS1* cohort. Cohort A included individuals with adenocarcinoma, median age of 55 years (range 29-86), predominantly female (61%) and never smokers (54%). Cohort B included older subjects (median age 68, range 39-78), predominantly male (65%), current/former smokers (77%) and with adenocarcinoma (92%). In both cohorts, the vast majority of patients (85%) presented ≥ 2 metastatic sites and crizotinib was mainly offered as second line treatment (74%). Time from end of first line therapy to crizotinib was 4.1 and 1.6 months for cohort A and B, respectively. In ITT population RR, median progression free-survival (PFS) and overall survival (OS) were 61.5%, 17.2 months and not reached in cohort A and 26.9%, 3.1 months and 5.3 months in cohort B, respectively. For cohort B, responses were observed in both *MET*$^{FISH+}$ and *MET*^{Ex14} (25% and 30%, respectively), with evidence of rapid progression in patients carrying *MET*$^{Ex14/KRAS}$. At present, for 2 *MET+* patients assessment is pending. Therapy was generally well tolerated with no unexpected adverse event. **Conclusion:** The METROS is the first prospective trial specifically conducted in *ROS1+* or *MET+* deregulated NSCLC. The study confirms remarkable efficacy of crizotinib in *ROS1*+ NSCLC. Responses observed in the *MET* cohort were of short duration confirming aggressiveness of the disease and the urgent needs for innovative therapies.

Keywords: NSCLC, MET, ROS1

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-016 NEXT-GENERATION SEQUENCING SHOWS MECHANISMS OF INTRINSIC RESISTANCE IN ALK-POSITIVE NSCLC PATIENTS TREATED WITH CRIZOTINIB

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Background: Crizotinib (XALKORI®) is a small molecule ALK, ROS1, and c-MET tyrosine kinase inhibitor approved for the treatment of patients with ALK-positive or ROS1-positive metastatic NSCLC. PROFILE 1005 was a single arm phase 2 study of the safety and efficacy of crizotinib in previously treated patients with advanced NSCLC that is ALK-positive as determined by the investigational use only FISH test or on a case-by-case basis using a local FISH, IHC or RT-PCR laboratory developed test. In this study 54.1% of patients exhibited a confirmed complete or partial response to crizotinib (responders) by investigator assessment, while 9.9% had a best overall tumor response of progressive disease (progressors). The objective of this analysis was to investigate mechanisms of intrinsic resistance to crizotinib by comparing progressors with responders through a targeted cancer gene panel of next-generation sequencing (NGS). **Method:** Archival tumor tissue used to screen patients for enrollment was analyzed using the FoundationOne NGS panel (Cambridge, MA). Results of the analyses from tumor tissue positive by ALK FISH were compared for a subgroup of progressors (N=22) with a randomly selected subgroup of responders (N=25). **Result:** There was a higher proportion of patients who were ALK-negative by NGS in progressors (8 of 22; 36%) as compared to responders (3 of 25; 12%) (p=0.083), including 5 patients with oncogenic driver mutations in KRAS (G12S, Q61H, amp), EGFR (L858R) and BRAF (G469A). Among responders, 4 patients (16%) had non-EML4 ALK fusions (KIDINS220, EDC4, DTWD2, AFF2) while no such case was detected in progressors. TP53 mutations were detected in 10 progressors (45%) and 5 responders (20%) (p=0.115). Excluding NGS-negative patients, TP53 mutations were detected in 7 of 14 progressors (50%) and 3 of 22 responders (13%) (p=0.026). **Conclusion:** In the small percentage of patients with ALK-positive NSCLC with a best response of progression upon treatment with crizotinib, a higher proportion are ALK-negative by NGS, representing either a technical false-positive or an accurate FISH result reflecting a non-activating gene rearrangement that is not detected by NGS. TP53 mutations were observed at a higher frequency in progressors than in responders in patients with ALK-positive NSCLC by both FISH and NGS. Both technical and biologic factors thus may contribute to apparent intrinsic resistance in patients with ALK-positive NSCLC treated with crizotinib.

Keywords: crizotinib, Intrinsic resistance

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-017 ALK-REARRANGED MAY PROMOTE VTE BY INCREASING THE EXPRESSION OF TF IN ADVANCED LUNG ADENOCARCINOMA

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Background: Patients with lung cancer are at increased risk for venous thromboembolism (VTE).About 8% to 15% of patients with advanced none small-cell lung cancer(NSCLC) experience a VTE in the course of their disease. However, the incidences of VTE in different molecular subtypes of NSCLC are rarely reported though they have big differentiation in clinical feature and therapeutic effect.Tissue Factor (TF) expressed in many solid tumors could bind and activate coagulation factor FVII and trigger the downstream coagulation cascade leading to thrombin generation and clot formation. **Method:** Here we extracted retrospective data from electronic medical records at Henan Cancer Hospital in China between January 2015 and January 2016. Lung adenocarcinomas with ALK-rearranged, EGFR mutation and both negative were classified. The incidence rate of VTE after diagnosed with lung adenocarcinoma was calculated and analyzed. Then we randomly selected ALK-rearranged and ALK-rearranged negative lung adenocarcinoma tissues and detected TF expression in them with imunohistochemistry. **Result:** At a median follow-up of 19 months, 5.85% (30 in 513) patients with advanced lung adenocarcinoma experienced VTE. Patients with different molecular subtypes put up different rate of VTE (P=0.0021). Among them ALK-rearranged were more likely to experience VTE (6 in 29, 20.69%). EGFR and both negative had lower rate of VTE and had no big difference between them (11 in 218, 5.05%; 13 in 266, 4.89% respectively).The expression of TF performed similar feature. TF high expression in ALK-rearranged tissues is 41.67% (10 in 24) dramatically higher than that in ALK-rearranged negative tissues (11.54%, 3 in 26, P=0.0152). **Conclusion:** The rate of VTE in ALK-rearranged advanced lung adenocarcinoma cohorts was about 4 fold higher than that in EGFR mutation and both negative patients. ALK-rearranged may promote that by increasing TF expression. The mechanism warrants further research.

Keywords: venous thromboembolism, lung adenocarcinoma, ALK-rearranged

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-018 ACQUIRED RESISTANCE TO CRIZOTINIB IN ADVANCED NSCLC WITH DE NOVO MET OVEREXPRESSION

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Background: MET exon14 skipping mutation has been regarded the driver mutation for MET activation, but with relatively low frequency of occurrence. MET overexpression can be a promising biomarker to predict the response to crizotinib. However, little is known about acquired resistance to treatments in tumors with de novo MET overexpression. **Method:** This prospective observational study included 33 NSCLC patients with MET IHC overexpression received crizotinib treatment From January 2013 to June 2017, 23 eligible patients evaluable for response . MET expression level were detected by immunohistochemistry (IHC) with antibody SP44, and ≥50% tumor cells with moderate to high intensity staining were defined as positive. Gene copy numbers were detected by FISH (Met probes from KREATECHTM.), and referring to Cappuzzo scoring system or MET/CEP7 ratio, ≥5 copies were positive or MET/CEP7 ratio ≥1.8 (low ≥1.8-≤2.2, Intermediate >2.2-<5 and High ≥5) was defined as MET amplification;. The status of EGFR, ALK, KRAS and ROS1 were also tested at baseline. Biopsy specimens obtained both at baseline and at the time of progression using targeted next-generation sequencing to assess for mechanisms of resistance. **Result:** Response were evaluable for 23 NSCLC patients with MET overexpression (4 female, 19 male). Fifteen of them achieved partial response (PR, 65.2%), 2 were stable disease (SD) and 6 were progressive disease (PD). All responders had high MET expression , and 12(52.2%) with FISH positive. The PFS and OS in the ITT population were 3.2 and 13.2 month respectively. Median PFS was 7.4m(95% CI,4.5-10.4) for MET IHC (100%+++) patients vs. MET IHC (50%++~100%+++) 1.9m (95% CI 0.9-2.9,P=0.053), For FISH positive patients, mPFS was 8.2 m(95% CI,5.2-11.1) m v.s. FISH negative 1.3m(95% CI,0.2-1.7,p=0.002). Two acquired resistance mechanisms were found after resistance, a 64 male patient with MET IHC 100%×3,FISH (+),crizotinib first line and the best response PR, rebiopsy after resistance showed the MET D1228N mutation by NGS, and the second patient was 50 years old male with MET IHC 100%×3,FISH (+),crizotinib first line and the best response was PR, EGFR amplification were found upon progression when rebiopsy after resistance. The patient acheived PR with subsequent treatment of cetuximab plus Taxel. **Conclusion:** Multiple mechanisms of acquired resistance to crizotinib were found in *de novo* MET overexpressed patients. A secondary mutation in the *MET* gene and *EGFR* amplification may be the two main mechanisms. MET overexpression could be as a biomarker for *de novo* MET positive NSCLC. FISH seems better in predicting efficacy for MET inhibitor.

Keywords: MET resistance, non small cell lung cancer, crizotinib

P1.01-019 ALK+ NON-SMALL CELL LUNG CANCER TREATED WITH FIRST LINE CRIZOTINIB: PATIENT CHARACTERISTICS, TREATMENT PATTERNS, AND SURVIVAL

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Background: This study describes the characteristics, treatment sequencing, and outcomes among locally advanced/metastatic crizotinib-treated ALK+ Non-small cell lung cancer (NSCLC) Hispanic patients. **Method:** From June 2014 to June 2017, a retrospective patient review was conducted among several centers from México (n=10), Costa Rica (n=4), Panamá (n=13), Colombia (n=16), Venezuela (n=10), and Argentina (n=20). Participating clinicians identified their ALK+ NSCLC patients who received crizotinib and reported their clinical characteristics, treatments, and survival using a pre-defined case report form. Kaplan-Meier analyses were used to describe overall survival (OS) and progression-free survival (PFS). **Result:** 73 ALK+ NSCLC patients treated with crizotinib as a first line were included. Median age at diagnosis was 62 years (range, 34-77), 60.3% were female and histological distribution was adenocarcinoma in 93.2%, squamous cell carcinomas in 2.7%, NOS in 2.7% and adenosquamous in 1.4%. Sixty-five patients (89%) were never or former smokers, 52 (71.1%) had ≥2 sites of metastasis and 15 (20.5%) had brain metastasis at diagnosis. Median PFS to treatment with first line crizotinib was 12.3 months (95%CI 9.4-15.3) and overall response rate (ORR) was 52% (CR 6.8% and PR 45.2%). Of those who discontinued crizotinib, 26.1% had brain progression, 35.6% switched to chemotherapy, 14% switched to a different ALK inhibitor and 59% received no further therapy. After starting crizotinib, median OS was 32.5 months (95%CI 25.6-39.4), 42.6 months (95%CI 31.8-53.5) for those who received ceritinib or/and alectinib, and 23.8 months (95%CI 19.0-28.6) among those treated with second line platinum based chemotherapy (p=0.003). **Conclusion:** The ORR and PFS observed in Hispanic patients with ALK+ NSCLC treated with first-line crizotinib was similar to that previously described. Limited access to new-generation ALK inhibitors affects OS. Those patients exposed to ceritinib or alectinib demonstrated a significant improvement in OS versus those treated with second-line platinum-based chemotherapy.

Keywords: crizotinib, ALK, First line therapy

P1.01-020 TRANSLOCATION ALK/EML4+ IN NON-SQUAMOUS NSCLC POPULATION AND CRIZOTINIB: WHAT CAN WE TELL?

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Background: Molecular analysis when managing a patient with lung cancer is important. This importance seems never stop increasing as the methods of testing are improving and our knowledge specially concerning therapeutic is expanding. In patients with non-small cell lung cancer (NSCLC) translocation anaplastic lymphoma kinase/echinoderm microtubule-associated protein-like 4 (ALK/EML4) is identified in 3-5% and those patients have their own epidemiology. Studies concerning ALK/EML4 are still few in Portugal but this is changing with new treatments, such as Crizotinib. The aim of our study was to analyse NSCLC ALK/EML4+ to find out their features and treatment responses to Crizotinib. **Method:** Retrospective study of 340 non-squamous NSCLC patients followed in our Thoracic Tumours Unit between 1 January of 2012 and 31 May of 2017. The translocation ALK/EML4 was analysed by FISH test. From ALK+ group an epidemiology characterization (age, gender, perform status and smoking habits) was made and were selected the ones treated with Crizotinib. From this last selection the adverse effects were registered and the progression free survival (PFS) was studied throw a Kaplan–Meier method. **Result:** The population included: 12% (41) patients ALK+, 68% (230) ALK- and 20% (69) inconclusive. Patients ALK+ were constituted by 51.2% women and 56% of non-smokers, with average age of 64 years old. Of this subgroup 20 patients were treated with Crizotinib: 45% as 1st line, 45% as 2nd line, 5% as 3rd line and 5% as 4th line of treatment. The response obtained was: 10% with partial remission, 35% with stable disease, 20% with progressive disease and 35% non-evaluated; no one achieved complete remission. The median of PFS was 273 days (± 111 days). Lateral effects were registered in 70% of the patients, the main ones being: nausea (25%) and elevations of transaminases (25%). Other side effects were visual alterations (15%), bradycardia (5%) and others (25%). Because toxicity 3 patients suspended Crizotinib. **Conclusion:** Lung oncology is reaching more and more a molecular level. However, the inadequacy of the samples and other errors are limiting the tests, as here is stand out by 20% of inconclusive results. Our study revealed a prevalence of ALK+ higher than is described in literature (12%), although the epidemiology is in concordance (majority of women and non-smokers). Under Crizotinib PFS is similar as previous described data (9,1months). In sum, more is yet to be known and improved.

Keywords: ALK, non small cell lung cancer, crizotinib

P1.01-021 FISH AND IHC DISCORDANCE IN ALK REARRANGED NON SMALL CELL LUNG CANCER

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Background: There is a small proportion of lung cancer patients who are ALK positive by IHC but negative by FISH, or vice versa. Outcome of this subset of patients when treated with crizotinib is not well known. This analysis was planned to study the FISH and IHC discordance in ALK rearranged NSCLC. **Method:** We retrospectively collected data from a prospectively maintained database in medical oncology department. We analyzed 257 patients who had been diagnosed with ALK rearranged NSCLC cancer. Patients who had discordant FISH and IHC findings for ALK were selected for this analysis. Their response rates, progression free survival and overall survival were calculated. Progression free survival and overall survival were estimated using Kaplan Meier method. **Result:** Out of 257 patients, 28 patients (10.9%) had discordance. 7 patients had IHC -ve status while had FISH positive status for ALK rearrangement. 21 patients had vice-versa. The response rate for crizotinib in IHC-/ FISH+ was 57.1% versus 71.4% in IHC+/FISH - group (p-0.331). The overall median progression free survival was 8.7 months and median overall survival was not reached. There was no statistical difference in PFS and OS between the 2 groups. **Conclusion:** In around 1/10th of ALK rearranged NSCLC patients, FISH and IHC have discordant findings, however these patients also benefit from crizotinib.

Keywords: Discordant results, ALK positive lung cancer, IHC and FISH for ALK

P1.01-022 PREDICTION OF CENTRAL NERVOUS SYSTEM PROGRESSION DURING CRIZOTINIB TREATMENT IN ALK+ NSCLC AMONG HISPANICS

A. Ruiz Patino[1], C. Martin[2], A. Cardona[3], O. Arrieta[4], O. Castillo-Fernandez[5], G. Oblitas[6], L. Corrales[7], L. Lupinacci[8], M.A. Pérez[9], L. Rojas[10], L. González[6], L. Chirinos[11], C. Ortiz[2], M. Lema[12], C. Vargas[13], C. Puparelli[2], H. Carranza[13], J. Otero[3], Z. Zatarain-Barron[4]

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Background: Crizotinib has offered patients with non-small cell lung cancer (NSCLC) positive to ALK rearrangements a powerful therapeutical option. Despite the benefit of crizotinib, most patients develop resistance and progression with special emphasis on the central nervous system. Early identification of patients that will present brain metastases could potentially lead to additional interventions preventing relapse. The objective of this study was to identify patients who would present with future CNS relapse after initiation of crizotinib. **Method:** A random forest tree model was constructed. Data from Hispanic patients with NSCLC harboring ALK rearrangements treated with crizotinib were collected from the CLICaP database. Clinical variables including age at diagnosis, sex, smoking status, number of metastasis and location and objective response were included. Based on these parameters, progression to central nervous system was predicted. **Result:** 66 patients were included in the analysis. Median age for the cohort was 55 years old (r, 33-85), 33 (59%) were women, 38 (58%) were never smokers and 29 (44%) presented disease progression during crizotinib treatment while 17 had central nervous system involvement. Median overall survival (OS) was 13.9 months (95%CI 11.6-19.3) in contrast to 8.3 months (95%CI 4.47-13.13) in terms of progression free survival (PFS) after crizotinib initiation. The best predictors for central nervous system progression were age, sex, number of metastasis, objective response to crizotinib and previous CNS involvement. With an AUC of 0.99, a sensitivity of 100% and a specificity of 88%, the model reached an overall accuracy of 97%. **Conclusion:** Central nervous system progression after crizotinib treatment can be accurately predicted. Validation for this model in larger cohorts is warranted.

Keywords: non small cell lung cancer, ALK, Random Forest Tree

P1.01-023 ALK-POSITIVE NSCLC: A TMH EXPERIENCE

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Background: ALK gene rearranged NSCLC are a rare subset of lung cancers. However, treatment with crizotinib leads to an improvement in outcomes. In this study, we have audited the outcomes of ALK-rearranged NSCLC at our institute. **Method:** This was a subset analysis of a prospective observational study. It was approved by the institutional ethics committee and was carried out in accordance with good clinical practice guidelines and declaration of Helsinki. For this analysis all Alk rearranged NSCLC patients, diagnosed at our center between November 2011-April 2017 were selected. The treatment received and the outcomes were noted. Progression-free survival and Overall survival were estimated using Kaplan-Meier method. **Result:** We had diagnosed 257 patients during this period. The median age was 50 years (23-77 years). There were 102 females (39.7%) and 155 males (60.3%). Only 49 patients were smokers (19.1%). The ECOG PS was 0-1 in 197 patients (76.7%), 2 in 28 patients (10.9%) and 3-4 in 32 patients (12.4%). The median number of sites of metastasis was 2 (0-7). Brain metastasis was seen in 36 patients (14.0%). The upfront treatment received was crizotinib in 168 patients (65.3%), pemetrexed -platinum doublet in 57 patients (22.2%), taxane-platinum in 4 patients (1.6%), gemcitabine-platinum in 4 patients (1.6%), others in 14 patients (5.4%). The crizotinib received was started upfront in 88 patients and after a few cycles chemotherapy in 80 patients. In these 80 patients, 53 patients were started as soon as the ALK rearrangement report was available while 27 patients were started after a few cycles once finances were available. The median PFS for crizotinib was 16.1 months versus 11.4 months in pemetrexed platinum (p-0.159) The median PFS in the patients receiving upfront crizotinib was 17.1 months versus 14.7 months in patients receiving crizotinib after the switch (p-0.399). The median overall OS was 39.9 months and it was similar between the two strategies of crizotinib(p-0.964). There were 57 patients (22.1%) who never received crizotinib. The median OS in patients who never received crizotinib was 11.0 months versus it was not reached in patients receiving crizotinib in any line (p-0.000). The 3 year OS in patients receiving crizotinib in any line was 67.0%. **Conclusion:** Crizotinib substantial improves outcomes in ALK-rearranged patients whether given upfront or post start of few cycles of chemotherapy.

Keywords: ALK, crizotinib, NSCLC

P1.01-024 PLASMA CIRCULATING CFDNA AS A POTENTIAL BIOMARKER IN CLINICAL MANAGEMENT OF NSCLC: EXPERIENCE OF TATA MEMORIAL HOSPITAL, INDIA

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Background: Circulating cell free tumor DNA (ctDNA) from liquid biopsy is a potential source of tumor genetic material in absence of tissue biopsy for EGFR testing. NSCLC patients with detectable levels of oncogenic driver mutations in peripheral blood are known to be associated with more advanced disease and poorer prognosis. Liquid biopsy was performed on132 NSCLC patients with matched tumor tissue for genomic analysis. An EGFR mutation of one major molecular subtype in NSCLC was performed on massive parallel sequencing. The Study's primary goals were to: (1) Derive high concordance between tissue biopsy and ctDNA for oncogenic driver mutations in Exon 19 and Exon 21 of the EGFR gene. (2) Establish and validate Liquid biopsy as a clinically useful surrogate for tissue biopsy in NSCLC whenever tissue biopsy is unavailable and (3) Treatment monitoring and detection of early recurrence. **Method:** Single gene EGFR mutation analysis was performed on the ctDNA by using ultra deep sequencing on the HiSeq platform. Then custom designed bioinformatics algorithms were used to detect somatic mutations at allele frequencies as low as 0.01%. **Result:** Overall concordance of mutation status between 132 pairs of tissue and plasma ctDNA samples for EGFR mutation status was about 97%. 34% (45/132) of the study subset was EGFR mutated on tissue typing and 31% (41/132) in ctDNA, with 100% specificity, 91.1% sensitivity. Positive predictive value was 100% and negative predictive value was 95.6% - with diagnostic accuracy of 97%. A false negative rate of 3% was observed in this study. 14 out of 132 (10%) samples which had rare Exon19 deletions and complex indels could be confidently detected by NGS methods. 6/31 patients (19%) who could not go for biopsy got the EGFR mutation testing on plasma alone, who were positive for Exon19/ Exon21 hotspot mutations could benefit from targeted therapy. An objective efficacy response rate for Gefitinib was estimated at 74%, with a disease control rate of 95.7%. Median period of follow-up was 13.9 months. Median PFS was 18.933 months (95% CI 11.168-26.198) and overall survival was 78.3%. **Conclusion:** 10% of newly diagnosed NSCLC patients could get the additional benefit of targeted therapy, by using the NGS which detected recurrent novel HOTSPOT mutations. Liquid Biopsy based tests will soon be as widespread as "standard" biopsies and imaging techniques, offering invaluable diagnostic, prognostic, and predictive information and would promisingly move from research into clinical practice in lung cancer.

Keywords: NSCLC, liquid biopsy, cfDNA, EGFR mutation analysis, Liquid Biopsy, EGFR, Next generation sequencing(NGS)

P1.01-025 BIOMARKER TESTING IN ADVANCED NSCLC: A SIMULATION-BASED ASSESSMENT OF MEDICAL ONCOLOGISTS

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Background: The past several years have seen a number of changes in standards of care for NSCLC, challenging oncologists to integrate evolving diagnostic paradigms into practice. A study was conducted using simulation-based technology to assess medical oncologists' current performance in ordering biomarker testing and diagnosing advanced NSCLC. **Method:** A virtual patient simulation (VPS) consisting of 2 patient cases was made available online via a website dedicated to continuous professional development. The VPS platform allowed oncologists to assess the patients and choose from an extensive database of diagnostic possibilities matching the scope and depth of practice. Clinical decisions made by participants in the VPS were analyzed using a sophisticated decision engine, and instantaneous, formative clinical guidance employing the current evidence-base and expert faculty recommendations were provided. After CG, oncologists had a second chance to address errors of omission. Data were collected between 1/29/2016 and 11/29/2016. **Result:** 197 oncologists fulfilled the participation criteria for completing the VPS. Assessment of their clinical decisions prior to CG revealed: · In a patient with newly diagnosed advanced NSCLC, 21% of oncologists did not order histopathology to determine subtype while 58% failed to order EGFR mutational testing Moreover, 30% ordered ROS1-translocation FISH testing and 39% PD-L1 IHC testing. Interestingly, although no approved targeted agent exists for MET amplified-, RET-translocated-, or BRAF-mutated NSCLC, 17%-28% ordered these molecular tests. · In a patient with EGFR-mutated NSCLC who had progressed on first line EGFR TKI, 40% did not order testing for T790M. Moreover, 40% ordered PD-L1 staining. Consistent with findings from the first case, between 11%-18% ordered testing for rarer mutations for which patients may qualify for a clinical trial. **Conclusion:** Histopathologic and biomarker testing are critical elements for selecting the most appropriate regimen for patients with advanced NSCLC across the continuum of care. Our analysis of current practice using a VPS platform that immerses and engages the clinician for an authentic, practical and consequence-free experience demonstrates that there is variability in biomarker testing by oncologists. In addition, our findings demonstrate a continued need to educate oncologists about prioritizing biomarker tests in order to select the most appropriate regimen for a patient with advanced NSCLC.

Keywords: biomarker testing, advanced NSCLC, Oncologists

P1.01-026 CIRCULATING MIR-206 IN ADVANCED STAGE LUNG CANCER PATIENTS AND ITS ASSOCIATION WITH CANCER CACHEXIA

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Background: Cancer cachexia is a common problem found in advanced stage cases. Pathophysiology of cachexia is complicated, involving cytokines and regulator molecules such as microRNA (miRNA). MiR-206, a specific miRNA in skeletal muscle cells was thought to play important role in regulating skeletal muscle loss but have not been studied well in cachectic patients. **Method:** A cross-sectional study was performed in Dharmais Cancer Hospital, Jakarta between September and December 2015. Subjects were patients with advanced lung cancers. Cachexia was defined as body mass index less than 20 kg/m^2 calculated after treatment. MiR-206 expression was assayed using quantitative real-time polymerase chain reaction (RT-PCR), whereas miR-16 served as internal control. Blood from health subjects were also taken for comparison. The results were expressed as cycle threshold (C_T) and fold change (FC) which was calculated using the $2^{-\Delta\Delta C_T}$ method. **Result:** Thirty-seven patients were enrolled; 27 (73.0%) were men. Patients' mean age was 51.7±11.1 years. Most of the patients (91.9%) were in stage IV. There were 16 (43.2%) patients with cachexia after treatment. Compared to normal healthy subjects, circulating miR-206 expression level was 13.7 times higher in lung cancer patients (FC=13.699). Among cancer patients, miR-206 expression was slightly up-regulated in cachectic than non-cachectic patients (FC=1.355). **Conclusion:** Circulating miR-206 is overexpressed in advanced stage lung cancer patients. Increased circulating miR-206 in cachectic patients may reflect extensive skeletal muscle loss associated with cancer cachexia.

Keywords: lungcancer, cancercachexia, miR-206

P1.01-027 COMBINATION OF BIOMARKER AND CLINICOPATHOLOGIC CHARACTERS MAY CIRCLE OUT BENEFICIARIES THROUGH SECOND-LINE IMMUNOTHERAPY: A META ANALYSE

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Background: Programmed cell death ligand 1 (PD-L1) expression had been proposed as predictive biomarker to immune-checkpoint inhibitors. Yet treatment responses are not always consistent with this single agent in the second-line therapy of NSCLC. Whether combination of PD-L1 and clinicopathologic characters could circle out optimal beneficiaries are still unknown. **Method:** We performed a meta-analysis of randomized control trials that compared immune-checkpoint inhibitors against chemotherapy in second-line therapy. Data including smoking status, EGFR status, KRAS status and histology were extracted as subgroup analyse to estimate the potential predictor of efficacy for anti PD-1/L1. **Result:** Five clinical trials that compared immune-checkpoint inhibitors against chemotherapy for second-line therapy were included. Both PD-L1 positive (HR=0.64, 95%CI=0.56-0.73, P<0.00001) and PD-L1 negative (HR=0.88, 95%CI=0.78-1.00, P=0.05) favored anti PD-1/L1. Subgroup analyse indicated that adenocarcinoma (ADC) as well as squamous cell carcinoma (SCC) preferred anti PD-1/L1. Never smokers may not benefit from anti PD-1/L1 but current/ever smokers did (HR=0.70, 95%CI=0.63-0.79, P<0.00001). Patients with EGFR mutation could not gain benefit from anti PD-1/L1 while the EGFR wild type could (HR=0.67, 95%CI=0.60-0.76, P<0.00001). Both KRAS mutation (HR=0.60, 95%CI=0.39-0.92, P=0.02) and wild type/unknown (HR=0.81, 95%CI=0.67-0.97, P=0.02) were apt to anti PD-1/L1.

A

Subgroup of trials	Weight	Hazard Ratio	HR (95%CI)	P value
PD-L1				
positive	47.4%		0.64 (0.56, 0.73)	<0.00001
negative	52.6%		0.88 (0.78, 1.00)	0.05
EGFR				
mutation	10.8%		1.12 (0.80, 1.56)	0.51
wild type/unknown	89.2%		0.67 (0.60, 0.76)	<0.00001
KRAS				
mutation	15.1%		0.60 (0.39, 0.92)	0.02
wild type/unknown	84.9%		0.81 (0.67, 0.97)	0.02

0 0.5 1 1.5
Favor anti-PD1/L1 Favor Docetaxel

B

Subgroup of trials	Weight	Hazard Ratio	HR (95%CI)	P value
Gender				
male	64.9%		0.74 (0.66, 0.84)	<0.00001
female	35.1%		0.80 (0.68, 0.94)	0.006
Age				
<65yrs	56.8%		0.75 (0.64, 0.88)	0.0004
65-75yrs	35.0%		0.62 (0.51, 0.76)	<0.00001
>75yrs	8.2%		0.99 (0.65, 1.50)	0.97
Smoking status				
Non-smoker	15.1%		0.81 (0.60, 1.10)	0.17
Current/former smoker	84.9%		0.70 (0.63, 0.79)	<0.00001
ECOG PS				
0	28.5%		0.70 (0.58, 0.85)	0.0002
1	71.5%		0.67 (0.60, 0.75)	<0.00001
Histology				
Adenocarcinoma	71.3%		0.71 (0.63, 0.80)	<0.00001
Squamous carcinoma	28.7%		0.67 (0.56, 0.81)	<0.0001

0 0.5 1 1.5
Favor anti-PD1/L1 Favor Docetaxel

Conclusion: Regardless of PD-L1 status, immune-checkpoint inhibitors could achieve better efficacy than chemotherapy in second-line therapy. Current/ever smokers without EGFR mutations may benefit more from anti PD-1/L1. Combination of PD-L1 and strongly relevant clinicopathologic characters should be considered to tailor optimal patients for anti PD-1/L1.

Keywords: biomarker and clinicopathologic characters, Immunotherapy, non-small cell lung cancer

P1.01-028 CHARACTERISTICS OF CELL FREE DNA IN LUNG CANCER PATIENTS

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Background: A third generation EGFR tyrosine kinase inhibitor, osimertinib, is effective for T790M positive lung cancer patients. Although the tissue re-biopsy of primary or metastatic tumors was required to use osimertinib, cell free DNA (cfDNA) has been recently approved for detection of T790M in Japan. We have reported that cfDNA size distribution was different between lung cancer and healthy individuals using a capillary electrophoresis system, that is one peak around the size of 170 bp in healthy individuals, and two peaks, 170 bp and 5 kb in advanced lung cancer patients. The purpose of this study is to clarify the clinical and biological characteristics of each sized cfDNA. **Method:** The plasma collected from 92 lung cancer patients, 18 benign pulmonary disease patients, 20 healthy individuals at Saga University Hospital were analyzed. cfDNA extraction was performed from 1000μl plasma by automated DNA extraction system using cellulose magnetic beads. We first compared the DNA concentrations and cfDNA size among three groups. The DNA concentrations were quantified by Quantus®, the fluorescent measurement of dsDNA intercalated dye, and cfDNA size was analyzed by the Agilent 2100 Bioanalyzer®. We next separately isolated cfDNA 170 bp and 5 kb fragments, and detected the epidermal growth factor receptor (*EGFR*) L858R point mutation by mutation-biased PCR and quenched probe system (MBP-QP) method. **Result:** The DNA concentration was higher in lung cancer patients compared to those in benign pulmonary disease and healthy individuals. Divided by histological types, DNA concentrations were highest in small cell carcinoma, and were increased in patients with advanced stages. Especially, DNA concentrations were higher in presence of metastasis, and 5 kb fragments were significantly increased in these cases. L858R positive patients showed higher DNA concentration with more obvious difference in 5 kb fragments. L858R was detected in both cfDNA fragments, 170 bp and 5 kb, which were separately isolated, suggesting that both sized DNA fragments contain circulating tumor-derived DNA (ctDNA). **Conclusion:** cfDNA concentrations were associated with progression of lung cancers, and bimodal characteristic was observed in terms of cfDNA size. Although the 170 bp short fragments of cfDNA are well known as an apoptotic product, the origin of 5 kb long fragments is still unclear. We have continuously examined how ctDNA was released from tumor cell.

Keywords: plasma DNA integrity, lung cancer, cell free DNA(cfDNA)

P1.01-029 LYMPHOCYTE MONOCYTE RATIO AS A PROGNOSTIC FACTOR IN NON SMALL CELL LUNG CANCER

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Background: Chronic state of inflammation is an important factor in advanced cancer which is used by tumor cells for maintaining survival and growth. Hematological parameters such as neutrophil/lymphocyte ratio (NLR), thrombocyte/ lymphocyte ratio (TLR) and lymphocyte / monocyte ratio (LMR) are reliable indicators of systemic inflammation. We aimed to elucidate the effect of hematological parameters and clinical features of patients on the prognosis of advanced stage non-small cell lung cancer (NSCLC) . **Method:** We included 102 stage IV NSCLC patients who presented to the oncology clinic between 2010-2016. Pretreatment clinical parameters and NLR, TLR, and LMR were retrieved from the medical records. The cut off values, calculated with ROC analysis, for NLR, LMR , TLR were 2.5, 3 and 183 , respectively. All patients were divided into two groups according to cut off values and analyzed accordingly. **Result:** Median OS and PFS were 10 and 6 months respectively. In univariate analysis high NLR, high TLR and low LMR were found to be significantly associated with survival . Among clinical parameters having ECOG performance score 0-1 , older age (≥70 years) single metastatic disease were prognostic. In multivariate cox regression analysis only the number of metastatic lesions and LMR were found to be independent predictors for survival. **Conclusion:** Although the interaction between tumor cells and the host immune system is a very complex process, LMR, NLR and TLR are hematological parameters that can be easily derived from total blood counts and can be used in daily clinical practice. Among these markers, we suggest that LMR holds the greatest potential as a viable prognostic factor in the setting of metastatic NSCLC.

Keywords: Advanced stage, Non Small Cell Lung Cancer (NSCLC), Lymphocyte monocyte ratio (LMR)

P1.01-030 PREDICTIVE BIOMARKERS IN NON-SMALLCELL CARCINOMA AND THEIR CLINICAL ASSOCIATION

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Background: Recognition of molecular targets, such as *EGFR, ALK, ROS* and MET involved in cell signaling have led to the development of new targeted therapies.Widespread use of predictive markers has generated new data on prevalence and clinicopathological correlates. However, there is a lack of comprehensive data from Indian subcontinent. This study identifies clinical, histomorphological and molecular corelates of biomarker positive NSCCl **Method:** Archival data of NSCC patients diagnosed with stage IV diseasea was retrieved. Those who tested positive for one of the four biomarkers EGFR, ALK, MET, ROS from January 2010 to December 2016 were included. EGFR testing was done using Qiagen EGFR TherascreenRGQ PCR KIT. ALK-1 protein was tested by FDA approved immunohistochemistry.Ros-1 gene rearrangement was assessed using Dual Color Break Apart DNA probe (Zytolight). C- MET gene amplification assay was done using Zytolight labeled LSI MET DNA probe(green)and cen-7 probe(orange). Epidemiological patient profile and tumor histomorphology on small biopsies was correlated with molecular signature and assessed with treatment response and overall survival. **Result:** Of the total 1938 lung cancer patients included in our study, 347 patients were observed to exhibit positivity for either one among four molecular markers. Among 347 patients, 77.8% had EGFR mutation. Of these del 19 was commonest and observed in 55% cases, L858R in 27.6% cases,Exon 20 Insertion in 5% and G719X in 3% cases. 7% of these EGFR mutants showed dual mutation. ALK-1 protein overexpression was seen in 19.3% . ROS rearrangement was present in 0.8% . MET amplification was observed in 2%. Predominant histological type was adenocarcinoma (87.6%) with predominant solid pattern. The median overall survival for EGFR, ALK, ROS, MET were 13.44,11.5, 17.2 and 15.1 months respectively. Sex, age, histology, mutation type and performance status affected overall survival.

	EGFR	ALK	ROS	MET
	DEL 19 L858R EXON 20I G719X DUAL OTHERS(L861Q) (T790M)			
CASES	151 76 14 10 19 01	67	03	07
%	55 27.6 5 3 7 0.3 19.3 0.8 2			
OS	13.4 12.5 14.5 13 12.6 11 11.5 17.2 15.1			

Conclusion: Biomarker testing has improved outcome and provides new insight to cancer clinicopathological profile.

Keywords: NSCLC, Predictive biomarker, Morphology

P1.01-031 UTILIZATION AND TIMING OF FOUNDATION MEDICINE (FMI) TESTING IN U.S. ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) PATIENTS

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Background: Actionable insights generated by FMI's hybrid capture-based next-generation sequencing (NGS) comprehensive genomic profiling services are increasingly important for navigating cancer care in aNSCLC patients. FMI and other NGS platforms support treatment decisions by detecting a variety of genetic alterations implicated in oncogenesis. We describe: 1) the characteristics of aNSCLC patients receiving FMI testing and 2) the utilization patterns and timing of FMI testing in relation to treatment and other molecular tests using a real world oncology electronic health record (EHR) database. **Method:** Flatiron Health has a longitudinal, demographically and geographically diverse database containing EHR data, reflecting routine clinical practice, from over 265 cancer clinics in the US. Inclusion criteria were aNSCLC diagnosis and ≥2 clinic visits within the Flatiron network on or after January 1, 2011. Data pertaining to molecular testing was available on 5 biomarkers (EGFR, ALK, KRAS, ROS1, PDL1) and used to identify 3 mutually exclusive testing groups: FMI, other NGS and non-NGS. **Result:** As of March 31, 2017, the aNSCLC cohort included 33,473 patients. Of 1,395 patients with FMI testing, 738 (53%) also had ≥1 non-FMI test (43% EGFR, 40% ALK, 20% ROS1, 17% PDL1, 16% KRAS). In FMI-tested patients, 45% received results before starting a first line of therapy (vs. 57% of other NGS tested and 79% of non-NGS tested patients). Table 1 details patient and testing characteristics for FMI tested patients, along with first treatments received after FMI testing.

Table 1. Patient, Testing and Treatment Characteristics for Patients Receiving FMI testing

	FMI	**Other NGS**	**Non-NGS**	**No tests**
Patient count (%) (Total N=33,473)	1,395 (4%)	1,946 (6%)	17,002 (51%)	13,128 (39%)
Patient and Testing characteristics				
Age at aNSCLC diagnosis (years) (median, [IQR])	67 [59, 73]	68 [60, 75]	69 [61, 76]	
No history of smoking	335 (24%)	376 (19%)	2,731 (16%)	
Squamous cell histology	194 (14%)	195 (10%)	1,532 (9%)	
No. of tests				
1	1,224 (88%)	1,587 (82%)	n/a	
≥2	171 (12%)	359 (18%)		
Year of testing[a]				
<2011	0 (0%)	1 (0%)	137 (1%)	
2011	0 (0%)	5 (0%)	1,215 (7%)	
2012	2 (0%)	16 (1%)	2,368 (14%)	
2013	59 (4%)	117 (6%)	2,894 (17%)	
2014	185 (13%)	235 (12%)	3,263 (19%)	
2015	377 (27%)	560 (29%)	3,099 (18%)	
2016	634 (45%)	818 (42%)	2,921 (17%)	
2017 (through March 31, 2017)	123 (9%)	186 (10%)	670 (4%)	
Number and Timing of Other Tests in patients with an FMI test	**FMI tested prior to start of 1st LoT**	**FMI tested during 1st and before start of 2nd LoT**	**FMI tested during 2nd and before start 3rd LoT**	**FMI tested during or after 3rd LoT**
Patient count (%) (Total N=1,386)[b]	626 (45%)	489 (35%)	157 (11%)	114 (8%)
Other tests conducted before FMI testing[c,d]				
ALK	111 (18%)	188 (38%)	100 (64%)	86 (75%)
EGFR	133 (21%)	204 (42%)	110 (70%)	86 (75%)
KRAS	51 (8%)	60 (12%)	25 (16%)	29 (25%)
PDL1	41 (7%)	44 (9%)	23 (15%)	22 (19%)
ROS1	53 (9%)	92 (19%)	40 (26%)	32 (28%)
Other tests conducted after FMI testing[c,d]				
ALK	48 (8%)	34 (7%)	8 (5%)	3 (3%)
EGFR	53 (9%)	38 (8%)	9 (6%)	5 (4%)
KRAS	35 (6%)	30 (6%)	7 (5%)	2 (2%)
PDL1	49 (8%)	33 (7%)	7 (5%)	3 (3%)
ROS1	37 (6%)	28 (6%)	6 (4%)	1 (1%)
First Treatment immediately following FMI testing				
Patient count (%) (Total N=802)[e]	424 (68%)	252 (52%)	77 (49%)	49 (43%)
NCCN-recommended targeted treatment for aNSCLC (N=196)[f,i]	105 (25%)	56 (22%)	20 (26%)	15 (31%)
NCCN-recommended immunotherapy (N=227)[g,i]	82 (19%)	110 (44%)	22 (29%)	13 (27%)
Non NCCN-recommended targeted treatment for aNSCLC (N=13)[h,i]	1 (0%)	7 (3%)	1 (1%)	4 (8%)

[a] If a patient had more than 1 FMI test, the year of the first FMI test is shown; similarly if a patient had more than 1 other NGS (ie. non-FMI), the first test is shown. If an FMI tested patient had both an FMI and non-FMI NGS test, the year of the first FMI test is shown; similarly if a other NGS tested patient has both an other NGS and non-NGS test, the year of the first other NGS test is shown. [b] 9 patients where the date of FMI test (ie. test result date or sample collection date) in relation to dates of treatment and line of therapy were missing or unknown are not included in this table. [c] Total of 738 patients (53% of all FMI tested patients) also received a non-FMI test in addition to their FMI test. [d] Percentages may not add up to 100% because of patients received more than one test. [e] Based on 802 total patients who received FMI testing and where treatment data was reported following their FMI test. [f] NCCN-recommended targeted treatments received included the following: erlotinib (N=63), gefitinib (N=10), afatinib (N=56), crizotinib (N=36), ceritinib (N=4), alectinib (N=8), trastuzumab (N=1), vemurafenib (N=2), dabrafenib (N=2), osimertinib (N=19), cabozantinib (N=0); it may be possible for patients to receive regimens containing more than 1 NCCN-recommended targeted treatment. [g] NCCN-recommended immunotherapy (immune checkpoint inhibitors) received included the following: nivolumab (N=189), pembrolizumab (N=29), atezolizumab (N=9); it may be possible for patients to receive regimens containing more than 1 NCCN-recommended immunotherapy. In addition, 2 patients received ipilimumab, an immune checkpoint inhibitor currently not recommended by NCCN for aNSCLC. [h] Non NCCN-recommended targeted treatments received included the following: olaparib (N=2), necitumumab (N=2), cetuximab (N=2), palbociclib (N=1), pazopanib (N=1), temsirolimus (N=1), trametinib (with no dabrafenib) (N=4) ; it may be possible for patients to receive regimens containing more than 1 non NCCN-recommended targeted treatment. [i] Based on the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC, version 6.2017 LoT: line of therapy as recorded in the Flatiron data, IQR: inter-quartile range. Patients with missing data are excluded from the table; Percentages are rounded to closest decimals.

Conclusion: Patients with FMI testing tended to be younger, non-smokers, and have squamous histology compared to patients receiving non-FMI tests. Nearly 50% of all FMI testing occurred prior to first treatment. Patients receiving FMI testing earlier were less likely to have a non-FMI biomarker test beforehand. Regardless of when FMI testing occurred, ~20-30% of patients received a NCCN-recommended targeted therapy immediately after the FMI test.

Keywords: Oncology electronic health record (EHR), next generation sequencing (NGS), advanced non small cell lung cancer (aNSCLC)

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-032 DETECTION OF EGFR, ALK AND OTHER DRIVER ONCOGENES FROM PLASMA CFDNA BY SINGLE MOLECULE AMPLIFICATION AND RE-SEQUENCING TECHNOLOGY (CSMART)

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Background: All patients with advanced stage NSCLC should have their EGFR and ALK mutation status known prior to initiation of first line therapy. Multiple plasma-based technologies such as ARMS and ddPCR are available for rapid detection of EGFR mutation, while only the more laborious Next Generation Sequencing (NGS) may cover EGFR, ALK and other uncommon mutations in a single blood test. cSMART is a novel NGS-based technology with rapid turnaround time that can detect EGFR, ALK and KRAS mutations plus others less common lung cancer specific driver oncogenes (BRAF, ROS-1, HER-2, PIK3CA, RET, MET14skipping). **Method:** Objectives of this study is to investigate the clinical application of cSMART on patients with advanced NSCLC. In cSMART assay, each cfDNA single allelic molecule is uniquely barcoded and universally amplified to make duplications. The amplified products are circularized and re-amplified with target-specific back-to-back primers. These DNA are then ligated with sequencing adapters and pair-end sequenced (>40,000x) with illumine sequencers. The original cfDNA molecules are reconstituted by multi-step bioinformatics pipeline for censor and correction. The final products are quantified for calculation of allele frequencies **Result:** Out of the 1664 samples tested, total of 1469 were of advanced stage NSCLC. We detected EGFR mutations in 758 (51.6%), ALK translocation in 34 (2.3%) and KRAS mutation in 78 (5.8%) patients. Among the patients with activating EGFR mutations, 301(39.7%) have exon 19 deletion and 279 (36.8%) have exon 21 point-mutation. Total of 6 (0.8%) patients with EGFR mutation have concurrent presence of ALK translocation. Incidence and mean allele frequency of the less common target mutation is summarized in Table. Median sample turnaround time is 7 days.

	Incidence (%)	Median Mutation Allele frequency (%)
BRAF	29 (1.97%)	0.08%
ROS1	2 (0.14%)	0.77%
HER-2	19 (1.29%)	0.20%
PIK3CA	70 (4.77%)	0.17%
RET	14 (0.95%)	0.57%
MET14skipping	63 (4.29%)	0.08%

Conclusion: cSMART is a novel plasma cfDNA-based technology that can detect the actionable target oncogenes for patients with advanced NSCLC. This is a sensitive method with capacity of detecting the uncommon targets at relatively low allele frequency.

Keywords: cSMART, Genome profiling, EGFR mutation

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-033 THROMBOGENIC BIOMARKERS IN PATIENTS WITH NSCLC – ASSOCIATIONS WITH THROMBOSIS, PROGRESSION, AND SURVIVAL

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Background: For patients with NSCLC, the risk of thromboembolism (TE) is high but heterogeneous. We aimed to profile biomarkers among NSCLC patients receiving anticancer therapy to identify patients and time periods of high TE risk where intervention with proven preventative strategies is likely to achieve maximal benefit. **Method:** We assessed the association between baseline biomarker levels and longitudinal biomarker changes, with subsequent incidence of TE (venous (VTE) or arterial (ATE)), disease progression and overall survival. Biomarkers (thromboelastography, d-dimer, fibrinogen, haemoglobin, white cell count, platelet count, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR)) were sequentially assessed at commencement of anticancer therapy (baseline), weeks 1, 4 and 12, and 3-monthly until 12 months. **Result:** During study follow-up (median 22 months, range 6-31), 129 patients were sequentially assessed over median 5 time points (range 1-9). Patients underwent surgery (n=12), chemo-radiotherapy (CRT, n=47), palliative chemotherapy (CHT, n=36), and single modality radiotherapy (RT, n=34) – only surgical patients received thromboprophylaxis. 24 patients (19%) had documented TE, 19 (15%) VTE and 5 (4%) ATE; 79% occurred within the first 6 months with median time to TE 48 days (range 1-151). Among ambulatory patients (CHT/CRT/RT), an initial model identified as high TE risk those patients with baseline fibrinogen ≥4g/L and d-dimer ≥0.5mg/L, or d-dimer ≥1.5mg/L. Hazard ratio (HR) for TE was 8.0 (p=0.04) for high versus low risk CHT/CRT patients and 6.5 (p=0.07) for high versus low risk for CHT/CRT/RT patients. Comparatively, using an established risk score, HR for TE with Khorana score ≥3 vs. <3 was 1.3 (p=0.68) for CHT/CRT and 1.1 (p=0.91) for CHT/CRT/RT. Considering temporal changes (d-dimer ≥1.5mg/L at week 4), risk assessment was enhanced with 100% sensitivity and 34% specificity for CHT/CRT. Specificity reduced to 27% when including RT patients. NLR, PLR and platelet count were not associated with TE. High TE risk patients (Fib≥4 + d-dimer ≥0.5, d-dimer ≥1.5) also had increased risk of cancer progression (HR 2.3, p<0.01) and mortality (HR 2.5, p<0.01). Baseline NLR≥2.5 and platelet count ≥350 were associated with progression (HR 2.0, p=0.01 and HR 2.0, p<0.01 respectively) and mortality (HR 2.6, p=0.01 and HR 1.9, p=0.01 respectively); PLR was not. **Conclusion:** For ambulatory patients with NSCLC, d-dimer and fibrinogen were associated with TE, cancer progression, and prognosis and could easily be applied in a simple algorithm, for real-time decision-making. In spite of low specificity, consideration of thromboprophylaxis is warranted for high risk patients given substantial TE-associated adverse clinical and economic consequences.

Keywords: Biomarkers, Risk prediction, thromboembolism

P1.01-034 CEREBROSPINAL FLUID AND PLASMA TUMOR DNA PROFILING REVEALS HETEROGENEITY OF CNS METASTASIS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Background: Tumor heterogeneity in central nervous system (CNS) metastases may lead to poor response to treatment in some patients with non-small-cell lung cancer (NSCLC), and genotyping of cell-free DNA (cfDNA) from cerebrospinal fluid is a promising method to reveal CNS metastasis specific gene alterations. **Method:** We conducted deep-sequencing on a 168-gene panel in cfDNA from matched cerebrospinal fluid (CSF) and plasma among 32 advanced or progressive NSCLC patients with indicated CNS metastases. **Result:** We detected single nucleotide variants (SNV) in 68.8% (22/32) of CSF samples and 77.4% (24/31) of plasma samples. The SNV detection rate was 100% in cytology positive CSF samples (11/11) or samples with cfDNA above 20ng (8/8), while it dropped to 53.3% (11/21) in cytology negative CSF samples and 58.3% (14/24) in samples with cfDNA below 20ng. Enriched copy number variations were detected in 10 patients. We also found CNS metastases specific driver gene alterations in 10 patients, including gene mutations (EGFR, TP53, RB1) or amplifications (MET, ERBB2). Among them, 3 patients carried common gene alterations with plasma. In two patients with only intracranial progression after targeted therapy or chemotherapy, driver gene mutations were detected in CSF samples but not in paired plasma. **Conclusion:** CSF profiling could successfully reflect genetic alterations for the CNS metastatic sites for both cytology positive or negative patients. Copy number amplifications and mutations on TP53 and RB1 are unique events identified in CSF. NGS on CSF and plasma ctDNA reveals tumor heterogeneity in NSCLC patients with CNS metastasis.

Keywords: Non-small-cell lung cancer, Circulating Tumor DNA, Central nervous system metastases

P1.01-035 A NEXT GENERATION SEQUENCING AND CHARACTERISTICS BASED MODEL FOR PREDICT CLINICAL BENEFIT OF ADVANCED NSCLC PATIENTS

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Background: The development of targeted therapies has revolutionized the treatment of non-small cell lung cancer. Interrogating the status of driver mutations has become routine practice. In this study, we applied next-generation sequencing to investigate the association between molecular signature and clinical benefit. **Method:** We performed capture-based targeted ultra-deep sequencing on 204 samples obtained from NSCLC patients at a single center, including 93 FFPE, 70 fresh tissue and 41 plasma samples. One hundred and twenty two samples were subjected to a panel consisting of 8 driver genes; 50 samples were subjected to a 56-gene panel. The remaining 32 samples were subject to a 168 gene panel. **Result:** In 159 TKI-naïve patients, driver mutation was identified in 95.2% of (79/83) patients using the 8-gene panel; among them, 65.1% (54/83) carried *EGFR* mutations. Larger panels identified mutations in 68.1% of patients; 21% carried mutations other than driver mutations. Treatment-naïve patients were primarily subject to the 8-gene panel; in contrast, patients progressed on chemotherapy were subject to larger panels. Seventy-two percent of patients (80/111) undergone matched targeted therapy (MTT) according to sequencing results had a significantly longer PFS than 29 patients who chose chemotherapies despite the fact of harboring driver ($p=4.58x10^{-4}$ HR=0.342, 95% CI: 0.158, 0.74). Next, we investigated whether the number of *EGFR* mutations a patient carries and the presence of concurrence *EGFR* amplification have an effect on PFS. Our data revealed that both parameters are not associated with PFS. Among 46 patients receiving chemotherapy, patients with *KRAS* mutations were associated with a shorter PFS, 133 days vs 207 days (p= 0.073, HR=2.06 95% CI; 0.791, 5.36). For TKI-naïve patients, primary tumor tissue was collected from 86 patients and tumor tissue from metastatic lymph nodes was collected from 35 patients. Interestingly, we observed that lymph node samples had a higher maximum mutation allelic fraction (MAF) than primary lung tumor samples in patients with distance metastasis, especially with visceral metastasis (p=0.0986); such trend was not observed in patients without distant metastasis. We also analyzed samples obtained after TKI-treatment. Among 36 TKI-treated patients, patients with visceral metastasis were more likely to harbor *TP53* mutations (p=0.04), which were primarily missense mutations not loss of function mutations, primarily seen in tumorigenesis. *TP53* missense mutations can potentially promote distant visceral metastasis after the development of resistance to TKIs. **Conclusion:** Our study highlighted the utility of sequencing-based screening technologies and characteristics in providing treatment guidance.

Keywords: PFS, next-generation sequencing, clinical parameters

P1.01-036 IDENTIFYING AND ADDRESSING GAPS IN MOLECULAR TESTING FOR PATIENTS WITH LUNG CANCER

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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. Yet previous studies indicate that not all patients with NSCLC are receiving testing, even for actionable mutations in EGFR, ALK, and ROS. We hypothesized that rates of molecular testing would be low for patients calling a community HelpLine and that we could potentially increase testing rates with one-on-one caller education and providing free precision medicine services. **Method:** Caller statistics were collected on the toll-free Lung Cancer Alliance (LCA) HelpLine from Sept 1, 2016 – May 31, 2017. Recruitment to the LungMATCH molecular testing program began Nov 10, 2017. Patients are recruited through conversations on the LCA HelpLine, then entered into Perthera Cancer Analysis (PCA) through consent into an IRB-approved registry protocol. PCA includes tissue acquisition, multi-omic molecular profiling, and medical review of testing results and clinical and treatment history. PCA reports are returned to both treating physicians and patients. Data is being collected longitudinally on treatment decisions, patient outcomes including progression-free and overall survival, and patient experience. **Result:** Data from the LCA Helpline identified a gap in molecular testing. 44% (100/228) of patients who were asked if they received any kind of molecular testing replied "No". Of 46 patients who were tested and knew the results, patients indicated changes in EGFR (25), PD-L1 (10), ALK (5), KRAS (4), MET(2), BRAF, and RET. Most of these alterations are potentially actionable. From Nov 10, 2016 – May 31, 2016, 63 interested patients were referred for PCA. Sixteen patients consented and eight more are currently in the consent process. Reasons for non-consent include: doctor refusal, initiation of testing at the treating institution, concern about financial implications, and seven deaths. Ten patients are actively undergoing PCA and six have received completed PCA reports. Of those six, three patients reported that treatment decisions were made using the molecular testing information. Updated results will be presented. **Conclusion:** Caller data indicate that patients with lung cancer are not receiving molecular testing in accordance to guidelines. To address this problem, we introduced a program through a nonprofit-corporate partnership that navigates patients and their physicians through a comprehensive precision therapy program. This type of program is feasible and there is patient interest.

Keywords: Biomarkers, molecular testing, non-small cell lung cancer

P1.01-037 CIRCULATING TUMOR DNA CLEARANCE DURING TREATMENT ASSOCIATES WITH IMPROVED PROGRESSION-FREE SURVIVAL

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Background: Therapeutic selection has been shown to lead to marked clonal evolution, thus revealing limitations in imaging scan as a monitoring method, which does not reflect biological processes at a molecular level. However, currently, response assessment of patients with non-small cell lung cancer (NSCLC) primarily relies on imaging scans, necessitating the development of methodologies for dynamic monitoring of treatment response. We evaluated ctDNA as a tumor clonal response biomarker. **Method:** We screened 831 advanced NSCLC patients with a mixture of prior treatment exposure by performing capture-based ultra-deep targeted sequencing on plasma samples using a panel consisting of 168 NSCLC-related genes. Eighty-six patients with driver mutations and a minimum of 2 evaluation points in addition to baseline were included for further analysis. **Result:** At baseline, 79.9% patients harbored at least one mutation from this panel; the remaining 20.1% had no mutation detected. Sixty-nine percent of patients (570/831) harbored driver mutation. Patients harboring 2 mutations or fewer at baseline had a median progression-free survival (PFS) of 7.4 months; in contrast, patients harboring more than 2 mutations had a median PFS of 3.8 months ($P=6.6x10^{-5}$ HR=0.34), suggesting a significant inverse correlation between number of mutations at baseline and PFS. Next, we evaluated the ability of ctDNA as a tumor clonal response biomarker in 86 patients with a minimum of 2 follow-ups. After a median follow-up of 314 days, 64 patients (74.4%)

reached disease progression. During treatment, 46 patients, treated with either matched targeted therapy (MTT) or chemotherapy, had a minimum of one time of ctDNA clearance, occurring from 1.6 months to 7.5 months after the commencement of treatment, with a median PFS of 8.07 months, an overall response rate (ORR) of 41% and a disease control rate (DCR) of 93%. Median overall survival (OS) for this group has not reached. In contrast, 40 patients who had consistent detectable ctDNA throughout the course of treatment had a median PFS of 3.47months, a median OS of 425 days, an ORR of 20% and a DCR of 53%. Our data revealed that patients with a minimum of one time ctDNA clearance are associated with a better ORR (p=0.05), DCR ($p=5.9x10^{-5}$), a longer PFS ($p=5.4x10^{-10}$HR=0.21) and OS ($p=2.3x10^{-5}$HR=0.21), regardless the type of treatment commenced and the time of evaluation. **Conclusion:** This real world study comprising a heterogeneous population reveals the predictive and prognostic value of ctDNA and warrants further investigations to explore its clearance as a surrogate endpoint of efficacy.

Keywords: CtDNA clearance, NSCLC, liquid biopsy

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-038 IDENTIFICATION AND CHARACTERIZATION OF CIRCULATING TUMOR CELLS FROM LUNG CANCER PATIENTS FOR SELECTING TARGET ANTICANCER DRUGS FOR RELAPSE

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Background: Metastasis was found in most of lung cancer patients resulting in death. Patient-derived xenograft model using tumor tissues and circulating tumor cells provides the opportunity to assess the biological features of cancer repeatedly during the cancer evolution, enabling clinicians to react quickly to treat the patient with the most suitable specific targeted therapy. **Method:** For setting up ex vivo culturing CTCs and establishment of patient-derived CTC xenograft model obtained from liquid biopsy of lung cancer patient, we plan to collect liquid biopsy (n>100) samples from each patient either once or several times before and after treatment. This study will be approved by our institutional review board and local ethics committee. All patient agree their informed consent for inclusion in this study. After collecting mononuclear cells, CTCs is isolated. Patient-derived CTC xenograft model will established using ex vivo cultured CTCs. Using both ex vivo cultured CTCs and patient-derived CTC xenograft model, various target anti-cancer drugs will be screened. And we then examined genetic variations and expression profile of CTC cells. **Result:** Based on these results, we identify the drugable target somatic mutations and characterizing the biologic behaviors of CTCs cells based on the results of consequence network via activation of somatic mutation. In case of lung cancer cells expressing EGFR mutation at diagnosis, we found that EGFR mutation was existed during chemotherapy. At the stage of metastasis, clonal evolution of lung cancer cells having EGFR mutation was detected. After examining the cytotoxicity of CTC cells by treatment of 3rd generation anti-EGRF inhibitor (3 different types) in vitro and in vivo model, we found a set of somatic mutations were we identified a set of somatic mutations associated with relapse and chemoresistance. These somatic mutations were involved in impairing DNA repair and activating EGFR-mediated cell signaling. Since effective anti-cancer drugs could be selected through screening of target anti-cancer drugs in PDX model following by identifying somatic mutation and expression profiles of CTC lung cancer cells, we suggest that our screening biosystem is useful to maintain the status of complete remission. **Conclusion:** CTC analysis can support the delivery of precision anticancer treatments, as specific biomarkers of response to targeted drugs can be appraised. Assuming that CTC induces the recurrence and metastasis, isolated CTC isolated from blood of lung cancer patients may have characteristics of cancer stem cells. Subsequently, CTC could be ex vivo cultured and apply to xenograft model to confirm genetic signatures of CTC.

Keywords: patient-derived xenograft model, Circulating tumor cell, Whole exome sequencing

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-039 SURVIVAL IMPACT OF NEXT-GENERATION SEQUENCING IN LUNG CANCER

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Background: Next-generation sequencing (NGS) enables a comprehensive genomic analysis of lung cancer patients. It has uncovered many novel genetic abnormalities and identified actionable genomic alterations in lung tumors that previously tested "negative" by conventional non-NGS tests. In this study, we evaluated the clinical impact of NGS, performed at different stages of the oncologic management, on overall survival of advanced lung cancer patients. **Method:** In this retrospective study, 178 consecutive non-small cell lung cancer (NSCLC) patients who performed hybrid capturing NGS were enrolled at the Thoracic Cancer Unit at Rabin Medical Center, Israel, between 2011-2017. Hybrid capture-based NGS was performed by Foundation Medicine and Gaurdant 360™ if tissue was not available. **Result:** 178 consecutive NSCLC patients were included in this study. Median age at diagnosis was 63±12.1 years. 83% had adenocarcinoma. NGS was performed upfront in 45.5% (81/178) and after 1st line failure in 54.5% (97/178). Treatment decision was taken toward targeted therapy subsequent to NGS analysis in 34% (61/178) of patients (29 and 32 respectively) with an objective response rate of 54%. Overall survival (OS) was evaluated for 51% (31/61) with a median of 12.2±14.1 months. For patients who performed upfront NGS, OS ranged between 1.8 to 32.5 months, with a median OS of 13.8 months. For patients who performed NGS on progression, OS ranged between 1.7 to 77.1, with a median OS of 12.7 months. **Conclusion:** Comprehensive tissue and liquid-based NGS have revealed targeted treatment options for one third of the patients. Overall Survival of patients treated with tailored therapy was positively impacted by earlier performed NGS.

Keywords: non-small cell lung cancer, next generation sequencing, overall survival

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-040 CLINICAL UTILITY OF PLASMA-BASED NGS FOR ADVANCED-STAGE NSCLC PATIENTS WITH INSUFFICIENT OR UNAVAILABLE TUMOR TISSUE

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Background: The failure rate of tissue-based NGS in newly diagnosed NSCLCs is approximately 20-25 %, reaching 40 % in the case of tumor biopsy samples collected at disease progression. In this study, we are analyzing the clinical utility of plasma-based NGS using cell-free circulating tumor DNA (ctDNA) for advanced-stage lung adenocarcinoma patients, as a complement or alternative to tissue-based molecular profiling. **Method:** Eight Academic Spanish Institutions are participating in patient recruitment. We are stratifying patients in three cohorts: 1) Patients with advanced-stage lung adenocarcinomas with insufficient tumor tissue for EGFR, ALK or ROS1 analysis; 2) Patients with EGFR, ALK or ROS1 altered tumors with acquired TKI resistance; 3) Patients with EGFR T790M positive cancers progressing on third generation EGFR TKIs. Next-generation ctDNA sequencing is being performed using GUARDANT360 73-gene panel at a CLIA certified central laboratory facility (Redwood City, California). We are stratifying gene variant actionability into four levels according to the OncoKB website criteria. **Result:** We have currently included 97 patients (January-June 2017). Complete clinical and molecular data are available at present for the first 37 patients. Twelve, 19 and 6 patients have been enrolled in cohorts 1, 2 and 3 respectively. Never smoker patients were overrepresented (n = 21, 56 %), predominantly at cohorts 2 and 3. A total of 30 cases (81 %) had detectable ctDNA. We have detected potentially actionable genetic alterations involved in mitogenic pathways in 16 patients (43 %). Level 1 alterations (variants with matched approved drugs) were found in three patients' tumors (25 %) from cohort 1 (two EGFR sensitizing mutations and one ROS1 rearrangement). Nine patients (36 %) from cohort 2 and 3 had tumors with potentially targetable acquired genetic alterations, including three cases with EGFR T790M mutations and one case with a ROS1 kinase domain mutation. Six patients (16 %) received matched targeted therapies, four (11 %) in genotype-driven clinical trials. Reasons for not receiving matched targeted therapies in patients with actionable tumors were clinical deterioration or death (n = 2), unavailability of matched clinical trials (n = 6), treatment with non-genotype-tailored therapies (n =1) or no disease progression to ongoing therapies (n =1). Final clinical and molecular data of the whole cohort will be provided at the meeting. **Conclusion:** On the basis of our preliminary data, next-generation ctDNA sequencing (GUARDANT 360) appears to detect actionable genetic alterations when tissue is unavailable, avoiding multiple biopsies and enabling rapid patient selection for genotype-tailored therapies.

Keywords: next generation sequencing, ctDNA, genotype-tailored treatment

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-041 ROLE OF RE-BIOPSY DURING DISEASE PROGRESSION NON-SMALL CELL LUNG CANCER FOR ACQUIRED RESISTANCE ANALYSIS AND DIRECTING ONCOLOGY TREATMENTS

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Background: It is not possible to properly target treatments in cases of relapse without knowing the nature of new lesions. Third-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) can overcome T790M-mediated resistance in non-small-cell lung cancer (NSCLC). But the re-biopsy to confirm T790M status is occasionally difficult. In Japan, transbronchial lung tissue biopsy (TBLB / TBB) is the most common sampling method used for re-biopsy to confirm patients eligible for treatment. We aimed to investigate the success rate of re-biopsy

and re-biopsy status of patients with advanced or metastatic NSCLC completing either 1st line chemotherapy or EGFR-TKI therapy. **Method:** We initially screened 39 consecutive patients with NSCLC harboring EGFR-sensitive mutations who had experienced PD after any chemotherapy at Tokyo Medical University Hospital January 2014 and December 2016. **Result:** 38 patients who had experienced PD after EGFR-TKI treatment were eligible. Among 30 patients, tumor progression sites included 3 pleural effusion, 9 thoracic primary/metastatic lesions, 2 hepatic metastases, 15 lymph node metastases. Of the 38 patients, 47.3% underwent rebiopsy sucessfully. Of the 38 biopsied patients, 18 (47.3%) were analyzed for EGFR mutation, using tissue or cytology samples; T790M mutations were identified in 10 (55%) of the 18 patients. Of the 38 biopsied patients, 18 (47.3%) were analyzed for EGFR mutation, using tissue or cytology samples; T790M mutations were identified in 10 (55%) of the 18 patients. **Conclusion:** Most re-biopsy samples were diagnosed with malignancy. T790M mutations were identified as much as same in previous studies. However, tissue samples were less available in previous studies. Skill and experience with re-biopsy and noninvasive alternative methods will be increasingly important.

Keywords: Disease progression, epidermal growth factor receptor mutation, Re-biopsy

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-042 DYNAMIC CTDNA ASSAY BY NEXT GENERATION SEQUENCING TO GUIDE TARGETED THERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: It is difficult to identify tumor driving genes in advanced non-small cell lung cancer (NSCLC) patients especially for those who were unable to obtain cancer tissue samples and had developed treatment resistance. Circulating tumor DNA (ctDNA) has garnered much excitement over the past few years for its potential clinical utility as a tumor therapy monitoring tool. Our study aims to evaluate the usefulness of ctDNA for serial monitoring actionable genetic alterations in NSCLC patients. **Method:** 34 pairs of matched cancer tissue and plasma samples were collected from patients with advanced NSCLC and applied to capture-based next generation sequencing (NGS) using the lung panel, consisting of critical exons and introns of 168 genes. Additional, serial monitoring of ctDNA was conducted in 11 NSCLC patients with actionable genetic alterations using the above NGS assay. **Result:** ctDNA yielded a close agreement of 85.3% (29/34) on actionable genetic alteration status when compared to cancer tissue at baseline in this study. Analysis of ctDNA at different time points showed a strong correlation to treatment efficacy. Interestingly, secondary genetic alterations such as EGFR mutation T790M were detected in 45.5% (5/11) of the patients during monitoring. **Conclusion:** ctDNA may be a potential alternative to conventional primary tissue based NGS assay. ctDNA assay by NGS could be clinically used to monitor the efficiency of personalized target therapy for NSCLC patients.

Keywords: non-small cell lung cancer, next generation sequencing, Circulating Tumor DNA

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-043 MOLECULAR TESTING FOR NON-SMALL CELL LUNG CANCER IN LATIN AMERICAN

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Background: According to IALSC/CAP guidelines EGFR and ALK testing is recommended for all non-squamous advanced lung cancers. However, the real access to molecular test and treatment, especially in LATAN is unknown. **Method:** We conducted an online survey with medical oncologists from LATAN during May 2017. The survey has 20 questions about molecular test and target treatment, but also clinical practice in the management of advanced non-squamous NSCLC. **Result:** 144 oncologists from 10 countries answer the survey, mostly of them (75%) from Brazil. Although 95% of the oncologists have access to EGFR mutation test and most of them can also test the ALK-fusion protein, only half of them test all patients. Usually these tests are supplied by the pharmaceutical industries (75% of EGFR and 78% of ALK). The mutation status are available in 2 weeks for the EGFR and in 3 weeks for the ALK. The main reason for not testing is lack of sufficient tissue (30% of oncologists), but also some difficulty in access and the long turn-around time where also an issue, 20% and 13% of the oncologist, respectively. Poor performance status and patient clinical characteristics were rarely considered a reason for not testing. Target therapy is available for mostly of the patients with private insurance, but only 50% in the public heath system have access to an anti-EGFR TKI and solely 20% can receive an anti-ALK TKI. New biopsies should be done in the progressive disease, but only 22% of the oncologists perform the procedure in more than 75% of their patient. Immunotherapy is a new treatment modality, especially in the develop countries, but it should be restricted as first line treatment to patients with high expression of PD-L1. In LATAN, immune checkpoints blockage is almost limited to the patients with private insurance (85%), being rare in the public heath system (15%). 83% of the oncologist considered to test the PD-L1 expression only after the results of EGFR /ALK are available. **Conclusion:** There are difficulties in the implementation of IALSC guidelines in LATAN. Mostly of the patients have access to EGFR mutation test, however the treatment is not available to everyone. It is clear the importance of the pharmaceutical industries in providing the molecular test by their voucher programs. The most important difficulty point out by the oncologists is the lack of tissue, but simple barriers as long time to get the results and access to the test should also be managed.

Keywords: Target therapy, molecular testing, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-044 DETECTION OF CIRCULATING TUMOR CELLS IS ASSOCIATED WITH DISEASE BURDEN IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Previous studies on the clinical value of circulating tumor cells (CTCs) enumeration as a predictor of prognosis in non-small cell lung cancer (NSCLC) have yielded controversial results. The purpose of this study was to further evaluate the prognostic relevance of CTC count in patients with advanced-stage NSCLC before and after first line chemotherapy. **Method:** A total of 43 patients with chemotherapy-naïve, advanced NSCLC and at least one available measurement of CTCs were enrolled in this single-center retrospective study. The presence of CTCs was evaluated by the use of the CellSearch System; CTC positivity was defined as ≥2 CTC in 7.5 ml of whole blood. CTC status was assessed at two different time points, i.e. at baseline (before administration of chemotherapy) and after completion of the first chemotherapy cycle. Baseline CTC count and its dynamic change between the above time points were correlated with clinicopathological features of patients, treatment response and survival, using univariate and multivariate regression analysis. **Result:** Eight (18.6%) out of 43 patients (mean age 67.1 ± 9.9 years, male/female ratio 39/4) harbored CTCs at baseline (mean 22.75 CTCs/patient, range: 2 - 108). Positive baseline CTC count was significantly associated with the presence of five or more metastatic sites (p=0.018). Response to treatment was recorded in 40.6% of patients and disease stabilization or progression in 59.4%. No significant associations were found between response or progression rates and baseline CTC counts (p=0.067 and p=0.083, respectively). On the contrary, progressive disease status and metastatic disease burden were significantly associated with the change in CTC count, (p=0.033 and p=0.035, respectively). No significant associations were found between survival (PFS or OS) and CTC count or the dynamic change of CTC status. Worse performance status (PS) and the presence of five or more metastatic sites were recognized as independent predictors of reduced PFS [HR=2.7; 95% CI: 1.1-6.8; p=0.035 and HR=2.9; 95% CI: 1.1-8.1; p=0.042, respectively], while PS was the only variable independently associated with OS (HR=16.9; 95% CI: 4.3-65.8; p<0.001). **Conclusion:** In our study, CTC count and the dynamic change of CTC status following chemotherapy administration were both associated with increased metastatic disease burden but not with PFS or OS. These data support the suggested role of CTCs in the metastatic cascade and underline the need for further validation of this candidate biomarker before its implementation into routine oncology practice.

Keywords: CTC count, Circulating tumor cells, non-small cell lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-045 COMPANION DIAGNOSTIC TESTS FOR EGFR, ALK AND ROS-1 VS NGS IN ADVANCED NSCLC PATIENTS - WHICH IS THE BEST IN TERMS OF COST AND EFFECTIVE?

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Background: Success of a target therapy is directly correlated with the accuracy of its companion diagnostic test. Without a corresponding biomarker, target therapy may yield shorter survival, waste time, increase burdens and costs. As important as conducting cost-effectiveness studies for therapies, it is also valuable to compare different molecular tests. In lung cancer, the mutational status of EGFR and translocation of ALK and ROS-1 are commonly tested to offer the best intervention. Our objective is to evaluate the cost-effectiveness of a unique exam using NGS versus other routinely used tests such as the ones which involve RT-PCR and FISH. **Method:** Target population is NSCLC, adenocarcinoma, and candidates to first-line therapy. Strategy 1: test EGFR mutation if EGFR test negative, individual follow to FISH for ALK; if FISH negative, follow to FISH for ROS-1. Strategy 2: differs from 1 since FISH for ALK and ROS are requested together. Strategy 3: all individuals are submitted to NGS (multicomplex platform which include EGFR/ALK/ROS-1 and other genes). Prevalence of biomarker, test accuracy and proportion of unknown results were used to calculate each decision tree branch. Sensitivity and specificity was obtained from literature review using Sanger as reference standard for RT-PCR tests and NGS. The study was analyzed from a healthcare-payer perspective based on

Brazilian private sector. Costs were based on data from diagnostic companies, ANS and AMB-CBHPM 2016. Survival time and utilities were based from randomized clinical trials. Decision tree model was designed to select an appropriate treatment regimen according to test results; and microsimulation model (M) simulate costs and survival from the corresponding treatment. If EGFR test was positive, M1: gefitinib 1ºline>pemetrexed+cisplatin>docetaxel; if ALK or ROS1 were positive, M2: crizotinib1 line>pemetrexed+cisplatin>docetaxel; if EGFR/ALK/ROS negative or test unknow, M3: pemetrexed+cisplatin>docetaxel>gemcitabine. **Result:** The use of NGS added 24% extra cases correct identified as well as extra costs (US$ 800.76; PPP 2015) attributed to the molecular testing. The ICER comparing NGS with sequential tests was US$ 3,381.82/correct case detected. Comparing strategy 2:1, the ICER was US$937.86/correct case detected. Therefore, when treatment was incorporated into the model, the effectiveness was diluted between arms. The NGS improves slight gain in life years and quality-adjusted life years, but this could be explained by minor differences in global survival time between treatments. **Conclusion:** this study is part of an effort to integrate companion diagnostics discussions on precision medicine and covered drugs in the Brazilian health system. Studies considering liquid biopsy could be worth value to highlight effectiveness between tests in clinical routine.

Keywords: companion diagnostic, non-small cell lung cancer, advanced

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-046 THE FEASIBILITY OF OSIMERTINIB TREATMENT ON BRAIN METASTASES IN NSCLC PATIENTS AFTER 1ST GENERATION EGFR-TKI RESISTANCE: A PRELIMINARY STUDY

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Background: NSCLC patients with activating EGFR mutations benefit from 1st generation EGFR-TKIs. It eventually develops acquire resistance after 10-12 months during of response. Of note, approximately one-third of those patients develop brain metastases, which deteriorate their quality of life and survival. Few effective therapeutic options are currently available for BM patients. Several case studies have showed the well response with osimertinib in BM patients. BM model also found the high penetration rate of Osimertinib into blood-brain barrier. This study evaluated the feasibility of osimertinib treatment on BM patients after 1st generation EGFR-TKI resistance. **Method:** Patients with advanced or recurrent NSCLC who had progressed during EGFR-TKIs treatment were collected from our previous clinical trial (NCT02418234) from March 2015 to March 2016. Blood samples were drawn within two weeks from PD occurred. T790M mutations were evaluated by droplet digital PCR. We undertook follow-up every 3 months by phone until April 2017. The median follow-up time was 11 months (range, 2 to 22 months). **Result:** Fifty NSCLC patients with BM after EGFR-TKI resistance were collected from our previous trials. After TKI resistance, ten patients received subsequent osimertinib treatment. Finally, ten patients included three males and seven females were included in the study. The median age was 66.5 (56 to 73). Seven were detected acquired T790M mutation. The median survival was 15.3 months (95% CI, 10.1 to 20.6 mo), 15.3 mo for T790M negative and 12.9 mo for T790M positive patients. **Conclusion:** Our preliminary study showed the well efficacy of osimertinib on NSCLC patients with BM. It provides well survival benefit. Randomized control trials should be required before it is widely used.

Keywords: osimertinib, Brain metastasis, lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-047 ANALYSIS OF EGFR MUTATION STATUS IN CSF AND BLOOD IN LUNG ADENOCARCINOMA PATIENTS WITH EGFR MUTATION AND CNS METASTASIS

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Background: Patients with non-small cell lung cancer (NSCLC)harboring epidermal growth factor receptor (EGFR) mutations benefit a great deal from EGFR tyrosine kinase inhibitors(TKIs). However, most patients get recrudesced within one or two years, and many of them progressed in central nerve system (CNS).Owing to the blood– brain barrier, detecting tumor-derived cell-free DNA (cfDNA) in the blood of brain metastasis tumor patients is challenging. Detecting tumor-specific mutations in cerebral spinal fluid (CSF) became an alternative method. **Method:** 41 initial or progressed lung adenocarcinoma patients with EGFR mutation and CNS metastasis from Henan Cancer Hospital were included in this study. 41 patients were all detected EGFR mutation status in CSF with dropplet digital PCR (ddPCR) and 37 in 41 patients were detected EGFR mutation status in blood with the same method. Their clinical informations were also collected at the same time. **Result:** The rate of EGFR mutations in CSF (15/41, 36.6%) were obviously lower than that in blood (24/37,64.9%) (P=0.013), especially in those with EGFR exon 19del mutation patients (7/18 vs 13/16, P = 0.017), without TKIs treated patients (3/13 vs 8/11,P = 0.038) and less than 60 years patients (10/25 vs 17/22, P = 0.010). In patients with CNS symptoms positive, the rate of EGFR mutations in CSF was higher than those negative (13/27 vs 2/14 , P=0.033). In patients with MRI indicating leptomeningeal metastasis, the rate of EGFR mutations in CSF was higher than those not indicating(8/11 vs 7/30 , P=0.003).

Clinical characteristics, EGFR mutation status in CSF and plasma (n = 41)	
Characteristic	**n(%)**
Gender	
Male	23 (56.1)
Female	18 (43.9)
Age	
≥ 60	16 (39)
< 60	25 (61)
Smoking status	
Yes	12 (29.3)
No	29 (70.7)
Brain metastases (MRI)	
Only metastatic tumors	30 (73.2)
With meningeal lesions	11 (26.8)
Brain metastatic tumor number	
Single	10 (24.4)
Multiple	31 (75.6)
Neurological symptoms	
Positive	15 (36.6)
Negtive	26 (63.4)
Prior TKIs treat	
Yes	28 (68.3)
No	13 (31.7)
CSF EGFR mution	
19	7 (17.1)
21	6 (14.6)
Both	2 (4.9)
Negtive	26 (63.4)
Blood EGFR mution	
19	13 (31.7)
21	10 (24.4)
Both	1 (2.4)
Negtive	13 (31.7)

Conclusion: The EGFR mutations status in CSF is different from that in blood in patients with EGFR mutation and CNS metastasis. This warrants confirmation in larger cohorts and further more studies are needed to find out the internal mechanism. Detecting EGFR mutations status in both blood and CSF will be helpful to make individualized treatment.

Keywords: EGFR mutation, Cerebral spinal fluid, lung adenocarcinoma

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-048 CLINICAL IMPACT OF EGFR MUTATION ON BRAIN METASTASIS IN NSCLC PATIENTS: A META-REGRESSION ANALYSIS

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Background: Though target agents like epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) have shown activity in patients with brain metastasis, the impact of EGFR mutation on incidence of non-small cell lung cancer (NSCLC) with brain metastasis and treatment outcome remain inconclusive. **Method:** MEDLINE, PubMed, and EBSCO Libraries were systematically searched until August 31, 2015. Retrospective studies including investigating the correlation between EGFR mutation status with brain metastasis from NSCLC were included. **Result:** The result of the fourteen studies including 4432 patients indicated NSCLC patients with EGFR mutation have higher incidence of brain metastasis (Figure 1, odd ratio = 2.09, 95% CI: 1.72–2.53). And, EGFR mutations were associated with better survival in patients with brain metastasis from five studies though not statistically significant (Figure 2, hazard ratio = 0.47, 95% CI: 0.16–1.35). Figure 1. Meta-analysis of the association between EGFR mutation status and the risk of brain metastasis.

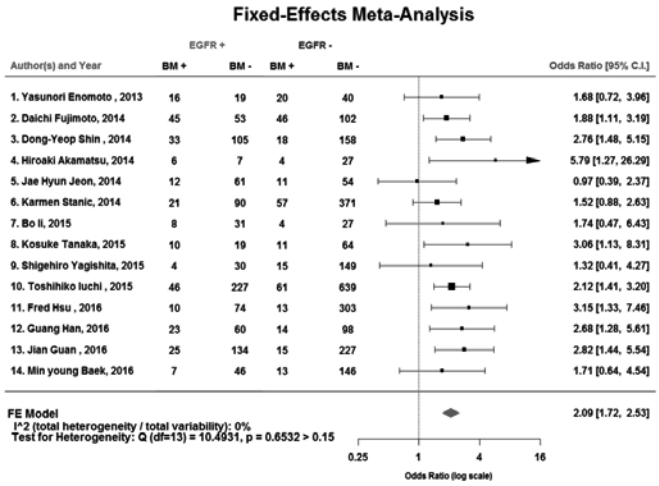
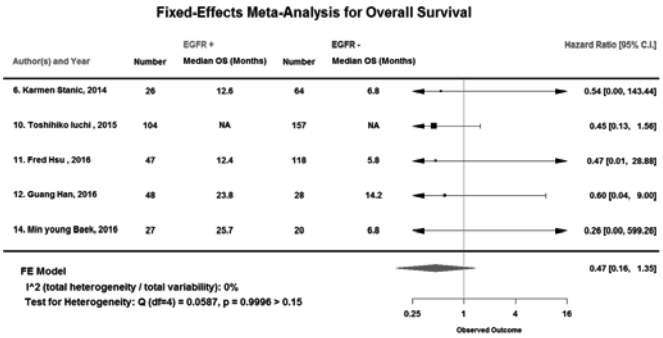


Figure 2. Meta-analysis on mean overall survival among NSCLC patients with brain metastasis according to EGFR mutation status.



Conclusion: We found that EGFR mutation increased risk of brain metastasis but EGFR mutation might predict better survival with appropriate treatments.

Keywords: EGFR mutation, NSCLC, Brain metastasis

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-049 CONFORMITY OF EGFR MUTATION STATUS BETWEEN BLOOD PLASMA AND TUMOR TISSUE SAMPLES AMONG NSCLC ADENOCARCINOMA PATIENTS, AT DR. H. A. ROTINSULU LUNG HOSPITAL. A PRELIMINARY STUDY

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Background: Lung cancer: the leading cause of cancer-related deaths worldwide About 85% of lung cancers are NSCLC with Adenocarcinoma in predominance EGFR-TKI became a current standard of care in adenocarcinoma, requires EGFR mutation test Biopsy needed to obtain tumor tissue for EGFR mutation test, with a failure rate of about 10-50% due to inadequate tumor tissue Blood plasma which contains circulating-free tumor DNA might be used as alternative DNA source for the EGFR mutation test To conduct a preliminary study to see the suitability between EGFR mutation examination in plasma samples with samples of tumor tissue (biopsy or cytology) **Method:** Design: descriptive cross sectional Subject: 10 Patients; Naive NSCLC adenocarcinoma patients (>18 y.o.) at dr. H. A. Rotinsulu Lung Hospital, Bandung Indonesia Examination: Kalgen Laboratory Jakarta-Indonesia and Prodia Diagnostic Molecular Laboratory Jakarta-Indonesia, using *therascreen* EGFR Kit Analyzed descriptively by comparing EGFR mutation from plasma sample with tumor or cytology tissue, calculated the conformity in percentage **Result:**

EGFR mutation test result between tumor tissue samples and blood plasma samples

EGFR mutation status of blood plasma samples	EGFR mutation status of tumor tissue samples				
	Exon 19del	L858R	T790M	No Mutation detected	Inadequate sample
Exon 19del	2				
L858R					1
T790M				1	
No mutation detected				5	1

Success rate: Plasma 100%, tissue 80% Mutation detected: Plasma 40%, tissue 20% No mutation detected: Plasma 50%, tissue 60%

Concordance of tumor tissue samples with blood plasma samples

Blood plasma samples	Tumor tissue samples		
	No mutation detected	Mutation detected	Inadequate sample
No mutation detected	5	0	1
Mutation detected	1	2	1
Conformity result: 70%			

Conclusion: This study has met the primary objective with conformity of 70% Needs further study with bigger population and design, although this study showed some trends favoring blood plasma samples

Keywords: EGFR, plasma, biopsy

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-050 COST-EFFECTIVENESS OF PDL1 BASED TEST-AND-TREAT STRATEGY WITH PEMBROLIZUMAB AS THE 1ST LINE TREATMENT FOR NSCLC IN HONG KONG

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Background: Pembrolizumab, a monoclonal antibody against PD-1, is approved by several regulatory agencies for first line treatment in metastatic NSCLC with a PD-L1 tumour proportion score (TPS) ≥50%. An economic model was developed to evaluate the cost-effectiveness of employing a biomarker (PD-L1) test-and-treat strategy (BTS), in which patients with TPS ≥50% are treated with pembrolizumab, and other patients receive standard-of-care (SoC) cytotoxic chemotherapies versus a non-BTS strategy with all patients receiving SoC. Patients with activating EGFR mutations and ALK translocations were excluded from the analysis. **Method:** The model was built with partitioned survival approach to estimate the incremental cost effectiveness ratio (ICER) expressed as cost per quality-adjusted life-year (QALY) gained. The clinical efficacy, utility and safety data used in this model were derived from the KN024 trial. The base case comparator in the model included five different platinum-based chemotherapy regimens used as SoC for advanced NSCLC in Hong Kong. The base-case time horizon for the model was 10 years with costs and health outcomes discounted at a rate of 3% per year. Utilities for the base case were based on utility data collected in KN024. Costs and disutility associated with grade 3-5 adverse effects of incidence rate 5%, including anaemia, neutropenia, pneumonia, thrombocytopenia and pneumonitis were considered in the model. Treatment was continued until disease progression or maximum 2 years for pembrolizumab. Local drug acquisition costs, PD-L1 testing costs, drug administration costs, disease management costs were applied. A series of sensitivity analyses were conducted to evaluate the uncertainty of cost-effectiveness results. **Result:** The BTS approach was projected to increase QALY by 0.29 with an additional total cost of HK$ 249,077 (USD 31,933) compared to non-BTS approach resulting in an incremental cost-effectiveness ratio (ICER) of HK$ 865,189 (USD 110,922) per QALY gained. This is lower than the World Health Organization (WHO) cost-effectiveness threshold of 3 times 2016 GDP per capita of Hong Kong, HK$ 1,017,819 (USD 130,490). Probabilistic sensitivity analysis showed 94.6% probability that the ICERs would be below this threshold. In a scenario analysis, a lower ICER of HK$ 859,284 (USD 110,165) was shown in comparison of pembrolizumab versus SoC among patients with TPS ≥50%. **Conclusion:** A BTS to identify a subset of NSCLC patients with PD-L1 TPS ≥50% to be treated with pembrolizumab in the first line setting can be considered cost-effective in Hong Kong.

Keywords: cost effectiveness, BTS in Hong Kong, pembrolizumab

P1.01-051 NIVOLUMAB VERSUS CHEMOTHERAPY AS POST-PLATINUM THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER IN A REAL-WORLD SETTING

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Background: Nivolumab, an immune checkpoint inhibitor, is approved for advanced non-small cell lung cancer (NSCLC) after platinum-based chemotherapy, based on results of 2 pivotal studies (CheckMate 017 and 057). This prospective observational study (CA209-118) compared outcomes with nivolumab versus chemotherapy as post-platinum therapy for NSCLC in a real-world community setting. **Method:** This analysis, as of May 16, 2017, included patients with advanced NSCLC who completed an initial course of platinum-based chemotherapy and started subsequent treatment prior to November 16, 2016, with a minimum of 6 months of potential follow-up. Patients receiving experimental therapy, immunotherapy other than nivolumab, or tyrosine kinase inhibitors for *EGFR/ALK*-mutated NSCLC were excluded. Patients in this non-randomized study were grouped by receipt of nivolumab or chemotherapy as first post-platinum therapy and followed until death, study discontinuation, or initiation of subsequent immunotherapy. Unadjusted and adjusted survival analyses were conducted. For adjusted analysis, multivariate regression was performed that included age, ECOG performance status score, time since stage IV diagnosis, smoking status, and squamous histology as covariates. **Result:** Of 383 eligible patients, 161 received post-platinum nivolumab and 222 received post-platinum chemotherapy, including 158 who received a regimen recommended by the National Comprehensive Cancer Network (docetaxel, pemetrexed, gemcitabine, ramucirumab + docetaxel, or erlotinib) and 40 who received a second platinum-based regimen. Baseline characteristics were well balanced between treatment groups, except that the percentage of men was higher in the nivolumab versus chemotherapy group (59% vs 49%). Mean age was 66 years, and 79% of patients had non-squamous histology. In all, 65% of patients in the nivolumab group and 69% in the chemotherapy group started post-initial platinum therapy ≤1 year after stage IV diagnosis. Median survival from the start of post-initial platinum therapy was 11.5 months (95% confidence interval [CI]: 7.9, not reached) in the nivolumab group and 8.3 months (95% CI: 6.1, 11.0) in the chemotherapy group. Unadjusted survival analyses showed a reduction in mortality risk of 20% with nivolumab versus chemotherapy (hazard ratio = 0.80; 95% CI: 0.59, 1.08); adjusted survival analyses yielded comparable results. In the nivolumab and chemotherapy groups, respectively, 9% and 18% of patients discontinued due to adverse effects; 41% and 49% discontinued due to death or disease progression. **Conclusion:** The results of this early survival analysis from a prospective study in a real-world community setting were similar to those seen in randomized trials, further supporting the benefit of nivolumab over chemotherapy in previously treated advanced NSCLC.

Keywords: Nivolumab, non-small cell lung cancer, Real-world

P1.01-052 PATIENT-REPORTED OUTCOMES (PROS) IN OAK: A PHASE III STUDY OF ATEZOLIZUMAB VS DOCETAXEL IN NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: The phase III OAK study in NSCLC (NCT02008227) demonstrated prolonged overall survival with atezolizumab (an anti-programmed death-ligand 1 antibody) versus docetaxel (median 13.8 vs 9.6 months; HR:0.73, 95% CI 0.62–0.87; p=0.0003). PROs were collected to support documentation of clinical benefit. We report data regarding symptom burden, functioning, and health-related quality of life (HRQoL). **Method:** Patients (n=850) with squamous/non-squamous, previously treated NSCLC, ≥18 years, with measurable disease (RECIST), and ECOG PS 0–1 were randomized to receive atezolizumab 1200mg or docetaxel 75mg/m^2 q3w. PROs were collected using two questionnaires: EORTC QLQ-C30 and its lung module, QLQ-LC13. Analyses included time-to-confirmed-deterioration (TTD) in lung cancer symptoms, physical and role function, HRQoL, longitudinal analyses of mean scores change from baseline to Cycles 5 and 6, proportion of patients with clinically meaningful worsening (≥10-point change from baseline) by Cycles 5 and 6. **Result:** High completion rates were observed throughout treatment (>80% for most cycles). Atezolizumab delayed TTD in physical (HR:0.75, 95% CI 0.58–0.98) and role function (HR:0.79, 95% CI 0.62–1.00). Prolonged TTD in chest pain (HR:0.71, 95% CI 0.49–1.05) was observed with atezolizumab; no differences in TTD were seen for other lung cancer symptoms and HRQoL. Longitudinal analyses demonstrated average changes from baseline in favor of atezolizumab for lung cancer symptoms (Cycle 6: dyspnea, fatigue), domains of functioning (Cycle 6: physical function, social function), HRQoL (Cycle 5); see Table. Fewer atezolizumab-treated patients experienced clinically meaningful worsening in possible treatment-related symptoms during treatment (Cycle 6: diarrhea [OR:0.51, p<0.0001], sore mouth [OR:0.40, p<0.0001], dysphagia [OR:0.61; p=0.0052], peripheral neuropathy [OR:0.50, p<0.0001], alopecia [OR:0.02; p<0.0001]). **Conclusion:** In OAK, atezolizumab delayed the time until NSCLC patients experience limitations in physical and role functioning versus docetaxel. Patient-reported data indicate atezolizumab maintained/improved lung cancer symptom burden and HRQoL compared with baseline, while demonstrating improved tolerability, versus docetaxel.

	By Cycle 5		By Cycle 6	
	LS means difference between treatment arms (average change from baseline)	**P value**	**LS means difference between treatment arms (average change from baseline)**	**P value**
EORTC QLQ-C30 Global Health Status and Function Scales (positive values indicate greater improvement with atezolizumab over docetaxel)				
Global Health Status	4.32*	p=0.0151	3.08	p=0.1257
Physical Function	3.33*	p=0.0290	6.64*	p<0.0001
Role Function	2.93	p=0.1959	4.72	p=0.0542
Emotional Function	2.66	p=0.1110	1.92	p=0.2868
Cognitive Function	-0.67	p=0.6790	-1.08	p=0.5309
Social Function	3.25	p=0.1159	4.68*	p=0.0319
EORTC QLQ-C30 Symptom Scales (negative values indicate greater improvement with atezolizumab over docetaxel)				
Fatigue	-6.27*	p=0.0015	-7.66*	p=0.0003
Nausea/Vomiting	-0.37	p=0.7824	-0.18	p=0.9040
Pain	1.44	p=0.5132	-1.67	p=0.4727
Dyspnea	-4.70*	p=0.0317	-5.92*	p=0.0138
Insomnia	3.50	p=0.1675	0.83	p=0.7564
Appetite Loss	-2.94	p=0.1994	-4.49	p=0.0586
Constipation	-0.31	p=0.8772	-0.33	p=0.8816
Diarrhea	-3.14*	p=0.0482	-2.05	p=0.1748
EORTC QLQ-LC13 Symptom Scales (negative values indicate greater improvement with atezolizumab over docetaxel)				
Dyspnea	-1.66	p=0.3146	-4.80*	p=0.0140
Coughing	-2.60	p=0.2572	-1.38	p=0.5772
Sore Mouth	-7.29*	p<0.0001	-9.23*	p<0.0001
Dysphagia	-0.08	p=0.9595	-2.01	p=0.1575
Peripheral Neuropathy	-12.98*	p<0.0001	-15.71*	p<0.0001
Hemoptysis	-0.24	p=0.7365	-0.91	p=0.2080
Alopecia	-50.59*	p<0.0001	-47.04*	p<0.0001
Chest Pain	-0.91	p=0.6064	-0.58	p=0.7779
Arm/Shoulder Pain	-2.27	p=0.3177	-0.58	p=0.8109
Pain in Other Parts	0.94	p=0.7197	-1.05	p=0.7034

*Values that are significantly in favor of atezolizumab versus docetaxel

Keywords: atezolizumab, NSCLC, PRO

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-053 ITALIAN NIVOLUMAB EXPANDED ACCESS PROGRAMME (EAP): DATA FROM PATIENTS WITH ADVANCED NON-SQUAMOUS NSCLC AND BRAIN METASTASES

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Background: Among patients (pts) affected by non-squamous non-small cell lung cancer (non-Sq-NSCLC), those with secondary brain metastases are very common and are characterized by a poor prognosis. As they are usually excluded from clinical trials, the EAP offered an opportunity to evaluate nivolumab efficacy and safety in these patients outside of a controlled clinical trial in Italy. **Method:** Nivolumab was available upon physician request for pts aged ≥18 years with a diagnosis of non-Sq-NSCLC who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events using Common Terminology Criteria for Adverse Events. Pts with brain metastasis were eligible if asymptomatic, neurologically stable and either off corticosteroids or on a stable dose or decreasing dose of ≤ 10 mg daily prednisone. **Result:** Out of 1588 patients with non-Sq-NSCLC participating in the EAP in Italy, 409 (26%) had asymptomatic and controlled secondary brain metastases. Pts received a median number of 7 doses (1-45) and had a median follow-up of 6.1 months (0.1-21.9). The disease control rate was 40%, including 3 pts with a complete response, 65 pts with a partial response and 96 with stable disease. Among these pts, 118 were receiving steroid therapy at baseline and 74 received concomitant radiotherapy. As of March 2017, median overall survival of this subpopulation was 8.1 months (6.2-10.1). Overall, among pts with brain metastasis, 337 discontinued treatment for any reason, with only 23 (7%) pts who discontinued treatment due to adverse events, in line with what observed in the general population and in previous studies. **Conclusion:** These data confirmed the activity of nivolumab in patients with non-Sq-NSCLC and brain metastases, supporting the use of nivolumab in this population with poor prognosis. Moreover, as already observed in other tumor types, safety results were consistent to what already reported and confirmed the favorable safety profile.

Keywords: Nivolumab, Brain metastasis, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-054 PD-L1 EXPRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER ACCORDING TO UNDERLYING PULMONARY DISEASE: A RETROSPECTIVE STUDY

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Background: Immune checkpoint inhibitors (ICIs) have good treatment outcomes for non-small cell lung cancer (NSCLC) especially with smoking history. The drug-induced interstitial lung diseases (ILDs) are frequently seen in patients treated with ICIs. The risk assessment for ILDs before ICIs treatment is important, however the pulmonary toxicities of ICIs in patients with smoking related pulmonary diseases such as emphysema and fibrosis are not known. In this study, we retrospectively analyzed PD-L1 expression of NSCLC according to underlying pulmonary disease. **Method:** We tested PD-L1 expressions in NSCLC using 22C3 antibody as tumor proportion score (TPS). We then compared PD-L1 expression TPS according to underlying pulmonary diseases assessed by chest CT (normal, fibrosis, emphysema). **Result:** We reviewed 44 NSCLC patients at NTT Medical Center Tokyo. The median age of all the patients was 71 years (range 46-90). Thirty-eight patients were male (86%). Adenocarcinoma was the most frequent with 26 patients (59%), followed by squamous cell carcinoma with 16 patients (36%). As to PD-L1 expression, 7 patients (16%) were TPS more than 50%, 12 patients (27%) were TPS 1-49% and 22 patients (50%) were TPS less than 1%. Three patients (7%) did not have evaluable material. All the patients with TPS >50% and 1-49% had smoking history. For patients with TPS <1%, there were three patients (14%) without smoking history. As to histology, there were 4 patients (57%) with squamous cell carcinoma for patients with TPS >50%, 4 patients (33%) for TPS 1-49% and 8 patients (36%) for TPS <1%. Among patients with TPS >50%, 2 patients (29%) had emphysema, 5 patients (23%) fibrosis, and no normal lung. Among patients with TPS 1-49%, there were 4 patients (33%) with normal lung, 6 patients (50%) with emphysema and 2 patients (17%) with fibrosis. For patients with TPS <1, there were 9 patients (41%) with normal lung, 10 patients (45%) with emphysema and 2 patients (9%) with fibrosis. **Conclusion:** No patients with normal lungs showed TPS >50%, whereas more than half of patients with TPS <1% had normal lung. Our results show that patients with higher PD-L1 expression has higher rate of underlying pulmonary disease which might be a higher risk for drug-related ILDs. Further treatment strategy is needed for use of ICIs with higher PD-L1 expression with underlying pulmonary diseases.

Keywords: PD-L1, emphysema, fibrosis

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-055 SPECTRUM OF EARLY PROGRESSION IN ADVANCED NSCLC PATIENTS TREATED WITH PD-1 INHIBITORS: IDENTIFYING MARKERS FOR POOR OUTCOME

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Background: While marked responses have been observed in patients with non-small-cell lung cancer (NSCLC) treated with PD-1 pathway inhibitors, anecdotal evidence indicates that rapid progression with dramatic tumor burden increase early in the course of therapy may be noted in a few patients. The study characterized the spectrum of early progression of advanced NSCLC treated with PD-1 inhibitors, and investigated quantitative imaging markers for poorer outcome. **Method:** The study included 134 patients (53 men, 81 women; median age: 66) with advanced NSCLC treated with commercially prescribed single-agent nivolumab or pembrolizumab, who had follow-up CT scans at 8 +/- 2 weeks of therapy. Tumor burden measurements were performed using RECIST1.1 on baseline and 8-week scans to characterize the spectrum of early progression during PD-1 therapy. Tumor burden changes at 8 weeks were studied for association with overall survival (OS), which was measured from the 8-week scan date. **Result:** The tumor burden changes at 8 weeks comparing to baseline ranged from -72.7% to +138.7% (median: +4.3%; the 90th percentile: +50.07%). OS of 15 patients with ≥50% increase of tumor burden at 8 weeks was significantly shorter compared to 119 patients with <50% increase at 8 weeks (median OS: 4.5 months [95%CI: 1.3-4.9] vs. 12.7 months [95%CI: 8.5-14.7]; log-rank p=0.0003). Among 42 patients who experienced tumor burden increase ≥20% (RECIST progression threshold) at 8 weeks, 15 patients with ≥50% increase had shorter OS than 27 patients with ≥20% but <50% increase (median OS: 4.5 months [95%CI: 1.3-4.9] vs. 6.8 months [95%CI: 5.4-20.1]; log-rank p=0.08), indicating that ≥50% increase threshold may identify a distinct group of early progressors with poorer prognosis. Never smokers were more likely to experience ≥50% increase at 8 weeks than former or current smokers (Fisher p=0.03). **Conclusion:** Tumor burden increase of ≥50% at 8 weeks of therapy was associated with significantly shorter OS in advanced NSCLC patients treated with commercial PD-1 inhibitors, indicating that it can serve as an imaging marker to identify a distinct subset of patients with poorer outcome of PD-1 inhibitor therapy, and may thus help guide treatment decisions.

Keywords: PD-1 inhibitor, progression, advanced non-small-cell cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-056 QUALITY OF LIFE AND CLINICAL OUTCOMES OF NIVOLUMAB AS 2+ LINE TREATMENT IN ADVANCED REFRACTORY NSCLC PTS: INTERIM ANALYSIS

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Background: We aimed to evaluate quality of life (QoL) and clinical outcomes of nivolumab (Nivo) as ≥ 2nd line treatment within the expanded access program in NSCLC pts. The QoL changes, response rates, survival and safety were studied within the multicenter prospective observational study. **Method:** Adult pts with advanced refractory NSCLC were enrolled in 7 centers in RF. All the pts received Nivo 3 mg/kg q2w. Tumor response was assessed using RECIST v. 1.1, adverse events (AEs) with NCI CTCAE v3.0; QoL by SF-36 and symptoms by ESAS-R at baseline, 4 and 12 weeks after treatment start. Overall survival (OS) and progression-free survival (PFS) curves were evaluated from the start of Nivo treatment by the Kaplan-Meyer method and compared by the log rank test. For QoL analysis Generalized Estimating Equations

(GEE) method was used. **Result:** The interim analysis was performed in the group of 172 pts with the median follow-up – 4.7 mos (65% – males; median age – 62 (29–80); ECOG PS 0-1/2-3 – 81%/19%; former/current smokers – 71%; non squamous NSCLC – 65%; ≥2 lines of previous treatment – 51%). After 2 cycles of Nivo QoL improvement was registered in 53% pts, after 6 cycles – in 60% pts; mean QoL index increased by 59% and 51%, respectively. Upon GEE, significant improvement of QoL index during 6 cycles was revealed (p<0.05)**.** The most severe and frequent baseline symptoms, fatigue and shortness of breath, decreased after 2 cycles in 44% and 33% of pts as compared to baseline, and after 6 cycles – in 54% and 46% pts, respectively.Efficacy was evaluated in 118 pts (median first evaluation – 2.2 mos): PR – 9%, SD – 44%, PD – 47%. 14 pts died before first efficacy evaluation. 40 pts were not evaluated for response on cut-off. In the group of pts who completed Nivo treatment (n=116) median PFS was 2.7 mos (95%CI 2.1–3.3), median OS – 8.4 mos (95%CI 6.2–10.7); median follow-up – 4.6 mos. Pts with brain mts (median OS 2.5 mos vs 9.0 mos) and pts with ECOG PS 2-3 (median PFS 2.5 mos vs 3.2 mos) had worse survival; p<0.05. AEs were registered in 54 pts; among them 14 had grades 3-4 AEs. **Conclusion:** Early data from this study supports the acceptable efficacy (53% pts had PR/SD) and safety of Nivo (11% pts with 3-4 grades AEs) in NSCLC pts. Nivo treatment leads to meaningful QoL improvement in this patient population.

Keywords: quality of life, advanced refractory non-small cell lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-057 NIVOLUMAB IN PREVIOUSLY TREATED ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Nivolumab, a monoclonal antibody against the Programmed Death 1 (PD-1) pathway, has been shown to improve outcome and safety compared to Docetaxel in second-line NSCLC. We evaluated the actual use of Nivolumab in routine clinical practice at a single center in patients with NSCLC. **Method:** Data from patients with a diagnosis of advanced NSCLC who were treated with Nivolumab at standard dose (3mg/kg every 14 days), between January 2016 and March 2017 in our Hospital, were retrospectively collected. We performed a descriptive analysis of multiple demographic, clinical and analytical variables, as well as seeking differences between progression-free survival (PFS) according to squamous (SqCC) and non-squamous (Non-SqCC) histology, ECOG Performance Status (PS) and prior lines received by log-rank, Kaplan-Meier methods and Cox proportional models. **Result:** Forty patients were treated. Median age was 67; 67.5% were male; 80% were smokers. Histologies: Non-SqCC 42.5%, SqCC 52.5%, 5% NOS. ECOG PS: 50% ECOG 2, 45% ECOG 1, 5% ECOG 0. Twenty patients were treated as second-line (50%), and 20 had received ≥ 2 prior systemic therapies (50%). Median PFS was 3 months. Response rate: 35% (2.5% of patients had complete response); 42.5% of patients had stable disease and 22.5% progression disease. Adverse events were mostly grade 1 and 2, as expected, just one patient discontinued treatment due to grade 4 inmuno-mediated colitis. Patients with SqCC achieved a longer median PFS than Non-SqCC patients (4.9 vs 2.8 months, HR 2.14, 95% CI 1.1-4.6, p <0.05). Median PFS in patients who received 1 prior line was 2 months vs 3.5 months in patients who received ≥2 prior lines (log-rank, p=0.5). PFS in ECOG PS 0-1 patients was 3 months vs 2 months in ECOG PS 2 (log-rank, p=0.2). **Conclusion:** Nivolumab in NSCLC routine clinical practice is a safe and active alternative to chemotherapy. Nivolumab achieve a good outcome in both histologies, SqCC and Non-SqCC, but we detected a longer PFS in SqCC. Adverse events were as expected, grade 1 and 2.

Keywords: anti PD-1, Nivolumab, Non-small-cell lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-058 REAL WORLD DATA WITH NIVOLUMAB: EXPERIENCE IN ARGENTINA

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Background: Nivolumab has improved overall survival (OS) in metastatic non-small cell lung cancer (NSCLC) patients. Analysis of the use of these drugs in real world provides more evidence about efficacy and toxicity. We describe here the experience of the use of nivolumab in NSCLC in Argentina. **Method:** NSCLC patients (pts) who received nivolumab between 6/2015 - 12/2016. Patients consented their respective physicians to be treated on a drug expanded access program. Data was collected retrospectively by the physician. Images and follow up were done according to physician´s discretion. Adverse events were classified according to CTC3.1. Responses were evaluated according to RECIST 1.1 criteria. DFS and OS was assessed. All pts who received at least one dose of Nivolumab were evaluated for toxicity. **Result:** N 109. Fup 8.83 m (IQR 3.4-12.67). 57.8% men, 29.4% current smoker, 78.0% non-squamous, 8.3% EGFR mutated. Chemotherapy lines before nivolumab 2 md (r 1-4), and 59.6% received radiotherapy. 89% received previously platinum based chemotherapy. Sites of relapse or progression before nivolumab were: lung (75.2%), lymph nodes (47.7%), bone (19.3%), liver (11.9%), central nervous system (11.0%), and adrenal gland (13.8%). PS 0 26.6%, 1 56.0%, 2 13.8% and 3 1.8%. Cycles of nivolumab 10 Md (IQR 3-18). Drug related toxicity 78.9%. Grade 2-3 28.4%. Corticoid use 33.9%. Responses were evaluated in 104 pts who had as best response CR 2/104 (2%), PR 28/104 (27. %), SD 33/104 (32%) and PD 41/104 (39.%). Time to the best response was 4.0 m (IQR 2.3-5.9). DFS 6.1 m (IQR 2.4-13.1) and OS 12.3 m (IQR 4.1-NR). Univariate analysis revealed that absence of corticoids use (p=0.034), toxicity grade 1-3 (p=0.0025), PS≤1 (p=0.049), age<=50 (p= 0.0011) were associated with longer DFS; PS≤1 (p<0.001) and toxicity grade 1-3 (p=0.001) were associated with longer OS. In multivariate cox regression analysis, toxicity grade 1-3 (HR 0.44 CI95% 0.24-0.81, p=0.008) and age<=50 (HR 0.28 CI95% 0.13-0.61, p=0.001) were associated with longer DFS while corticoids use was associated with shorter DFS (HR 2.06 CI95% 1.22-3.48, p=0.007); toxicity grade 1-3 (HR 0.28 CI95% 0.14-0.54, p<0.0001) and PS≤1 (HR 0.16 CI95% 0.08-0.31, p<0.0001) were associated with longer OS. **Conclusion:** The use of Nivolumab in a real world setting, in heavily pre-treated NSCLC patients was well tolerated and showed promising clinical efficacy. PS, the use of corticoids and immune-mediated toxicity seem to be conditions which could affect clinical outcomes.

Keywords: Nivolumab Argentina

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-059 COMBINATION PEMBROLIZUMAB AND LOW DOSE WEEKLY CARBOPLATIN/PACLITAXEL FOR PATIENTS WITH RECURRENT/ METASTATIC NSCLC AND PS OF 2

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Background: Chemotherapy and immunotherapy have been shown to be beneficial for patients with non-small cell lung cancer (NSCLC) and performance status (PS) of 0 or 1; there still is debate, however, regarding its efficacy for patients with a PS of 2 which comprises approximately 30% of the NSCLC population. Pre-clinical data have demonstrated that low dose carboplatin/paclitaxel have resulted in superior immune efficacy compared to the maximum tolerated dose regimen. Given the significant unmet need for treatment options in this patient population, our study evaluated low-dose weekly carboplatin/paclitaxel combined with pembrolizumab in patients with NSCLC and a PS of 2. **Method:** Patients with metastatic or recurrent NSCLC and PS of 2 were randomized to single agent pembrolizumab at 200mg every 3 weeks or pembrolizumab plus weekly carboplatin AUC 1 and paclitaxel 25 mg/m^2 irrespective to PDL-1 status. Response was determined using immune-related RECIST, and toxicity was graded using CTCAE 4.0. **Result:** Between 6/2016 and 2/2017, 20 patients were enrolled, and 19 patients were evaluable for response. The median age was 69 years (54-83). All 19 patients (100%) had a PS of 2. Ten patients were randomized to the single agent arm and 9 patients to the combination arm. Six patients received the therapy as second line (2 combination arm and 4 single agent arm). Mean 3 week cycles per patient: 9 (4-16) in combination arm and 7 (2-14) in single arm group. Response at 9 weeks in the combination arm: partial response (PR) 6 (67%), stable disease (SD) 2 (22%), and progressive disease (PD) 1 (11%). Response at 9 weeks in the single agent arm, PR 2 (20%), SD 4 (40%), and PD 4 (40%). Adverse events in combination arm: 1 (11%) discontinued therapy due to grade 3 fatigue, 3 (33%) discontinued carboplatin due to allergic reactions at 7, 9, and 10 months of treatment but continued pembrolizumab and paclitaxel, and 1 (11%) on hormone replacement therapy due to treatment-induced hypothyroidism. Adverse events in single agent arm: 1 (10%) discontinued treatment due to complete A-V block successfully resolved with pacemaker insertion, and 2 (20%) are on hormone replacement therapy due to treatment-induced hypothyroidism. **Conclusion:** Combination pembrolizumab and weekly low dose carboplatin/paclitaxel is an active and well tolerated regimen in patients with advanced NSCLC with PS of 2.

Keywords: NSCLC, poor performance status, Immunotherapy

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-060 NIVOLUMAB AFTER PROGRESSION TO PLATINUM- BASED CHEMOTHERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: In patients with advanced non–small-cell lung cancer (NSCLC), docetaxel has been established as the second line of treatment after progression to platinum-based regimens. Following the results of the CheckMate 017 and 057 studies, Nivolumab, an anti-PD-1, has been second in line approved. This has increased overall survival in comparison with Docetaxel. This paper analyzes the experience with Nivolumab in second and successive lines of advanced NSCLC within the service of Medical Oncology from the Complejo Asistencial Universitario of León, Spain. **Method:** 25 patients diagnosed with advanced NSCLC were included in the period from July 2015 to November 2016. The clinical-pathological characteristics, efficacy, objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), and safety were analyzed. The dose of Nivolumab used was 3 mg/kg every 15 days. **Result:** The median age was 64 years old. All subjects had an ECOG performance status <2. 84% had stage IV cancer. 96% were current smokers or former smokers, in the same proportion (Table 1). 72% received a single pre-treatment line. A median of 7 cycles were administered (range: 2-28). The ORR was 28% (CR 4%, PR 24%) with a disease control rate of 44%. The median DOR was not reached at the time of analysis (range: 2.5+ - 10.4+ months). The median PFS was 5.4 months (95% CI 4.86-6). The rate of immune-related adverse events (IR-AE) of any grade was 36%, with endocrinopathies (hypothyroidism and hyperthyroidism) being the most common IR-AE (24%). The rate of IR-AE G3 was 8% (1 patient pneumonitis, 1 patient hepatotoxicity). There were no toxic deaths.

Table 1: Baseline clinical-pathological characteristics	
Age (years)	
Median	64
Rank	43-80
Age ≥ 75 years, n (%)	2 (8%)
Sex, no (%):	
Male sex	20 (80%)
Female sex	5 (20%)
Smoking status, no (%)	
Current smoker	12 (48%)
Former smoker	12 (48%)
Never smoked	1(4%)
ECOG performance status score, no (%)	
0	19 (76%)
1	6 (24%)
Histology of the tumor, no (%)	
Adenocarcinoma	11 (44%)
Squamous carcinoma	12 (48%)
NOS	2 (8%)
Disease stage, no (%)	
IIIA	3 (12%)
IIIB	1 (4%)
IV	21 (84%)
Positive EGFR mutation status, no (%)	1 (4%)
Positive KRAS mutation status, no (%)	2 (8%)
Number of prior therapies, no (%):	
1	18 (72%)
≥2	7 (28%)
Type of prior systemic therapies, no (%):	
Platinum-based regimen	17 (68%)
Taxanes	3 (12%)
Others	1 (4%)
Best response to most recent prior systemic regimen according to the investigator: no (%)	
Complete response	1 (4%)
Partial response	11 (44%)
Stable disease	10 (40%)
Progressive disease	3 (12%)

Conclusion: Nivolumab represents a standard of treatment in advanced NSCLC. Its results of efficacy and safety in this retrospective real-time observational analysis (RWD), with 25 consecutive patients,are consistent with published studies. More patients and extended follow-up are required to draw more precise conclusions.

Keywords: lung cancer, Nivolumab

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-061 THE EFFICACY AND SAFETY OF ANTI-PD-1 IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER (NSCLC): SYSTEMATIC REVIEW

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Background: Non-small cell lung cancer (NSCLC) patients treated with standard chemotherapies experience progression rapidly. A novel therapy based on programed death 1 (PD-1) inhibitors showed an increasing potential in several malignancies including advanced NSCLC.This article is a meta-analysis aiming to systematically evaluate the efficacy and safety profiles of PD-1 agents in patients with NSCLC. **Method:** Data sources: Data were collected from eligible studies searched from PubMed, Embase, and Cochrane. Synthesis methods: Pooled hazard ratio (HR) for overall survival (OS) and progression-free survival (PFS) was estimated to assess the efficacy of PD-1 inhibitors versus docetaxel, pooled odds ratio (OR) was calculated for objective response rate (ORR). OR for occurrence of any grade and grade 3 to 5 treatment related adverse effect was calculated for evaluating the safety of PD-1 therapies. **Result:** Five studies were included in this analysis. The pooled HRs for OS and PFS were 0.66 (95% CI 0.60–0.74; P<0.00001) and 0.78 (95% CI 0.71–0.86; P<0.00001) respectively, the pooled OR for ORR was 2.12 (95% CI 1.50–2.98; P<0.0001), indicating a significant improvement in OS, PFS, and ORR. OR for occurrence was 0.78 (95% CI 0.63–0.96; P=0.02) in any grade treatment-related adverse effect and 0.27(95% CI 0.23–0.33; P<0.00001) in grade 3 to 5 treatment-related adverse effect, suggesting a superior safety profile of PD-1 inhibitors. **Conclusion:** The anti-PD-1 therapy can significantly prolonge the OS,PFS,improve the ORR and can also reduce the treatment-related adverse effect events versus standard chemotherapies.

Keywords: non-small cell lung cancer, Anti-PD-1, PD-1

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-062 KRAS MUTATIONS (KRAS-MUT) AND ANTIPD1/PDL1 THERAPY IN A COHORT OF LUNG CANCER (LC) PATIENTS (P). EXPERIENCE FROM A SINGLE INSTITUTION

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Background: AntiPD1/antiPDL1-based immunotherapy has changed dramatically the prognosis of LC p with a substantial improvement of overall survival (OS) and even presenting long lasting responses in a subset of p. Several factors have been associated with the likelihood of better survival, which include the smoking exposure and the presence of KRAS-mut according to data from randomized clinical trials that compared chemotherapy to these immunotherapeutic agents. **Method:** By reviewing the clinical records of all stage IV LC p treated with antiPD1/antiPDL1 agents, we identified p with KRAS-mut and evaluated their clinical outocomes. **Result:** 129 p with advanced NSCLC were treated with nivolumab, pembrolizumab or atezolizumab (65.1%, 17.1% and 17.8 %, respectively) from November 2013 to April 2017. 14 p were identified as adenocarcinomas with KRAS-mut (20.3%) of all non-squamous NSCLC (60p), once squamous cell carcinoma (39 p), p with Kras status unknown (15p), other reasons (6p) were excluded. KRAS-mut subgroup include 28.5% of female, median (m) age of 62.3 years, 92.8% of ever smokers, and PS0-1. The immunotherapy consisted of nivolumab (71.4%) and pembrolizumab and atezolizumab (14.3% each) and was administered as 1st, 2nd and ≥3rd therapy in 7.1,78.6 and 14.3% of p, respectively. 71.4% of p responded to therapy (64.3% partial response) and in 42.8% of p this response lasted ≥12 months (range 12-32). For this cohort of p m progression-free survival was 7.65 months and OS was 58 months. At the time of analysis 57.1% were still receiving treatment. **Conclusion:** Although the number of p is small, KRAS-mut p represent a subgroup of p that seem to substantially benefit from antiPD1/PDL1 agents in terms of both response and survival.

Keywords: antiPD1/PDL1, KRAS mutations

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-063 ARE THE REAL WORLD PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER REPRESENTED IN PHASE III IMMUNOTHERAPY TRIALS?

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Background: Several randomized phase III trials with immune checkpoints inhibitors have accrued patients with metastatic non-small cell lung cancer (NSCLC). These trials employed strict patient selection criteria, and it is currently unknown how it represents the 'real-world' population. **Method:** From January 2011 to December 2016, all patients with metastatic NSCLC referred for first oncological evaluation at two University Hospitals in South of Brazil were identified by electronic database and included in the analysis. Twelve pre-defined eligibility criteria, all used in the recent first line phase III immunotherapy trial, were analyzed. OS and PFS were estimated by Kaplan-Meier curves. Multivariate analysis was performed to identify factors associated with survival. Statistical analysis was performed with SPSS 22.0. **Result:** Three hundred and nine patients were collected for this analysis. Patient characteristics revealed a mean age of 63.73 ± 09.47 years, 56% male and 65% had adenocarcinoma. One hundred ninety-seven (64%) patients did not meet one or more eligible criteria at first evaluation. ECOG performance status ≥2 (118 patients) and active brain metastasis (69 patients) accounted alone for 79.7% of non-eligibility cases. One hundred (50.76%), 53 (26.9%), 30 (15.22%) and 14 (7.1%) had 1, 2, 3 or 4 non-eligible criteria respectively. The median survival after the diagnosis of metastatic disease was 6.34 (95% IC, 5.59 to 7.08) months in the non-eligible group

and 11.07 (95% IC, 8.65 to 13.48; p<0.001) in the eligible group. The hazard ratio of 1.90 (95% IC, 1.46 to 2.47) to mortality in the non-eligible group should reflect the worse baseline prognostic features in this group. **Conclusion:** To our knowledge, this is the first report of metastatic NSCLC patients analyzed regarding the eligible criteria of the phase III trials. It is clear that clinical trials do not represent the "real world" population and its outcomes have an important selection bias. Phase III clinical trials eligibility criteria should be reviewed to better represent the NSCLC population.

Keywords: clinical trial eligibility, metastatic non-small cell lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-064 EFFICACY AND TOLERABILITY OF NIVOLUMAB IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors are a novel group of immunotherapeutic agents. Antibodies to programmed death-1 (PD-1), such as nivolumab, have shown promising clinical activity in patients with advanced non-small-cell lung cancer (NSCLC), but their efficacy and safety in elderly patients with advanced NSCLC are unclear, because available major clinical trials involved a small number of elderly patients. **Method:** A total of 34 patients received nivolumab for advanced NSCLC from February 2016 to June 2017 in our hospital. We retrospectively reviewed the clinical medical records of these patients. They were divided into two groups; patients aged > 70 and < 70 years. Overall response rates (ORR), progression-free survival (PFS), major adverse effects and discontinuation rate due to adverse effects were compared between in two groups. **Result:** All of them were included in this study (median age was 64 years). Almost all patients had been previously treated with cytotoxic chemotherapy. They included 10 patients in aged > 70 years and 24 patients in aged < 70 years. There was no significant difference in histological type, performance status (PS), smoking history, line of therapy, and laboratory data between the two groups. Comparison between patients aged > 70 years and aged < 70 years in advanced NSCLC shows no statistically significant difference in median PFS (140 vs. 128, HR: 0.96, 95 % CI, 0.37-2.46, p = 0.93), ORR (40 % vs. 32 %, p = 0.70). The treatment was discontinued in 40 % (4/10) and 13 % (3/24) owing to adverse effect; however, there was no significant difference in two groups, and there was no adverse effect death in both groups. **Conclusion:** Nivolumab is tolerable and effective treatment for elderly patients with advanced NSCLC.

Keywords: Nivolumab, Elderly patients

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-065 TREATMENT BEYOND PROGRESSION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED NON-SQUAMOUS NSCLC: RESULTS FROM THE ITALIAN EXPANDED ACCESS PROGRAM

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Background: Because of the novel mechanism of action of immunotherapies like nivolumab, response patterns may differ from other therapies and may provide a rationale for considering treatment beyond progression. Immunotherapy protocols generally allow patients (pts) to continue treatment beyond investigator-assessed progressive disease (PD) as long as there is ongoing clinical benefit. Here we report the analysis of pts treated beyond PD in the Italian nivolumab EAP for pts with non-squamous non small cell lung cancer (Non-Sq-NSCLC). **Method:** Nivolumab was provided upon physicians' request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months. Pts included in the analysis received ≥1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events. Patients were allowed to continue treatment beyond initial PD as long as they met the following criteria: investigator-assessed clinical benefit, absence of rapid PD, tolerance of program drug, stable performance status and no delay of an imminent intervention to prevent serious complications of PD. **Result:** In total, 1588 Italian pts with advanced Non-Sq-NSCLC received at least one dose of nivolumab in the EAP across 168 sites and 1056 (66%) had PD. Of those, 274 pts (26%) were treated beyond progression. Before being treated beyond PD, the disease control rates (DCR) was 28%, with 1 complete response (CR), 27 partial responses (PR) and 49 stable diseases (SD). Post PD, 58 of all pts treated beyond PD achieved a non-conventional benefit, meaning a subsequent tumor reduction or stabilization in tumor lesions. With a median follow-up of 10.3 months (0.1-21.9) and a median of 11 (4-44) doses, median overall survival for pts treated beyond PD was 15.5 months (range: 13.1-17.9). Overall, among pts treated beyond PD, 200 discontinued treatment for any reason, with only 11 (5.5%) pts who discontinued treatment due to adverse events, suggesting no increased safety signals. **Conclusion:** As already observed in clinical trials, these preliminary EAP data seem to confirm that a proportion of pts who continued treatment beyond PD demonstrated sustained reductions or stabilization of tumor burden, with an acceptable safety profile. Further investigations are warranted in order to better define and identify pts who can benefit from this treatment strategy.

Keywords: Advanced non small cell lung cancer, progressive disease, Nivolumab

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-066 PDL-1 EXPRESSION OF TUMOR CELL, MACROPHAGE, AND IMMUNE CELLS ON PLEURAL EFFUSION

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Background: Immune checkpoint inhibitors provide a new treatment strategy for lung cancer. Therefore, microenvironment of tumor and interaction between immune cells and tumor cells become more important. Until now, the most frequently used marker to predict treatment response is immunohistochemical (IHC) stain of tumor PD-L1. However, the microenvironment of malignant pleural effusion is not clear. Weather we could use IHC stain of PD-L1 on cells of pleural effusion to predict treatment response have not been studied, either. **Method:** We retrospective enrolled patients who received malignant pleural effusion drainage and had cell blocks specimens from 2014-2016. IHC stain for PD-L1 was performed for tumor cells, immune cells, and macrophage of all cell block specimens. An experienced pathologist reviewed all the cell block cytology. The intensity of IHC stain was graded into grade 0, 1, 2, and 3. We also collected the clinicopathological characteristics of all patients. **Result:** PD-L1 expression of pleural effusion tumor cells was associated with the PD-L1 expression of pleural effusion macrophage (p=0.003) and immune cells (p<0.001). However, PD-L1 expression of immune cells is not associated with that of macrophages. PD-L1 expression of tumor cells is correlated with gender (p=0.012), smoking status (p=0.032), and ECOG performance status (p=0.017). Finally, PD-L1 expression of immune cells was associated with overall survival of our patients (p=0.004). **Conclusion:** These results suggested that there might be an immune interaction of pleural effusion tumor cells with macrophage/immune cells, and low expression of PDL1 expression of immune cell are associated with poor survival of lung cancer patients with malignant pleural effusion.

Keywords: PD-L1, malignant pleural effusion, lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-067 CHARACTERISTICS AND SURVIVAL RATE OF NON-SMALL CELL LUNG CANCER IN PATIENTS 45 YEARS OF AGE OR YOUNGER

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Background: Lung cancer in younger patients (45 years of age and younger) is rarely found and has different characteristics with older patients. In this study we are looking for characteristics and survival rate of younger NSCLC patients at Indonesia. **Method:** NSCLC patients that came to Dharmais Cancer Center during January 2005 – December 2015 aged 45 years or younger were included in this study. We analyzed patients' age, gender, history of smoking, histology type, stage, therapy and survival rate. **Result:** Out of 956 NSCLC patients, there were 134 young patients (13.9%). Median age of patient is 39 years old. The most common range of age is 41-45 years old (n=57, 42.5%) with more male patients compared to female patients (n=92, 68.7%). 108 young NSCLC patients (80.6%) did not have history of smoking. Adenocarcinoma is the most common histology type found (59%) and stage IV (52.2%) is most frequent in this study. There is no significant difference between gender and diagnosis (p=0.737), stage (p=0.170), history of smoking and type of histology (p=0.534) in younger NSCLC patients. Median survival rate of the younger patients is 12.2 months (95% CI: 11.045 – 13.355), compared with older patients being 13.2 months (95% CI: 11.547 – 14.853). There is no significant difference between survival rate of younger NSCLC patients and older patients (p=0.543). Patients with EGFR mutation does not have significant association with gender (p=0.07), history of smoking (p=0.259), amount of cigarettes per day (p=0.942), and Brinkman Index (p=0.366). There is a significant difference of survival rate between patients who have EGFR mutation and those who do not (27.4 months VS. 12.2 months; p=0.05). There is no significant difference between patients with EGFR mutation who received target therapy and those who did not (p=0.426). However, there is a significant difference between patients without EGFR mutation who received chemotherapy and those who did not (15.2 months vs. 11.5 months, p=0.05). **Conclusion:** NSCLC in younger patients

have shorter survival rate compared with older patients. Survival rate in patients with EGFR mutation who received chemotherapy is better.

Keywords: NSCLC, survival, lung cancer

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-068 IMPACT OF CASE-BASED CME ON PHYSICIAN PERFORMANCE IN THE DIAGNOSIS AND MANAGEMENT OF NSCLC

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Background: Lung cancer is the leading cause of cancer-related mortality in the United States. Over the last decade an improved understanding of the pathways that drive malignancy and disease progression have fundamentally altered the NSCLC treatment paradigm. We sought to determine if participating in a case-based online educational intervention related to NSCLC diagnosis and management improved the clinical decision-making of oncologists and pathologists in the US. **Method:** Oncologists participated in an innovative online CME activity using branching logic that assessed clinical decisions in management of patients with NSCLC and provided tailored feedback. Two patient cases were presented and clinicians were assessed on answers to multiple-choice questions pre- and post-education. If first attempt answers were incorrect, clinicians received feedback and clinical consequences for their choices, and provided a second opportunity to answer. The CME activity launched May 5, 2016 and data were collected through June 6, 2016. **Result:** For oncologists (n=149), between 52% and 70% answered clinical decision questions correctly on the first attempt, while 27% to 94% of pathologists (n=44), answered correctly . After consequence-based feedback, between 12% and 41% of both oncologists and pathologists improved their decision-making. Specific improvements seen include: 20% oncologists and 23% pathologists increased their ability to identify the need to order IHC staining to identify the tumor's histopathology 23% more oncologists and 29% more pathologists selected the most appropriate regimen for a patient with adenocarcinoma without actionable mutations after 30% of oncologists and 41% pathologists increased in their ability to select the most appropriate therapy for a patient who has progressed on a first-line regimen based on prior treatment and the PD-L1 status of their tumor **Conclusion:** This innovative, case-based CME activity using branching logic with tailored consequence-based feedback improved clinical decision-making in management of patients with NSCLC to drive learning. It is anticipated that improved clinical decisions among oncologists and pathologists in diagnosis and management of NSCLC will lead to translation in practice and better patient outcomes. Future education using a similar design could be used to translate ongoing developments in NSCLC into clinical decisions for comprehensive management of NSCLC.

Keywords: pan-negative, NSCLC, Education

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-069 CLINICAL EXPERIENCE WITH IBM WATSON FOR ONCOLOGY (WFO) COGNITIVE SYSTEM FOR LUNG CANCER TREATMENT IN CHINA

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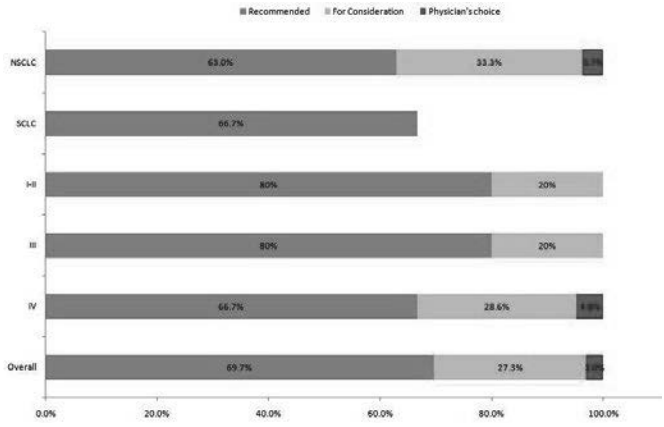
Background: IBM Watson for Oncology (WFO) is a Memorial Sloan Kettering-trained cognitive computing system. Watson provides evidence-based treatment options and ranks them into three categories for oncologist decision making as "Recommended "."For Consideration" and "Not Recommended". We examined the concordance of treatment options in Lung cancer patients between WFO and tumor board in the Affiliated Hospital of Qingdao University, China. **Method:** 33patients with stage I-IV lung cancer were enrolled in this study. By tumor stage, 15.1% (5 of 33) patients are Phase I or II, 15.1% (5 of 33) are Phase III and the rest of the patients (23 of 33) are Phase IV. By histology, 18.2% (6 of 33) are small cell lung cancer (SCLC) and 81.8% (27 of 33) are non-small cell lung cancer (NSCLC). Options were considered concordant when it was included in the "Recommended" or "For Consideration" categories. **Result:** Overall, treatment recommendations were concordant in 96.9% (32 of 33) of cases. By histology, 100% of SCLC patients' therapy regimes were concordant with the recommended one, and treatment recommendations were concordant in 96.3% of NSCLC patients. By tumor stage, treatment recommendations were concordant in 100% of I- III and 96% of Phase IV lung cancer. Of the whole cases, 69.7% were recommended and 27.3% were for consideration (figure1). The majority reason for choosing consideration option is that the immunotherapy drugs targeted PD-1 or PD-L1 such as Nivolumab, Pembrolizumab and Atezolizumab recommended by Watson for Oncology had not been launched in China.



Conclusion: Treatment recommendations made by the Affiliated Hospital of Qingdao University and Watson for Oncology were highly concordant in lung cancer. We'll make further analysis for this cognitive computing system in more cases and other types of carcinomas.

Keywords: WFO cognitive system; concordance; China

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-070 BIW-8962, AN ANTI-GM2 GANGLIOSIDE MONOCLONAL ANTIBODY, IN ADVANCED/RECURRENT LUNG CANCER: A PHASE I/II STUDY

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Background: GM2 ganglioside is a tumor-associated antigen that is overexpressed in a high proportion of several malignancies, e.g. SCLC, NSCLC, mesothelioma, melanoma, neuroblastoma, multiple myeloma. BIW-8962 is a recombinant, humanized, non-fucosylated immunoglobulin G1 monoclonal antibody to GM2 ganglioside that shows pre-clinical activity towards lung cancer cell lines and in an animal model bearing SCLC xenografts. The aim of this study was to determine the safety and preliminary clinical efficacy of BIW-8962 administered as monotherapy in patients with previously treated lung cancer. **Method:** In phase I, patients (N=16) with advanced, recurrent lung cancer (8 each with SCLC and NSCLC) received increasing doses of BIW-8962 (1–10 mg/kg) intravenously every 3 weeks using a standard 3+3 design to determine the maximum tolerated dose (MTD). The highest dose (10 mg/kg) was administered to patients with advanced, recurrent SCLC (N=21) in phase II. **Result:** It was only possible to obtain pre-study biopsy samples for two patients, both of which showed cell surface GM2 overexpression of moderate intensity on immunohistochemistry testing. In phase I and II, all patients received the total planned dose. There were no dose-limiting toxicities in phase I and the MTD was not established. BIW-8982 10 mg/kg therefore used as the recommended phase II dose. The phase II study was prematurely terminated due to lack of efficacy. The objective response rate was 5.0% (95% CI, 0.1%–24.9%) in the efficacy evaluable population (N=20). Median overall survival was 304.0 days (95% CI, 70.0–406 days) and median progression free survival (PFS) was 43.0 days (95% CI, 38.0–43.0 days). One patient showed a durable partial response with PFS of 463 days and response duration of 382 days. There were a few patients with stable disease, which was generally not durable. No pattern of consistent toxicity was observed across the phases: there were no treatment-related adverse events (AEs) Grade ≥3, serious AEs, AEs leading to discontinuation of BIW-8962, or deaths. No unexpected trends or safety concerns were identified from laboratory parameter, vital sign, or electrocardiogram assessments. Anti-BIW-8962 antibodies were not detected in serum of any patient before or following treatment. Exploratory analysis of circulating tumor cells and other potentially predictive or pharmacodynamic markers did not reveal any results consistent with an effect from BIW-8962. **Conclusion:** This study was prematurely terminated due to lack of efficacy, for which the reason is unknown. Clinical development of BIW-8962 has been discontinued.

Keywords: BIW-8962, anti-GM2 ganglioside monoclonal antibody, advanced/recurrent lung cancer

P1.01-071 HIGH DOSE IVAA SYNERGY WITH MEHT IN PATIENTS WITH STAGE III-IV NSCLC: A PHASE I STUDY

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Background: Ascorbic acid (AA) infusion and modulated electrohyperthermia (mEHT) are widely used by integrative cancer practitioners for many years. However, there are no sufficient data in safety, quality of life and clinical response of the above treatments in patients with stage III-IV Non-Small Cell Lung Cancer (NSCLC).We designed a Phase I trial to provide the evidence. **Method:** Blood ascorbic acid in the fasting state was obtained from 35 NSCLC patients; selecting from them 15 patients with stage III-IV entered the phase I -II study. They were randomized allocated into 3 groups, and received doses 1.0, 1.2, 1.5g/kgAA infusions. Pharmacokinetic profiles were obtained when they received solely IVAA at concentrations of 1g/kg, 1.2g/kg, and 1.5g/kg, and when IVAA in combination with mEHT. The process was applied 3 times a week (every other day, weekend days off) for 8 weeks. Participants in the first group received intravenous AA (IVAA) when mEHT was finished, in the second group IVAA was administered simultaneously with mEHT and in the third group IVAA was applied first, and followed with mEHT. DLT was defined as any reversible grade ≥3 adverse events, whether haematological or non-haematological. CT enhanced scan were collected from the patients before the treatment and one month after the treatment finished. **Result:** Fasting plasma AA levels were significantly correlated with stage of the disease. The overall toxicity was marginal.Thirstiness was the major symptom during all of the treatments.Peak concentration of AA were significantly higher in the simultaneous treatments than in other combinations with mEHT or in solely IV AA-managed groups. The average scores for the functioning scales continuously increased and the symptoms gradually decrease over the full cycle of the study.By using RECIST 1.1 criteria, two of four subjects diagnosed with lung squamous cell carcinoma had partial response (PR), two of four had stable disease(SD). Two of ten patients diagnosed with lung adenocarcinomahad had PR, three of ten had SD, five of ten had progressive disease. **Conclusion:** IVAA synergies with simultaneous mEHT were safe and can be well tolerated in patients. Patients diagnosed with squamous cell lung cancer were sensitive to the above two treatments.There's a need for a phase II study with advanced NSCLC patients administering mEHT simultaneously with IVAA to assess for the efficacy and progression free survival time.

Keywords: stage III-IV NSCLC, Ascorbic acid, mEHT

P1.01-072 EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT) IN LUNG CANCER: CLASSIC REPRODUCTION

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Background: Lung cancer is the one of the highest incidence and fatality disease in the world wide. Although several of treatments have been found such as chemotherapy, radiotherapy and target therapy, lung cancer treatments remain many obstacles, for instance, drug resistant and gene mutant. **Method:** Epithelial-to-mesenchymal transition (EMT) process is a traditional pathway in cells program, during this process cells loss epithelial marker and acquire mesenchymal characteristic. EMT associates with cancer cell migration and invasion, more EMT process predicts poor prognosis and the resistant to chemotherapy even target treatment. More therapy target to EMT process such as some markers or signaling pathway. In this review, we discussed the new relationship of EMT and lung cancer. Some compounds which inhibited cancer cells acted with regulator of EMT or EMT process. Recent years, the target treatment and even the immune therapy were appeared in National Comprehensive Cancer Network guideline. **Result:** The effective treatment of lung cancer is correlated with EMT process. In vivo and in vitro research showed that occurrence of EMT process predicted poor prognosis and treatment failure in target and immune therapy. **Conclusion:** With the development of lung cancer treatment, EMT process may become a key research target.

Keywords: Epithelial-to-mesenchymal transition, lung cancer

P1.01-073 OVER-EXPRESSION OF GGPPS CONTRIBUTES TO TUMOR METASTASIS AND CORRELATES WITH POOR PROGNOSIS OF LUNG ADENOCARCINOMA

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Background: This study aimed to evaluate the biological role of geranylgeranyl diphosphate synthase (GGPPS) in the progression of lung adenocarcinoma **Method:** GGPPS expression was detected in lung adenocarcinoma tissues by qRT-PCR, tissue microarray (TMA), and western blotting. The relationship between GGPPS expression and the clinicopathological characteristics and prognosis of lung adenocarcinoma patients was assessed. GGPPS was downregulated in SPCA-1, PC9, and A549 cells, using siRNA, and upregulated in A549 cells, using an adenoviral vector. The biological role of GGPPS in cell proliferation, apoptosis, migration, and invasion was determined by MTT and colony formation assays, flow cytometry, and transwell and wound-healing assays, respectively. In addition, the regulatory role of GGPPS on the expression of several EMT markers was determined **Result:** GGPPS expression was significantly increased in lung adenocarcinoma tissues compared to that in adjacent normal tissues. Over-expression of GGPPS correlated with patients with large tumors, high TNM stage, lymph node metastasis and poor prognosis. Knockdown of GGPPS inhibited migration and invasion of lung adenocarcinoma cells, but did not affect cell proliferation and apoptosis. Meanwhile, GGPPS inhibition significantly increased the expression of E-cadherin, and reduced the expression of N-cadherin and vimentin in lung adenocarcinoma cells **Conclusion:** Over-expression of GGPPS correlates with poor prognosis of lung adenocarcinoma, and contributes to metastasis through the regulation of EMT

Keywords: EMT, GGPPS, lung adenocarcinoma, prognosis, metastasis

P1.01-074 EXOSOMAL RNA-PROFILING OF LUNG PLEURAL EFFUSIONS IDENTIFIES ADENOCARCINOMA PATIENTS THROUGH ELEVATED MIR-200 EXPRESSION

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Background: The inherent challenges associated with lung tissue biopsies have spurred an enormous interest in the use of liquid biopsies. Pleural effusions are one such liquid biopsy which may enable lung cancer profiling and also assess if the patient suffers from a benign or malignant process in the lungs. Recently extracellular vesicles of endocytic origin, exosomes, have attracted interest as liquid biopsy of tumors since they can be used to look at tumor derived mutations as well as tumor cell activity represented by the RNA transcriptome. The RNA cargo carried in exosomes is known to resemble the RNA profile of the primary tumor. Here we aimed to analyze if microRNA and targeted cancer mRNA profiling of exosomes isolated from pleural effusions could decipher biomarkers associated with lung adenocarcinoma. **Method:** A systematic microRNA profiling of matured processed microRNAs along with targeted cancer mRNA profiling was carried out on extracellular vesicles, including exosomes, derived from 36 clinical pleural effusions, separated into 18 benign and 18 lung adenocarcinoma samples. Benign pleural effusion consisted of unspecific inflammation in the majority of cases. The two groups were well balanced with respect to age (median = 72Y) and smoking history (ever smokers in circa 70% of cases). However, males were overrepresented in the benign group (83% vs 44%). Both microRNA and mRNA profiling was conducted using TaqMan RT-qPCR Open Arrays (containing 800 genes each) followed by statistical ranking (Wilcoxon test) of differentially regulated transcripts between the two patient groups. **Result:** Systematic RNA profiling revealed a substantial, and highly significant ($p<0.0001$), elevated expression of all members from the extended miR-200 family in pleural effusions collected from patients with NSCLC adenocarcinoma. By cross-analyzing the obtained microRNA profiling data to the mRNA cancer panel expression, statistical enrichment between miR-200 family members and predicted miR-200 target genes, including *PIK3CA*, *NOTCH1* and *KRAS* was observed (Fisher's exact test, $p=0.0105$). **Conclusion:** Our study demonstrates the usage of exosomal RNA profiling from pleural effusions to define patients with lung adenocarcinoma and further highlights miR-200 microRNAs as diagnostic markers in lung cancer liquid biopsies. Acknowledgment: This study was supported from the following funding bodies: Swedish Cancer Society, Stockholm Cancer Society, Stockholm County Council, Knut and Alice Wallenberg Foundation and Erling Persson Family Foundation.

Keywords: pleural effusions, lung adenocarcinomas, MicroRNAs

P1.01-075 SIMULTANEOUS MULTIPLEX PROFILING OF GENE FUSIONS, METE14 MUTATIONS AND IMMUNE GENES IN ADVANCED NSCLC BY NCOUNTER TECHNOLOGY

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Background: Assessment of several immune-genes and tumor drivers is critical

for individualized treatment of non-small cell lung cancer (NSCLC). We have previously demonstrated the ability of the transcript-based nCounter Technology for the detection of *ALK, ROS1* and RET gene fusions, using a customized codeset (Reguart *et al*. Clinical Chemistry 2017). Here, we present the first results of the validation in advanced NSCLC samples of a new CodeSet designed to simultaneously characterize clinically relevant gene fusions, *MET* alterations and the expression of immune genes. **Method:** We have designed an in-house custom set to detect driver fusions involving 4 genes (*ALK, ROS, RET, NTRK*), *MET* exon 14 skipping mutation, *MET* overexpression and immune genes (*PD1, PDL-1, CD4, CD8, FOXP3, GZMM, IFNG*). A panel of *ALK-ROS-RET-NTRK* positive cell lines (H2228, H3122, SU-DHL-1, HCC78, BaF3 pBABE, LC2/ad and a *NTRK*-positive cell line), Hs746T (METex14), EBC-1 (overexpressing *MET*) and a negative cell line (PC9) were used for the initial validation of the panel. Subsequently, 58 FFPE samples from advanced NSCLC patients, previously characterized by FISH, RT-PCR and IHC, have been analyzed. Total amount of 100-150 ng RNA was used for detection. Workflow includes RNA isolation, hybridization and digital counting with for a total turnaround of 3 days. Raw counts were normalized using positive controls, negative controls and house-keeping genes. **Result:** .Results obtained with the cell lines positive for *ALK, ROS1, RET* and *NTRK1* fusion genes were exactly coincident with their genotypes, with fusion transcripts successfully detected in all cases by 3'/5' imbalance and direct fusion probes. In addition, *MET*ex14 splicing transcripts were detected in the Hs746T cells at significant levels, higher than those of wt *MET* mRNA. In contrast, *MET*ex14 mRNA counts were almost undetectable in the rest of cell lines. Regarding FFPE samples from advanced patients, 46 could be successfully analyzed by nCounter. Among 13 patients positive for *ALK* and *ROS1* fusions, 12 were confirmed by nCounter. Regarding the *MET*ex14 splicing variant, 5 out of 6 patients previously detected by RT-PCR were also positive by nCounter. **Conclusion:** Preliminary data suggest that multiplex detection of clinically relevant drivers can be successfully achieved using nCounter Technology. The assay is simple, requires short hands-on-time, needs low input RNA and is highly efficient in detecting gene rearrangements and *MET*ex14 splicing variants. Results will be prospectively validated in a larger cohort of advanced NSCLC patients and we will determine if clusters of different inmune-phenotypes exist among oncogenic-driven NSCLC tumors.

Keywords: gene fusions, METe14, NSCLC

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-076 COMPARISON OF PANA MUTYPER AND PNA CLAMPING FOR DETECTING KRAS MUTATIONS IN TUMOR TISSUE, CELL BLOCK AND PLEURAL EFFUSION FROM CANCER

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Background: Recently, target therapy for cancer patients should be considered according to the individual mutational status. Therefore, detection of mutations is clinically important for patients' outcome. Molecular testing of lung cancer is one of the most important standard of care and treatment. However, it is not always easy to get enough tumor tissue from patients. There is a promising novel mutation detection technology, which is PANA Mutyper. We compared effectiveness of both methods for the detection of KRAS mutation using tumor tissues, cell blocks and pleural effusions with patients with malignant pleural effusion. **Method:** KRAS mutations were assessed by PANA Mutyper and PNA clamping using tumor tissues, cell blocks and pleural effusions. The diagnostic usefulness of two methods were analyzed. **Result:** A total of 104 patients with malignant pleural effusion were enrolled which includes 56 adenocarcinoma of lung, 11 squamous carcinoma of lung, 17 small cell lung cancer, 3 large cell lung cancer, 3 stomach cancer, 2 ovary cancer, etc. PANA Mutyper showed more superior detection rate than PNA clamping through tumor tissues, cell blocks and pleural effusions. **Conclusion:** PANA Mutyper had a diagnostic superiority for the detection of KRAS mutations in patients with malignant pleural effusion. This method can be used as more sensitive and accurate detection of KRAS mutations. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014R1A2A1A11052422).

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-077 ONCOGENIC POTENTIAL OF A NOVEL HER2 755PL IN-FRAME (HER2PL) MUTATION IN LUNG ADENOCARCINOMA

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Background: Never smoking Asian patients with lung adenocarcinoma are usually accompanied with recurrent occurring mutations of oncogenic drivers, such as EGFR, HER2, ALK fusions, ROS1 fusions etc. HER2 mutations were identified in approximately 2–4% of NSCLCs and these mutations were usually mutually exclusive with other driver mutations. Preclinical studies have suggested that overexpression of HER2 or mutations of the HER2 kinase domain are critical in oncogenic transformation and tumorigenesis. We found a novel HER2 755^{PL} in-frame (also called HER2^{PL}) mutation in a 52-year old never smoking lung adenocarcinoma patient. She did not have EGFR mutation. Patient was treated with a second generation of EGFR tyrosine kinase inhibitor (TKI), afatinib and had responded. However, the role of HER2^{PL} mutation in lung tumorigenesis and its response to EGFR TKIs have never been addressed before. **Method:** We established a plasmid construct carrying a HER2 gene with HER2^{PL} and transfected into normal murine fibroblasts, NIH/3T3 and human lung adenocarcinoma, NCI-H358 which express wide type EGFR. HER2 activation pathways were examined by western blots of phosphorylation of down-stream molecules with and without gefitinib and afatinib treatment. **Result:** Overexpression of HER2^{PL} mutation can activate HER signaling pathways in both NIH/3T3 and NCI-H358. HER2^{PL} mutation induces much higher phosphorylation of HER2 and downstream AKT signaling pathway compared to wide-type HER2. In addition, we found that HER2PL mutation can trigger HER2 signaling in ligand-independent manner and afatinib can significantly decrease HER2^{PL} mutation-induced HER2 signaling pathway compared to a first generation of EGFR TKI, gefitinib. Furthermore, we found that the distribution of HER2^{PL} mutation is in cytosol as well as on the membrane and the expression of p-HER2 (Tyr1221/1222) can be effectively attenuated with afatinib treatment in NCI-H358 stable lines using immunofluorescence assay. The cell growth and drug sensitivity to different generations of EGFR TKI in NCI-H358 lines transfected with HER2^{PL} mutation are under investigation. **Conclusion:** This research may bring us new insights to understand the oncogenic significance of HER2^{PL} mutation and be applied to relevant therapeutics.

Keywords: afatinib, HER2 mutation

P1.01: ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.01-078 LONGITUDINAL STUDIES OF QUALITY OF LIFE IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS UNDERGOING FIRST-LINE TARGET THERAPY

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Background: This paper studies the quality of Life (QoL) of taiwan advanced non-small-cell lung cancer (NSCLC) patients receiving first-line target therapy; QoL data into sexual scores using the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire EORTC QLQ-C30 and the QLQ-13 in patients with NSCLC. **Method:** From March 2016 to March 2017, patients with in a teaching hospital in southern Taiwan were recruited as the research participants, the patients with advanced or metastatic EGFR mutation-positive NSCLC who received gefitinib, erlotinib, or afatinib as first-line treatment, were invited to complete the EORTC QLQ-C30 and QLQ-C13 on a 5 time visit, the data was analyzed by using SPSS 20.0 software. **Result:** A total of 30 patients with NSCLC, The global health status showed differences between QOL before Target therapy and 4 and 12 weeks after commencing therapy, compared to baseline. Quality of life-30 scores were 35.6 ± 8.3 before therapy, 38.1 ± 7 after 4 weeks and 43.4 ± 6.8 after 12 weeks (P <0.000) (Table 1). For the other scales, at 12 weeks, improvement of insomnia, Pain, Dyspnoea, Fatigue and Appetite loss, but worsening of diarrhea, Sore mouth and Dysphagia were observed (P <0.05). **Conclusion:** Longitudinal QoL assessments are important in advanced lung cancer patients because the data they provide could, for example, help to assess more patient areas and enable early recognition of arising symptom aggravation, there support for case management and health education.

Table 1 Evaluation of the quality of life of patients using the QLQ-C30 and QLQ-LC13 questionnaire

	Before therapy Mean (SD) (N = 30)	After 1 weeks Mean (SD) (N = 30)	After 4 weeks Mean (SD) (N = 30)	After 8 weeks Mean (SD) (N = 30)	After 12 weeks Mean (SD) (N = 29)
QLQ-C30 areas					
Global	35.6±8.3	38.6±5.9**	38.1±7	38.2±5.6	43.4±6.8***
Physical	72.2±25.1	72.4±24	72.7±23.9	73.8±23.2*	74.7±22.9**
Role	71.1±25.1	75±23.1	75.6±20.5	74.4±20.1	76.4±19.8
Emotional	86.7±10.5	89.7±9.5*	91.7±9.9**	91.4±8.7*	92±8.3*
Cognitive	66.1±15.8	67.2±15.2	68.3±15.7	68.9±14.7	70.1±14.1*
Social	63.3±26.3	66.7±19.2	71.1±16.6	71.1±18.7	71.3±19
Symptom scales/items					
Fatigue	20.4±20.1	15.9±14.8	10±12.6**	10±13.3**	11.5±13.8***
Pain	16.7±16.7	7.8±18.6*	6.1±15.2**	3.3±10***	3.4±10.2***
Nausea	0±0	0.6±3	0.6±3	0±0	0±0
Dyspnoea	21.1±23.5	10±15.3**	4.4±14.2***	2.2±8.3***	1.1±6.1***
Sleep disturbance	22.2±19.9	12.2±16.1*	6.7±13.3***	6.7±13.3***	8±14.3***
Appetite loss	21.1±20.2	14.4±16.5	12.2±18.2*	8.9±14.7**	9.2±17.3***
Constipation	1.1±6	1.1±6	0±0	0±0	0±0
Diarrhoea	1.1±6	22.2±23.3***	30±18***	32.2±18.2***	18.4±16.6***
Financial impact	16.7±18.8	14.4±16.5	7.8±14.1	7.8±14.1	9.2±14.9
QLQ-LC13 areas					
Coughing	32.2±20.2	16.7±16.7***	8.9±14.7***	10±15.3***	10.3±17.7***
Dyspnoea	17±19.2	10.7±12.3*	4.4±8.4***	3.3±7.1***	4.2±8.5***
Haemoptysis	0±0	0±0	0±0	0±0	0±0
Sore mouth	0±0	12.2±21.9**	10±15.3**	6.7±13.3	6.9±13.5**
Dysphagia	0±0	5.6±12.4	8.9±14.7*	5.6±12.4*	4.6±11.5*
Peripheral neuropathy	0±0	0±0	0±0	0±0	0±0
Hair loss	0±0	0±0	0±0	0±0	0±0
Chest pain	10±15.3	1.1±6***	0±0	0±0	0±0
Pain in arm or shoulder	2.2±8.3	0±0	0±0	1.1±6	0±0
Other pain sites	6.7±18.1	7.8±18.6	4.4±14.2	2.2±8.3	1.1±6.1*

*P<0.05,**p<0.01, ***P<0.001, compared with before therapy.

P1.02-001 SLFN11 EXPRESSION IN EARLY STAGE NON-SMALL CELL LUNG CANCER PREDICTS BENEFIT FROM ADJUVANT CHEMOTHERAPY WITH TAXANE AND PLATINUM

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Background: No predictive biomarker for cytotoxic chemotherapy is approved for clinical use. Schlafen family member 11 (SLFN11) protein is widely reported as sensitizing to DNA-damaging agents. Epigenetically mediated suppression of SLFN11 is associated with poor response to platinum in patients with ovarian and lung cancer. Pre-clinical lung cancer models suggest that SLFN11 expression may be a useful biomarker of response to cisplatin, PARP inhibitors and topoisomerase inhibitors. Tumor expression of SLFN11 is assessed by immunohistochemistry, RNA expression or DNA methylation; no standard method exists. We used mass spectrometry to quantify SLFN11 protein in archived samples of patients with early stage NSCLC treated with taxane plus platinum (TP) and correlated proteomic expression of SLFN11 with survival. **Method:** We obtained archived tissue sections representing 594 patients with lung cancers of multiple subtypes. A board-certified pathologist marked the tumor areas, which were microdissected and solubilized. In each liquefied tumor sample, 60 protein biomarkers including SLFN11 were quantified with selected reaction monitoring mass spectrometry. Patients were stratified by a SLFN11 cutoff of 100 amol/ug, based on the proteomic assay's limit of quantification. Survival outcomes were assessed with Kaplan-Meier and Mantel-Cox log-rank analyses. **Result:** Among 86 TP-treated early stage NSCLC patients, those with SLFN11 protein levels above the cutoff (n=51) had better progression-free survival (PFS) than patients with SLFN11 levels below the cutoff (HR: 2.26; 95%CI: 1.08-4.72; p=0.052). Similar differences in PFS were found in the subset of patients with NSCLC (n=77) (HR: 2.79; 95%CI: 1.29-6.05; p=0.030). Differences in overall survival by SLFN11 expression were not statistically significant. In a group of untreated patients (n=440), there were no differences in PFS between patients with high and low expression of SLFN11. **Conclusion:** Mass spectrometric evaluation of SLFN11 retrospectively identified responders to platinum-containing chemotherapy and could be used to predict response for platinum-containing therapy and warrants further validation. Multiplexed proteomics can quantitate SLFN11 simultaneously with other therapeutically relevant proteins (eg, HER2, ALK, ROS1) to inform therapy selection at initial diagnosis and upon relapse.

Keywords: chemotherapy, SLFN11, Predictive biomarker

P1.02-002 DIAGNOSTIC UTILITY OF MUC4 EXPRESSION TO DIFFERENTIATE EPITHELIOID MESOTHELIOMA FROM LUNG ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA

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Background: Malignant mesothelioma is a highly aggressive asbestos related cancer with poor prognosis and its diagnosis and differentiatiation from various cancers is challenging. In addition to histological features, many positive and negative immunohisotchemical markers are needed to differentiate epitheioid mesothelioma from lung adenocarcinoma and/or squamous cell carcinoma. The positive mesothelial markers calretinin, WT-1, D2-40, CK5/6; positive lung adenocarcinoma markers, TTF-1, Napsin-A, Claudin-4, CEA; and positive squamous cell markers, P40, P63, CK5/6, MOC31 are routinely used. However, these markers are not sufficient and novel markers have to be identified. **Method:** Patients and Histologic Samples Pathological specimens (formalin-fixed paraffin-embedded tissue blocks) of 65 epithelioid mesothelioma and 60 lung adenocarcinoma and 57 squamous cell carcinoma were obtained from the archives of the Department of Pathology, Hiroshima University. All histological sections were reviewed and reclassified according to recent 2015 WHO classification and was confirmed by histologic findings and an immunohistochemical marker panel recommended by 2012 IMIG update to practical guidelines Immunohistochemical Procedures and Evaluation of Expression of MUC4 Immunohistochemical staining was performed using the Ventana Benchmark GX automated immunohistochemical station (Roche Diagnostics, Tokyo, Japan). Cells showing nuclear staining for calretinin, WT1, p40, p63, and TTF-1, cytoplasmic staining for MUC4 and napsin A, membranous staining for D2-40, MOC-31, and claudin-4 or membranous and/or cytoplasmic staining for CK5/6 and CEA were regarded as 'positive'. Positive Immunoreactivity was semiquantified scored from 0 to 3+. **Result:** MUC4 positivity was present in 50/60(83.3%) cases, case of adenocarcinoma and 50/56(89.3%) cases of squamous cell carcinoma but none of 65 epithelioid mesotheliomas (0%). Among lung adenocarcinoma cases, 21 cases showed score 3+, 9 cases 2+ and 20 cases score +1. In lung squamous cell carcinoma, 21 cases score 3+, 10 cases score 2+ and 19 cases score 1+. The sensitivity and specificity of MUC4 to differentiate epithelioid mesothelioma from lung adenocarcinoma were 100% and 83.3% respectively with accuracy rate of 92%. Similarly, sensitivity and specificity of MUC4 to differentiate epithelioid mesothelioma from lung squamous cell carcinoma 100% and 89.3% respectively with accuracy rate of 95%. MUC4 expression showed sensitivity of 100%, but lower specificity of 86.2% and accuracy rate of 91.2% than CEA or Claudin-4 expression. However, it showed better sensitivity, specificity and accuracy rate than that of MOC-31. **Conclusion:** MUC4 is an additional negative immunohistochemical marker to differentiate epithelioid mesothelioma from lung adenocarcinoma and/or squamous cell carcinoma.

Keywords: MUC4, Epithelioid mesothelioma, lung adenocarcinoma & squamous cell carcinoma

P1.02-003 PREVENTION OF ADRIAMYCIN-INDUCED CARDIAC DAMAGE BY NAD-MODULATIONPREVENTION OF ADRIAMYCIN-INDUCED CARDIAC DAMAGE BY NAD-MODULATION

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Background: Adriamycin (ADR), a potent anticancer chemotherapeutic agent, is used to treat a variety of human neoplasms. However, its clinical use is hampered by severe side effects including cardiotoxicity. It has been reported that ADR-induced cardiotoxicity is related to myocardial oxidative stress, disruption of cellular and mitochondrial Ca^{2+} homeostasis and DNA damage. Nevertheless, the remedy for ADR cardiotoxicity is still not developed. Here we describe the effect of NAD^+/NADH modulation by NQO1 enzymatic action on ADR-induced cardiotoxicity in mice. **Method:** C57BL/6 male mice were intraperitoneally injected with ADR. Before and after exposure to ADR, the mice were orally administrated with WK0202, a substrate of NQO1, (20 mg/kg body weight of mice). Cardiac biomarkers (CPK, Trop I, LDH and SGOT) in plasma levels, oxidative biomarkers and mRNA levels of pro-inflammatory cytokines were determined to compare cardiac toxicity of each experimental group.C57BL/6 male mice were intraperitoneally injected with ADR. Before and after exposure to ADR, the mice were orally administrated with WK0202, a substrate of NQO1, (20 mg/kg body weight of mice). Cardiac biomarkers (CPK, Trop I, LDH and SGOT) in plasma levels, oxidative biomarkers and mRNA levels of pro-inflammatory cytokines were determined to compare cardiac toxicity of each experimental group. **Result:** Cardiac biomarkers in sera, oxidative biomarkers, and mRNA levels of pro-inflammatory cytokines were significantly increased in ADR-treated mice. However, these increases were significantly alleviated by WK0202. We also demonstrated that the downfall in SIRT1 and SIRT3 activities is critically involved in ADR-induced cardiotoxicity through acetylation of NF-κB p65 and p53. However, increase of NAD^+/NADH by WK0202 through NQO1 enzymatic action attenuated ADR-induced cardiotoxicity through recovery of SIRT1 and SIRT3 activities and subsequent deacetylation of NF-κB p65 and p53. . **Conclusion:** WK0202 has a protective effect against ADR-induced acute cardiotoxicity through NQO1 enzymatic action. Therefore, WK0202 might be a new therapeutic option for preventing chemotherapy-associated side effects.

Keywords: Cardiotoxicity, NQO1, Adriamycin

P1.02-004 LONG NON-CODING RNA XLOC_000090 PROMOTES LUNG CANCER MIGRATION THROUGH MODULATION OF MIR-4505

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Background: Many studies have shown that long non-coding RNAs (lncRNAs) are implicated in cancer progress including lung cancer. In our previous studies, we screened the differentially expressed lncRNAs between lung adenocarcinoma with lymph node metastasis and lung adenocarcinoma without lymph node metastasis by microarray analysis. XLOC_000090, an lncRNA without a known function, was identified. Here, we investigated the functions of XLOC_000090 in lung cancer. **Method:** The expression of XLOC_000090 was detected by qRT-PCR in 96 pairs of NSCLC tissues and the adjacent normal lung tissues. Then, we investigated the correlation between XLOC_000090 expression and clinicopathological variables and prognosis. Cell invasion and migration assay was used to detect cell invasion and migration ability in vitro. Murine model of lung cancer was used to detect the effect of XLOC_000090 on pulmonary metastasis in vivo. Dual luciferase reporter assay was used to determine the direct binding between XLOC_000090 and miR-4505. **Result:** Compared with normal lung tissues, XLOC_000090 expression was higher in NSCLC tissues (P<0.05). XLOC_000090 expression was associated with lymph node metastasis (P<0.05) and pathological stage (P<0.05). Patients with high XLOC_000090 expression exhibited significantly poorer disease-free survival and overall survival (P<0.05). XLOC_000090 overexpression increased tumor cell migration and invasion ability, whereas downregulation of XLOC_000090 expression decreased tumor cell migration and invasion ability in both A549 and Calu3 lung cancer cells. Murine model of lung cancer also showed that XLOC_000090 promoted metastasis of lung cancer cells in vivo. Furthermore, a potential XLOC_000090-

targeting miRNA, miR-4505, was identified by ceRNA regulatory network prediction analysis. miR-4505 expression was significantly downregulated in lung cells transfected with XLOC_000090, and significantly upregulated in lung cells transfected with sh-XLOC_000090. Dual-luciferase reporter assay showed the direct binding between miR-4505 and XLOC_000090. XLOC_000090-promoted cell migration and invasion ability was diminished in miR-4505 overexpressed cells. **Conclusion:** Our results demonstrated that XLOC_000090 promoted the migration and invasion of lung cancer cells through regulating miR-4505. XLOC_000090 could be served as a new molecular marker for the progression and prognosis of patients with NSCLC.

Keywords: lncRNA, lung cancer, cell migration

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-005 SOLVING THE INTERFERING PROBLEM OF TISSUE EMBEDDING OCT COMPOUND IN ACTIVITY BASED MULTIPLEX PROFILING OF TYROSINE KINASE SUBSTRATES

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Background: The analysis of clinically relevant human tissue preserved in optimal cutting temperature (OCT) medium with activity based proteomic approaches are promising for the discovery of novel druggable disease biomarkers for the diagnosis, prognosis and prediction of response to therapeutic interventions. Nonetheless, and for many different proteomic approaches, there are important signal interferences observed in the presence of the OCT compound. **Method:** We tested activity based multiplex profiling tyrosine kinase substrates in a large batch of neoplastic and non-neoplastic lung resection specimen embedded with or without OCT. Since January 2003 we collected fresh frozen matched pairs from malignant adenocarcinoma and non-neoplastic lung biopsies. In 2007, we started to embedded all our samples in OCT. We obtained all clinical characteristics of 47 patients with early TNM stage 1 lung adenocarcinoma. We observed significant differences in overall phosphorylation levels and searched for reasons explaining such a large effect. **Result:** We ruled out the implication of either short versus long storage time after sample extraction or of nonhomogeneous batch processing of samples. We documented that the clear downward shift in overall phosphorylation levels coincided with the introduction of OCT as an improved embedding medium for resection specimen. For all the kinomes extracted, we developed a corrective procedure where a median centering was performed on the values of each peptide, separately for the with or without OCT samples. **Conclusion:** We applied corrective filtering of data to the multiplex profiling approach of well characterised tyrosine kinase substrates obtained in lung resection specimen embedded with or without OCT. With the OCT correction parameters applied, the quantitation of molecular prognosis signature based on tyrosine kinase activity differences found in lung adenocarcinoma resection specimens may result in the identification of novel targets for future anti-lung cancer therapies.

Keywords: proteomics, biomarker

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-006 ARSENIC PROMOTES PERSISTENT ALTERATIONS IN THE LUNG PIRNA TRANSCRIPTOME TO TARGET EPIGENETIC PATHWAYS

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Background: Chronic exposure to arsenic leads to the onset of different diseases, including lung cancer. Arsenic-induced lung tumors have been associated with a high-frequency of lung squamous-cell carcinomas among never smokers (a rare epidemiological pattern), suggesting a unique underlying biology. Epigenetic alterations are known to play a role in this process; however, detailed mechanisms are not yet fully elucidated. Piwi-interacting RNAs (piRNAs), a novel class of small non-coding RNAs (sncRNAs), play a key role in epigenetic regulation and maintenance of genome integrity. Here, we examine the impact of different arsenic species in the human piRNA transcriptome, using lung cell models mirroring chronic, low dose exposure. We also investigate the interaction network of deregulated piRNAs and identified biological pathways potentially affected. **Method:** One normal lung (HBEC) and two lung cancer cell lines: A459 (adenocarcinoma) and H520 (squamous-cell carcinoma) were grown in 10 ppm of sodium arsenite (AsIII) or arsenate (AsV) for six passages. Total RNA was extracted at different time points and sequenced. piRNA expression was deduced using our custom sncRNA analysis pipeline, which interrogates >23K piRNA-encoding human loci. piRNA/DNA binding prediction was performed using two different algorithms (miRanda/ThermoBLAST). Network analysis was performed using Partek Pathways. **Result:** Overall, 691 piRNAs were expressed. Persistent changes in piRNA expression over time were identified, with specific patterns associated with the different arsenic species. In HBECs (non-malignant lung tissue), 14 piRNAs were persistently upregulated and 16 downregulated in response to AsIII. Similarly, 6 were up- and 11 downregulated when the same cells were exposed to AsV. Only 1 piRNA, DQ598008, was commonly upregulated in response to both arsenic species, while 4 piRNAs were commonly downregulated. Lung cancer cell lines follow the same arsenic species-specific trends, with a high subtype-specificity indicating these species maintain a role during lung tumor development. Remarkably, we found an enrichment of genes associated with methyltransferase activities predicted to be targeted by piRNAs altered by AsIII (a biologically-relevant form of arsenic), evidencing their role in arsenic-related carcinogenic mechanisms. **Conclusion:** Arsenic induces persistent alterations in the lung sncRNA transcriptome, particularly piRNAs, impacting pathways linked to epigenetic regulation. Together, these results provide insights into sncRNA-related mechanisms in arsenic-induced lung carcinogenesis. Moreover, different arsenic species induce distinct alteration patterns, highlighting the relevance of the source of exposure. piRNAs, as with other sncRNAs, are stable in biofluids, circulating tumour cells, and archival clinical materials. Therefore, piRNAs hold great promise as potential exposure and monitoring biomarkers for arsenic-related health effects.

Keywords: arsenic, Epigenetic, non-coding RNAs

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-007 TP53 AND DNA-REPAIR GENE POLYMORPHISMS AS RISK FACTORS FOR THE DEVELOPMENT OF ADVANCED LUNG ADENOCARCINOMA IN SERBIA

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Background: *TP53* and DNA repair genes polymorphisms have been proposed as clinically significant cancer risk factors. The TP53 gene, coding for a known tumor suppressor, is found to be mutated in over 30% of human cancers. Impaired DNA repair efficiency caused by differences in expression, methylation and polymorphisms of DNA repair genes *XRCC1* and *Rad51* is likely to affect cancer occurence. This study aimed to evaluate the association of the *TP53* Arg72Pro single-nucleotide polymorphism (SNP) (rs1042522), X*RCC1* Arg399Gln SNP (rs25487) and *Rad51* G135C SNP (rs1801320) with the occurrence of lung adenocarcinoma in Serbia, both individually and in combination. **Method:** This case-control study included 65 advanced lung adenocarcinoma patients treated at two Institutes in Serbia, stage IIIB or IV, and ECOG performance status 0, 1 or 2, and 68 healthy matched controls. All subjects were of Caucasian descent. *TP53*, *XRCC1* and *Rad51* genotyping was done by polymerase chain reaction followed by restriction length polymorphism (PCR-RFLP). Statistical analysis was performed using the Chi-square test and descriptive analyses included genotype and allelic frequencies. Deviations of the genotype frequencies from those expected under Hardy-Weinberg equilibrium were assessed using the χ^2 test. The odds ratio (OR) and 95 % confidence intervals (CI) were also calculated as an estimate of relative risk, with significance set at $p < 0.05$ for all analyses. **Result:** The frequencies of *XRCC1* alleles in patients vs. controls were 0.75 vs. 0.6 for Arg, and 0.25 vs. 0.4 for Gln. *XRCC1* Arg allele was significantly associated with the development of lung adenocarcinoma only in the recessive model [p=0.019; OR (95% CI) = 2.47 (1.21 - 5.05)]. The frequencies of *Rad51* alleles in patients vs. controls were 0.78 vs. 0.76 for G, and 0.22 vs. 0.24 for C. The frequencies of *TP53* alleles in patients vs. controls were 0.52 vs. 0.63 for Arg, and 0.48 vs. 0.37 for Pro. We found no statistically significant associations of *Rad51* and *TP53* polymorphisms with lung adenocarcinoma. Investigating all possible gene-gene interactions, we also found no statistically significant associations with lung adenocarcinoma. **Conclusion:** In this study, homozygous carriers of the *XRCC1* Arg allele were found to be more susceptible to the development of lung adenocarcinoma during lifetime. Thus, *XRCC1* genotyping might be useful as an additional tool for predicting individual lung cancer risk

Keywords: lung adenocarcinoma, GENE POLYMORPHISMS, XRCC1, Rad51, TP53

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-008 EXPRESSION OF MISMATCH REPAIR PROTEINS ASSOCIATES WITH SURVIVAL AND RESPONSE TO EGFR TYROSINE KINASE INHIBITORS IN LUNG ADENOCARCINOMA PATIENTS

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Background: Mismatch repair (MMR) pathway is a fundamental cellular process required for the maintenance of genomic stability. Recently, a growing body of evidence suggests that a non-canonical MMR (ncMMR) function may be present as a source of mutations in human cells, which could lead to tumorigenesis. The dual functions of MMR with anti-mutagenic and mutagenic activities complicate its role in disease. Given that the functional role of MMR in lung cancer was rarely reported and is still controversial, the current study aimed to address the clinical significance of MMR proteins and their associations with therapeutic biomarkers in lung adenocarcinoma. **Method:** A panel of tissue microarrays containing 442 lung adenocarcinomas was examined for the expression of MMR proteins MLH1, PMS2, MSH2 and MSH6 using immunohistochemistry. The associations between MMR expression and clinicopathological features, patients' survival as well as therapeutic biomarkers including EGFR mutation and PD-L1 expression were

analyzed. **Result:** MLH1, PMS2, MSH2 and MSH6 protein expression significantly correlated with one another in lung adenocarcinoma (*p<0.001*). Neither age nor sex nor predominant histological pattern correlated with their expression, except that only MSH2 expression positively associated with the solid-pattern growth (*p<0.05*). Survival analyses showed that high expression of each MMR protein statistically correlated with poor patients' overall and progression-free survivals (*p<0.05*). For therapeutic biomarker analysis, expression of MMR or PD-L1 independently associated with poor patients' overall survival, but no significant correlation between their expression was observed. High expression of MLH1, MSH2 and MSH6 (*p<0.05*) but not PMS2 (*p=0.12*) was linked to poor survival in EGFR mutation-positive patients. To examine EGFR-TKI treatment response, the outcomes of 50 patients with EGFR mutation-positive tumors treated with EGFR-TKI were included for further analysis. Interestingly, patients with high expression of MLH1 in tumors showed a worse progression-free survival after EGFR-TKI treatment (*n* = 23, 13.8 months, 95% CI: 6.5 to 21.1 months) than those with low expression (*n =27*, 25.6 months, 95% CI: 10.9 to 40.3 months). **Conclusion:** MMR proteins are overexpressed in lung adenocarcinoma and significantly associate with poor patients' survival, which may have a prognostic value in predicting patients' drug response and clinical outcomes. Our results also raise a possibility that ncMMR function may participate in the tumorigenesis of lung adenocarcinoma.

Keywords: EGFR-TKI, Mismatch repair, lung adenocarcinoma

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-009 ACCUMULATION OF MUTATIONS IN BACKGROUND NORMAL LUNG TISSUE CONSTITUTES A MAJOR LUNG CANCER RISK

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Background: Accumulation of mutations in normal-appearing lung tissue is believed to be important for development of lung cancer, and to be heavily influenced by smoking. However, their very low levels have been hampering their measurement, and their links with cancer risk and smoking history have not been demonstrated. To overcome this limitation, we recently developed a novel method that can measure levels of somatic mutations at 10^{-6}/bp levels [Yamashita et al., Cancer Lett, online]. **Method:** Eleven healthy lung tissues (Group1:G1) were collected from the normal lungs of metastatic lung cancer patients without smoking history, and 11 exposed lung tissues (Group2:G2) were collected from those with smoking history. 11 high-risk lung tissues (Group3:G3) were collected from the lungs of lung cancer patients with smoking history. A sequence library (15,552 bases of 291 regions of 55 cancer-related genes) was prepared by multiplex PCR using 100 DNA molecules, and was sequenced using a next generation sequencer. **Result:** The accumulation levels of mutations were significantly higher in G3 ($2.7 \pm 0.8\times10^{-5}$ mutations/base) than those in G1 ($1.8 \pm 0.5\times10^{-5}$ mutations/base) ($p = 0.0189$). The accumulation appeared to be associated with smoking history (OR = 3.2; 95 % CI = 0.54–18.98), and the C>T mutation, a signature reported in cancer tissues [Alexandrov *et al*., Science, 354:2016], was significantly more frequent in G2 than in G1. The GCC>GTC and CCC>CTC mutations, a signature of exposure to the nitrosamines contained in tobacco smoke, were significantly more frequent in G2 and G3. **Conclusion:** The accumulation level of mutations was increased in exposed lung tissues, and the mutation accumulation was associated with cancer risk.

Keywords: smoking, normal-appearing lung tissue, accumulation of mutations

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-010 NOVEL ROLE OF HSSB2 IN THE BASE EXCISION REPAIR PATHWAY (BER)

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Background: The base excision repair (BER) pathway is responsible for removing damaged or incorrectly incorporated uracil bases in the genome. Mismatched bases that persist in the genome and remain unrepaired may result in either lethal mutations or cytotoxic DNA double strand breaks. Previous studies have determined that hSSB1 is critical for the detection, signaling and repair of cytotoxic double strand DNA breaks and oxidized DNA lesions within the genome. The role of hSSB2 is, however, less clear. In this study, we have identified that the single stranded DNA binding proteins, hSSB1 and 2, are involved in the detection and removal of uracils within the genome and function as part of the BER pathway. **Method:** We identified a novel role for hSSB1 and hSSB2 in BER. EMSA and incision biochemical assays were used to determine the ability of hSSB1/2 to bind uracil containing mismatches. Incision assays were used to determine the effect hSSB2 and hSSB1 have on UNG2 activity. Two cytotoxic drugs (5-fluorouracil and pemetrexed), which induce uracil misincorporation in the genome, were used to determine the cell sensitivity in control and hSSB1/2-depleted cells using a live and dead cell assay. Immunoprecipitation, immunofluorescence and Protein-Protein interactions were carried out to determine whether hSSB2 and hSSB1 interacts with key regulatory proteins of the BER pathway. **Result:** This study demonstrates that hSSB1 and hSSB2 proteins can recognize and bind to double stranded DNA substrates containing a uracil mismatch. Interestingly, we have identified that hSSB1 and hSSB2 have a differential preference for uracil mismatches, with hSSB1 preferentially binding UA and hSSB2 UG mismatches. Furthermore, hSSB2 induces the incision activity of UNG2 by approximately two fold for a U:G mismatch but not a U:A mismatch. A549 lung adenocarcinoma cells depleted of both hSSB1 and hSSB2 are hypersensitive to 5-fluorouracil and pemetrexed. Loss of either hSSB1 or hSSB2 alone by siRNA results in a compensatory upregulation of hSSB2 or hSSB1 respectively, suggesting over-lapping functionality and substrate specificity. **Conclusion:** This study highlights the importance of hSSB2 and hSSB1 in the removal of uracil from the genome. Currently, pemetrexed and fluorouracil based agents are in use for treating lung cancer. This study raises the possibility that hSSB2 and hSSB1 may be biological indicators of response to fluorouracil and pemetrexed. Further, it may be possible to develop future hSSB2/hSSB1 inhibitors that could enhance the activity of these agents in the treatment of lung cancer.

Keywords: Human Single stranded DNA binding protein, Base excision repair, fluorouracil

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-011 XRCC6BP1: A KEY PLAYER IN THE DNA REPAIR OF CISPLATIN RESISTANT NSCLC CELLS

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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 previously established in our laboratory. DNA repair genes significantly altered in CisR cells were validated at the mRNA and protein level, using RT-PCR and Western blot analysis, respectively. 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 using Annexin-V/PI staining. Cellular expression and localisation of XRCC6BP1 protein and H2AX foci in response to cisplatin were examined by immunofluorescence using the Cytell Imaging System. To investigate a role for XRCC6BP1 in lung cancer stem cells, Side Population (SP) studies were used to characterise stem-like cells in a panel of chemoresistant cell lines. XRCC6BP1 mRNA analysis was also examined in ALDH1$^+$ and ALDH1$^-$ subpopulations. Immunohistochemistry analysis was carried out on a cohort of resected lung tumour tissues (n=20) and XRCC6BP1 expression was correlated with clinicopathological parameters. **Result:** We identified a number of critical DNA repair genes that were differentially regulated between H460 PT and CisR NSCLC cells, where XRCC6BP1 mRNA and protein expression was significantly increased (mRNA; 19.4-fold) in 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 CisR cells and reduced the DNA repair capacity of these cells relative to scrambled (negative) controls. Immunofluorescence studies showed an increase in XRCC6BP1 protein expression and H2AX foci in CisR cells relative to their PT counterparts. While SP analysis revealed a significantly higher stem cell population in CisR cells, XRCC6BP1 mRNA expression was considerably increased in SKMES-1, H460 and H1299 ALDH1$^+$ CisR cells compared to ALDH1$^-$ cells. Data analysis of XRCC6BP1 immunohistochemistry is currently ongoing. **Conclusion:** We identified XRCC6BP1 as key DNA repair gene implicated in cisplatin resistant NSCLC. Our data highlight the potential of targeting components of the DNA repair pathway in chemoresistant lung cancer, in particular XRCC6BP1, either alone or in combination with conventional cytotoxic therapies.

Keywords: dna repair, XRCC6BP1, Resistance

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-012 PROFILING DNA REPAIR IN LUNG CANCER

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Background: We hypothesised that some lung cancers have DNA repair alterations that either are therapeutically targetable, or that result in resistance to particular DNA damaging therapies. Expression profiling of DNA repair genes may thus enable better matching of patients with the current chemotherapeutic options. Furthermore, profiling may identify tumours that will be more responsive to other DNA repair-directed therapies not normally used in treating NSCLCs e.g. PARP or CDKN4/6 inhibitors. **Method:** We tested RNA of more than 166 samples from tumour cores of 107 patients and 12 normals on the Nanostring platform. We developed a new approach to normalising Nanostring data based on the RUV (removing unwanted variation) method so that we could better identify differences between the patients. **Result:** Many interesting findings emerged indicating some new therapeutic

options. The conclusions obtained from Nanostring analysis were verified by examination of the TCGA lung adenocarcinoma RNA-Seq data. **Conclusion:** This is the first systematic study of DNA repair gene deficiencies in NSCLC. There are important implications for the rational use of chemotherapy and radiotherapy. This work was funded by Cancer Australia.

Keywords: dna repair, rational chemotherapy

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-013 ATM MUTATION AS A PREDICTOR FOR MUTATION BURDEN IN NSCLC

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Background: Ataxia telangiectasia-mutated (ATM) is a critical first responder to DNA damage in the cell, but despite being one of the most mutated genes in lung cancer, no specific mutation hotspots have been linked with disease development. Our own quantitative analysis of ATM protein levels in patient samples suggests that ATM is lost in 20-25% of cases and that this loss correlates with poor overall survival and increased response to adjuvant chemotherapy treatments. We believe that this may be the result of increased genomic instability within the cancer cells caused by a lack of adequate DNA repair. Given that ATM-deficient cancers may have higher genetic instability, and that ATM is so highly mutated in lung cancer, we sought to quantify the relationship between ATM mutations and genomic instability, as measured by somatic mutation burden. **Method:** Using genomic and sequencing data available from publically available databases including the Broad Institute Cancer Cell Line Encyclopedia (CCLE) and the NIH Cancer Genome Atlas (TCGA), we correlated mutations in ATM and other genes involved with the DNA damage response with the total number of mutations annotated in ~900 cancer cell lines and ~200 lung adenocarcinomas. **Result:** We show that in cell lines across all cancer types, and particularly in lung, breast, and esophageal cancers, mutations in ATM correlate with a significantly higher number of total mutations. Only mutations in the direct damage response genes appeared to associate with total mutations, whereas p53 – while more commonly mutated – did not correlate with higher mutations in cell lines or patients. In lung cancer patients, however, neither ATM mutations nor ATM protein levels were similarly correlated with higher mutation burden. **Conclusion:** We have identified a potential relationship between ATM mutation and total somatic mutations in cancer cell lines which may be indicative of overall genetic instability. Analysis of the ATM mutations in both cell lines and patient samples clearly shows that there are no specific hotspots for mutation in ATM that correlate with increased total mutations. Thus screening for ATM mutations alone may not be sufficient to indicate loss of function or instability. However, this data may prove useful in developing panels of targets to screen as mutation hotspots of instability, and ultimately to help identify patients that may benefit from targeted or modified therapy options based on ATM-deficiency or higher genetic instability.

Keywords: ATM, Mutation burden, Genomic instability

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-014 TGFALPHA PROMOTES GROWTH OF LUNG TUMORS CARRYING EGFR MUTATION BUT NOT KRAS MUTATION IN TRANSGENIC MOUSE MODELS IN VIVO

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Background: TGFalpha, one of the EGFR ligands (EGF, TGFA, AREG, EREG, HBEGF, BTC and EPGN), is known to be associated with poor survival in human lung adenocarcinoma (Tateishi et al., Cancer Res 1990). However, it remains unknown whether TGFalpha promotes EGFR-mutant lung adenocarcinoma and/or KRAS-mutant lung adenocarcinoma in vivo. **Method:** In order to understand the role of TGFalpha in lung cancer in vivo, we developed transgenic mice that conditionally induce mutant EGFR (Politi et al., Gene Dev 2006) or mutant KRAS (Fisher et al., Gene Dev 2001) along with TGFalpha (Hardie et al., Am J Physiol Lung Cell Mol Physiol 2004) in lung epithelium and analyzed the survival and histology of the mice. Based on the mouse study, we also investigated the association of TGFalpha with EGFR mutation or KRAS mutation in human lung cancer using TCGA databases (TCGA, Nature 2012; 2014), lung cancer cell lines and lung cancer specimens. **Result:** TGFalpha enhanced the growth of EGFR-mutant lung tumors but not that of KRAS-mutant lung tumors in the transgenic mice. The growth of EGFR-mutant lung tumors enhanced by TGFalpha was accompanied by the expression of two key tumor-promoting regulators p63 (a marker for airway basal cells and lung squamous cell carcinoma cells) and AGR2 (disulphide isomerase). TGFalpha was associated with poor survival in EGFR-mutant lung adenocarcinoma but not in EGFR wild-type adenocarcinoma (e.g., KRAS-mutant lung adenocarcinoma) in human lung cancer. Although osimertinib and brigatinib have been shown to be clinically and preclinically effective for the treatment of gefitinib and erlotinib-resistant EGFR-mutant lung adenocarcinoma, including EGFR.T790M or EGFR.C797S (Goss et al., Lancet Oncol 2016; Mok et al., N Engl J Med 2017; Uchidori et al., Nat Commun 2017), the history of moleculary-targeted therapy for EGFR-mutant lung adenocarcinoma indicates that lung tumor clones resistant to osimertinib and brigatinib would likely emerge. Our results suggest that blocking EGFR ligands (e.g., TGFalpha and/or EGF) may provide therapeutic benefit to treat such drug-resistant EGFR-mutant lung adenocarcinoma. However, such a strategy may not work for KRAS-mutant lung adenocarcinoma. **Conclusion:** TGFalpha (an EGFR ligand) promoted growth of EGFR-mutant lung tumors but not that of KRAS-mutant lung tumors in vivo. Importantly, the growth of EGFR-mutant lung tumors promoted by TGFalpha was accompanied by the expression of p63, which may suggest initiation of lung tumor lineage alteration from adenocarcinoma (p63 negative) to adenosquamous carcinoma (p63 positive).

Keywords: KRAS, TGFalpha, EGFR

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-015 COMPARISON OF STUDY MODELS OF LUNG CANCER

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Background: Lung cancer is the most prominent cancer in human with high mortality rate. Although chemo-radiation therapies have been improved, the patient survival is still poor. Thus, not only developing therapeutic medications, but also biomarkers of early diagnosis have been desired. Several models of primary lung cancer research are in use, however, systematic evaluation and characterization of models are required to have suitability and relevance based on study aims. To provide research environment for lung cancer, we reappraise relevant models for lung cancer. **Method:** Three concepts of primary lung cancer models were evaluated: (I) Urethane induced lung tumor. (II) Cell line induced tumor model via intravenous (iv) or subcutaneous (sc) injection. (III) *ex vivo* 3D primary cell culture model. 20 weeks after urethane injection, the animals were harvested to analyze tumor incidence and tumor immunity. Lewis Lung Carcinoma (LLC) cell line was employed for the orthotopic development of lung tumor in 2 weeks after the injection. Hanging drop method was used for the 3D culture of primary cells from LLC sc induced tumor. Immunohistochemistry (IHC) of proliferation markers (pH3 and Ki67), tumor immunity (CD4, CD8, B220, F4/80, NKp46, and PDL-1) were performed for a finer characterization of tumors. **Result:** Urethane and iv injection of LLC cell line developed heterogeneously distributed tumors in lung. sc injection stably developed single tumor nodule. 3D cultured primary cells formed spheroids within 5 days. IHC revealed that all tumors were consistently proliferating with less extend in urethane and 3D model. F4/80$^+$cells and CD4$^+$cells infiltrated into tumors significantly more than CD8$^+$, B220$^+$, or NKp46$^+$cells. T cell populations (CD4$^+$and CD8$^+$) were much more prominent in LLC iv model than other models. Interestingly the expression of PDL-1 was found only in 3D model. **Conclusion:** The urethane-induced primary lung tumor is reliable with a high rate of development, but needs longer time period to develop tumor compared to iv and sc models. iv injection model develops lung tumor in the original location. With relatively more convenience, sc model allows the analysis of tumor without adjacent tissue bias. 3D primary cell culture model enable for conferring characterization of individual tumor and strategic design of therapy, namely personalized medicine. The involvement and characteristics of immune cells found within tumors were comparable across all models. Injections by i.v. or s.c. of cell line to mouse can be considered as an alternative yet convenient model to develop various different types of lung cancers.

Keywords: lung, Cancer, model

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-016 ESTABLISHMENT OF LUNG ADENOCARCINOMA ORGANOID CULTURES

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Background: Effective non immune- oncology targeted therapies are available only for less than 25% (non-Asian) and 60% (East Asian) of lung adenocarcinoma (ADC) patients. ADC has one of the largest burdens of genetic abnormalities among all cancers. It is understood that ADC arise from the accumulation of abnormalities which dysregulate key cellular processes to permit a growth and survival. Further improvement in our ability to develop novel therapies requires additional lung cancer models that closer mimic the genetic alterations found in patient tumors. Three-dimensional organoid culture ("mini organs") of tumor cells recently has generated great interest as such a novel preclinical model. **Method:** We experimented to develop novel media formulation to generate organoid models from 10 established ADC cell lines, 7 primary culture ADC cell lines developed from patient-derived xenograft (PDX) models, 8 ADC PDX models, and 20 resected patient ADC tissues. Organoid cultures that could be serially passaged for at least 5 passages were defined as long-term organoid models. Organoids were characterized for their histopathological features and immunomarker expression (p40, TTF-1, p53), growth rate and drug sensitivities. **Result:** Long-term organoid cultures were developed from 9/10 (90%) of established ADC cell lines, 3/7 (42%) of PDX-derived cell lines, 2/8 (25%) of

ADC PDX models, and 1/20 (5%) of primary patient ADC tissues. Established organoid cultures recapitulated the histological features of ADC. We are currently collecting the data on growth rates and drug sensitivities of selected organoid cultures. **Conclusion:** Lung adenocarcinoma organoid cultures can be established for both established cell lines and patient tumor tissues but with variable success rates. Further studies are necessary to understand the discrepancy in the establishment rates from different sources of the tumor cells.

Keywords: lung adenocarcinoma, Organoid, patient-derived xenografts

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-017 FREELY FLOATING CANCER CELLS IN LYMPH NODE SINUSES OF HILAR LYMPH NODE POSITIVE LUNG CANCER PATIENTS

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Background: Previous studies demonstrated that freely floating cancer cells (FFCCs) in the lymph node sinuses were of prognostic significance for colorectal and gastric cancers. The goal of the study is to assess the clinical significance of detecting FFCCs using Fast Red staining for cytokeratin in both stage I/II lung cancer patients and hilar lymph node positive lung cancer patients who underwent curative resection. **Method:** Between 2002 and 2011, a total of 167 patients (including 23 hilar lymph node positive patients) were enrolled. Resected lymph nodes were stained for cytokeratin in order to achieve a clear distinction from coal dust. An anti-cytokeratin antibody was labeled with a secondary antibody conjugated with alkaline phosphatase, which was detected by a reaction with Fast Red/naphthol that produced a red color. Patients were considered to be positive for FFCCs (FFCC+) if more than one freely floating cytokeratin-positive cell was detected in the lymph node sinuses. **Result:** Among all 167 patients, a significant difference was observed in Five-year relapse-free survival rates (5Y-RFS), with 75.9% and 31.6% being achieved by FFCC- and FFCC+ patients, respectively (P<0.001). Similarly, the 5-year overall survival rate (5Y-OS) was significantly lower in FFCC+ patients, with 85.4% being achieved by FFCC- and 62.3% by FFCC+ patients, respectively (P=0.007). Among 23 hilar lymph node positive patients, a significant difference was also observed in 5Y-RFS, with 50.0% and 0.0% being achieved by FFCC- and FFCC+ patients, respectively (P=0.013). The 5Y-OS tended to be lower in FFCC+ patients, with 64.3% being achieved by FFCC- and 53.3% by FFCC+ patients, respectively (P=0.595). **Conclusion:** The presence of FFCCs in stage I/II lung cancer patients was associated with a poor prognosis. In addition, FFCCs in hilar lymph node positive patients also have potential as a useful marker foreseeing the recurrence.

Keywords: Freely floating cancer cells, Hilar lymph node positive, lung cancer

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-018 NUMBER OF CANCER CELLS IN LUNG ADENOCARCINOMA SPECIMEN – CORRELATION WITH NOGUCHI'S CLASSIFICATION, WHO PATHOLOGIC TYPE, AND PROGNOSIS

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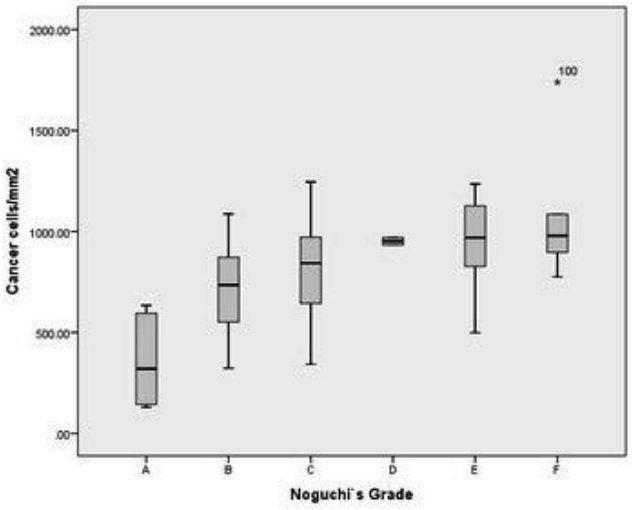
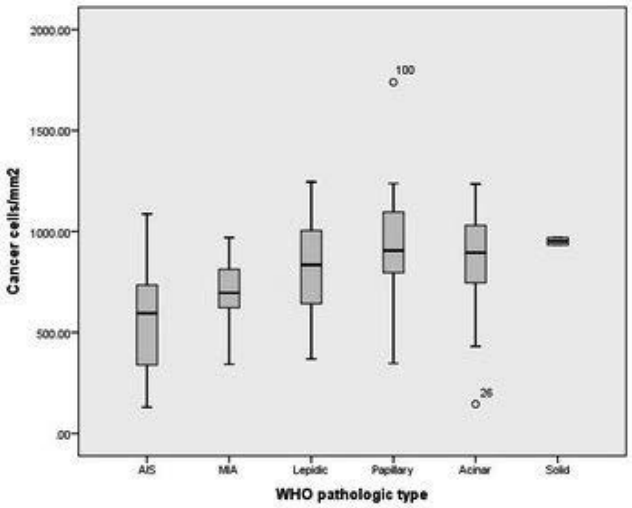
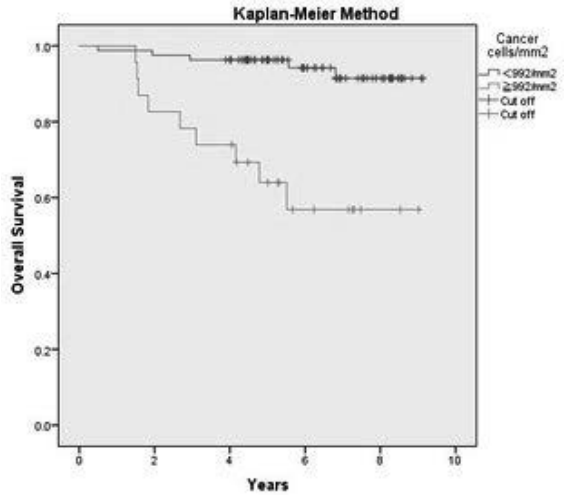
Background: Patients with completely resected lung adenocarcinomas smaller than 2 cm have a good prognosis, though some develop recurrence. It has been shown that Noguchi's classification and WHO pathologic type are correlated with prognosis. We examined the correlation of number of cancer cells/mm^2 in adenocarcinoma specimens with prognosis, Noguchi's classification, and WHO pathologic type. **Method:** Primary tumors were obtained from 104 patients who underwent surgery from January 2006 through December 2010 and had pulmonary adenocarcinomas ≤2 cm in maximum diameter. This prognostic investigation was performed in November 2016. All specimens were stained with hematoxylin-eosin and evaluated using Noguchi's classification and WHO pathologic type. We also determined the number of cancer cells/mm^2 in the specimens, with those findings evaluated using receiver operator characteristic (ROC) curve analysis and tumor size. Overall survival curves were produced using the Kaplan-Meier method and analyzed using a log rank test according to number of cancer cells, Noguchi's classification, and WHO pathologic type. The relationship among those 3 parameters was investigated with Pearson's correlation coefficient. A p-value <0.05 was considered to indicate significance. **Result:** At the time of the examination, 90 patients were alive and 14 had died due to lung cancer. The average number of cancer cells/mm^2 was 791.3 (range 129.4-1739.5) and that was strongly correlated with progression of Noguchi's grade (correlation coefficient 0.519, p<0.001) and WHO pathologic type (correlation coefficient 0.436, p<0.001). ROC curve analysis established a cut-off of 992/mm^2. In general, cases with cancer cells above the cut-off had worse prognosis (5-year survival 64.0% vs. 94.2%, p<0.001).







Conclusion: The number of cancer cells/mm^2 in lung adenocarcinoma specimens was found to be correlated with Noguchi's classification and WHO pathologic type, and is considered useful for prognostic evaluation of affected patients.

Keywords: Adenocarcinomas, Cancer cells, Prognosis

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-019 DUAL ROLE OF NOTCH IN LUNG CANCER

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Background: Anomalies in the family of Notch receptors (1, 2, 3, and 4) have

been implicated in a range of solid tumors, including lung cancer. There is growing evidence that Notch plays an oncogenic and tumor suppressor role in adenocarcinoma and lung squamous cell carcinoma, respectively. Gaining a complete understanding of the mechanisms underlying these opposing activities in lung cancer is key to the development of novel targeted therapy approaches. **Method:** The Cancer Genome Atlas (TCGA) datasets were used to look at gene co-expression patterns of Notch in lung adenocarcinoma and lung squamous cell carcinoma. Biological pathways implicated by gene families were assessed using functional annotation tools (DAVID, ToppGene, and IPA). In vitro and in vivo knockdown studies assessed the functional role of Notch in lung cancer. **Result:** Co-expression analysis supports the hypothesis that Notch is co-expressed with different genes in lung adenocarcinoma and squamous cell carcinoma. Knockdown of Notch in vitro and in vivo support our in silico finding of opposing effects of Notch. Our analysis implicates genes associated with metabolic pathways, angiogenesis and cell cycle that may underlie the differential role of Notch in lung adenocarcinoma and squamous cell carcinoma. **Conclusion:** These results support the hypothesis differences in the Notch co-expression may underlie its opposing roles in lung adenocarcinoma and squamous cell carcinoma. These finding help unravel the context dependent role of Notch as an oncogene and tumor suppressor in subtypes of lung cancer. Understanding the similarities and differences in co-expression patterns can improve our understanding of the regulatory mechanisms of Notch and strategies for its clinical development as single agent or in combination.

Keywords: co-expression, NSCLC, NOTCH

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-020 ACINAR-PREDOMINANT PATTERN CORRELATES WITH POORER PROGNOSIS IN INVASIVE MUCINOUS ADENOCARCINOMA OF THE LUNG

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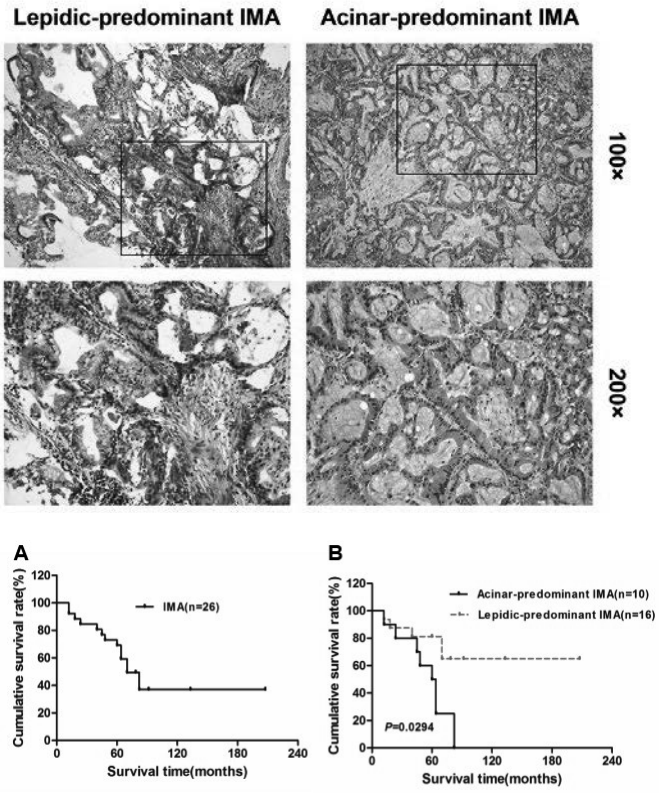
Background: Invasive mucinous adenocarcinoma (IMA) is a variant of lung adenocarcinoma. Growth pattern such as lepidic, acinar, papillary and micropapillary can be seen in IMA. However, no study regarding prognostic and clinicopathologic aspects of IMAs with different growth pattern has been reported. **Method:** From January 1999 to July 2011, of 2236 patients with newly diagnosed primary lung adenocarcinoma, 16 patients were identified as lepidic-predominant IMA and 10 patients as acinar-predominant IMA. Data regarding the clinicopathological characteristics, CT features and prognosis was collected. **Result:** No statistically significant difference was noted in gender, age as well as smoker proportion between lepidic-predominant and acinar-predominant IMA. There was no statistically significant difference in T classification. The proportion of lymph node metastasis was significantly higher in acinar-predominant IMA (P=0.046). Both the tumors shared many signs in CT findings. Air-bronchgram was a relatively specific sign for lepidic-predominant IMA. Survival analysis showed that lepidic-predominant IMA also have a more favorable outcome than acinar-predominant IMA (P=0.0294).



Conclusion: Lepidic-predominant and acinar-predominant IMA are two different subtypes of IMA. Acinar-predominant IMA is associated with lymph node metastasis and has a poorer prognosis than lepidic-predominant IMA.

Keywords: invasive mucinous adenocarcinoma, Prognosis, pathological subtype

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-021 CAN ^{18}F-FDG PET/CT PREDICT THE PATHOLOGICAL NECROSIS AND MICROVESSEL DENSITY IN LUNG ADENOCARCINOMAS

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Background: Tumor hypoxia is characterized by necrosis and a low microvessel density (MVD). Necrosis and MVD are invaluable tools for predicting survival outcomes in non-small-cell lung cancer (NSCLC). Furthermore, hypoxia increases the extent of resistance to gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in lung adenocarcinomas. However, the invasive nature of tumor sampling remains a major clinical obstacle. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) accumulation is a well-validated *in vivo* measure of tissue glucose metabolism and hypoxia. We hypothesized that ^{18}F-FDG PET could identify tumor necrosis of, and quantify the MVD in lung adenocarcinoma. Therefore, we investigated the relationship between preoperative ^{18}F-FDG PET parameters and tumor necrosis and MVD. Hypoxia biomarkers including glucose transporter type 1 (GLUT1), carbonic anhydrase IX and vascular endothelial growth factor were also evaluated. **Method:** Data on 164 patients who underwent the surgical resection of pulmonary adenocarcinomas were retrospectively reviewed. Preoperative ^{18}F-FDG-PET data, the extent of tumor necrosis, and immunohistochemical measures of the expression of GLUT1, carbonic anhydrase IX, vascular endothelial growth factor, and CD31 for detecting MVD were evaluated. The associations between PET parameters and the levels of pathological markers, and the prognostic significance of necrosis, were evaluated. **Result:** The standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) level were significantly lower in patients exhibiting no necrosis compared to those with partial or diffuse necrosis. When we divided the patients into two groups based on high *vs*. low PET parameter values, elevated SUVmax, MTV, and TLG values were significantly more associated with partial or diffuse necrosis than were lower values ($p<0.001$). A negative correlation was evident between the MVD and SUVmax ($p=0.002$), MVD and MTV ($p=0.038$), and MVD and TLG ($p=0.019$). GLUT1 expression correlated with high PET parameter values, a low MVD, and the presence of necrosis. Patients without necrosis exhibited better 5-year recurrence-free survival and overall survival than patients with necrosis ($p<0.001$ and $p=0.007$, respectively). However, a multivariate analysis revealed that necrosis was not of prognostic significance. **Conclusion:** High-level FDG accumulation predicted tumor necrosis. Clinicians can thus predict prognosis and improve treatment policies by reference to PET parameters.

Keywords: Positron emission tomography, necrosis, lung adenocarcinoma

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-022 SPONTANEOUS REGRESSION OF PRIMARY PULMONARY SYNOVIAL SARCOMA; A CASE REPORT

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Background: Primary pulmonary synovial sarcoma is rare, comprising 0.5% of all primary lung malignancies, and spontaneous regression, defined as tumor disappearance without treatment, is very unusual. **Method:** This is a case report of a primary pulmonary synovial sarcoma showing spontaneous regression. The clinical and pathologic records were reviewed, and histologic analysis of the resected specimens was performed. **Result:** Clinical summary: A 38-year-old woman had no history of smoking and no respiratory symptoms. Chest computed tomography revealed a well-demarcated peripheral part-solid nodule measuring 3.8cm in the right lower lobe. Transbronchial biopsy was performed and the diagnosis was synovial sarcoma (*SYT-SSX1* variants). She underwent thoracoscopic right lower lobectomy and systematic lymph node dissection. Pathological findings: The cut surface of the resected specimen showed a smooth walled cyst measuring 2.7 × 2.0 cm containing necrotic tissue. The histological examination revealed a widespread coagulative necrosis of tumor cells with peripheral granulation. Only a few regenerated residual tumor cells were observed. **Conclusion:** This is the first report of spontaneous regression of primary pulmonary synovial sarcoma. Although the mechanism is unknown, blood flow obstruction after the transbronchial biopsy may affect the tumor regression.

Keywords: Transbronchial biopsy, Primary pulmonary synovial sarcoma, Spontaneous regression

P1.02-023 TGF-β SIGNALING MEDIATED BY FIBROBLASTS IS ASSOCIATED WITH THE HISTOLOGICAL SUBTYPES OF LUNG ADENOCARCINOMA

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Background: About 90% of invasive lung adenocarcinoma cases contain several histologic subtypes and demonstrate heterogenous histologic patterns. How such histological heterogeneity is formed remains unclear. The histological subtypes are associated with the prognosis in lung adenocarcinoma patients. Understanding the molecular mechanisms contributing to the pathological subtypes may provide a basis for developing new therapeutic strategies. Tumor microenvironments (TME) including endothelial cells, immune cells, and fibroblasts, have all been recognized as key components regulating cancer progression. TME influences tumor cells via direct cell-cell contact or their products, such as cytokines and extracellular matrixes. In this study, we determined the role of TME in the histological heterogeneity of lung adenocarcinoma. **Method:** We inoculated GFP-labeled A549 human lung adenocarcinoma cells into tissues in four different sites of immunodeficient mice including; the pleural cavity, subcutaneous region, intracardial, and the renal capsule. We then compared the histopathological features of those xenograft tumors. We established immortalized αSMA-positive cancer associated fibroblasts (CAFs) from the xenograft tumors, and co-cultured them with A549 cells in 3D culture conditions so as to analyze the interaction between the tumor cells and the stromal cells. **Result:** We found that the xenografted A549 cells developed distinct histological types of tumors; solid types and acinar types, depending on the inoculated sites. The solid type tumors contained an abundance of acidic mucins stained with Alcian blue, and they expressed MUC5AC, which is one of the common mucin core proteins. The acinar type tumors showed gland-like structures encircled by stromal cells. We found that the phosphorylation of Smad3 were upregulated in the acinar type tumors, especially αSMA-positive CAFs. Smad3 is the downstream of the transforming growth factor-β (TGF-β) signal. These data indicate that the TGF-β/Smad pathway is activated in acinar type tumors. CAFs derived from acinar type tumors induced acinar formations of A549 cells under in vitro 3D culture conditions. We also found that the inhibitor of TGF-β receptor I suppressed such acinar formations, suggesting that TGF-β signaling is associated with the histological subtypes of lung adenocarcinoma. **Conclusion:** Our data show that the histological heterogeneity of lung adenocarcinoma is dependent on TGF-β signaling mediated by the αSMA-positive CAFs. Inhibition of TGF-β signaling might block interactions between cancer cells and αSMA-positive CAFs, and TGF-β signaling inhibitors might suppress tumor heterogeneity in lung adenocarcinoma.

Keywords: histological heterogeneity, cancer associated fibroblasts, lung adenocarcinoma

P1.02-024 CORRELATION OF MAXIMAL TUMOR DIAMETER BETWEEN PATHOLOGY SPECIMEN AND CT IN NONSMALL CELL LUNG CANCER: A PILOT STUDY

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Background: Tumor size has been recognized as an important prognostic factor. In renal tumor, CT imaging generally overestimates pathological tumor size. However, systematic correlation of tumor size between pathology and radiology in lung cancer has not been studied yet. Herein, we compared the maximal tumor diameter between surgically resected fresh lung tissue and chest CT. **Method:** Our study included 75 surgically resected nonsmall cell lung cancer specimens submitted in a fresh state. Pathologic tumor size (PTS) was obtained by measuring the largest cross-sectional tumor diameters in the fresh specimen. Radiologic tumor size (RTS) was retrospectively measured in axial (RTSax) and reconstructed oblique (RTSrecon) image of chest CT. Tumors larger than 4 cm, tumors with uncertain margins owing to underlying lung fibrosis or pneumonia, and tumors sectioned in formalin-fixed state were excluded. **Result:** The mean PTS, RTSax, and RTSrecon with standard deviation were 2.1cm ± 0.815, 2.068cm ± 0.822, and 2.26cm ± 0.871, respectively. PTS and RTrecon was significantly different (PTS-RTSrecon: -1.179±0.404, $p<0.001$), while there was no statistically significant difference between PTS and RTSax. Scatter plot and linear regression analysis demonstrated a strong positive correlation between PTS and RTS (PTS = 0.395+0.824xRTSax, $p<0.001$; PTS=0.233+0.818xRTSrecon, $p<0.001$). The intraclass correlation coefficient (ICC) between PTS and RTSax was 0.832 (95% confidence interval, 0.747-0.890). The ICC between PTS and RTSrecon was 0.884 (95% confidence interval, 0.822-0.925). There was no significant difference between PTS and RTS associated with histologic subtype, specimen type, warm ischemic time, predominant lepidic histology, pleura invasion, and gross feature. **Conclusion:** Both RTSax and RTSrecon were significantly correlated with PTS. Reliability analysis showed that RTSrecon correlated with PTS slightly better than RTSax, although RTSrecom tended to overestimate PTS. Further study with larger sample size would be needed.

Keywords: pathologic specimen, Chest CT, Tumor size

P1.02-025 A CASE OF PRIMARY PERIPHERAL EPITHELIAL–MYOEPITHELIAL CARCINOMA OF THE LUNG

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Background: Primary epithelial-myoepithelial carcinoma (EMC) of the lung is extremely rare carcinoma of salivary type lung cancer. Only 16 cases were reported for peripheral pulmonary EMC in literatures in the world, at present. **Method:** We report a resected case of primary peripheral EMC of the lung existed in right S2 with considerations of literature. **Result:** The patient was 63-year old male, received medical check-up at nearby clinic and an abnormal shadow was pointed out on chest X-ray film. He was referred to our hospital for more detailed examinations and therapy. He had no past history, symptoms nor abnormal physical findings. Chest CT scan showed a 56 x 24 mm mass in right S2. Transbronchial lung biopsy (TBLB) was performed and the tumor was diagnosed as adenoid cystic carcinoma. There was no metastasis to other organs in detailed examinations. Right upper lobectomy and lymph node dissection (ND2a-2) was performed. He was discharged our hospital at 8 post operative days with no post-operative complications. Macroscopically the tumor was 32x30x22 mm in size, white-colored, homogeneous, and well-defined surrounding pulmonary substance. Microscopically the tumor was composed of double tubular layers. Inner tubular layer showed epithelial cell characteristics, whereas the outer layer showed myoepithelial cell characteristics. Immunohistochemical examinations revealed positive for cytokeratin AE1/3 at inner tubular layer, and positive for SMA, p63, and calponin at outer tubular layer. Finally, the diagnosis of the tumor was determined as peripheral pulmonary EMC. There were no metastases in dissected lymph nodes. Epidermal growth factor receptor (EGFR) was wild type and anaplastic lymphoma kinase (ALK) was negative. Pathological stage was IB because of T2aN0M0. He was followed up with no adjuvant therapy, and disease free for 2 years after operation. **Conclusion:** Primary salivary gland type tumors of the lung are rare. Among them, primary peripheral EMC is extremely rare. Differential diagnoses of pulmonary EMC include mucoepidermoid carcinoma, adenoid cystic carcinoma, pleomorphic adenoma and so on. There is a possibility of misdiagnosis in small specimens. EMC of the lung is regarded as a low-grade malignant neoplasm. For diagnosis of EMC, it is necessary to obtain large specimen and/or resect by operation. In this paper, we report a completely resected case of primary peripheral EMC. It is thought that a biological characteristic of EMC will be elucidated by the further accumulation of EMC case.

Keywords: epithelial-myoepithelial carcinoma

P1.02-026 THE CHARACTERISTICS OF LYMPH NODE METASTASIS IN RESECTED ADENOSQUAMOUS LUNG CANCER

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Background: The aim of this study was to retrospectively analyze the clinical data of resected Adenosquamous lung cancer (ASLC) and to explore the influencing factors and clinicopathological characteristics of the metastasis lymph nodes. **Method:** A total of 1156 consecutive patients with surgically resected lung cancer in the three institutions from January 2009 to June 2014 were studied. Fifty-four previously diagnosed ASLC patients were re-evaluated by experienced pathologists. IHC and H&E staining were employed to examine the primary focus and metastasis lymph nodes. The relationship between lymph node metastasis and clinicopathological characteristics of ASLC patients was then analyzed and the pathological type of metastasis lymph node was also determined. **Result:** Thirty-seven cases of typical ASLC were included in the study. Of the 37 ASLC patients, 20 cases presented lymph node metastasis. Lymph node metastasis was not associated with gender, smoking, tumor distribution, histological type of primary focus, and preoperative CEA level, but was associated with age (p=0.023) and tumor size (p=0.012). Lymph node metastasis was more frequently (90% of lymph node metastasis patients) presented in patients <65 yrs, and only 2 patients aged ≥65 presented metastatic lymph node. Moreover, metastatic lymph nodes were more frequently presented in patients with ≥ 3 cm tumor size. In addition, 19 cases (95%) of metastasis lymph nodes were adenocarcinoma and only 1 patient presented with N1 adenosquamous carcinoma. **Conclusion:** Lymph node metastasis adenocarcinoma was the main type in ASLC patients, and was related to the age and tumor size of the primary focus. Further large sample studies are necessary to identify influencing factors and clinicopathological characteristics of the metastasis lymph nodes.

P1.02-027 MINUTE PULMONARY MENINGOTHELIAL-LIKE NODULES PRESENTING AS MULTIPLE GROUND-GLASS DENSITY NODULES (GGNS): A CASE REPORT

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Background: Minute pulmonary meningothelial-like nodules (MPMNs) are generally detected incidentally in resected lung specimens. Recently, with increased use of high-resolution computer tomography (HRCT), MPMNs have occasionally been detected before surgery. They may appear as mild restrictive lung disease or randomly distributed micronodules of ground-glass attenuation on HRCT. **Method:** In this study, we retrospectively evaluated a case in which multiple ground glass density nodules (GGNs) were detected incidentally and operated for diagnosis in our hospital with the final diagnosis of MPMNs. **Result:** A 58-year-old non-smoking woman was referred to our hospital for multiple GGNs in bilateral lower lobes detected on a chest CT scan. HRCT was obtained for further evaluation. Numerous tiny GGNs were seen in the both lower lungs with centrilobular, subpleural and gravitational distribution. Many of them showed cystic or cavitary changes. Three differential diagnoses were presented by HRCT findings. The first was multifocal adenocarcinoma in situ or adenocarcinoma, the second was multifocal micronodular pneumocyte hyperplasia, and the third was atypical manifestation of langerhans cell histiocytosis or respiratory bronchiolitis interstitial lung disease. A follow up HRCT was reobtained after 2 months to determine diagnostic strategy and there was no significant change or mild prominence. For pathologic confirmation, video-assisted thoracoscopic surgery (VATS) right lower lobe wedge resection was performed. Microscopically, the surgical lung biopsy specimen showed multifocal ovoid cell proliferation along alveolar interstitium. The cells were bland, and no mitotic activity was identified. Immunohistochemical analysis was performed, and the sample was positive for epithelial membrane antigen (EMA), progesterone (PR) and CD56. Cytokerain, thyroid transcription factor-1, and S100 were negative. Finally the diagnosis of MPMNs was established, and there was no evidence of malignancy. On the second postoperative day, the patient was discharged without any complications. **Conclusion:** MPMNs are not uncommon incidental pathologic findings but the HRCT findings are nonspecific. They can occasionally manifest as multiple GGNs on HRCT, mimicking multifocal adenocarcinoma in situ or interstitial lung disease. Although most cases do not require special treatment, when there is no confident clinical diagnosis, such as in our case, a pathological correlation could be performed. An awareness of MPMNs presenting as GGNs is important because it may simulate neoplastic or other nonneoplastic diseases.

Keywords: Minute Pulmonary Meningothelial-Like Nodules, Multiple ground-glass density nodules

P1.02-028 PATHWAYS INVOLVED IN EARLY STAGE LUNG CANCERS

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Background: Lung cancer is a heterogeneous disease and we have few good markers of therapy prediction for chemotherapy and even immunotherapy. The biological mechanisms driving the tumour growth of different tumours even within the same histology are likely to vary and cause the diversity in therapy response. Pathifier is an algorithm developed by Eaton Domany's group (Drier Y et al. PNAS, 2013) to estimate the deregulation of pathways of tumour samples based on mRNA expression levels of the genes in the pathway. Briefly, the algorithm estimates the deviation of the pathway in the tumour samples compared with normal samples. We analyse pathways deregulated in early stage squamous cell carcinomas to identify pathways potentially linked to therapy response. Such analyses have been performed for breast cancer (Livshits A et al, MolOnc, 2015), but have so far not been applied to lung carcinomas. **Method:** A total of 198 patients undergoing surgery for squamous cell lung cancer were included in the study. mRNA was extracted from the surgically resected tumour from all patients and from adjacent normal lung tissue from 22 patients. An adjustment of the pathifier algorithm was developed to avoid over-estimation of pathway deregulation. The samples were clustered according to adjusted pathway deregulation. Extensive clinical information such as mutation status, smoking history and survival was available. **Result:** Hierarchial clustering of the adjusted pathway deregulation scores identified separate clusters of squamous cell carcinomas of the lung dominated by different biological pathway with putative difference in clinical behaviour. Based on the biological activity, subgroups of patients are suggested to respond to immunotherapy and cell cycle inhibitors. The clusters are linked with survival, smoking history and expression of immune-related genes including PD-L1. **Conclusion:** Subgroups of lung squamous cell carcinomas have different biology represented by deregulation of groups of pathways. These biological differences can be used to identify clinically relevant markers of prognosis and therapy prediction. The results should be validated in functional studies.

Keywords: Squamous cell carcinoma, pathways

P1.02-029 PULMONARY ADENOFIBROMA WITH CYSTIC CHANGE: A CASE REPORT

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Background: Pulmonary adenofibroma is a rare benign tumor with biphasic pattern resembling adenofibroma of female genital tract and fibroepithelial lesion of breast. Since Scarff and Gowar first described it as a fibroadenoma of lung in 1944, only 10 cases have been reported in English literature. It is generally detected in middle-aged patients with solitary subpleural nodule. Histogenesis of this lesion is controversial, whether it is hamartomatous lesion or benign neoplasm. We report a case of a pulmonary adenofibroma in a 77-year-old male, presented with a subpleural bulla. **Method:** Section not applicable **Result:** A 77-year-old male, an ex-smoker, presented with chronic cough. Chest computed tomography revealed a 7-cm sized bulla in right middle lobe. As the large bulla had a thick wall and increased with lapse of time, resection was done. Frozen diagnosis suggested a proliferative lesion which cannot exclude mesothelioma or a parenchymal epithelial neoplasm. Grossly, the tumor was subpleural cystic lesion with central solid portion. Histologically, the lesion was characterized by a leaf-like branching and glandular pattern composed of a single layer of bland ciliated cuboidal lining epithelium and fibrous stroma. Immunohistochemical analysis revealed epithelium that stained positively for cytokeratin 7 and TTF-1, and stroma stained positively for SMA and nonspecific for CD34. The patient was diagnosed as pulmonary adenofibroma and discharged without any complications. **Conclusion:** Pulmonary adenofibroma is a rare biphasic tumor that could be misinterpreted as other benign or malignant tumors. Pulmonary hamartoma and solitary fibrous tumor could contain entrapped bronchial epithelium in the periphery of the tumor, which is distinguished from diffusely distributed epithelial component of adenofibroma. Pulmonary blastoma is another biphasic tumor which has a distinctive primitive appearance of epithelial and mesenchymal components. Moreover, this case presented as a thick-walled bulla that the possibility of primary mucinous adenocarcinoma or cystic metastasis was suspected in the radiological examination. Although pulmonary adenofibroma is recommended minimal surgical resection, lobectomy was done in this case due to its diagnostic difficulty in radiology and intraoperative frozen pathology. To avoid any inappropriate treatment, pulmonary adenofibroma should be regarded as a differential diagnosis of a solitary pulmonary nodule showing biphasic appearance.

Keywords: Pulmonary adenofibroma, biphasic tumor, solitary pulmonary nodule

P1.02-030 THE EFFECT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE ON THE TUMOR STROMA IN NON-SMALL CELL LUNG CANCER

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Background: Inflammatory cytokines, including tumor necrosis factor-α (TNFα), interleukin(IL)-6, IL-8, and IL-18 in the blood are elevated in patients with chronic obstructive pulmonary disease (COPD), but the influence of COPD on the differentiation and function of cancer-associated fibroblasts (CAFs), which are the dominant stromal component in the tumor microenvironment, remains to be elucidated in non-small cell lung cancer (NSCLC) patients. The purpose of this study is to examined the relationship between degree of COPD and CAFs in NSCLC patients who had undergone the lung surgery. **Method:** The expression of αSMA in tumor tissue was analyzed by immunohistochemistry for 45 cases with COPD and 8 cases without COPD who had undergone lung cancer surgery between 2014 and 2015 to evaluate the frequency of CAFs. We evaluated the correlations between low attenuation area (LAA), Brinkman index (BI), FEV1/FVC, GOLD COPD Stages and frequency of CAFs in tumor tissue. **Result:** Univariate analysis showed a strong correlation between the frequency of CAFs and LAA ($P<0.001$), BI ($P<0.001$), FEV1/FVC ($P<0.001$) except for GOLD COPD Stages ($P=0.208$). Multivariate analysis showed that LAA was significant predictors of frequency of CAFs in tumor tissue. **Conclusion:** Parameters obtained from the pulmonary function test and smoking index are often affected by the skill and memory of the patients. It was suggested that the LAA which objectively quantified the degree of emphysematous change was more related by the frequency of CAFs in tumor microenvironment.

Keywords: copd, CAFs, LAA

P1.02-031 CLINICOPATHOLOGICAL STUDY OF 16 CASES WITH PULMONARY PLEOMORPHIC CARCINOMA

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Background: Pulmonary pleomorphic carcinoma is a rare histologic type with poor prognosis, proposed in the third edition of the 1999 WHO histologic classification of lung tumors. **Method:** We performed surgical treatment for 16 cases with pulmonary pleomorphic carcinoma between April 2000 and April 2017, and investigated the patients' characteristics and perioperative outcomes. **Result:** The male-to-female ratio was 14 to two. The median age was 68 years, ranging from 55 to 88. All cases had a smoking habit. The locations of tumors were RUL in 5 cases, RML in 3, RLL in 4, LUL in 4 and LLL in 2. Pathological stages were IA2 in1, IA3 in 1, IB in 2, IIA in 3, IIB in 1, IIIA in 6 and IIIB in 2, based on eighth of the TNM classification for lung cancer. Nodal status was classified as pN0 in 11, pN1 in 1 and pN2 in 4. Epithelial components were squamous cell carcinoma in 5 (31%), adenocarcinoma in 5 (31%), double-cell components in 2 (12.5%), no epithelial components in 2 (12.5%) and indistinct in 2 (12.5%), while sarcomatous elements, spindle cells in 8 (50%), giant cells in 1 (6%), double-cell elements in 5 (31%) and indistinct in 2 (13%). Eight cases received adjuvant treatments, including chemotherapy in 5, radiotherapy in 1 and chemoradiotherapy in 2. Postoperative recurrence was detected in 9 cases (56%). And 7 of the nine cases had the recurrence within 6 months after the surgical resection. On the contrary, no recurrence was detected in 7 cases comprised of pN0 in 5 cases and pN1-2 in 2. And 2 of the 7 cases have been disease-free for more than two and a half years. **Conclusion:** Although pulmonary pleomorphic carcinoma has poor prognosis, patients without lymph node metastasis have the possibility of having favorable prognosis compared to the patients with lymph node metastasis. It is important to observe the postoperative courses carefully during 6 months from surgical resection in order to detect the early recurrences promptly.

Keywords: Pulmonary pleomorphic carcinoma, recurrence, lymph node metastasis

P1.02-032 CLINICOPATHOLOGICAL PROFILE OF INVASIVE MUCINOUS ADENOCARCINOMA BASED ON EVALUATION OF INVASIVE COMPONENTS

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Background: In the new 2015 WHO classification, invasive mucinous adenocarcinoma (IMA), formerly referred to as mucinous BAC, is categorized as variant of invasive adenocarcinoma. IMA has goblet or columnar cell feature with abundant intracytoplasmic mucin and may show the same heterogeneous mixture of histologic subtypes (lepidic, acinar, papillary, and micropapillary) as non-mucinous tumors. In the 8th edition of TNM classification, invasive tumor size is used for T factor, but few comprehensive studies about invasive components of IMA are reported. **Method:** We evaluated 460 patients with lung adenocarcinoma surgically resected at our facility from Jan 1, 2000 to Jan 31, 2017. In cases identified as IMA, invasive components (the predominant histologic subtypes, the size of invasive area and the presence of spread through air spaces (STAS)) were noted. We classified all cases with the 8th TNM system and investigated the clinical course retrospectively. **Result:** 24 cases (5.2%) were diagnosed as IMA. Of 24 IMAs, 21 cases (91.3%) expressed CK20 with lack of TTF-1. KRAS mutation was found in 2 of the examined 3 cases. 23 cases (96.3%) were found histologic subtype other than lepidic pattern. All cases of IMA were classified into 16 cases of lepidic predominant IMA and 8 cases of non-lepidic predominant IMA (3 cases of acinar predominant, 5 cases of papillary predominant) depending on the predominant histologic subtype. The proportions of lepidic predominant and non-lepidic predominant IMA in each stages were as follows; IA: 68.8% vs 12.5%, IB: 12.5% vs 37.5%, II: 6.3% vs 25.0%, IIIA: 12.5% vs 25.0%. Lymph node metastasis was observed in only one case of non-lepidic predominant IMA. The recurrence was observed 37.5% (6 of 16, included 3 relapsed cases of Stage I) and 37.5% (3 of 8) respectively in the period. STAS was found with a high probability in both category (71.4% vs 100%) and a total of 7 cases were pulmonary recurrence. 5-year DFS did not differ significantly (48.5% vs 51.4%, log rank test p=0.76). 5-year OS was a high tendency for lepidic predominant IMA, but no significant difference was observed (73.9% vs 43.8%, log rank test p=0.14). **Conclusion:** Lepidic predominant IMA seemed to be more frequent in early-stage cancer than non-lepidic predominant IMA, but the frequency of relapse in the clinical course was similar in both groups. These results suggest that IMA have a prognostic factor other than patterns of the histologic subtypes and invasive size.

Keywords: invasive mucinous adenocarcinoma, the 8th edition of TNM classification, STAS

P1.02-033 DIFFERENTIATING OF CYTOMORPHOLOGICAL CHARACTERISTICS IN NON-SMALL CELL LUNG CANCER PREDICTS VALUE OF RADIOLOGIC FEATURES

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Background: In the 2011 IASLC/ATS/ERS classification, guidelines recommend that the major adenocarcinoma (ADC) subtypes should be classified according to the predominant histologic pattern. In published papers, the ADC classification has significant prognostic and predictive value regarding death or recurrence has been reported. The purpose of this study was to retrospectively evaluate characteristic differences between cytomorphological findings among histological subtypes in the preoperative bronchoscopic materials and radiologic features on high-resolution computed tomography (HRCT) and [(18)F]-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) /CT examinations in our database. **Method:** Forty-four consecutive lung cancer patients with peripheral lung nodules diagnosed by bronchoscopic biopsies underwent surgery in our hospital from April 2011 to May 2016. The cyotologic material obtained by brushing bronchoscopically was placed onto a glass slide, immediately fixed in 95% ethanol, and stained with Papanicolaou stain. The cytomorphological studies were retrospectively performed separately by two experienced cytotechnicians. Clinicopathological data with preoperative radiologic features on HRCT and 18F-FDG PET/CT in the patients was utilized for comparing to cytomorphological analyses. **Result:** Out of the forty-four patients with lung cancer, by excluding one typical carcinoid and four not otherwise specified (NOS), thirty-nine specimens in the patients consisted of ADC (n=32) and squamous cell carcinoma (SQCC, n=7) were analyzed. Thirty-two ADC were subclassified cytomorphologically into acinar (n=22), solid (n=8), papillary (n=1) and lepidic (n=1). The subtypes of ADC except for eight solids were categorized as nonsolid of ADC on comparisons of analyzed data. Specimens classified as solid pattern of ADC had a predominant 3D clusters (8 of 8 specimens, 100%) and conspicuous nucleoli (7 of 8 specimens, 87.5%) than nonsolid patterns of ADC. There were statistically significant differences between the nonsolid and the solid patterns about the two features (P=0.0011 and 0.0007, respectively). C/T ratio (a diameter of consolidation divided by a diameter tumor size) of the nonsolid pattern (0.9±0.1) was significantly lower than that for the solid pattern and the SQCC (1.0±0.0) (p=0.01). Maximum standardized uptake value (SUVmax) of the SQCC at 60 and 120 minutes (12.3±4.0 and 16.9±7.3) was significantly higher than that for the nonsolid pattern of ADC (7.0±3.6 and 9.0±4.6; P=0.003 and 0.004, respectively).

Clinicopathologic Characteristics and Radiologic Features in Patients with Nonsolid, Solid Patterns (ADC) and SQCC

Cytologic features	ADC		SQCC (n=7)	P value		
	Nonsolid (n=24)	Solid (n=8)		Non- vs Solid	Non- vs SQ	Solid vs SQ
Age						
Mean (yrs, mean±SD)	70.2±9.4	62.5±8.3	72.9±3.5	0.047[a]	0.4729	<0.0001[b]
Gender						
Male	13	4	5	0.8379	0.4159	0.398
Female	11	4	2			
Smoking index						
≧600	10	3	6	0.8354	0.0402[c]	0.572
<600	14	5	1			
Clinical stage						
IA	8	2	2	0.0782	0.3662	0.2919
IB	12	1	3			
IIA	2	2	0			
IIB	0	0	1			
IIIA	2	3	1			
CT characteristics						
GGO	0	0	0	0.084	0.1044	–
Part Solid	7	0	0			
Solid	17	8	7			
CT						
Tumor size (cm, mean±SD)	3.2±0.7	3.9±2.1	3.5±1.4	0.359	0.4169	0.598
Consolidation size (cm, mean±SD)	3.0±0.8	3.9±2.1	3.5±1.4	0.257	0.1992	0.598
C/T ratio	0.9±0.1	1.0±0	1.0±0	0.01[d]	0.01[e]	0
PET						
SUV max (60 min)	7.0±3.6	9.0±4.4	12.3±4.0	0.218	0.003[f]	0.152
SUV max (120min)	9.0±4.6	11.9±5.8	16.9±7.3	0.194	0.004[g]	0.172

Abbreviations: ADC, Adenocarcinoma; SQCC, Squamous cell carcinoma; Non-, Nonsolid; SQ, Squamous cell carcinoma; yrs, years; SD, Standard deviation; GGO, Ground glass opacity; C/T ratio, Consolidation / Tumor ratio (a diameter of consolidation divided by a diameter tumor size) ; *= Statistical significance was defined as p<0.05.

Conclusion: Preoperative cytomorphological subtyping might predict value of radiologic features on CT and PET examinations, therefore their features also could provide information about a degree of pathological invasiveness or biological malignancy of tumor with some decisions for treatments.

Keywords: Cytomorphological analyses, Positron emission tomography, high resolution computed tomography

P1.02-034 NON-INVASIVE QUALITATIVE DIAGNOSIS OF LUNG CANCER ENABLED BY SPECTRUM ANALYSIS OF ULTRASOUND

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Background: Ultrasound has been widely utilized in clinical to visualize the internal

structure of the objective non-invasively. However ultrasound image can't distinguish malignant lesion from the normal tissue. Spectrum analysis of ultrasound is a newly developed technology which may reflect on the histological feature. We examine if the spectrum analysis is able to distinguish malignant tissue from normal tissue. **Method:** Spectrum was measured using a prototype ultrasound processor EUME5 given by Olympus Japan. three parameters of spectrum such as Midband-fit(M), Intercept(I), and Slope(S) were measured for the objective tissue. In animal study, human lung cancer Xenograft were created in nude mice for each lung cancer cell line (A549, H460, HCC827, and H3122). In clinical setting, surgically excised lungs including lung cancers were examined spectrum analysis for both lung cancers (n=19, 106 slices) and normal lungs (n=17, 65 slices). **Result:** Four different Xenografts exhibited significant differences of spectrum data. In the clinical study, the mean value of M, I and S of both lung cancers and normal lungs were M: -43.22 ±4.09 vs -39.31±3.87($p<0.01$,) I: -55.28±3.19 vs -54.13±2.4 (N.S), S: -1.43±0.35 vs -1.73±0.30 ($p<0.01$) **Conclusion:** Each lung cancer Xenograft of different histology showed different spectrum value. Spectrum analysis is likely to reflect the histological feature. In clinical, M and S showed statistically different values between lung cancer and normal lung. Based on spectrum value, a malignant tumor can be distinguished from the normal lung in the ultrasound image.

Keywords: Ultrasound spectrum analysis, lung cancer

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-035 HUMAN PAPILLOMAVIRUS INFECTION IN LUNG SQUAMOUS CELL CARCINOMA AND CORRELATION TO P16 INK4A EXPRESSION FROM AN ARGENTINE POPULATION

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Background: Lung cancer is the leading cause of cancer death worldwide. In 1979, Syrjänen suggested a role for human papillomavirus (HPV) infection in bronchial carcinoma. Many studies have found HPV on lung carcinoma, predominantly in squamous cell carcinoma (SCC). There seems to be a geographical factor determining prevalence rates. In Latin America, only 2 studies, altogether including 51 cases of lung SCC, examined this association. However, data from Argentina is lacking. The aim of this study is to asses the incidence of HPV infection in lung SCC of Argentinean population, and to correlate with $p16^{INK4a}$expression from an Argentine population. **Method:** The study was approved by CEMIC's Ethics Committee. Informed consent was obtained. Materials consisted of formalin-fixed paraffin-embedded (FFPE) tissue from 29 surgically excised and 11 transbronchial biopsies of primary L-SCC evaluated between 2006-2016. *HPV Genotyping:* On 50µm-thick slides, tumor was microdissected and DNA was extracted (columns method). Wide-spectrum HPV DNA (L1-ORF) was amplified by PCR. Positive specimens were genotyped by PCR for types 16 and 18. *Immunohistochemistry:* All p16 staining's were performed on VENTANA BenchMark GX using antibody CINtec® p16. Staining patterns were interpreted on a binary way (positive or negative). Only cases with diffusely intense cytoplasmic and/or nucleic staining on tumor cell (TC) were considered positive. Cases in which the normal bronchial epithelium resulted p16 positive but TC were negative, were also registered. **Result:** HPV was isolated in 10/40 cases (25%). The details of HPV infection and the clinicopathological data is depicted on table 1.

Clinicopathological features of SCC		
	HPV positive (n=10)	HPV negative (n=30)
Gender		
Female	5	11
Male	5	19
Age		
<50	1	-
50-60	-	21
>60	9	9
Smoking		
Never-smoker	-	-
Smoker	-	-
Unknown	10	30
Tumor cell differentiation		
Well	1	-
Moderate	-	10
Poorly	9	20
Keratinizing		
Non-keratinizing	9	27
Keratinizing	1	3
p16 positive on tumor cellls		
Positive	3	2
Negative	7	28
p16 on bronchial epithelium		
Positive	3	2
Negative	7	28
HPV type		
HPV 16	3	-
HPV 18	5	-
Co-infection HPV 16 and 18	2	-
Specimen type		
Transbronchial biopsy	3	8
Surgical excision	7	22

Conclusion: We detected an HPV infection rate of 25%. HPV18 was the common genotype. On 7 cases, normal bronchial epithelium was both p16 and HPV positive, suggesting that adjacent tumor tissue may be HPV infected. p16 should not be used as a surrogate marker for HPV infection, since it is only positive on 60% of cases.

Keywords: p16INK4a, Squamous cell carcinoma, HPV

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-036 FINE NEEDLE ASPIRATION AS A DIAGNOSTIC TOOL IN LUNG CANCER: WORTH PURSUING?

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Background: The diagnosis of lung cancer can be challenging due to different forms of disease presentation, coupled with institutional familiarity with specific techniques. Transthoracic fine needle aspiration (FNA) is relatively simple and inexpensive, yielding diagnostic material in 70-95% of cases. In the era of personalized oncology where immunohistochemical and molecular assays may be required, the role of FNA to provide enough material should be reassessed. **Method:** This is a prospective study designed to evaluate the feasibility and safety of FNA as a primary technique in the diagnosis of lung tumors. Patients were randomized in a 1:1 ratio into two arms, one using conventional FNA needle (control arm) and another using coaxial needle (experimental arm). Eligible patients were at least 18 years old and had a lung mass suspicious of lung cancer. The procedure was performed in an outpatient clinic, under local anesthesia, by an experienced thoracic surgeon in the presence of a pathologist. The primary endpoint was a positive cell block containing at least 40% of neoplastic cells, a surrogate for successful additional assays. We present the first interim analysis. This study was approved by the Ethics Committee. **Result:** Between January 2013 and May 2015, 34 patients were enrolled, 17 in each arm. The cohort was mostly comprised of males (62%) and smokers (91%), with a median age of 66 years (range 51-85). Most cases were assessed with a computed tomography (94%), with target tumor measuring a median of 8.2 cm (range 1-13 cm). Baseline characteristics were well balanced between the 2 arms, except for gender (82% males in the experimental arm, 41% in the control arm). A positive cell block was acquired in 9 (53%) and 7 (41%) cases in the experimental and control arms, respectively. Altogether, a positive cell block was acquired in 16 cases (47%). A diagnosis was obtained in 82% of cases, but histological subtyping was only possible in 73%. The cell block positivity rate was significantly associated with histological subtyping ($p<0.001$). Local pain was the only adverse event, reported in 2 cases in each arm. **Conclusion:** FNA was a safe procedure in both arms, but yielded enough tumor material in less than half patients and was less than optimal to determine histological subtyping. No relevant difference was observed between conventional and coaxial needle, neither for safety nor for efficacy. FNA alone should not be considered a standard procedure in most cases suspicious for lung cancer.

Keywords: diagnosis, fine needle aspiration, Lung neoplasms

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-037 PULMONARY CARCINOID TUMORS: A PROGNOSTIC IMPLICATIONS OF KI-67 PROLIFERATIVE INDEX

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Background: Division of typical (TC) and atypical (AC) carcinoids is based on the mitotic index and/or the presence of necrosis. A mitotic rate is a well-established and highly prognostic factor, but many studies indicate that assessment of proliferative activity based on Ki-67 value could be easier and more reproducible. The aim of the study was: •assessment of Ki-67 index in PC and its usefulness in distinguishing TC from AC, •to determine whether the mean Ki-67 index is significantly different in TC and AC, •selection the optimal cut-off Ki-67 value that would help predict overall survival in pulmonary carcinoids (PC). **Method:** The clinicopathological features from 329 resected PC were correlated and survival analysis were performed. Mitoses and the proliferative index (PI) were analyzed. For mitotic counting, a scale bar depicting an area of 2 mm^2 was provided and for PI assessment, the percentage of positively stained cells by Ki-67 in the area with the highest proliferative activity was counted. **Result:** There were 217 (66%) TC and 112 (34%) AC, with a median follow-up time of 7,6 ys (230 females and 99 males). The mean age at diagnosis was 52,8 years, median 55 y. Most tumors were localized centrally (73,7%). AC were larger than TC (2,54 vs 1,9cm) and more common located peripherally. Lymph nodes involvement was present in 49 cases (15%), N1-34 (10%) and N2-15 (5%), frequently in AC.The high cellular atypia, cartilage destruction, invasion of peribronchial tissue or adjacent lung parenchyma, presence of pleural, perineural and vascular invasion correlated with AC. ACs were associated with significantly higher Ki-67 indices (8,7%, median 7%) than TCs (3,1%, median 2%). There were significant correlations between high PI and: large tumor size, mitotic activity, vascular invasion and lymph node metastases. The Ki-67 index was a good factor differentiating TC from AC, with cut-off ≤ 4% for TC and > 4% for AC, with high specifity (90%) and sensitivity (70%) and with high likelihood ratio (2,97).The number of deaths among the patients with TC and AC was 7 (6,3%) and 31 (14,3%) respectively. The 5-,10- and 15 year overall survivals for the entire group were 92,8%, 86,8% and 78,6% respectively. **Conclusion:** Ki-67 is an effective grading tool for PC and for differentiation between TC from AC. Apart the mitotic count and necrosis, the Ki-67 index should be incorporated into the mandatory histological criteria for diagnosis PC. The optimal cut-off value of Ki-67 that helps distinguish TC from AC is 4%.

Keywords: carcinoid, pulmonary, Ki-67

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-038 BILATERAL COMBINED LYMPHANGIOLEIOMYOMATOSIS AND DIFFUSE IDIOPATHIC PULMONARY NEUROENDOCRINE CELL HYPERPLASIA WITH TYPICAL CARCINOIDS

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Background: Both lymphangioleiomyomatosis (LAM) and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) are rare entities of diffuse intra-pulmonary cellular proliferation. Thus far, these have not been reported to occur synchronously in the same patient. **Method:** We investigated the lungs of a 54 year old woman who underwent bilateral lung transplantation for radiologically and histologically diagnosed sporadic LAM by routine histological and molecular diagnostic procedures. **Result:** Upon macroscopic inspection both explanted lungs had a multicystic appearance, with multiple nodules, with a max. diameter of 1.0 cm in the left lung, and a max. diameter of 2.9 cm in the right lung. Microscopically, both lungs contained extensive lesions consistent with LAM, with cystic change and surrounding monomorphic spindle cell proliferations immunohistochemically positive for SMA, ER and HMB-45. In addition, diffuse intraepithelial and nodular proliferations of neuro-endocrine cells were seen, positive for TTF-1, CD56, chromogranin A, and synaptophysin, amounting to DIPNECH with multiple neuroendocrine tumourlets and foci of typical carcinoid. There were no lymph node metastases and SSTR-2A staining was negative in neuro-endocrine cell proliferations. Upon mutation analysis by next generation sequencing using an extended diagnostic panel, no pathogenic mutations were found in the largest carcinoid, but the LAM component contained 2 different TSC2 gene splice variants (TSC2 c.599+1G>A; and TSC2 c.1119+1G>C). In view of these genetic findings the two different disease processes were thought not to be clonally related. **Conclusion:** In summary, we present the first case of bilateral combined pulmonary LAM and DIPNECH, which were histomorphologically intricately related but by mutation analysis deemed to be separate entities with presumably distinct histogenesis.

Keywords: TSC2 mutation, lymphangioleiomyomatosis, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-039 MAIN BRONCHUS LOCATION IS A PREDICTOR FOR METASTASIS AND PROGNOSIS IN LUNG ADENOCARCINOMA: A LARGE NORTH AMERICAN COHORT ANALYSIS

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Background: Primary location of lung adenocarcinomas (ADCs) has been reported to be associated with good or bad prognosis due to various definitions for central and peripheral. However, as a definite central location, main bronchus receives few focus. We investigated the clinical features and prognosis of central ADCs known to be located in the main bronchus. **Method:** A total of 397,189 lung adenocarcinomas registered from 2004-2013 in National Cancer Database(NCDB) were extracted for current analysis, and were divided into main bronchus location (2.5%, N=10,111) and non-main bronchus location(97.5%,N=387,078).Univariate and multivariate analyses were performed for survival analysis between the two groups, and Chi-square analysis was performed to identify whether main bronchus group has different lymph node and distant metastases stratified by tumor size. **Result:** ADCs located in the main-bronchus showed more advanced stages than non-main bronchus locations, with a significantly worse survival both for all patients (5.8m vs. 13.6m) and those undergoing curative resection (21.9m vs. 70.9m)) ($p<0.001$), and a significantly higher rate of lymph node involvement and distant metastasis as stratified by tumor size (trend test, $p<1E-16$). Multivariate analysis of overall survival showed that main bronchus location is a stage-independent prognostic factor (HR=1.15, $p<0.001$). **Conclusion:** Primary location has clinical and prognostic impact for lung adenocarcinoma. Main bronchus location is a predictor for worse prognosis irrespective of stage and curative intent-surgery, which is indicative of some underlying biological mechanism to be further studied.

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-040 GENETIC RISK EVALUATION IN FAMILIES WITH LUNG CANCER HISTORY IN HIGH LUNG CANCER MORTALITY REGION OF XUANWEI, CHINA

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Background: Compared with the numerous studies of somatic mutations using sporadic lung cancer, the research into germline mutations using familial lung cancer (FLC) is very limited. In the present study, we used FLC samples obtained from the Chinese population in highly air-polluted regions to screen for novel germline mutations in lung cancer. **Method:** Through a whole genome sequencing (WGS) analysis of the nine subjects (four lung cancer patients and five normal family members of FLC), we obtained a whole genome dataset of DNA alterations in FLC samples. A total of 1218 genes were identified with mutations of multiple types. Subsequently, the top 12 highly mutated genes were selected for validation by PCR and DNA sequencing in an expanded sample set including FLC, sporadic lung cancer, and healthy population. **Result:** Mutations of the five genes (*ARHGEF5*, *ANKRD20A2*, *ZNF595*, *ZNF812*, *MYO18B*) may be potential germline mutations of lung cancer. We also analyzed specific mutations within the 12 genes and found that some specific mutations within the *MUC12*, *FOXD4L3* and *FOXD4L5* genes showed higher frequencies in the samples of FLC and/or lung cancer tissue, compared with the healthy population. Moreover, some genes with copy number variation may be potentially associated with a predisposition to lung cancer. Furthermore, non-coding DNA alterations of the WGS data in FLC were systematically analyzed and arranged. Interestingly, we found that germline mutations also occurred in many non-coding genes. **Conclusion:** Our study uncovered the mutation spectrum in FLC of the Chinese population. The investigation of novel and known gene mutations detected by the present study may contribute to evaluate functional impacts of these mutations not only in FLC but in sporadic lung cancer as well.

Keywords: whole genome sequencing, Genetic predisposition, familial lung cancer

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-041 MUTATION OF SWI/SNF COMPLEX GENES IS FREQUENT IN POORLY DIFFERENTIATED, MESENCHYMAL-LIKE LUNG CANCER WITHOUT MAJOR DRIVER MUTATION

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Background: Recently, components of the switch/sucrose non-fermenting (SWI/SNF) complex have emerged as novel tumor suppressors in non-small cell lung cancer (NSCLC). However, the detailed genotypic and phenotypic features of NSCLC with mutations of SWI/SNF subunits remain unclear. In this study, we intended to clarify detailed morphologic and phenotypic features of NSCLC with mutations of SWI/SNF subunits through analysis of a panel of NSCLC cell lines and primary NSCLC. **Method:** We used 38 NSCLC cell lines which had been analysed for mRNA profiles and major driver mutations in our previous studies (Matsubara et al. AJP 2010, JTO 2010). The genetic status of SWI/SNF subunits was interrogated and retrieved from the public databases (COSMIC, CCLE). Morphological features of these cell lines were examined by 3-D cell culture and xenografts in NOD/SCID mice. We

also immunohistochemically analyzed the expressions of multiple SWI/SNF subunits (BRG1, BRM, BAF47, ARID1A, and ARID1B.) in primary 133 NSCLC consisting of 25 squamous cell carcinomas, 70 adenocarcinomas, 16 large cell carcinomas, and 22 pleomorphic carcinomas. **Result:** In a panel of 38 NSCLC cell lines, mutations of SWI/SNF subunits tended to be found in the cell lines without major driver mutations and with mesenchymal (E-cadherin-low, vimentin-high) phenotypes. Consistently, these cell lines formed grape-like or stellate spheroid in 3-D cell culture, and poorly differentiated, solid or medullary tumors in xenograft models. In the primary tumors, reduced expression of BRG1 and BRM was significantly more frequent in large cell carcinomas and pleomorphic carcinomas than in squamous carcinomas and adenocarcinomas. Loss of expression of ARID1A, ARID1B and BAF47 was only rarely found only in a fraction of NSCLC cases. **Conclusion:** Collectively, these results indicate that loss of the SWI/SNF complex components is found in driver mutation pauci tumors and correlates with dedifferentiation and mesenchymal phenotype in NSCLC.

Keywords: epithelial-mesenchymal transition, Non-small cell carcinoma, SWI/SNF complex

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-042 CIRCADIAN CLOCK GENE PER2 OVER-EXPRESSION INHIBITS TUMOR PROGRESSION IN HUMAN NON-SMALL CELL LUNG CANCER

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Background: The Period clock gene family has three family members, including Per1, Per2 and Per3. Among them, *Per2* is an indispensable component of the circadian clock, which not only modulates circadian oscillations, but also has a decreased expression in many types of cancers and functions as a tumor suppressor gene. However, the expression and specific roles of Per2 in human non-small cell lung cancer(NSCLC) is still unknown. And the present study is aimed to investigate the roles of Per2 porced expression in NSCLC in vitro and in vivo. **Method:** Per2 expression level in tissues was examined by immunohistochemistry. mRNA and protein expression alterations were teste by RT-PCR and Western blot. To clarify the specific roles of Per2 in A549 cell line, we construct the stable overexpressed cell line by lentivirus transfection. And the roles of Per2 porced expression in tumor proliferation and migration were examined by CCK8, colony formation, cell wound, cell migration and invasion, and we also detected the alterations in cell cycle and apoptosis by flow cytometric analysis. Furthermore, we established subcutaneous tumor animal mode to test the tumorgenesis and migration ability of Per2 overexpressed A459 cell in vivo. **Result:** We found that Per2 has a commonly higher expression in para-carcinoma tissues than carcinoma tissues in 26 NSCLC patients(P=0.0001). And Per2 expression in NSCLC patients were correlated with some clinicopathological features(P=0.0000). Then, function assay showed that forced expression of Per2 in A549 cells markedly decreased the ability of cancer cell proliferation, migration and invasion in vitro(P<0.05), and also increased the apoptosis and the number of cells in G1/G0 phase(P<0.05). Furthermore, overexpression of Per2 altered the proliferation and migration related protein expression(P<0.05). Consistent with the in vitro study, we also showed that Per2 overexpression decreased the tumorigenicity of A549 cells in vivo(P<0.05). **Conclusion:** Per2 has a lower expression in NSCLC tissues and also funtions as a tumor supressor gene. It regulates the numerous important downstream tumor-related genes, which may be a novel molecular target for cancer treatment.

Keywords: Per2, non-small cell lung cancer, Circadian clock gene

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-043 A COMPARISON OF CONSISTENCY OF DETECTING BRAF GENE MUTATIONS IN PERIPHERAL BLOOD AND TUMOR TISSUE OF NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: BRAF, one of the three members of the RAF kinase family, belongs to the group of serine-threonine kinases and plays a vital role in mitogen-activated protein kinase (MAPK) pathways. Mutations of BRAF have been found in 0.5-3% of non-small-cell lung cancer (NSCLC). Among the different mutations occurring in the BRAF gene, BRAF V600E is the most common. A number of BRAF inhibitors, including sorafenib, vemurafenib and dabrafenib, are under clinical development. Thus, the detection of genetic driver mutation in lung cancer patients has become the most important tool in clinical practice. The aim is to detect the consistency of the BRAF gene mutation in peripheral blood and tumor tissue of patients with NSCLC and discuss the clinical application value of BRAF gene mutation in peripheral blood. **Method:** Real-time fluorescent quantitative polymerase chain reaction (RT-PCR) was used to detect the tissues in 257 patients of NSCLC and the peripheral blood samples in 318 patients of NSCLC, of which 185 cases of peripheral blood specimens could match the tissue samples, and detected the BRAF gene mutation in them by comparison of mutations consistency in blood and tissue samples, and analyzed the correlation between BRAF gene mutations and clinical characteristics of patients. **Result:** The BRAF gene mutation rate was 7.23% in peripheral blood of 23 patients with NSCLC, and was 5.45% in 14 cancer tissues, the mutation consistency was 80.00% in peripheral blood tumor tissue matched samples. The consistency was statistically significant (κ=0.710, P<0.001). **Conclusion:** The consistency of the BRAF gene mutation in peripheral blood and tissue is high. BRAF gene mutations of peripheral blood could be used for clinical diagnosis and treatment in cases when tissue specimen is hard to get.

Keywords: blood, non-small-cell lung cancer, BRAF

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-044 RELATIONSHIP BETWEEN RET REARRANGEMENT AND THYMIDYLATE SYNTHASE MRNA EXPRESSION IN NON-SMALL CELL LUNG CANCER TISSUES

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Background: RET fusion gene is identified as a novel oncogene in a subset of non-small cell lung cancer (NSCLC). However, few datas are available about the prevalence and clinicopathologic characteristics in RET rearrangement lung adenocarcinoma patients. The aim of this study is to investigate mRNA expressions and relationship of RET rearrangement and thymidylate synthase (TYMS) genes in NSCLC tissues. **Method:** The positive rate of RET rearrangement and the mRNA expressions of of TYMS gene in NSCLC tissues of 642 patients were detected by using real-time fluorescent quantitative PCR method, and the relationship and its correlation between the expression and clinicopathological features were also analyzed. **Result:** The positive rate of RET rearrangement in NSCLC was 0.93% (6/642); High mRNA expression of TYMS gene was 63.55%(408/642). The expressions showed no relationship with gender, age, smoking, tumor size, lymph node metastasis and clinical stages (P>0.05). The mRNA expressions between RET rearrangement and TYMS genes showed positive correlation (P<0.05). **Conclusion:** Thymidylate synthase gene shows low expression level in NSCLC patients with positive RET fusion gene, which may benefit from pemetrexed of first-line chemotherapy drug.

Keywords: Molecular, RET fusion gene, Thymidylate synthetase

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-045 PIK3CA MUTATIONS IN CHINESE PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Background: PIK3CA mutation represents a clinical subset of diverse carcinomas. We explored the status of PIK3CA mutation and evaluated its genetic variability and prognosis in patients with lung adenocarcinoma. The aim of this study is to investigate mutations and prognosis of non-small-cell lung cancer(NSCLC) harboring PIK3CA mutations. **Method:** A total of 517 patients with NSCLC were recruited between July 2012 and December 2014. The status of PIK3CA mutation and other genes were detected by reverse transcription polymerase chain reaction(RT-PCR) or next generation sequencing. **Result:** PIK3CA gene mutation was detected in 3.09% (16/517) NSCLC patients, including H1047R (4 patients), E545A (2 patients), E453K (2 patients), H1065Y (2 patients), E545K (1 patient), E39K (1 patient), E542K (1 patient), C420R (1 patient), K111E (1 patient) and E545K plus L781F (1 patient), and median overall survival (OS) for these patients was 23.0 months. Among them, 12 patients with co-occurring mutations had a median OS of 28.0 months, and median OS of the 4 patients without complex mutations was 21.0 months. No statistically significant difference was found between the two groups (P=0.06). Briefly, patients with (n=5) or without (n=11) co-occurring EGFR mutations had a median OS of 28.5 months and 21.0 months respectively (P=0.45); patients with (n=4) or without (n=12) co-occurring TP53 mutations had a median OS of 30.6 months and 21.0 months respectively (P=0.51). **Conclusion:** There is no significant difference of molecular features in PIK3CA gene mutations in NSCLC. Patients with complex mutations benefited more from therapy than those with single mutations.

Keywords: Prognosis, PIK3CA, clinical features

P1.02-046 MUTATIONAL SUBTYPES AND PROGNOSIS OF NON-SMALL-CELL LUNG CANCER HARBORING HER2 MUTATIONS

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Background: HER2 is a driver gene identified in non-small-cell lung cancer(NSCLC). The prevalence, clinicopathology and genetic variability of HER2 mutation non-small cell lung cancer patients are unclear. The aim of this study is to investigate mutational subtypes and prognosis of NSCLC harboring HER2 mutations. **Method:** A total of 781 patients with NSCLC were recruited between July 2012 and December 2014. The status of HER2 mutation and other genes were detected by reverse transcription polymerase chain reaction (RT-PCR) or next generation sequencing. **Result:** HER2 gene mutation rate was 1.92%(15/781) in NSCLC, including S310F (2 patients), A775_G776insYVM (2 patients), S280F (2 patients), P780_Y781insGSP (1 patient), C630Y (1 patient), L755P (1 patient), T327S (1 patient), K907R (1 patient), R70W (1 patient), E117D (1 patient), L970V (1 patient), and C965S (1 patient). Mutation rate of female was much higher than male(3.76% vs 1.23%, P=0.022), and current-smoker was much higher than no-smoker(3.17% vs 0.74%, P=0.027), and median overall survival (OS) for these patients was 42.6 months. Among them, 12 patients with co-occurring mutations had a median OS of 42.6 months, and median OS of the 3 patients without cpmplex mutations was 40.3 months. No statistically significant difference was found between the two groups(P=0.43). Briefly, patients with (n=8) or without (n=7) co-occurring EGFR mutations had a median OS of 50.6 months and 42.6 months respectively (P=0.19); patients with (n=9) or without (n=6) co-occurring TP53 mutations had a median OS of 40.4 months and 46.7 months respectively (P=0.39); patients with (n=2) or without (n=13) co-occurring SMARCA4 mutations had a median OS of 50.6 months and 42.6 months respectively (P=0.33); patients with (n=2) or without (n=13) co-occurring MTOR mutations had a median OS of 44.3 months and 42.6 months respectively (P=0.71); patients with (n=2) or without (n=13) co-occurring SMARCA4 mutations had a median OS of 50.6 months and 42.6 months respectively (P=0.33); patients with (n=2) or without (n=13) co-occurring APC mutations had a median OS of 39.0 months and 42.6 months respectively (P=0.92). **Conclusion:** There are some significant difference of molecular features in HER2 gene mutations with non-smoking women in NSCLC, along with the state of HER2 gene mutations little influence on prognosis. Afatinib treatment may displayed moderate efficacy in patients with HER2 mutations.

Keywords: Non-small-cell lung cancer, Prognosis, HER2 mutation

P1.02-047 MUTATIONAL FEATURES AND PROGNOSIS OF NON-SMALL-CELL LUNG CANCER HARBORING RAS MUTATIONS

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Background: In non-small cell lung cancer (NSCLC) RAS-mutant status is a negative prognostic and predictive factor. The prevalence, clinicopathology and genetic variability of RAS mutation NSCLC patients are unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring RAS mutations. **Method:** We retrospectively reviewed clinical features from 41 patients with RAS gene mutation NSCLC, and the survival rate was calculated by Kaplan-Meier method and log-rank test was used to compare the survival rates. **Result:** KRAS gene mutation rate was 8.00% (38/475) in NSCLC, including G12C (9 patients), G12D (8 patients), G12V (7 patients), G12A (2 patients), G12S (2 patients), G13D (2 patients), Q61H (2 patients), G12L (1 patient), G12 (1 patient), G12K (1 patient), G12fs*3 plus G12V (1 patient), G13C plus V14I(1 patient) and K5N(1 patient). Mutation rate of current-smoker was much higher than no-smoker(15.76% and 4.41%, P<0.01), and median overall survival (OS) for these patients was 18.3 months; NRAS gene mutation rate was 0.29% (1/346), G12D, and OS for these patients was 14.2 months; HRAS gene mutation rate was 0.63% (2/315), including H27N and N85I, and median OS for both patients was 19.2 months. Among them, 18 cases of the 41 RAS mutation patients with co-occurring mutations had a median OS of 28.0 months, and median OS of the 23 patients without cpmplex mutations was 21.0 months. No statistically significant difference was found between the two groups(P=0.06). Briefly, patients of KRAS mutations with (n=4) or without (n=34) co-occurring EGFR mutations had a median OS of 40.0 months and 16.3 months respectively (P=0.07); patients with (n=3) or without (n=35) co-occurring TP53 mutations had a median OS of 36.4 months and 18.3 months respectively (P=0.22); patients with (n=3) or without (n=35) co-occurring STK11 mutations had a median OS of not reached so far and 16.3 months respectively (P=0.22); patients with (n=2) or without (n=36) co-occurring KEAP1 mutations had a median OS of 43.6 months and 16.3 months respectively (P=0.06). **Conclusion:** Mutation rate of KRAS gene in current-smoker NSCLC patients was higher than no-smoker, there is no other significant difference of molecular features in RAS gene mutations in NSCLC. Patients with complex mutations benefited more from therapy than those with single mutations. Immunotherapy may displayed moderate efficacy in patients with TP53 and RAS co-exist mutations.

Keywords: Non-small-cell lung cancer, Prognosis, RAS

P1.02-048 SOMATIC MUTATION ANALYSIS OF RB1 GENE IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: RB1 (retinoblastoma 1) was reportedly one of the major determinative factors for sensitivity to taxanes in previous studies. The dephosphorylated RB1 protein confers the higher sensitivity to chemotherapy drug, but the RB1 mutation non-small-cell lung cancer (NSCLC) genetic variability and prognosis is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring RB1 mutations. **Method:** A total of 728 patients with NSCLC were recruited between July 2012 and December 2014. The status of RB1 mutation and other genes were detected by next generation sequencing. **Result:** RB1 gene mutation was detected in 0.96% (7/728) NSCLC patients, including p.G449E (1 patient), p.L542stop (1 patient), p.R552* (1 patient), p.Y6511fs*7 (1 patient), c.2663+2T>C (1 patient), p.P23del (1 patient) and F684fs*7 plus R418T (1 patient), and median overall survival (OS) for these patients was 32.7 months. Among them, all patients were RB1 gene with co-occurring mutations. Briefly, patients with (n=3) or without (n=4) co-occurring EGFR mutations had a median OS of 34.9 months and 30.4 months respectively (P=0.95); patients with (n=5) or without (n=2) co-occurring TP53 mutations had a median OS of 32.7 months and 31.7 months respectively (P=0.90). **Conclusion:** EGFR or TP53 gene accompanied may have less correlation with RB1 mutation in NSCLC patients. Chemotherapy drugs may displayed moderated efficacy in patients with RB1 mutation, especially, accompanied with TP53. These data have implications for both clinical trial design and therapeutic strategies.

Keywords: RB1 genen mutation, Non-small-cell lung cancer, Prognosis

P1.02-049 DETECTION OF CDKN2A GENE MUTATIONS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER PATIENTS

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Background: CDKN2A is the tumor suppressor, which regulates cell cycle progression by inhibiting cyclinD-CDK4 and cyclinD-CDK6 complexes responsible for initiating the G1/S phase transition. CDKN2A gene disruption happens by different types of mutations, such as the loss of heterozygosity, homozygous deletion, or promoter silencing. There is some clinical evidence for the use of CDKN2A mutations as prognostic and predictive biomarker. The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer(NSCLC) harboring CDKN2A mutations. **Method:** A total of 1046 patients with NSCLC were recruited between July 2012 and December 2014. The status of CDKN2A mutation and other genes were detected by next generation sequencing. **Result:** CDKN2A gene mutation was detected in 0.77% (8/1046) NSCLC patients, including p.M53I (1 patient), p.R58* (2 patients), p.R80* (2 patients), c.193+2T>C (1 patient), p.A127T (1 patient) and p.D74Y (1 patient), and median overall survival (OS) for these patients was 29.8 months. Among them, all patients were CDKN2A gene with co-occurring mutations. Briefly, patients with (n=4) or without (n=4) co-occurring EGFR mutations had a median OS of 23.4 months and 33.6 months respectively (P=0.32); patients with (n=6) or without (n=2) co-occurring TP53 mutations had a median OS of 23.4 months and 34.8 months respectively (P=0.27). **Conclusion:** EGFR and TP53 gene accompanied may have less correlation with CDKN2A mutation in NSCLC patients. CDK4/6 inhibitor palbociclib drugs may displayed moderated efficacy in patients with CDKN2A mutation. The findings of this study could facilitate the identification of therapeutic target candidates for precision medicine of NSCLC

Keywords: Non-small-cell lung cancer, Prognosis, CDKN2A mutation

P1.02-050 PAN-CAN ANALYSIS OF MIRNAS AT THE IMPRINTED CHROMOSOME 14Q32 LOCUS REVEALS A UNIQUE PATTERN OF DEREGULATION IN NSCLC

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Background: Genes expressed at the imprinted chromosome 14q32 locus play crucial roles in both fetal and adult development. The protein-coding genes expressed by the paternal allele are required for proper placentation and organogenesis; while the expression of non-coding genes encoded by the maternal allele were found to be temporally active in the brain. Previous reports identified few miRNAs at the locus that were able to stratify low and high risk patients with non-small cell lung carcinoma (NSCLC). However, a locus-wide analysis of miRNA deregulation across smoking-associated tumours still remains unexplored. To address this, we quantified the expression of 51 miRNAs in 10 smoking-associated cancer types and assessed their differential expression in unpaired normal and malignant tissues. **Method:** We analyzed the small RNA transcriptome in 10 cancer types from The Cancer Genome Atlas (TCGA) clinical cohorts (i.e. LUAD, LUSC, HNSC, kidney, stomach, esophagus, bladder, cervical, pancreas and liver). All small RNA sequencing reads were aligned on the human genome build 19 (hg19) and normalized using our in-house bioinformatics pipeline. miRNAs with expressions greater than or equal to 1.0 RPM in 10 percent of samples were included for further analysis. Zeta-score values were calculated and used for unsupervised hierarchical clustering to identify distinct patterns of deregulation across different cancer types. We validated our findings using 132 paired NSCLC samples from the British Columbia Cancer Agency (BCCA). Small RNA sequencing of the validation cohort was performed using Illumina Hi-seq 2000 platform. All samples were microdissected prior to RNA isolation. **Result:** We identified 39 miRNAs that are expressed in all cancer types included in this study. Unsupervised hierarchical clustering based on miRNA z-score values revealed a distinct pattern of deregulation in NSCLC compared to other smoking-associated malignancies. Many of these miRNAs were upregulated in both lung adenocarcinoma and squamous carcinoma while other cancers showed either repression or unchanged expression. We further assessed the expression of these miRNAs in metastatic (with lymph node/distant organ invasion) and non-metastatic lung adenocarcinoma (LUAD) cases using TCGA and BCCA clinical cohorts. From this analysis, we found miR-323b, miR-433 and miR-889 consistently unregulated (p value ≤ 0.01) in metastatic tumours. **Conclusion:** NSCLC tumours showed a unique pattern of deregulation in chromosome 14q32 small non-coding genes when compared with other smoking-associated malignancies. Also, we identified three miRNAs that were significantly upregulated in metastatic LUAD cases. Target prediction and thorough functional assays of these miRNAs may reveal novel pathways disrupted during the metastatic progression of LUAD.

Keywords: chromosome 14q32, non-small cell lung cancer, miRNAs

P1.02-051 ULTRA-DEEP SEQUENCING DEPICTS THE GENOMIC LANDSCAPE OF GROUND-GLASS NODULES IN EARLY STAGE LUNG ADENOCARCINOMA

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Background: Ground-glass nodule (GGN) is a type of nonspecific abnormality in lung parenchyma detected by computed tomography (CT) as hazy lesion with preservation of bronchial structures and vascular margins, which has a high correlation with lung adenocarcinoma. Different from typical lung cancer, malignant GGN appears a very early stage characteristic with long and indolent course. Large-scale radiological, pathological, and genetic studies on GGNs have broadened our knowledge to develop strategies of management. However, the molecular pathogenesis of GGNs remains unclear, leaving several questions of great clinical significance unsolved. **Method:** Motivated by this, we collected a cohort of 29 GGN patients diagnosed as early stage lung adenocarcinoma and performed whole exome sequencing (WES) to clarify the comprehensive genomic features and underlying molecular mechanism of GGNs. With the expectation of low purity of these samples, we adopted an ultra-deep sequencing depth to ~1000x, which is the deepest WES strategy so far in a single sample of single sequencing experiment to our knowledge, and got a high resolution landscape of genomic alterations in GGNs. **Result:** We found the extreme heterogeneity within each GGN patient, most of mutations manifesting as low frequency, indicating that GGNs grew under neutral evolutionary dynamics. Next we analyzed the mutation signature of these mutations and identified two novel signatures, Cp*C>A and Gp*CPC>T/Gp*CpG>T. These two signatures can reflect the mutation accumulating process within a growing tumor after initiation. Seven driver genes calculated in our cohort were all known lung cancer related genes, including *EGFR*, *MGA*, *PIK3CA*, *PPP2R1A*, *RBM10*, *SETD* and TP53. Of note, copy number alterations in GGNs were significantly less than other late stage lung cancers and this would result in the specific nature of GGNs. **Conclusion:** In summary, this analysis of exome sequencing data highlights the repertoire of cancer genes and mutational processes in GGN patients, and progresses towards a comprehensive account of the somatic genetic basis of GGNs. These results, combined with further study efforts, will accelerate the pace to the achievement of accurate diagnosis and treatment for GGN patients. Also, the endeavor here provides a framework for the research on early stage tumors and low purity tumors, which will become a subject of active investigation in the near future.

Keywords: Whole exome sequencing, lung adenocarcinoma, ground glass nodule

P1.02-052 IDENTIFICATION OF DAB2 AND INTELECTIN-1 AS NOVEL POSITIVE IMMUNOHISTOCHEMICAL MARKERS OF EPITHELIOID MESOTHELIOMA

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Background: Malignant mesothelioma is a fatal malignant tumor. It is often difficult to diagnose and to differentiate from other carcinomas, especially pulmonary adenocarcinoma. As there are currently no absolute immunohistochemical positive markers for the definite diagnosis of epithelioid mesothelioma, the identification of additional "positive" markers that may facilitate this diagnosis becomes of clinical importance. **Method: Gene Expression Analysis** Formalin-fixed paraffin-embedded tissue sections from 6 epithelioid mesothelioma and 6 pulmonary adenocarcinoma cases were used for gene expression analysis. RNA extraction for gene expression analysis was performed from papillary or solid growth of tumor cells in each specimen. The Human Transcriptome 2.0 GeneChip Array containing gene transcript sets of 44,699 protein coding and 22,829 nonprotein coding clusters was used to analyze gene expression profiles. Validation by Real-time RT PCR & Western Blotting The increased mRNA expression of DAB2 and Intelectin-1 was validated by reverse transcriptase polymerase chain reaction of RNA from tumor tissue and protein expression was validated by Western blotting of 5 mesothelioma cell lines. Immunohistochemical Procedures and Evaluation of Expression of DAB2 and Intelectin-1 The utility of DAB2 and Intelectin-1 in the differential diagnosis of epithelioid mesothelioma and pulmonary adenocarcinoma was examined by an immunohistochemical study of 75 cases of epithelioid mesothelioma and 67 cases of pulmonary adenocarcinoma. **Result:** Differential Gene Expression Of the 44,699 protein coding and 22,829 nonprotein coding transcripts on the Human Transcriptome 2.0 GeneChip Array, 902 statistically significant mRNA transcripts were differentially expressed, with a greater than 1.3-fold difference, between epithelioid mesothelioma and pulmonary adenocarcinoma. Validation Realtime RT-PCR showed relative mRNA expression of DAB2 and Intelectin-1 was significantly higher in epithelioid mesothelioma than that in pulmonary adenocarcinoma. Western blot analysis showed DAB2 and Intelectin-1 protein expression in all 5 commercially available mesothelioma cells lines with anti-DAB2 and anti-Intelectin-1 antibody. Immunohistochemical Expression Profiles in Epithelioid Mesothelioma and Pulmonary Adenocarcinoma The expression of DAB2 and Intelectin-1 was localized in the cytoplasm of tumor cells in epithelioid mesothelioma cases. Positive DAB2 expression was observed in 60 of 75 epithelioid mesotheliomas (80.0%) and 2 of 67 pulmonary adenocarcinomas (3.0%). In half of epithelioid mesotheliomas, DAB2 immunoreactivity was generally strong and diffuse (score 3+). In contrast, pulmonary adenocarcinomas showing DAB2 expression was focal (score 1+). **Conclusion:** We identified 2 novel positive markers of epithelioid mesothelioma, DAB2 and Intelectin-1, by using gene expression microarray analysis and confirmed their utility to differentiate epithelioid mesothelioma from pulmonary adenocarcinoma by immunohistochemical study.

Keywords: DAB2 & Intelectin-1, Epithelioid mesothelioma, gene expression analysis

P1.02-053 A NEW STRATEGY OF ADJUVANT CHEMOTHERAPY FOR LUNG CANCER BASED ON THE EXPRESSION OF ANTI-AGING GENE KLOTHO

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Background: Adjuvant chemotherapy of lung cancer including cisplatin is recommended for patients with lung cancer p-stage II-IIIA in case of complete resection. However, at the present, treatment outcomes are not necessarily satisfactory, and there is not effective chemotherapy resume for each patient individually. Establishing effective chemotherapy resume for each patients individually and practicing personalized medicine of lung cancer are expected for improving treatment outcomes after operation of p-stage II-IIIA patients. 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 aimed at revealing possibility of the Klotho gene expression as prognostic factor and effect prediction factor of the chemotherapy, and establishing personalized medicine for adjuvant chemotherapy of lung

cancer. **Method:** We introduced the Klotho-plasmid into lung cancer cell A549 and established Klotho overexpressing cell, A549/Klotho. We examined the sensitivity test for various anticancer agents including pemetrexed, CDDP, paclitaxel, gefitinib, etc, using A549 cells and A549/Klotho cells. **Result:** 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). A549/Klotho cells were a little sensitive against docetaxel. There is no difference of sensitivity between A549/Klotho cells and A549 cells against molecular target drugs such as afatinib, alectinib, ceritinib, gefitinib, and osimertinib. In A549/Klotho cells expression of N-cadherin was completely inhibited by Western blot analysis. **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: lung cancer, Klotho, N-cadherin

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-054 THE MOLECULAR CHARACTERISATION OF LUNG ADENOCARCINOMA SUBGROUPS

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Background: Lung adenocarcinoma is a heterogeneous disease which can be challenging to classify accurately, yet precise histological subtyping is becoming increasingly important. Subgroup patterns have been shown to confer important prognostic information. In this study, we sort to identify gene expression profiles for the six predominant subtypes within adenocarcinoma, in a sequential cohort of resected tumours, to explore whether molecular markers could enhance standard histological diagnosis. **Method:** 89 paired (fresh frozen tumour and normal tissue) lung adenocarcinomas were profiled both histologically and by global gene expression and correlated with multiple clinical parameters including stage, age, gender and smoking status. The tumour samples were reviewed by a thoracic pathologist to determine the predominant subtype and assigned into lepidic, acinar, papillary, micropapillary, solid or cribriform predominant groups. Gene expression was generated using Affymetrix Human gene 1.1ST arrays and the Genetitan platform. All RINs > 6. The data was rma treated using Affymetrix Power Tools and poor quality arrays were detected and excluded using Array Quality Metrics. Low expressed probes and control probes were removed. Differential gene expression of the adenocarcinoma predominant subtypes was evaluated using Limma. **Result:** Survival analysis confirms that age and stage are the most significant predictors of outcome. Application of a highly stringent threshold (adj. P value 0.0001) identified 4805 gene transcripts that were significantly differentially expressed among the six predominant adenocarcinoma subtypes. We determined that 3887 of these transcripts are unique to one of the adenocarcinoma subgroups and therefore have the potential to contribute to a predominant subtype defining transcriptional signature. These unique transcripts include functionally interesting genes such as transcriptional factors SOX2/4/7/13/18 involved in determination of cell fate and ROR1 a receptor tyrosine kinase-like orphan receptor among others. A pairwise comparison of the individual subgroups identified that the most significant gene variation is seen between lepidic predominant and solid predominant, indicating that these subgroups are transcriptionally the most disparate to one another. **Conclusion:** In this study multiple highly significant gene transcripts that allow differentiation between the adenocarcinoma subgroups have been identified. These adenocarcinoma subtype gene signatures have the potential to augment current histological diagnosis of lung adenocarcinoma and provide valuable insights into the different biological processes underpinning the six adenocarcinoma subtypes.

Keywords: Genomics, adenocarcinoma subtypes, transcriptomics

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-055 GENOTYPING SQUAMOUS CELL LUNG CARCINOMA AMONG HISPANICS (GENO1.1-CLICAP)

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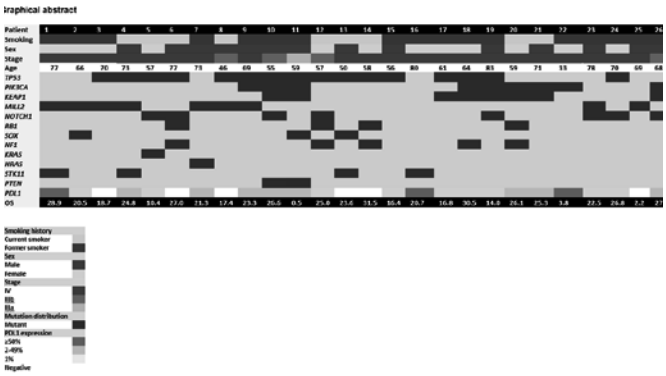
Background: Lung squamous cell carcinoma (SCC) is the second most prevalent type of lung cancer. Currently, no targeted therapeutics are approved for treatment of this cancer subgroup, largely because of a lack understanding of the molecular pathogenesis of the disease. To characterize SCC genomic profile among Hispanics we tested diverse alterations using a validated next generation sequencing (NGS) platform. **Method:** We performed sequencing using a comprehensive NGS assay (*TruSight Tumor 170*) targeting the full coding regions of 170 cancer-related genes on 26 squamous cell lung cancer samples from Hispanic patients. PD-L1 expression in tumor cells (TCs) was assessed using clone 22C3 (Dako) and main clinical outcomes like progression free survival (PFS), overall response rate (ORR), and overall survival (OS) were recorded. **Result:** Median age was 67 years (range, 33-83), 53.8% were men and all patients had previous exposure to tobacco (former 69.2%/current 30.8%) with a mean consumption rate of 34-year package. Almost all patients (80.8%) received cisplatin or carboplatin plus gemcitabine as first line with an ORR of 61.5%, a median PFS of 12.0 months (95% CI 10.9-13.2) and OS of 24.8 months (95% CI 20.8-28.7). We found a relatively high prevalence of inactivating mutations in TP53 (61.5%), PIK3CA (34.6%), MLL2 (34.6%), KEAP1 (30.8%) and NOTCH1 (26.9%). In addition, genetic alterations in the NF1 (19.2%), RB1 (15.4%), STK11 (15.4%), SOX2 (11.5%), PTEN (7.7%), KRAS (3.8%) and HRAS (3.8%). Distribution of PD-L1 expression were: negative, 1%, 2-49% and ≥50% in 23.1%, 38.5%, 26.9% and 11.5%, respectively. None of the genetic alterations affected PFS, OS or ORR and PDL1 expression was lower among those who had mutations in TP53 (p=0.037) and PIK3CA (p=0.05). **Conclusion:** We identified previously described mutations among Hispanic patients with SCC. Lower PDL1 expression was also found among those who had alterations in TP53 and PIK3CA.



Keywords: next-generation sequencing, PDL1, Squamous cell carcinoma

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-056 BRAF NON-V600E MUTATIONS RECURRENTLY FOUND IN NON-SMALL CELL LUNG CANCER IN CHINESE PATIENTS

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Background: Approximately half of BRAF-mutated non-small cell lung cancer (NSCLC) harbor a BRAF non-V600E mutation. Because of the rarity of those mutations, associated clinical features and prognostic significance have not been thoroughly described so far. **Method:** A total of 2979 patients with non-small-cell lung cancer were recruited between July 2012 and December 2014. The status of BRAF mutation and other genes were detected by pyrophosphate sequencing or the next generation sequencing. **Result:** BRAF gene mutation rate was 0.91% (27/2979) in NSCLC, and median overall survival (OS) for these patients was 14.0 months. Among them, 17 BRAF non-V600E patients (A308T, A569T, V377D, R626K, P345T, Q530*, A320T, G652E, N581S, T167I, G466V, L597V, D594G, D594G, R389C, G469A, W531S, 62.96%) had a median OS of 11.9 months, and median OS of the 10 BRAF V600E patients (37.04%) was 24.3 months. Statistically significant difference was found between the two groups (P=0.03). Briefly, patients with (n=2)(non-V600E), (n=3)(V600E) or without (n=22) co-occurring EGFR mutations had a median OS of 25.6 months, 14.8 months and 14.8 months respectively (P=0.43); patients with (n=12)(non-V600E), (n=4)(V600E) or without (n=11) co-occurring TP53 mutations had a median OS of 11.9 months, 26.8 months and 13.9 months respectively (P=0.23); patients with (n=2)(non-V600E), (n=1)(V600E) or without (n=24) co-occurring ATM mutations had a median OS of 25.8 months, 16.0 months and 12.9 months respectively (P=0.71); patients with (n=3)(non-V600E), or without (n=24) co-occurring KRAS mutations had a median OS of 10.4 months and 15.3 months respectively (P=0.14); patients with (n=5)(non-V600E), or without (n=22) co-occurring DNMT3A mutations had a median OS of 13.4 months and 15.3 months respectively (P=0.22). **Conclusion:** This one of the largest series of patients with BRAF mutant NSCLC. Our clinical datas suggest that BRAF non-V600E mutations define specific subsets of patients with NSCLC, the value of BRAF non-V600E mutations are poor prognosis than V600E mutations. And it may benefit from combined targeted therapy with a RAF inhibitor and a MEK-inhibitor in treating BRAF non-V600E mutantion NSCLC.

Keywords: Non-small-cell lung cancer, BRAF mutation, Prognosis

P1.02-057 ANALYSIS OF C-MET AMPLIFICATION NON-SMALL CELL LUNG CANCER CELL BLOCKS FROM PLEURAL EFFUSION

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Background: The MET receptor tyrosine kinase and its ligand, hepatocyte growth factor, is identified as a treatment target in lung cancer. c-MET gene abnormality can be distributed to various mechanisms including: overexpression, kinase activation, exon mutation, and amplification. c-MET gene amplification has been described as one of the reasons responsible for acquired EGFR tyrosine kinase inhibitor resistance. The aim of this study is to investigate the clinical value of c-MET gene amplification non-small cell lung cancer (NSCLC) blocks cell from pleural effusion. **Method:** Two hundred and fifeen cases of c-MET gene amplification 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 c-MET amplification was examined in 74 cases of patients with tissues and cell blocks. **Result:** c-MET amplification was found in 31 of 215 cell blocks (positive detection rate of 14.42%). c-MET amplification was detected in 35 of 404 tissue blocks (positive detection rate of 8.66%). There were 68cases in the 74 (91.89%) cases had the same consistency as tissue block. c-MET amplification was detected in 9 of 74 (12.16%) cell blocks, and 13 of 74 (17.57%) tissue blocks. **Conclusion:** The rate of c-MET amplification in cell blocks of NSCLC is higher than in matched tissue blocks. The patients with malignant pleural effusion are likely to tend c-MET amplification.

Keywords: non-small cell lung cancer, cell block, c-Met

P1.02-058 MOLECULAR CHARACTERISTICS AND OUTCOME OF CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER HARBORING NFE2L2 MUTATIONS

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Background: Recently, the nuclear factor (erythroid derived 2)-like 2 (NFE2L2) gene mutations are identified in non-small-cell lung cancer(NSCLC). While the genetic variability of NFE2L2 mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring NFE2L2 mutations. **Method:** A total of 375 patients with non-small-cell lung cancer were recruited between July 2012 and December 2014. The status of NFE2L2 mutation and other genes were detected by the next generation sequencing. **Result:** NFE2L2 gene mutation was detected in 2.40% (9/375) in NSCLC patients, including R34Q (2 patients), R34G (2 patient), D77Y (2 patients), D29N (1 patient), E79Q (1 patient) and D29H (1 patient), stage of IIIB-IV was much higher than IA-IIIA (9.76% *vs* 0.34%, P<0.001), and smoker was much higher than no-smoker (4.14% *vs* 0.97%, P<0.001). The median overall survival (OS) for these patients was 33.6 months. Among them, 7 patients with co-occurring mutations had a median OS of 37.4 months, and median OS of the 2 patient without complex mutations was 18.1 months. No statistically significant difference was found between the two groups (P=0.12). Briefly, patients with (n=4) or without (n=5) co-occurring EGFR mutations had a median OS of 33.6 months and 28.6 months respectively (P=0.76); patients with (n=4) or without (n=5) co-occurring TP53 mutations had a median OS of 33.6 months and 19.7 months respectively (P=0.88); patients with (n=2) or without (n=7) co-occurring DNMT3A mutations had a median OS of 37.4 months and 26.7 months respectively (P=0.72). **Conclusion:** There are some significant difference of clinical features in NFE2L2 gene mutations with smoking advance non-small-cell lung cancer. TP53 accompanied mutations might play a good prognosis in NFE2L2 gene mutation non-small cell lung cancer.

Keywords: Prognosis, NFE2L2 mutation, Non-small-cell lung cancer

P1.02-059 MOLECULAR CHARACTERISTICS OF SMARCA4 MUTATIONS DETECTION IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The SMARCA4 gene encodes an ATP-dependent helicase BRG1 and it belongs to SWI/SNF (switching defective/sucrose nonfermenting) complex. According to previous researches, SMARCA4 is one of the most broadly mutated subunits, developing an understanding of the mechanisms by which mutation of SMARCA4 drives cancer. The aim of this study is to investigate mutations and prognosis of NSCLC harboring SMARCA4 mutations. **Method:** A total of 1190 patients with non-small-cell lung cancer were recruited between July 2012 and December 2014. The status of SMARCA4 mutation and other genes were detected by next generation sequencing. **Result:** SMARCA4 gene mutation was detected in 0.84% (10/1190) NSCLC patients, including R370P (1 patient), N519Kfs*15 (1 patient), Q464K (1 patient), Q1440* (2 patients), E959* (1 patient), I1400M (1 patient), E882K (1 patient), D656H (1 patient) and A379T plus A39T (1 patient), and median overall survival (OS) for these patients was 17.9 months. Among them, all patients were RB1 gene with co-occurring mutations. Briefly, patients with (n=5) or without (n=5) co-occurring EGFR mutations had a median OS of 22.1 months and 14.7 months respectively (P=0.79); patients with (n=6) or without (n=4) co-occurring TP53 mutations had a median OS of 26.2 months and 16.3 months respectively (P=0.43); patients with (n=2) or without (n=8) co-occurring HER2 mutations had a median OS of 28.9 months and 14.7 months respectively (P=0.28);patients with (n=2)or without (n=9) co-occurring STK11 mutations had a median OS of 14.2 months and 26.2 months respectively (P=0.04);patients with (n=2) or without (n=8) co-occurring DNMT3A mutations had a median OS of 16.3 months and 26.2 months respectively (P=0.34); patients with (n=2) or without (n=8) co-occurring TERT mutations had a median OS of 22.1 months and 14.7 months respectively (P=0.88). **Conclusion:** mTOR pathway may play a poor prognosis in SMARCA4 gene mutation non-small cell lung cancer. HDAC inhibitor treatment may displayed moderated efficacy in patients with SMARCA4 gene mutations. Further research on SMARCA4 gene mutation is required. Maybe a panel of biomarkers will be necessary in the future.

Keywords: HER2 mutation, Non-small-cell lung cancer, Prognosis

P1.02-060 PODOPLANIN EXPRESSION IN CANCER-ASSOCIATED FIBROBLASTS PREDICTS POOR PROGNOSIS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE LUNG

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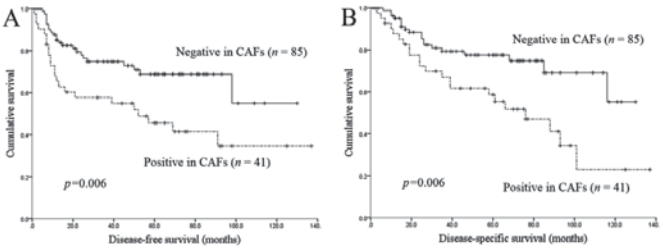
Background: Podoplanin is a candidate cancer stem cell marker in squamous cell carcinoma (SCC). Several studies have reported the prognostic value of podoplanin expression in tumor cells in lung SCC but few have focused on its expression in cancer-associated fibroblasts (CAFs). The aim of this study was to analyze the prognostic significance of podoplanin expression, with special reference to the expression pattern in both tumor cells and CAFs. **Method:** Immunohistochemical analyses using anti-podoplanin antibody were performed on 126 resected specimens of lung SCC. When more than 10% of tumor cells or CAFs showed immunoreactivity with podoplanin levels as strong as those of the positive controls, the specimens were classified as a podoplanin-positive. **Result:** Podoplanin-positive status in tumor cells (n=54) was correlated with a lower incidence of lymphatic invasion (p=0.031) but there were no significant differences in disease free survival (DFS) and disease-specific survival (DSS) by the log-rank test. Podoplanin-positive status in CAFs (n=41) was correlated with more advanced stage (p=0.008), higher frequency of pleural invasion (p=0.002) and both shorter DFS (p=0.006) and DSS (p=0.006). In Cox's multivariate analysis, podoplanin-positive status in CAFs was an independent negative prognostic factor for DFS (p=0.027) and DSS (p=0.027).



Conclusion: Podoplanin expression in CAFs might be an independent unfavorable prognostic indicator in patients with lung SCC, irrespective of the expression status of tumor cells.

Keywords: Squamous cell carcinoma, cancer-associated fibroblast, podoplanin

P1.02-061 PODOPLANIN EXPRESSION IN CANCER-ASSOCIATED FIBROBLASTS PREDICTS UNFAVOURABLE PROGNOSIS IN PATIENTS WITH STAGE IA ADENOCARCINOMA

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Background: Podoplanin expression in cancer-associated fibroblasts (CAFs) has been proposed as an unfavourable indicator in squamous cell carcinoma of the lung, but little is known about its clinical significance in early-stage lung adenocarcinoma. The aim of the present study was to evaluate the prognostic impact of podoplanin expression in patients with pathological stage IA lung adenocarcinoma classified by the new tumour-node-metastasis (TNM) system. **Method:** Paraffin-embedded tissue samples from 148 curatively resected patients with pathological stage IA1-3 lung adenocarcinoma were analyzed immunohistochemically using an antibody for podoplanin. When more than 10% of cancer cells or CAFs showed immunoreactivity with podoplanin, the specimens were classified as podoplanin-positive. The association between podoplanin expression status and clinicopathological factors was evaluated by the performing non-parametric tests. For the survival analysis, two different endopoints, cancer relapse and cancer-related death, were used to calculate disease-free survival (DFS) and disease-specific survival (DSS), respectively. **Result:** Podoplanin-positive status in cancer cells (n= 8) correlated with neither clinicopathological factors nor patients' prognosis. Podoplanin-positive status in CAFs (n= 43) was significantly correlated with poorer differentiation (P= 0.003), the presence of lymphatic invasion (P< 0.001) and high-grade (solid and/or micropapillary) component (P= 0.005). The log-rank test showed that podoplanin expression in CAFs was significantly associated with both shorter disease-free survival (DFS) (P< 0.001) and disease-specific survival (DSS) (P= 0.002). According to Cox's multivariate analysis, podoplanin-positive status in CAFs had the most significant effect on shorter DFS (hazard ratio [HR] = 6.037, P= 0.001) followed by the presence of high-grade component (HR = 3.82, P= 0.009). **Conclusion:** Podoplanin expression in CAFs could be an independent predictor of increased risk of recurrence in patients with pathological stage IA1-3 lung adenocarcinoma. Our result suggested that immunohistochemical analysis using antibodies to podoplanin, which has been routinely performed, could be useful not only for the detection of lymphatic vessel invasion but also for predicting an aggressive tumour phenotype in patients with lung adenocarcinoma.

Keywords: cancer associated fibroblast, podoplanin, CAF

P1.02-062 RING FINGER PROTEIN 38 PROMOTE NON-SMALL CELL LUNG CANCER PROGRESSION BY ENDOWING CELL EMT PHENOTYPE

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Background: RNF38, as an E3 ubiquitin ligase, plays an essential role in multiple biological processes by controlling cell apoptosis, cell cycle and DNA repair, .this study set out to investigate the and clinical implications of Ring finger protein 38 (RNF38) in non-small cell lung cancer (NSCLC). **Method:** We examined RNF38 expression pattern in in multiple cancers by Oncomine expression analysis,Immunohistochemistry, quantitative real-time polymerase chain reaction (qRT-PCR) and western blot were used to detect the levels of RNF38 protein and mRNA in NSCLC and corresponding paratumorous tissues.After RNF38 was knocked down using small hairpin RNAs (shRNA) in NSCLC cell lines (A549 and 95D), Wound-healing assays and trans-well assays were used to assess cell migration and invasion ability. Colony formation assays and CCK8 were used to detect proliferative abilities. The analysis of epithelial-to-mesenchymal transition (EMT) phenotype was carried out by immunofluorescence staining and western blot. **Result:** Our data revealed that elevated expression of RNF38 were more common in NSCLC tissue than paired normal tissues in both mRNA (2.82 ± 0.29 vs. 1.23 ± 0.13) and protein (2.75 ± 0.09 vs. 1.24 ± 0.02) level. Higher levels of RNF38 expression were significantly associated with lymph node metastases, higher TNM stages (p=2.09E-04) and predicted poor prognosis. We also observed that RNF38 expression was inversely correlated with E-cadherin expression (P= 0.025). Moreover, downregulation of RNF38 in NSCLC cells, the proliferation, metastatic and invasive abilities were significantly impaired. In addition, aberrant RNF38 expression could modulate the key molecules of EMT. **Conclusion:** Our results indicate that elevated expression of RNF38 is significantly associated with the proliferation and metastatic capacity of NSCLC cells, and RNF38 overexpression can serve as a biomarker of NSCLC poor prognosis.

Keywords: EMT, RNF38, Non-small cell carcinoma

P1.02-063 TUMOR HETEROGENEITY ANALYSES BY INTEGRATED PROTEO-GENOMICS OF THORACIC TUMORS FROM SEQUENTIAL BIOPSIES AND WARM AUTOPSIES

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Background: Tumor heterogeneity modulates treatment response to targeted therapy. Both intra-tumor and inter-tumor heterogeneity is well characterized in various cancers, including lung cancer, the commonest cause of cancer death in both men and women. Tumor heterogeneity studies have been conducted mostly for early stage lung cancer. Furthermore, these studies have focused primarily on next-generation sequencing (NGS). **Method:** We applied whole exome sequencing (WES), RNA-seq, OncoScan CNV and mass spectrometry-based proteomic analyses on 46 tumor regions from metastatic sites including lung, liver and kidney, obtained by rapid/warm autopsy from 4 patients with stage IV lung adenocarcinoma, 1 patient each with pleural mesothelioma and thymic carcinoma. 3/6 patients were admitted to NIH Clinical Center to receive in-patient hospice care before death under this study and the autopsy procedure was initiated between 2-4 hours of death in all patients. We have also performed similar integrated proteogenomics analyses on 11 different biopsies, including at autopsy of an "exceptional responder" lung adenocarcinoma patient who survived with metastatic lung adenocarcinoma for 7 years. We used the "super-SILAC" and TMT labeling strategies for quantitative proteomics using a Thermo Orbitrap Elite mass spectrometer. Patient-specific databases were built incorporating all somatic variants identified by NGS to interrogate the mass spectrometry data and an extensive validation pipeline was built for confirmation of variant peptides. **Result:** Here, we report an integrated analysis at the level of somatic variants, copy number, transcript, protein expression, and the phosphoproteome to demonstrate the extent of tumor heterogeneity and its potential impact on tumor biology. All tumors displayed organ-specific, branched evolution that was consistent across exome, transcriptome and proteomic analyses. RNA-seq, CNV-seq and proteomics analyses complemented the clonal evolution analyses performed using WES. The degree of heterogeneity at the genomic and proteomic level was patient-specific. There was extreme heterogeneity within the tumors of one of four patients with lung adenocarcinoma and in the thymic carcinoma patient (both non-smokers). Further examination of the heterogenous thymic and lung adenocarcinoma tumors showed strong enrichment of APOBEC-mutagenesis signature and high APOBEC3B mRNA levels. We identified a high risk *APOBEC3AB* germline allele in the thymic carcinoma patient that results in increased APOBEC expression and mutagenesis. **Conclusion:** Our integrated proteo-genomics analyses reveal significant differences in the genomic and proteomic intra-tumor and inter-tumor heterogeneity. APOBEC-mutagenesis is a significant driver of extreme cases of heterogeneity. High risk *APOBEC* germline alleles and increased APOBEC expression drive APOBEC mutagenesis in select patients.

Keywords: Proteo-genomics, Autopsy, Tumor-heterogeneity

P1.02-064 PROTEOMIC ANALYSIS OF EXOSOME PURIFIED USING A NOVEL REAGENT

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Background: Exosomes are a type of extracellular vesicles secreted from all types of cells via endosomal pathway and found in most body fluids, including blood, urine, saliva, blood, breast milk, and cerebrospinal fluid. Many biologically active molecules such as protein, mRNA, miRNA, DNA and phospholipid are found in exosomes. Exosomes have been suggested to mediate cell-to-cell communication and breast cancer metastasis to lung via integrin of exosome. In order to explore the function of exosomes, highly efficient, comprehensive proteomic analysis is essential. To this end, surfactants are generally used to enhance protein digestion efficiency, which results in the increased total sequence coverage and number of identified peptides and proteins in LC-MS. In this study, we compared the efficiency of commercially available surfactants using cancer cell conditioned medium. We have also assessed the presence of cancer marker within the exosomes. **Method:** A novel reagent was added to serum, plasma, urine and conditioned medium, and exosomes were recovered by ultracentrifugation or immunoprecipitation. Obtained highly pure exosomes were subjected to immunoblotting, nanoparticle tracking analysis (NTA) and proteomic analysis using mass spectrometry. Obtained exosomes are collected from conditioned medium by ultracentrifugation, and lysed using commercially available MS-compatible detergents (e.g., RapiGest SF, AALS, NALS and ZALS) before being digested by proteases. Obtained peptides were analyzed using LC-MS. **Result:** LC-MS analysis has shown that the number of proteins identified from exosomes collected from the conditioned medium has increased by the addition of lysis step using various kinds of MS-compatible detergents compared to guanidine-HCl treatment, with the exception of CALS I and ZALS I. **Conclusion:** Highly pure exosomes can be isolated from cell culture supernatants and body fluids at high yield using our solution in immunoprecipitation and ultracentrifugation. Addition of solubilization step using detergents for proteomic analysis has increased the number of identified proteins from exosomes. However, the

lysis efficiencies of exosomes varied depend on the type of surfactants.

Keywords: LC-MS, surfactant, Exosome

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-065 HISTONE DEACETYLASE INHIBITION ALTERS STEM CELL PHENOTYPE IN GEFITINIB-RESISTANT LUNG CANCER CELLS WITH EGFR MUTATION

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Background: Cancer stem cells (CSCs) are epigenetically altered by histone deacetylase (HDAC), resulting in chromatin condensation. We have reported that gefitinib-resistant-persisters (GRP) population within non-small cell lung cancer (NSCLC) cells possesses CSCs features. The purpose of this study is to examine the role of HDAC in the gefitinib-resistant lung CSC. **Method:** We used HDAC1, HDAC2, and HDAC5 as markers of chromatin compaction in GRP of EGFR-mutant NSCLC cells PC9 and HCC827. Gefitinib-resistant tumor (GRT) was established by obtaining the remaining tumor in PC9-injected NOG mice after two weeks of gefitinib treatment. Quantitative real-time PCR were performed to analyze gene expressions. immunofluorescence and fluorescence-immunohistochemistry were performed to analyze protein expressions in the NSCLC cell lines and *in vivo* biopsy specimens, respectively. HDAC inhibitor Trichostatin-A was used to study the impact on the sensitivity of GRP to gefitinib and the implication on the CSC features. **Result:** PC9-GRP and HCC827-GRP cells expressed high level of HDAC1, HDAC2, and HDAC5. GRT also showed upregulation of HDAC1 compared to naïve PC9 tumor. Inhibition of HDAC reduced CSC-related factors and, reduced sphere formation of GRP, and increased sensitivity to gefitinib. Specimens from lung cancer patients with acquired resistance to gefitinib displayed high expression of HDAC1. **Conclusion:** HDAC is implicated in the CSC phenotype and is involved in the resistance to EGFR-TKI in NSCLC. Inhition of HDAC could be considered to reverse acquired resistance of EGFR-mutant to EGFR-TKI that is mediated by CSC.

Keywords: Cancer Stem Cells, acquired resistance to EGFR-TKI, HDACs

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-066 CANCER STEM CELLS IN PULMONARY HIGH GRADE NEUROENDOCRINE CARCINOMA: A SERIES OF 23 CASES FROM EASTERN INDIA

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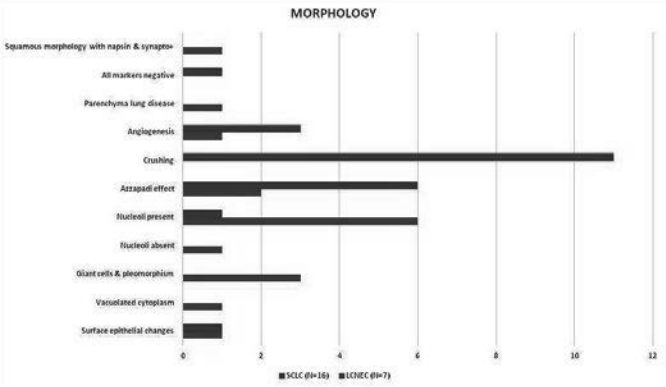
Background: As per WHO 2015 classification, high grade neuroendocrine carcinomas (HGNEC) [both large cell (LCNEC) and small cell (SCLC)] constitute around 20% of the total lung carcinomas. These tumours are biologically aggressive with early metastasis; have a tendency to recur and develop resistance to conventional chemotherapy. The aggressive behaviour is postulated to be due to the presence of stem cell like cancer cells [cancer stem cell (CSC)].This study was aimed to determine the clinicopathological significance of CSC markers in HGNEC on small lung biopsies. **Method:** Twenty three cases of HGNEC (7 LCNEC, 16 SCLC) diagnosed over a period of 2 ½ years at AIIMS, Bhubaneswar were analysed retrospectively. Bronchoscopic and transthoracic biopsies were subjected to routine morphological and immunohistochemical analysis by using synaptophysin, chromogranin, CD 56/NCAM, and Mib-1. Subcategorization was done as per WHO 2015 guidelines. CSC markers such as ALDH1, CD 34, and CD 117 were used for further analysis. **Result:** As follows



Neuroendocrine panel including CSC markers:

Markers	LCNEC=7		SCLC=16	
CD56	2		5/8	
Synaptophysin	7		13/16	
Chromogranin	3		6/10	
TTF1	4		5/9	
Mib-1	<50%	,>50%	<50%	>50%
	3/6 (50%)	3/6 (50%)	1/9 (11%)	8/9 (89%)
ALDH1	4/6 (66.6%)		3/13(23%)	
CD-117	3/6 (50%)		6/10 (60%)	
CD-34	1/6 (16%)		0/10 (0%)	

Conclusion: A high proportion (16/23, 68%) of HGNECs were positive for at least one CSC marker. ALDH1 expression noted more in LCNEC. Immunohistochemical expression of CSC markers on small biopsies may be used for prognostication and management in pulmonary neuroendocrine carcinomas.

Keywords: Cancer stem cells, neuroendocrine carcinoma, lung

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-067 FGF1 AND IGF1 CO-STIMULATION PROMOTED THE AMPLIFICATION AND CANCER STEMNESS OF LUNG CANCER CELLS UNDER 3D CULTURE CONDITION

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Background: Lung cancer stem cells (LCSCs) are considered as the cellular origins of metastasis and relapse of lung cancer. However, because of relative few amount of stationary LCSCs in primary cancer tissues, it is difficult to conduct large-scale mechanical and translational studies directly without any amplification of LCSCs *in vitro*. Routine two-dimentional culture system(2D-culture) hardly mimics the growth and functions of LCSCs *in vivo* and therefore significantly decreases the stemness activity of LCSCs. **Method:** We cultured human lung adenocarcinoma cell line A549 in basal medium eagle (BME) to establish three-dimentional (3D) culture condition, followed by screening cytokines that promote cancer stem cells' growth under 3D condition culture. To investigate their functions in enrichment of lung cancer stem-like cells, we constructed a conditioned 3D culture model and performed a serious of assays. We detected expression of stemness markers by flow cytometry and RT-qPCR, and stem cell like phenotypes including cell proliferation, colony formation, mammosphere culture, cell apoptosis, migration, invasion and drug resistance *in vitro*, as well as tumorigenicity *in vivo*. Furthermore, we explored the signaling pathways involved in regulating enrichment and amplification of lung cancer stem-like cells by Affymetrix HTA 2.0 Array. **Result:** We found 3D-culture promoted the enrichment and amplification of LCSCs in A549 cells which displaying higher proliferation and invasion activity, but lower apoptosis. The expression and secretion levels of FGF1 and IGF1 were dramatically elevated in 3D-culture compared to 2D-culture. After growing in FGF1 and IGF1-conditioned 3D-culture, the proportion of LCSCs with specific stemness phenotypes in A549 cells significantly increased compared to that in either traditional 2D or conventional 3D system. FGF1 and IGF1 promoted proliferation and invasion activity, as well as elevated drug resistance of LCSCs. Further results indicated that FGF1 and IGF1 promoted the amplification and cancer stemness of LCSCs dependent on MAPK signaling pathway. **Conclusion:** Our data firstly established a cytokines-conditioned 3D-culture for LCSCs and demonstrated the effects of FGF1 and IGF1 in promoting the enrichment and amplification of LCSCs which might provide a feasible cell models *in vitro* for both mechanical and translational researches on lung cancer.

Keywords: 3D culture, FGF1 and IGF1, Lung cancer stem cells

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-068 EFFECTS OF PIRFENIDONE TARGETING EMT AND TUMOR-STROMA INTERACTION AS NOVEL TREATMENT FOR NON-SMALL CELL LUNG CANCER

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Background: Epithelial-to-mesenchymal transition (EMT) is related to the malignant behavior of cancer. Interaction between cancer-associated fibroblasts (CAFs) and tumor cells has been shown to increase tumor cell survival via several pathways including EMT. Pirfenidone (PFD) is an anti-fibrotic agent for idiopathic pulmonary fibrosis and one of its functions may be to inhibit fibrotic EMT. We evaluated the effects of PFD on EMT using non-small cell lung cancer (NSCLC) cells, as well as interactions between CAFs and NSCLC cells *in vitro* and *in vivo*. **Method:** NSCLC cells (A549, NCI-H358) were used to evaluate the effects of PFD on EMT. Primary human fibroblasts obtained from tumors as well as normal tissues were isolated from surgically resected lungs of three patients with lung cancer, and defined as CAFs and LNFs, respectively. The effects of PFD on activation of CAFs and LNFs were determined by analyzing the expression of hallmarks of fibroblast activation and

pro-inflammatory markers. In addition, the impact of PFD on interactions between NSCLC cells and CAFs was also determined in vitro using a co-culture technique, as well as *in vivo* using co-implantation of those cells. **Result:** PFD significantly inhibited TGF-β1-induced EMT in NSCLC cells, and also the activation levels of α-SMA and collagen I, as well as cytokine productions of IL-6 and TGF-β1 by LNFs and CAFs. qRT-PCR results showed that the median diminution rates for three patients by PFD were 0.303 in LNFs and 0.69 in CAFs for α-SMA, and 0.316 in LNFs and 0.627 in CAFs for collagen I. Medium conditioned with LNFs or CAFs significantly induced EMT in NSCLC cells, while pretreatment of LNFs or CAFs with PFD inhibited the EMT change in NSCLC cells. *In vivo* findings showed that co-implantation of CAFs promoted tumor progression, which was suppressed by PFD via inhibition of EMT and stroma outgrowth. Immunohistological analysis showed that the Ki67 labelling index was higher in the co-implantation group than in the control group. Administration of PFD reduced the Ki67 labelling index by 27.1% in A549 tumors and 27.0% in NCI-H358 tumors in the co-implantation group. PFD also decreased α-SMA positive area with restoration of E-cadherin expression. **Conclusion:** Our findings suggest that PFD inhibits EMT and fibroblast activity, as well as cross-talk between cancer cells and fibroblasts. PFD may have great potential as a novel agent with a wide variety of actions for treatment of NSCLC.

Keywords: epithelial-to- mesenchymal transition, tumor-stroma interaction, pirfenidone

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-069 PEMETREXED-RESISTANT NON-SMALL CELL LUNG CANCER CELL LINES HAVE NOVEL DRUG-RESISTANT MECHANISMS

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Background: Pemetrexed (PEM) is an anti-folate drug that is widely used as a first-line chemotherapy for non-squamous non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) mutation that treated with EGFR tyrosine kinase inhibitors (TKIs). Beyond that, PEM has still important role for second- or third-line chemotherapy after the occurring EGFR-TKI resistant mutations. While several proteins such as a folate enzyme thymidylate synthase (TYMS) were reported as contributing factors of PEM resistance in NSCLC cells, we still need a maker with high specificity for drug sensitivity to PEM to use in clinical setting. We aimed finding novel factors of PEM-resistance by using NSCLC cell lines *in vitro*. **Method:** We established two different sets of PEM resistant NSCLC cell lines by long-term continuously PEM exposure in vitro from those parental cell lines A549 and PC-9. We analyzed the effects of PEM in those parental and resistant cell lines, also identified mechanisms of the resistance in PEM-resistant cell lines by molecular-biological analysis. **Result:** One of the PEM-resistant cell line that is derived from A549 has obviously decreased mRNA expression of a folate transporter protein SLC19A1 in qRT-PCR analysis. Additionally, we also confirmed that the siRNA knockdown of SLC19A1 endowed parental NSCLC cell lines with PEM resistance. Surprisingly, another PEM-resistant cell line derived from EGFR mutant PC-9 has not only the significantly increased TYMS that is most reported protein in PEM-resistant NSCLC cell lines but also EGFR-independent Akt activation on PI3K signaling pathway. Importantly, this Akt activation carried low sensitivity to EGFR-TKI and PI3K inhibitor in the PEM-resistant PC-9 cells. **Conclusion:** In conclusion, SLC19A1 negatively regulates PEM resistance in NSCLC cell lines and long-term PEM treatment encompasses EGFR-TKI resistance in EGFR mutant NSCLC cell line.

Keywords: pemetrexed, drug resistance, EGFR-TKI

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-070 IDENTIFICATION OF LUNG CANCER SPECIFIC DIFFERENTIALLY METHYLATED REGIONS USING GENOME-WIDE DNA METHYLATION STUDY

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Background: The development of lung cancer is resulted by the interaction between genetic mutations and dynamic epigenetic alterations, although its mechanisms are not fully understood. Among the epigenetic alterations, DNA methylation is the most studied epigenetic regulatory mechanism. DNA methylation changes may be promising biomarker for early detection and prognosis in lung cancer. We evaluated serial changes of genome wide DNA methylation pattern in blood of lung cancer patients. **Method:** Blood samples were obtained for three consecutive years from 3 patients (2 years before, 1 year before, and after lung cancer detection) and from 3 control subjects without lung cancer. We conducted an epigenome-wide analysis using the MethylationEPIC BeadChip which covers 850,000 cytosine-phosphate-guanine (CpG) site. The methylation value (β), a ratio between methylated probe intensity and total probe intensity, is interpreted as the proportion of methylation and ranges between 0 (unmethylated) and 1 (methylated). Significant differentially methylated regions (DMRs) were identified using p values < 0.05 in correlation test for serial methylation changes and serial increase or decrease of β value above 0.1 for three consecutive years. **Result:** We found significant 3 CpG sites with serial changed β values of differentially methylated regions and 7105 CpG sites with significant correlation for serial methylation changes from control patients without lung cancer. However, there were no significant DMRs met both conditions. In contrast, we found significant 11 CpG sites with serial changed β values of differentially methylated regions and 10562 CpG sites with significant correlation for serial methylations changes from patients with lung cancer. There were two significant DMRs met both conditions, cg21126229 (RNF212), cg27098574 (BCAR1). **Conclusion:** This genome-wide DNA methylation study showed DNA methylations changes that might be implicated in lung cancer development. The DNA methylation changes may be candidate target regions for early detection and prevention in lung cancer. Further investigation of these regions and related genes may lead development of a biomarker for lung cancer.

Keywords: DNA methylation, lung cancer, biomarker

P1.02: BIOLOGY/PATHOLOGY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.02-071 SFN STABILIZES ONCOPROTEINS THROUGH BINDING WITH SKP1 TO BLOCK SCF^{FBW7} UBIQUITING LIGASE

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Background: Lung adenocarcinoma is the most common subtype of non-small cell lung cancer (NSCLC) and accounts for about 50% of them. Although EGFR or EML4-ALK has been identified as oncogenic driver mutation and translocation for advanced adenocarcinoma, trigger or mechanism of its early progression is still unclear. Previously, we revealed that stratifin (SFN, 14-3-3 sigma) has tissue-specific functions and regulate cell cycle progression in a positive manner in lung adenocarcinoma (Shiba-Ishii A et al. *Mol Cancer* 2015). Moreover, S-phase kinase-associated protein 1 (SKP 1) which is an adaptor part of SCF-type E3 ubiquitin ligase complex including SCF^{FBW7}, SCF^{SKP2} and SCF$^{\beta\text{-TRCP}}$ was identified as one of the SFN binding protein by pull-down assay and LC-MS/MS analysis. The aim of this study is to analyze the molecular mechanism of tumor progression in lung adenocarcinoma associated with SFN binding with SKP1. We have hypothesized that SFN binds with SKP1 among various SCF complexes and specifically blocks SCF^{FBW7} function to ubiquitinate oncoproteins such as cyclin E1, c-Myc, c-Jun, and notch 1. **Method:** Endogenous interaction of SKP1 and SFN or FBW7 was examined by co-immunoprecipitation using A549, lung adenocarcinoma cells. We performed ubiquitination assay under the treatment of proteosome inhibitor, MG132 to induce accumulation of ubiquitinated oncoproteins after siRNA-SFN transfection. Moreover, to investigate whether SFN regulates the localization of SKP1, we performed immunofluorescence staining of A549 after siRNA-SFN treatment. **Result:** We found that SKP1 interacted with SFN and FBW7, respectively in lung adenocarcinoma cells. The binding activity of FBW7 with SKP1 increased after suppression of SFN, indicating that SFN and FBW7 might competitively bind with SKP1. Moreover, knockdown of SFN led to reduction of oncoproteins such as cyclin E1, c-Myc, c-Jun and notch 1 and showed accumulation of poly-ubiquitinated oncoproteins relative to the control by blocking proteosome degradation. However, p27^{Kip1} (substrate of SCF^{SKP2}) and IKB (substrate of SCF$^{\beta\text{-TRCP}}$) showed no expression change after knockdown of SFN. While SKP1 mainly localized in cytoplasm of A549, knockdown of SFN induced translocation of SKP1 to nucleus. **Conclusion:** SFN induces the stabilization of oncoproteins by blocking SCF^{FBW7} ubiquitin ligase in lung adenocarcinoma and associated with its malignant progression. SFN will be a promising theraputic target for lung adenocarcinoma.

Keywords: SFN, Adenocarcinoma, Ubiquitination

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-001 VERIFICATION AND IMPLEMENTATION OF THE VENTANA ANTI-ALK D5F3 ANTIBODY IN DETECTING ALK REARRANGEMENT IN NSCLC

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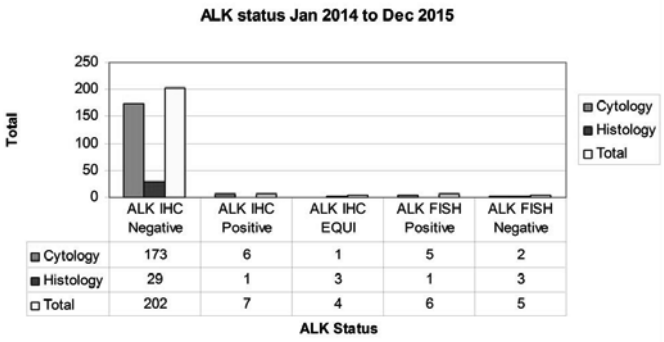
Background: NSCLC patients with ALK rearrangement (2-7%) are usually young, non-smokers and benefit from targeted first and second lines tyrosine kinase inhibitor e.g. Crizotinib. The gold standard test for ALK in patients with proven metastatic or locally advanced NSCLC is fluorescence in situ hybridisation (FISH), however, immunohistochemistry (IHC) for ALK protein overexpression such as the VENTANA anti-ALK (D5F3) antibody is a useful screening test for ALK status in NSCLC patients as it has a high negative predictive value. Positive or equivocal cases can be confirmed by FISH. **Method:** Accreditation standards require laboratories to verify equipment and reagent performance before adopting into routine practice. We tested cytology and histology NSCLC samples of primary lung origin using anti-ALK (D5F3) antibody for ALK status using the VENTANA IHC platform and compared the findings against the gold standard FISH methodology. We tested 50 consecutive NSCLC

samples of which 3 were excluded as FISH failed. **Result:** Of the remaining 47 samples, one was ALK positive by IHC and FISH and the remaining 46 were negative by both methods. As there were no false positive or negative cases by IHC, sensitivity, specificity, PPV and NPV were all 100%. We then proceeded to adopt reflex ALK testing by IHC as verification was achieved and confirmed equivocal and positive cases by FISH. In total we have tested 213 cases with ALK IHC equivocal in only 4 instances and one false positive (PPV = 85.7%). All 5 cases were negative by FISH (table below).



Conclusion: ALK by IHC can be implemented to identify patients' ALK status with confirmatory reflex testing by FISH for equivocal or positive cases in a cost effective and efficient process so that ALK positive patients can receive targeted TKI. Established cutting protocol to maximise tissue use is essential for tissue preservation and turn around times.

Keywords: ALK, IHC, FISH

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-002 CRIZOTINIB-ASSOCIATED TOXIC EPIDERMAL NECROLYSIS IN AN ALK-POSITIVE ADVANCED NSCLC PATIENT

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Background: Crizotinib is an oral small-molecule inhibitor of anaplastic lymphoma kinase (ALK) tyrosine-kinase that has been approved for treating patients with advanced echinoderm microtubule associated protein like 4-anaplasitic lymphoma kinase (EML4-ALK) rearranged non-small-cell lung cancer (NSCLC). *T*oxic epidermal necrolysis (TEN) is a rare adverse event related to crizotinib. **Method:** We report a case of 75-year-old Chinese male patient of advanced NSCLC harboring with ALK fusion, who developed TEN after 56 days of crizotinib treatment **Result:** the patient demised due to this dermatological adverse event **Conclusion:** The occurrence of severe cutaneous necrolysis that predominantly involve skin and mucous membranes during crizotinib treatment should alert clinicians to be aware of TEN and take prompt actions.

Keywords: toxic epidermal necrolysis, crizotinib, EML4-ALK rearranged

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-003 CLINICAL IMPLICATIONS OF AN ANALYSIS OF CRIZOTINIB PHARMACOKINETICS CO-ADMINISTERED WITH DEXAMETHASONE IN PATIENTS WITH NSCLC

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Background: Dexamethasone is a systemic corticosteroid often used in non-small cell lung cancer (NSCLC) patients to treat disease and treatment-related complications. It is a known weak-to-moderate cytochrome P-450 (CYP) 3A inducer that may decrease exposure of CYP3A substrate tyrosine kinase inhibitors (TKIs). Crizotinib (Xalkori®) is a selective inhibitor of anaplastic lymphoma kinase (ALK) and ROS1 and is approved for treating ALK-positive and ROS1-positive NSCLC. Crizotinib is a substrate and time-dependent inhibitor of CYP3A. Co-administration of crizotinib 250 mg BID with a strong CYP3A inducer, rifampin 600 mg QD, resulted in an 84% decrease in steady-state crizotinib exposure. In this analysis, we evaluated the effect of dexamethasone on steady-state crizotinib exposure from clinical studies in patients with ALK-positive and ROS1-positive NSCLC. **Method:** Data were from 4 clinical studies (PROFILE 1001, 1005, 1007, and 1014) with 1669 ALK-positive and 53 ROS1-positive NSCLC patients treated with crizotinib at the recommended starting dose of 250 mg BID. For each patient, multiple steady-state trough concentrations ($C_{trough,ss}$) of crizotinib were measured after ≥ 14 days of consecutive crizotinib 250 mg BID dosing. Withinpatient comparison of crizotinib $C_{trough,ss}$ between crizotinib dosing alone and crizotinib coadministered with dexamethasone consecutively for ≥ 21 days was performed using a linear mixed effects model. **Result:** There were a total of 514 (29.8%) patients who received dexamethasone from the 4 PROFILE studies. Other less commonly used (< 10%) weak-to-moderate CYP3A inducers included: methylprednisolone, prednisone, ginkgo/ginseng and efavirenz. In this analysis, a total of 15 patients had crizotinib $C_{trough,ss}$ for both crizotinib dosing alone and crizotinib co-administered with dexamethasone consecutively for ≥ 21 days. The adjusted geometric mean of crizotinib $C_{trough,ss}$ following co-administration with dexamethasone was 98.2% (90% CI: 79.1%-122.0%) relative to crizotinib dosing alone, with the lower limit just below the typical bioequivalence limits of 80%-125%. **Conclusion:** Dexamethasone was the most commonly used CYP3A inducer across the 4 PROFILE studies. Long-term (≥ 21 days) use of dexamethasone in NSCLC patients treated with crizotinib had no statistically significant effect on crizotinib exposure and thus would not compromise treatment efficacy. Other weak-to-moderate CYP3A inducers are not expected to have an effect on crizotinib, similar to the findings with dexamethasone. The framework of this analysis can be applied when dexamethasone or other weak-to-moderate CYP3A inducers are concomitantly used with CYP3A substrate TKIs.

Keywords: crizotinib, dexamethasone, ALK

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-004 ALECTINIB FOR PATIENTS WITH ALK REARRANGEMENT–POSITIVE NON–SMALL CELL LUNG CANCER AND A POOR PERFORMANCE STATUS

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Background: Alectinib is a potent and highly selective inhibitor of the tyrosine kinase ALK and has shown marked efficacy and safety in patients with *ALK* rearrangement–positive non–small cell lung cancer (NSCLC) and a good performance status (PS). It has remained unclear whether alectinib might also be beneficial for such patients with a poor PS. **Method:** Eligible patients with advanced ALK rearrangement–positive NSCLC and a PS of 2 to 4 received alectinib orally at 300 mg twice daily. The primary end point of the study was objective response rate (ORR), and the most informative secondary end point was rate of PS improvement. Plasma concentrations of alectinib were measured by liquid chromatography-mass spectrometry (LC-MS/MS). **Result:** Between September 2014 and December 2015, 18 patients were enrolled in this phase II study (Lung Oncology Group in Kyushu 1401). Twelve, five, and one patients had a PS of 2, 3, or 4, respectively, whereas four patients had received prior crizotinib treatment. The median follow-up time for all patients was 9.8 months (range, 5.6 to 18.0 months) at the time of the primary analysis. The ORR was 72.2% (90% confidence interval [CI], 52.9–85.8%), and the disease control rate was 77.8% (90% CI, 58.7–89.6%). The ORR did not differ significantly between patients with a PS of 2 and those with a PS of ≥3 (58.8% and 100%, respectively, $P = 0.114$). The PS improvement rate was 83.3% (90% CI, 64.8–93.1%, $P < 0.0001$), with the frequency of improvement to a PS of 0 or 1 being 72.2%. The median progression-free survival (PFS) was 10.1 months (95% CI, 7.1 to17.8 months), with no difference between the patients with a PS of 2 and those with a PS of ≥3 (median PFS, 10.1 and 17.8 months, respectively, $P = 0.24$). Toxicity was mild, with the frequency of adverse events of grade ≥3 being low. Neither dose reduction nor withdrawal of alectinib because of toxicity was necessary. The trough concentration of alectinib in plasma was 235 ± 65 ng/mL (mean ± SD), which is slightly lower than that previously reported in patients with a good PS, supporting the tolerability of alectinib administration in those with a poor PS. **Conclusion:** Alectinib is a treatment option for patients with *ALK* rearrangement–positive NSCLC and a poor PS. Updated data and that for overall survival will be available at presentation.

Keywords: Alectinib, poor performance status, ALK rearrangement

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-005 PHASE 2 STUDY OF CERITINIB IN PATIENTS WITH ALK+ NSCLC WITH PRIOR ALECTINIB TREATMENT IN JAPAN: ASCEND-9

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Background: ALK inhibitors are a standard of care for ALK-positive metastatic NSCLC and several ALK inhibitors are currently available. Alectinib is one of the recommended therapies as 1st line treatment for ALK-positive metastatic NSCLC in Japan based on robust progression-free survival (PFS) prolongation and favorable safety profile. However, even with treatment with alectinib, these cancers eventually progress after acquiring resistance against alectinib. Therefore, which drug should be chosen after alectinib is relevant clinical question. Recently, ceritinib, which is a highly selective oral ALK inhibitor, has demonstrated superior activity compared to chemotherapy in the 1st line setting for patients with ALK-positive metastatic NSCLC (ASCEND-4, Soria et al. Lancet 2017). It also showed clinically meaningful benefit in patients who failed to prior ALK inhibitor treatment including alectinib (Nishio et al. J Thorac Oncol 2015). In this study, we tried to evaluate efficacy and safety of ceritinib in ALK-positive metastatic NSCLC patients who progressed on alectinib treatment. **Method:** ASCEND-9 (NCT02450903) is a single-arm, open-label, multicenter, phase 2 study of ceritinib 750 mg/day (fasted) in adult patients with *ALK*+ (Vysis ALK Break Apart FISH Probe kit test), stage IIIB/IV NSCLC previously treated with alectinib and had subsequent disease progression. Other key inclusion criteria are ≥ 1 measurable lesion per RECIST 1.1 and WHO PS 0-1. Patients must have received previous treatment with alectinib, but prior crizotinib and/or up to 1 chemotherapy regimen are allowed. Patients with asymptomatic CNS metastases are eligible. Ceritinib may be continued beyond RECIST-defined PD. Primary endpoint is investigator assessed-overall response rate (ORR) per RECIST 1.1. Secondary endpoints include disease control rate (DCR), time to response (TTR), duration of response (DOR), PFS and safety. Biomarkers are evaluated for exploratory purpose. **Result:** Twenty patients were enrolled at 10 centers in Japan from Aug 2015 to Feb 2017. At present, the study is underway, and the results including ORR, DCR, TTR, DOR, PFS, safety and exploratory biomarker data will be presented at the 2017 WCLC. **Conclusion:** Section not applicable.

Keywords: Ceritinib, ALK+NSCLC, ALK sequential therapy

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-006 CLINICOPATHOLOGICAL FEATURES AND POOR OUTCOME FOR ALK INHIBITORS OF SQUAMOUS CELL LUNG CANCER WITH ALK-REARRANGEMENT

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Background: Anaplastic lymphoma kinase (ALK)-rearrangements are mainly encountered in 5% of adenocarcinomas lung cancer (Ad-LC) patients and anti-ALK targeted therapy dramatically improves therapeutic responses. The prevalence of ALK rearrangement in squamous cell lung carcinomas (Sq-LC) is extremely rare and thus, clinicopathological features and clinical outcomes for ALK inhibitors of ALK-rearranged Sq-LC were still unknown. Accordingly, in this study, we compared clinical features and clinical outcomes in patients with Sq-LC and Ad-LC. **Method:** We retrospectively analysed the clinical features of five patients with ALK-rearranged Sq-LCs including two ALK-rearranged adenosquamous cell lung carcinomas (AdSq-LC) and compared the results with ALK-rearranged Ad-LC. We also evaluated representative cases of both responder and nonresponder to ALK inhibitors. **Result:** The prevalence of ALK rearrangement in Sq-LCs was 1.36%. The population in ALK rearrangement NSCLC with smoking history was higher in ALK-rearranged Sq-LC than in ALK-rearranged Ad-LCs (80.0% and 68.0%). Progression-free survival (PFS) after initial treatment with the ALK inhibitor crizotinib was significantly shorter in ALK-rearranged Sq-LC than in ALK-rearranged Ad-LC (6.4±4.7 months and 13.4±12.8 months: p=0.033). Notably, two ALK fluorescence in situ hybridization (FISH)-positive/immunohistochemistry-negative cases did not respond to crizotinb, and PFS following alectinib treatment of ALK-rearranged Sq-LC was short (p = 0.045). The responder to ceritinib showed the presence of the L1196M mutation, which causes other ALK inhibitor resistance, by rebiopsy and successes to maintain CR response, even if detected off-target resistance marker of both EGFR and vimentin, a marker of EMT, for ALK inhibitors. However, the nonresponder did not respond to all ALK inhibitors, despite the presence of ALK FISH-positive circulating tumor cells and circulating free DNA without the mutation for ALK inhibitors resistance by liquid-biopsy. **Conclusion:** ALK-rearranged Sq-LC was associated with poor outcomes in ALK inhibitor-treated patients, suggesting that complexity of resistance mechanisms including off-target mechanisms for ALK inhibitors may exist. Oncologists should be aware of the possibility of ALK-rearranged Sq-LC based on clinicopathological features and plan the next therapeutic strategy by as much of re-biopsy accordingly to improve clinical outcomes.

Keywords: Squamous cell lung cancer, anaplastic lymphoma kinase rearrangement, Circulating tumor cells

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-007 A REAL-WORLD STUDY OF CLINICOPATHOLOGICAL CHARACTERISTICS AND SURVIVAL OUTCOME IN ADVANCED ALK-POSITIVE NON-SMALL-CELL LUNG CANCER

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Background: Crizotinib has resulted in substantial benefits for advanced non-small-cell lung cancer (NSCLC) patients harboring anaplastic lymphoma kinase (ALK) rearrangement. With limited real-world data available, the present work aimed to explore the clinicopathological characteristics and survival outcome of patients with advanced ALK+ NSCLC in a single center in China. **Method:** Data of 83 advanced ALK-rearranged NSCLC patients treated in Zhejiang Cancer Hospital were collected and analyzed retrospectively. Survivals were analyzed using the Kaplan-Meier method and were compared using the log-rank test. Multivariate analysis were performed by the Cox proportional hazard model. **Result:** Of the 83 patients enrolled, 33(39.8%) patients received crizotinib, and the other 50(60.2%) patients received chemotherapy as the initial treatment. The first-line use of crizotinib prolonged PFS compared with chemotherapy (median PFS 19.0 m vs. 5.7 m, P < 0.001), but not OS (46.0 m vs. 30.6 m, P=0.797). Till the last follow up, 71(85.5%) patients had received crizotinib, and 12(14.5%) patients were crizotinib-naïve. Patients who had received crizotinib had significantly longer OS than those who did not (48.9 m vs. 19.8 m, P < 0.05). Among the 71 patients who had received crizotinib,33(46.5%) used in first-line therapy, 22(31.0%) used in second-line therapy, and 16(22.5%) used after second-line therapy. There were not significant difference of OS among the three groups (30.6 m vs. 57.7 m vs. 40.8 m, *P*=0.583). The Cox multivariate analysis identified the following independent negative prognostic factors for OS: smoking (HR=4.725), liver metastasis(HR=4.570), bone metastasis (HR=2.651), and use of crizotinib (HR=0.295). **Conclusion:** Our real-world study showed that the use of crizotinib improved long-term survival of patients with advanced ALK-rearrangement NSCLC. There were no difference in survival outcome between patients with initial crizotinib and those with non-initial crizotinib.

Keywords: ALK, NSCLC, crizotinib

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-008 ANALYSIS OF DATA ON INTERSTITIAL LUNG DISEASE ONSET AND ITS RISK FOLLOWING TREATMENT OF ALK-POSITIVE NSCLC WITH XALKORI

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Background: Incidence and potential risk factors of interstitial lung disease (ILD) were evaluated in patients with *ALK*-positive non-small cell lung cancer (NSCLC) enrolled for all-case surveillance of Xalkori. **Method:** The survey was conducted on all patients treated with XALKORI® 200mg/250mg capsules. The observation period was 52 weeks from the initiation of treatment with Xalkori, or time from treatment commencement until treatment discontinuation in patients who discontinued treatment prematurely. Investigator-reported cases of ILD were assessed by the ILD independent review committee consisting of external experts to evaluate background risk factors potentially associated with the onset of ILD. **Result:** Among 2059 patients enrolled for this survey from May 2012 to October 2014, 1972 were included in a safety analysis. Among 139 reported cases of patients developing ILD following Xalkori treatment, 116 patients were confirmed to have ILD (incidence rate of 5.9%). The breakdown of these cases was mainly as follows: 63 (54%) patients were male, 52 (45%) were female, 57 (49%) were aged at least 65 years, 3 (2.6%) had a previous history of ILD, and 63 (54%) had smoking history, including former smokers. Giving the breakdown by Grade, 46 patients had Grade 2 or lower ILD, and 70 patients had Grade 3 or higher, including 22 with Grade 5 (mortality rate of 1.1%). Ninety-one patients (78.4%) developed ILD within 12 weeks after treatment commencement. The background factors with statistically significant differences among patients included age, body surface area, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and smoking history. Also the multivariate analysis revealed that aging, poor ECOG PS, former smokers and previous history or complications of ILD were correlated with the occurrence of ILD. **Conclusion:** The onset time, the incidence of ILD and risk factors obtained from this surveillance didn't seem to be significant difference with those of EGFR TKIs reported previously.

Keywords: interstitial lung disease, Xalkori, risk factors

P1.03-009 A LUNG ADENOCARCINOMA WITH A STRN-ALK REARRANGEMENT WAS POORLY RESPONSIVE TO ALECTINIB TREATMENT

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Background: Patients with advanced-stage non-small cell lung cancer (NSCLC) can receive benefits from treatment with anaplastic lymphoma kinase (ALK) inhibitors, if the tumor harbors a rearrangement of the ALK-encoding gene. Alectinib, a second-generation ALK inhibitor, is generally an effective therapy for ALK-rearranged NSCLC, but not all patients are responsive to Alectinib treatment. The aim of the present study was to assess the clinical and genetic characteristics of ALK-positive lung adenocarcinoma (ADC) that showed poor response to Alectinib treatment. **Method:** Patients with ALK-rearranged NSCLC, who received Alectinib treatment at Nihon University Itabashi Hospital (Tokyo, Japan) between 2015 and 2017, were included in the study. Demographic and clinical data including year, sex, stage, smoking history, treatment response, and survival were collected. Pleural effusion from a poorly responsive patient was further examined for secondary ALK mutations and ALK fusion partners. Secondary ALK mutations were analyzed using Sanger sequencing, and ALK fusion partners were identified by RNA sequencing. Furthermore, p-glycoprotein (p-gp)/ATP binding cassette subfamily B member 1 (ABCB1) mRNA levels were quantified by quantitative RT-PCR. The study was approved by the institutional review board. **Result:** Five patients (three men and two women; median age, 51 years) with adenocarcinoma were studied. Two patients received first-line treatment, two received second-line treatment, and one received fourth-line treatment. Four patients achieved partial response, and one patient did not respond to the treatment. The median progression-free survival (PFS) rate was 204 days. In the poorly responsive patient, PFS rate was 92 days, which was much shorter than previously reported. No secondary gatekeeper mutations in the ALK tyrosine kinase domain was detected in carcinoma cells obtained from pleural effusion of one poorly responsive patient. However, Striatin (STRN)/ALK, a rare fusion of the aggressive rearranged ALK, was identified, it was confirmed that one end of STRN exon3 was fused with the beginning of ALK exon 20. ABCB1 overexpression was also detected. **Conclusion:** A rare ALK rearrangement, STRN/ALK, and overexpression of the multidrug-resistant ABCB1 are possible candidates for predictive factors for poor response to Alectinib treatment.

Keywords: non-small cell lung cancer, Resistance, STRN/ALK

P1.03-010 EFFICACY AND SAFETY OF ANAPLASTIC LYMPHOMA KINASE (ALK) TYROSINE KINASE INHIBITORS IN ALK-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Anaplastic lymphoma kinase (ALK) gene rearrangements occur in 3-5% of non-small cell lung cancer (NSCLC) cases. ALK tyrosine kinase inhibitors (ALK-TKIs), such as crizotinib and alectinib, are recommended for the treatment of ALK-positive NSCLC. However, acquired resistance to the ALK-TKIs develops after treatment with these agents. Therefore, it is necessary to consider the alteration of the therapeutic approach against ALK-positive NSCLC. This investigation, reviewed patients with ALK-positive NSCLC treated at Hiratsuka Kyosai Hospital in 2016, to determine the efficacy and safety of ALK-TKIs in this setting. **Method:** The medical data of 11 patients who had been diagnosed with ALK-positive advanced NSCLC and treated with ALK-TKIs at Hiratsuka Kyosai Hospital in 2016 were reviewed retrospectively. **Result:** A total of 11 patients (3 males and 8 females; mean age: 62 years) with ALK-positive NSCLC were investigated. All the pathological types were adenocarcinomas. Eight patients were treated with crizotinib as first-line therapy, and 3 out of those patients were treated with alectinib as second-line therapy. The remaining 3 patients were treated with alectinib as first-line therapy. The overall response rate was 87.5%, and the median progression-free survival was not reached. Four patients had developed PD while receiving crizotinib. Two out of those patients have developed brain metastasis, and were administered local radiotherapy to the brain. Patients who progressed following treatment with ALK-TKIs, were treated with pemetrexed-based chemotherapy. Although adverse events (AEs) of crizotinib were more than those of alectinib, most of them were of Grade 1 to 2 severity. Most common AEs of crizotinib included vision disorder (62.5%), diarrhea (50%), elevated aminotransferases (50%), and nausea (37.5%). Grade 3 to 4 adverse events were reported in 4 cases. However, all of them were controlled by withdrawal of treatment or reduction of dosage. **Conclusion:** ALK-TKIs demonstrate good efficacy and safety in patients with ALK-positive NSCLC.

Keywords: ALK tyrosine kinase inhibitors, crizotinib, Alectinib

P1.03-011 CLINICAL OUTCOMES CORRELATED WITH PERCENTAGE OF POSITIVE ANAPLASTIC-LYMPHOMA KINASE CELLS TESTED BY FISH ANALYSIS IN NSCLC.

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Background: Testing for Anaplastic Lymphoma Kinase (ALK) rearrangement in patients diagnosed with Non-Small Cell lung Cancer (NSCLC) is the standard of care in the UK. 2-7% of tumours are positive and subsequently patients may be eligible for treatment with Tyrosine Kinase Inhibitors (TKIs). Response rates to TKIs range from 65-75% with a median PFS of 7.7-10.7 Months. We investigated the relationship between the percentage of ALK positive cells and clinical outcomes in a local patient cohort. **Method:** All patients found to have an ALK rearrangement between 1/1/13 - 1/4/17 in the Leeds Cancer Centre, UK were included. ALK analysis was performed using Fluorescent in situ Hybridisation (FISH) and the percentage of positive abnormal cells was recorded. Retrospective review of the medical notes was performed and outcomes documented including, whether the patient received a TKI, response to TKI, duration of response and overall survival. Chi-squared, Kaplan-Meier survival curves and log-rank test were used to assess survival outcomes. **Result:** 75 patients were found to have an ALK rearrangement in total. Median age was 66 (range 51-92). Only 23 patients received a TKI. Until 2016 TKIs were not available in the first line setting in the UK and many patients were unable to receive a TKI either because first line chemotherapy was contra-indicated or because their performance status had deteriorated during first line chemotherapy making them unsuitable for a TKI. Some patients had early stage disease and therefore a TKI was not indicated (n=7). Median percentage of ALK positive cells was 27% and this was used as a cut off for further statistical analysis. Patients with > 26% of cells positive for ALK had a significantly higher chance of response (91.67% Vs. 42.86% p= 0.025). There was a trend towards improved PFS (107 vs 70 days) for those patients with >26% positivity. This was not statistically significant (PFS p=0.102) and no difference in overall survival was observed (OS p=0.421). **Conclusion:** In this small cohort, patients whose tumours had a higher proportion of tumour cells with an ALK rearrangement, were more likely to respond to TKI. They also had better PFS, though this was not significant. This study was limited by small numbers. TKIs are now available in the first-line setting, allowing more patients to access them. Future investigations will benefit from these increased numbers and if confirmed prospective studies, assessing more targeted use of TKIs on the basis of cellular positivity, could be considered.

Keywords: ALK rearrangement, non-small cell lung cancer, Treatment response

P1.03-012 USING COMPUTATIONAL MODELING TO SIMULATE CLINICAL RESPONSE OF ALK INHIBITORS TO G1202R ALK AND POSSIBLE MECHANISMS OF RESISTANCE

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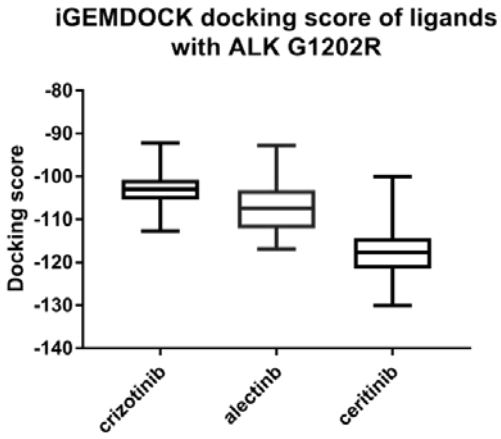
Background: Chromosomal inverse translocation of anaplastic lymphoma kinase (*ALK*) have induced constitutively active ALK fusion proteins. Lung cancers with *ALK* rearrangements are highly sensitive to ALK tyrosine kinase inhibition(TKI). The multi-targeted TKI crizotinib, ceritinib and alectinib were approved by the FDA in 2011 , 2014 and 2015 to treat patients with advanced ALK positive NSCLC. However, most patients develop resistance within 1 to 2 years. The purpose of current study is to utilize computational modeling to simulate clinical response of ALK inhibitors and to investigate possible resistant mechanisms. **Method:** The X-ray crystal structure of ALK complexed with crizotinib (PDB code 2xp2) was used for the simulations. The residue G1202 was mutated into R1202 by using the SWISS-MODEL software. iGEMDOCK v2.1 was used to generate the docked conformation of ligands and to rank the conformations according to their docking scores. We used its molecular docking platform to dock the crizotinib or ceritinib or alectinib to the active cavity of the ALK models (wild type and mutation type). Molecular dynamic (MD) simulations were performed using the GROMACS package. **Result:** The trajectories of ligands binding with ALK protein were analyzed for : (a) the root mean square deviation (RMSD) of the activation sites; (b) the pocket distances between the mass center of residues DFG of activation site and the mass center of ligands. The RMSD was found to increase for R1202 ALK protein with three compounds when compared with G1202 ALK protein with crizotinib. By monitoring the pocket distances between the center of residues DFG and the mass center of ligands, we found that the G1202R ALK protein was more open than that of the wild type. Table 1 show docking score using iGEMDOCK v2.1 for three ligands with G1202R ALK protein.



IC 50 (nM)	crizotinib	alectinib	ceritinib
G1202R mutation	617	695	354

Conclusion: Computation modeling may simulate the clinical response but need further investigation.

Keywords: tyrosine kinase inhibition(TKI), molecular dynamics simulation, EML4-ALK–positive lung cancer

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P1.03-013 MONITORING OF ALK FUSIONS AND MUTATIONS IN ADVANCED ALK POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Co-isolated exosomal RNA and cfDNA from plasma can be used for detection of genomic alteration such as EML4-ALK fusion RNA and ALK resistance mutations in NSCLC patients. The clinical utility of this liquid biopsy for response monitoring is under investigation. The aim of this study was to evaluate liquid biopsy as tool for monitoring response to treatment in a prospective cohort of ALK-positive NSCLC patients. **Method:** Consecutive ALK positive NSCLC patients treated with systemic therapies in our institution were enrolled. After informed consent, blood samples were prospectively collected for longitudinal analysis during treatment and at progression. Exosomal RNA and cfDNA co-isolated from plasma was used for detection of EML4-ALK fusion RNAs by the qPCR-based ExoDx Lung(ALK)™-test as well as for analysis of ALK-resistance mutations by ExoDx NGS sequencing. **Result:** From Aug 2016 to date, 23 patients were enrolled in the study, 14 (61%) were females, 15 (65%) non-smokers, median age of 50 years (23-76). All patients had adenocarcinoma and were tissue positive for ALK by immunohistochemistry 14 (61%) and/or FISH 16 (70%). Nineteen patients (83%) had stage IV disease at diagnosis, with brain involvement in 7 patients (37%), bone in 11 (48%) and liver in 2 (11%). The median number of ALK inhibitors received was 2 (0-4). Twenty-one patients (91%) received ALK inhibitors (5 crizotinib, 3 ceritinib, 13 next-generation inhibitors) and 2 chemotherapy, with an objective response rate of 48%. Five out of 8 patients (63%) that were treatment naïve (baseline) or progressive disease (PD) at the time of collection, were positive for EML4-ALK by liquid biopsy, 1 of 4 samples (25%) at baseline, and 4 of 4 samples (100%) at PD, were positive by liquid biopsy. EML4-ALK variant 1 was detected in two (40%) and variant 3 in three patients (60%). All 26 samples collected during objective response or stable disease (100%) were negative for EML4-ALK by liquid biopsy. The ALK resistance mutation panel was performed on 2 samples from patients with PD, and both were detected positive for ALK resistance mutations, L1196M (variant 1) and G1202R (variant 3), respectively. **Conclusion:** The monitoring of ALK fusions on exosomal RNA by liquid biopsy is applicable in the clinic and closely correlated to disease control. ALK mutations detection using liquid biopsy can be an accurate tool for assessing the resistance to ALK inhibitors. Updated results from up to 30 patients will be available for the final presentation.

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P1.03-014 SALINE ALONE VS SALINE PLUS MANNITOL HYDRATION FOR THE PREVENTION OF ACUTE CISPLATIN NEPHROTOXICITY: A RANDOMIZED TRIAL

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Background: Cisplatin is widely used as an effective chemotherapy in diverse neoplasms and is associated with renal toxicity. Several studies suggest that pre-hydration plus mannitol prior to chemotherapy with cisplatin prevents nephrotoxicity. The aim of this study is to determine the acute effects of hydration plus mannitol on renal function in patients receiving cisplatin. **Method:** Fifty patients who were eligible to receive chemotherapy with cisplatin alone or in combination with other chemotherapy were randomized to receive 1L saline alone (A) or saline plus mannitol before and after chemotherapy. The mannitol group received 12.5 g of mannitol in saline solution. Serum Creatinine (Ser Cr), BUN, and GFR were measured at baseline (no more than 3 days prior to therapy) and on Day 1, 5, and 14. Baseline characteristics were analyzed using t-tests or chi-squared tests. Repeated Measures (RM) ANOVA was used to compare the change in BUN, creatinine, GFR, and BUN to Creatinine ratio. **Result:** Data for 48 patients (36 male and 12 female) were collected. The median age is 57 (range 18 to 78); 23 received saline alone and 25 received mannitol. There are no difference between randomized groups between Age, Gender, and Race. The mean BUN and BUN to creatinine ratio significantly increased by 46% and 37% respectively ($p < 0.001$), while the corresponding mean Serum Cr did not significantly change over time and mean GFR peaked at day 1 then decreased by day 5 ($p=0.001$). All variables returned to baseline by Day 15. Twenty patients (42%) had grade 1 increase in Ser Cr (25% in A and 17% in B, $p=0.078$). No patients had grade 2 or greater in the mannitol group, while 2 patients had grade 2 or grade 3 in saline only group. RM ANOVA analysis show no difference between randomized groups from baseline through Day 1, Day 5, and Day 14 for BUN, creatinine, GFR, and BUN to Creatinine ratio. **Conclusion:** Cisplatin caused acute decline in renal function as determined by BUN, BUN to Ser Cr ratio and GFR, however, addition of mannitol to pre-hydration fluid did not change the outcome.

Keywords: Cisplatin, Cisplatin, acute renal toxicity, mannitol, Mannitol

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P1.03-015 THE RELATIONSHIP BETWEEN THE UGT1A1*27 AND UGT1A1*7 GENETIC POLYMORPHISMS AND IRINOTECAN-RELATED TOXICITIES IN PATIENTS WITH LUNG CANCER

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Background: Genetic polymorphisms in the UDP-glucuronosyltransferase 1A1 (UGT1A1), UGT1A7, and UGT1A9 genes are associated with interindividual differences in irinotecan toxicities. Purpose: To evaluate the effects of gene polymorphisms, including UGT1A1*7, *27, and *29, on the safety of irinotecan therapy. **Method:** The eligibility criteria were as follows: lung cancer patients who were scheduled to undergo irinotecan therapy, aged ≥20 years, and had a performance status of 0-2. After informed consent had been obtained, patients were enrolled, and their blood was collected and used to examine the frequency of the UGT1A1*6, *7, *27, *28, and *29 polymorphisms and the drug concentrations of irinotecan, SN-38, and SN-38G after irinotecan therapy. **Result:** Thirty-one patients were enrolled. The patients' characteristics were as follows: male/female = 25/6, median age (range) = 71 (55-84), stage IIB/IIIA/IIIB/IV = 2/6/11/12, and Ad/Sq/Sm/Oth = 14/10/3/4. The -/-, *6/-, *7/-, *27/-, *28/-, and *29/- UGT1A1 gene polymorphisms were observed in 10 (32%), 10 (32%), 2 (6%), 2 (6%), 7 (23%), and 0 (0%) cases, respectively. There were no homozygous or complex heterozygous polymorphisms. The UGT1A1*27 polymorphism occurred separately from the UGT1A1*28 polymorphism. The lowest leukocyte counts of the patients with the UGT1A1*27 and UGT1A1*6 gene polymorphisms were lower than those seen in the wild-type patients. SN-38 tended to remain in the blood for a prolonged period after the infusion of irinotecan in patients with the UGT1A1*27 or UGT1A1*28 polymorphism. No severe myelotoxicity was seen in the patients with UGT1A1*7. **Conclusion:** UGT1A1*27 and UGT1A1*7 are both rare gene polymorphisms. UGT1A1*27 can occur separately from UGT1A1*28 in some circumstances and is related to leukopenia during irinotecan treatment. UGT1A1*7 is less relevant to irinotecan-induced toxicities, and UGT1A1*29 seems to have little clinical impact.

Keywords: polymorphism, UGT1A1*27, UGT1A1*7

P1.03-016 VIDEO-THORACOSCOPIC PULMONARY RESECTION AVOIDS DELAY AND INCREASE ADJUVANT CHEMOTHERAPY COMPLIANCE FOR NON-SMALL CELL LUNG CARCINOMA

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Background: Adjuvant chemotherapy compliance and the full dose delivery of agents are believed to be superior after video-thoracoscopic lobectomy (VATS-L) for operable non-small cell lung carcinoma (NSCLC), compared with thoracotomy. The purpose of this study was to determine the role of minimally invasive lobectomy on when to start and the percentage of provided planned regimen. **Method:** All patients undergoing pulmonary resection for NSCLC between January 2010 and May 2016 were reviewed retrospectively. For comparison, analyses were performed only on patients receiving sole adjuvant chemotherapy, after the final pathology. Chemotherapy was planned according to Adjuvant Navelbine International Trialist Association (ANITA) trial. The analyzed variables were the duration between the discharged day form surgical unit and the initial chemotherapy day, the planned and the received chemotherapy doses. **Result:** Total of 74 patients were subsequently underwent adjuvant chemotherapy for NSCLC either after thoracoscopic surgery (n=26) or thoracotomy (n=48). Patients undergoing VATS-L had a shorter median length of hospital stay (4.4 versus 7.3 days; P<0.001), that leads significantly reduced time delay on chemotherapy commencement (29.4 versus 37.0 days; P=0.002). VATS-L group received 83.0% of planned Cisplatin and 81.7% of Navelbine dose. In the thoracotomy group, the compliance to planned doses of Cisplatin and Navelbine was 77.6% and 75.0%, respectively. Both of the drug regime tolerance was significantly (Cisplatin P=0.005; Navelbine P=0.020) increased in the VATS-L group (Table 1).

Table 1. Comparison of different variables between groups

		n	Median	SD	P*
Hospital LOS (days)	VATS	26	4.35	1.77	**<0.001**
	T	48	7.33	3.00	
%C	VATS	26	82.96	4.56	**0.005**
	T	48	77.63	8.64	
%N	VATS	26	81.65	7.85	**0.020**
	T	48	75.00	13.03	
Time to chemotherapy (days)	VATS	26	29.38	9.41	**0.002**
	T	48	36.98	9.74	

C: Cisplatin, N: Navelbine, LOS: length of stay, SD: standard deviation, T: thoracotomy, VATS: video-assisted thoracoscopic surgery

Conclusion: It is known that VATS-L has several advantages over conventional open surgery. Moreover, our data presented that it also allows more accurate and rapid adjuvant chemotherapy in terms of treatment initiation timing and compliance, by enabling quick postoperative recovery.

Keywords: chemotherapy, VATS-L, compliance

P1.03-017 BENZYL ISOTHIOCYANATE INDUCES PROTECTIVE AUTOPHAGY IN HUMAN LUNG CANCER CELLS THROUGH ENDOPLASMIC RETICULUM STRESS-MEDIATED MECHANISM

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Background: Benzyl isothiocyanate (BITC) inhibits the growth of various human cancer cells, however, the mechanism underlying growth inhibitory effect of BITC is not fully understood. In the present study, we investigated the effect of BITC on autophagy induction in human lung cancer cells *in vitro* and *in vivo*. **Method:** Autophagy was characterized by detection of the formation of acidic vesicular organelles (AVOs), the accumulation of microtubule-associated protein 1 light chain 3-II (LC3-II), the punctuate pattern of LC3, and expression of Atg5. Endoplasmic reticulum (ER) stress was determined by measurement of cytosolic calcium level, and phorphorylation of ER stress marker proteins PERK and eIF2α. The effect of BITC on lung tumor growth was examined by lung cancer cell xenograft experiments. **Result:** Our data showed that BITC inhibited the growth of human lung cancer cells. BITC induced autophagy in lung cancer cells, pretreatment with autophagy inhibitor 3-MA enhanced the inhibitory effect of BITC. ER stress was also caused by BITC, suppression of ER stress by ER stress inhibitor 4-PBA attenuated autophagy induction, and further potentiated the cell growth inhibition by BITC. Xenograft experiments showed that BITC inhibited lung tumor growth in vivo, and induced both autophagy and ER stress in lung tumor cells. **Conclusion:** Our results indicated that BITC inhibits lung cancer cell growth both in vitro and *in vivo*. BITC induces autophagy in lung cancer cells, and autophagy plays a protective role in the inhibition effect of BITC. The autophagy induction is mediated by ER stress response.

Keywords: human lung cancer, benzyl isothiocyanate, Autophagy

P1.03-018 EFFECTIVENESS OF SUPPORTIVE CARE DRUGS IN LUNG CANCER PATIENTS UNDERGOING 1ST LINE CHEMOTHERAPY IN A RESOURCE LIMITED SETTING

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Background: Lung cancer(LC) chemotherapy is associated with several adverse effects(AEs). Data regarding supportive care medications(SCMs) offered to prevent/treat chemotherapy-related AEs in resource-limited settings and compliance to these therapies is lacking. A prospective observational study was therefore carried out in an attempt to ascertain effectiveness of SCMs in real life setting. **Method:** Consecutive patients with newly-diagnosed LC initiated on first-line chemotherapy at a tertiary referral centre in North India (from July 2014-September 2015) were enrolled. Details of chemotherapy-related AEs including incidence, timing of onset, duration and grades were recorded. Compliance with use of mandatory SCMs prescribed after each chemotherapy cycle was assessed by a structured questionnaire. Patients were also instructed to maintain a symptom diary to record various symptoms, frequency of use of need-based SCMs, visits to local health-care providers and hospitalization(if any) during the inter-cycle period. **Result:** Of 112 patients enrolled, majority were males(83.9%,n=94), current/ex-smokers(82.1%,n=92), had advanced stage [IIIB=33.9%(n=38), IV=46.4%(n=52)] and of non-small-cell type (NSCLC; 72.3%,n=81). A total of 602 chemotherapy cycles were administered with AEs being reported in 580 cycles(96.3%). Diarrhea was the commonest AE(180 cycles,29.9%) developing after a mean (SD) duration of 3.6(2.5) days and lasting for 4(3.3) days. Vomiting(138 cycles,22.9%) beginning after a mean (SD) of 3.5(2.7) days, lasting for 3.8(3.1) days; and constipation(121 cycles,20.1% mean[SD] onset after 2.9[1.7] days, lasting for mean[SD] of 6.5[6 .1]) were the other common AEs. Grade3/4 AEs occurred in 6.7%(39/580) cycles. Compliance to dexamethasone and proton-pump inhibitors prescribed as part of mandatory SCMs was 98.2% and 98.3% respectively. Need based SCMs were required in 479 of the 580 cycles(82.6%) reporting AEs. Need-based SCMs were effective in relieving most symptoms (100% episodes of pain, cough and epigastric pain). Local physician consultation was sought in 18.1% and 15.8% episodes of vomiting and pain respectively. Proportion of patients with grade 3/4 AEs and requiring hospitalization was highest for mucositis(16.1% grade 3/4 and 9.7% hospitalized); followed by vomiting(10.1% grade3/4 and 8.7% hospitalized) and diarrhea(10.6% grade 3/4 and6.7% hospitalized). Hiccups, despite occurring in only 5 chemotherapy cycles(0.9%) did not improve with need based SCMs in 40%. Anemia was observed in 441(73.3% prevalence) chemotherapy cycles and was treated with blood transfusions, erythropoiesis-stimulating agents and intravenous iron supplementation in 47(10.7%), 30(6.8%) and four(0.9%) cycles respectively. **Conclusion:** This study highlights a high prevalence of AEs during LC chemotherapy. However, majority of episodes were grade 1-2 and were controlled with need-based SCMs, without requiring hospitalization or local physician consultation.

P1.03-019 SOPHORIDINE INHIBITS LUNG CANCER CELL PROLIFERATION THROUGH ACTIVATING HIPPO SIGNALING AND P53 PATHWAY

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Background: Lung cancer is regarded as the most commonly diagnosed malignant disease with the leading cause of cancer-associated death. Sophoridine is a quinolizidine alkaloid extracted from *Sophora alopecuroides* L, a traditional Chinese medicine, which was found to have diverse pharmacological properties such as anti-inflammatory and anti-cancer. In our current research, we evaluated the effect of sophoridine alone and in combination with cisplatin on various human lung cancer cell lines and also explored the possible anti-cancer mechanisms underlie. **Method:** Colony formation assay, CCK-8 assay as well as transwell invasion and migration assay were adopted to investigate the anti-cancer effects of Sophoridine through a series of human lung cancer cell lines. Western-blot and Quantitative Real-time PCR were used to explore the possible underlying mechanisms of the inhibitory effect of Sophoridine on lung cancer progress. **Result:** We confirmed that Sophoridine can inhibit lung cancer cell proliferation, invasion and migration significantly. In addition, the Hippo-YAP pathway and p53 signaling might be involved in the inhibitory effect of Sophoridine in NCI-H446, NCI-H460 and A549 cell lines but not in the p53-deficient NCI-H1299 cells. Quantitative Real-time PCR showed that Sophoridine can dramatically suppress the downstream targets of Hippo-YAP1 pathway such as CYR61, CDX2, FOXM1, c-Myc and VEGF. **Conclusion:** In conclusion, our study first suggested that sophoridine might be used as a novel agent for lung cancer.

Keywords: lung cancer, Traditional Chinese medicine, Hippo and P53 signaling

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-020 DETECTION OF HYPOXIA USING EF5 PET/CT IN 10 PATIENTS WITH ADVANCED NSCLC RECEIVING CHEMOTHERAPY WITH AND WITHOUT BEVACIZUMAB

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Background: Hypoxia is associated with increased resistance to radiation and chemotherapy treatments and may be an important prognostic factor in non-small cell lung cancer (NSCLC). Antiangiogenic drugs such as bevacizumab can have the paradoxical effect of transiently improving perfusion by normalizing blood vessels and reducing interstitial pressure, which may improve chemotherapy delivery and tumor cell killing. The aim of this study was to non-invasively assess tumor hypoxia with ^{18}F-EF5 PET/CT imaging in patients with advanced-stage NSCLC prior to systemic therapy and to compare changes during and after chemotherapy treatments with and without bevacizumab. ^{18}F-EF5 is a 2-nitroimidazole-based PET tracer reported as a good surrogate for hypoxia. **Method:** Eligibility included patients with incurable stage III/IV NSCLC who were to receive first-line platinum-based doublet chemotherapy alone or in combination with bevacizumab; prior radiation therapy was not allowed. 10 patients completed the study; 5 were treated with standard chemotherapy alone and 5 with chemotherapy plus bevacizumab. Each patient had three ^{18}F-EF5 PET/CT studies: one baseline pre-treatment, one at day 15 after the first cycle and one post-treatment study after 4-6 cycles of therapy. The investigators reading the PET/CT studies were blinded as to whether patients were treated with bevacizumab or not and no clinical information was available. ^{18}F-EF5 PET/CT images were acquired from shoulders to upper abdomen and analyzed by calculating tumor-to-muscle (T/M) uptake ratios. A ratio ≥1.50 was considered positive for hypoxia. **Result:** A total of 64 lesions were analyzed on baseline ^{18}F-EF5 PET/CT scans: 42 in the bevacizumab group and 22 in the control group. 51 of these lesions were positive for hypoxia (79.7%): 37 in the bevacizumab group (88.1%) and 14 in the control group (63.6%). Using a Dunn's multiple comparisons test, there was a significant decrease in ^{18}F-EF5 uptake only on post-treatment study versus baseline in the group treated with chemotherapy alone ($p=0.009$). On the other hand, in the group treated with chemotherapy plus bevacizumab, T/M ratios obtained after one cycle of chemotherapy and after treatment completion were statistically lower when compared to baseline ($p<0.0001$). **Conclusion:** Preliminary data suggest that many advanced NSCLC are hypoxic and that the combination of bevacizumab and chemotherapy leads to a greater decrease in ^{18}F-EF5 accumulation compared to chemotherapy alone in primary tumors and metastatic lymph nodes. Further studies are necessary to understand the clinical significance of this finding and to explore this as a potential predictive marker for the use of bevacizumab.

Keywords: Hypoxia, bevacizumab (Avastin), 18F-EF5 PET/CT

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-021 A PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE INCIDENCE OF THROMBOEMBOLIC EVENTS DURING PLATINUM BASED CHEMOTHERAPY IN LUNG CANCER

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Background: Lung Cancer is a prothrombotic state with its treatment frequently complicated by thromboembolism leading to shorter life expectancy, worsening of the quality of life and may delay, interrupt, or completely halt the cancer therapy. Based on many retrospectives and prospective analyses in patients with lung cancer, thromboembolic complications are a common event with incidences ranging from 10-17 %. It is possible to identify those with the highest risk of venous thromboembolism suitable for antithrombotic prophylaxis, which could favorably affect their morbidity and mortality **Method:** All patients with advanced lung cancer who were started on platinum-based chemotherapy were included. Those patients who had prior TEs or inherited coagulopathy or those on therapeutic anticoagulation, regular NSAIDs / aspirin or those on bevacizumab were excluded.A thromboembolic event was considered associated with chemotherapy if it occurred between the time of the first dose and 4 weeks after the last dose **Result:** A total 188 patients were screened for the study and 167 patients were enrolled in the study. Since 2 patients were lost to follow-up after accrual, 165 patients were included in the final analysis. Of the 165 patients, 67.8% (112/165) received chemotherapy regimen of carboplatin with gemcitabine, 30.3% (50/167) received carboplatin with pemetrexed, 1.2 % (2/165) received cisplatin with pemetrexed and 0.6 % (1/165) received carboplatin with paclitaxel. A median number of days on platinum were 94 (range 10-478). The median number of chemotherapy cycles administered was 4 (range 1–6). Thromboembolic events occurred in 4.8% of patients (8 out of 165 patients) which were related to the platinum chemotherapy. Among 8 patients with thromboembolic events, 3 patients developed venous pulmonary thromboembolism and 5 patients developed cerebral infarction, out of which 4 had arterial cerebral infarction and one patient had a superior sagittal sinus thrombosis. All eight patients were symptomatic and one patient with cerebral infarction died because of the infarction. The majority of events (7 out of 8) occurred within the first 100 days of starting platinum chemotherapy. Overall, the median time until occurrence of a thromboembolic event was 24 days (range, 8 to 129days). None of the presumed risk factors associated with thrombosis were found be related to the occurrence of TEs on univariate analysis. **Conclusion:** The incidence of thromboembolic events were 4.8 % in our study was low due to the use of carboplatin-based regimens in the majority of patients. The majority of thromboembolic events occurred within 3 months from the initiation of chemotherapy.

Keywords: thromboembolic events, platinum chemotherapy, prospective

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-022 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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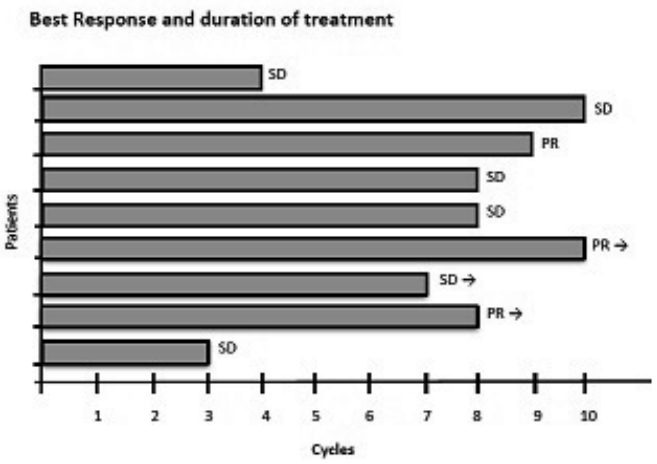
Background: Given the modest/transitory benefit of bevacizumab(B)/chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) and the tendency of tumors to develop escape pathways of angiogenesis,investigation of dual anti-angiogenic therapy may result in more effective angiogenesis inhibition. TRC105 is an antibody to endoglin,an essential angiogenic target expressed on proliferating endothelial cells,and overexpresed in response to VEFG inhibition.This phase 1b study of TRC105 in combination with standard (STD) dose of B with paclitaxel/carboplatin (P/Crb) in advanced non-squamous (NSQ) NSCLC had the primary objectives of safety/tolerability and to determine a recommended phase 2 dose.Secondary objectives included preliminary evidence of antitumor activity and pharmacokinetic (Pks) profile of TRC105. **Method:** A dose finding study (3+3 design) of TRC105 with B(15mg/kg), P(200mg/m2),and Crb(AUC6), given iv on day 1 of each 21 day cycle.Two dose levels of TRC105 were evaluated: 8mg/kg (cohort 1) and 10mg/kg (cohort 2), administered iv weekly. An expanded cohort at dose level 2 is being evaluated. A maintenance phase with TRC105 + B was considered after of induction therapy in those pts without evidence of progressive disease. Safety and efficacy assessments were determined by the NCI-CTCAE (v 4),and RECIST 1.1, respectively.Eligible pts had PS 0-1, chemotherapy naive stage 4 NSQ-NSCLC, measurable disease, and no significant cardiovascular comorbidities. Pts with asymptomatic treated CNS metastases were allowed. Other parameters assessed included Pks, immunogenicity,and angiogenic biomarkers in plasma.Descriptive statistics were used to summarize pt characteristics, safety, efficacy, Pks and biomarkers. **Result:** Overall safety population comprised 9 pts receiving ≥ 1 cycle of treatment. Median age was 65 years, 55% were women, and one pt had brain metastases. A total of 67 cycles of treatment were delivered (median of 8 cycles). The most frequent grade (G) 3 adverse events:anemia (55%), fatigue (55%), and neuropathy (44%). There was a G3 epistaxis and a G5 neutropenic event. Responses shown below:



Conclusion: TRC105 with STD CT was associated with an acceptable safety profile.

Keywords: antiangiogenesis, non-small cell lung cancer, Targeted therapy

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-023 THE REAL-WORLD PRACTICE OF BEVACIZUMAB PLUS CHEMOTHERAPY IN STAGE IV LUNG ADENOCARCINOMA: A SINGLE INSTITUTE EXPERIENCE

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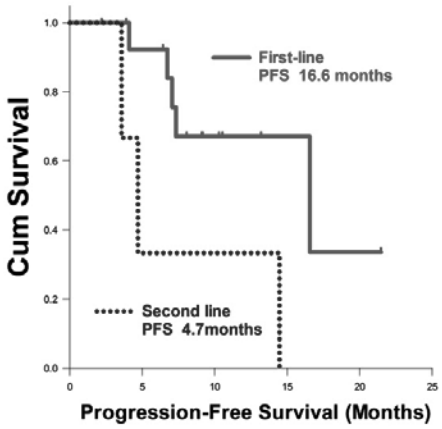
Background: Non- small-cell lung cancer (NSCLC) is the most frequent histologic type of lung cancer, and adenocarcinoma is the predominant subtype. The ECOG 4599 trial showed bevacizumab, carboplatin, and paclitaxel is regarded as a new standard regimen.[1] The AVAil study showed bevacizumab in combination with gemcitabine/cisplatin significantly increased PFS compared to chemotherapy alone, but did not demonstrate a statistically significant prolongation of overall survival.[2] A previous meta-analysis showed that bevacizumab plus first-line platinum-based chemotherapy was able to significantly prolong the overall survival (OS) and progression-free survival (PFS) of NSCLC patients.[3] However, bevacizumab is not covered by health Insurance in Taiwan, so the real-world efficacy of bevacizumab plus chemotherapy remains unclear. **Method:** We retrospectively reviewed lung cancer database at Kaohsiung Chang Gung Memorial Hospital between January 2015 and May 2017, and a total of 18 patients with lung adenocarcinoma receiving bevacizumab plus chemotherapy were identified. **Result:**



All patients were stage IV disease, and most of them were female (67%), epidermal growth factor receptor (EGFR) wild type (78%) and ALK wild type (94%). There were 15 patients receiving bevacizumab plus first-line chemotherapy, and the remaining 3 patients underwent second-line chemotherapy in combination with bevacizumab. In first-line chemotherapy group, the chemotherapy regimen included pemetrexed/platinum/bevacizumab (73%) and docetaxel/platinum/bevacizumab (27%); the response rate was 27%, and disease control rate was high to 94%. There were only three patients in second-line chemotherapy group, including one patient treating with pemetrexed/bevacizumab and two patients treating with docetaxel/bevacizumab; only one patient responded to treatment (response rate: 33%). The PFS was 16.6 and 4.7 months in first-line and second-line chemotherapy groups, respectively. **Conclusion:** Our data showed the chemotherapy plus bevacizumab as the first-line treatment, led to better response rates and disease control rates in stage IV lung adenocarcinoma patients. Bevacizumab combined with cytotoxic drugs was also suitable as the second-line treatment for such patients.

Keywords: bevacizumab, lung adenocarcinoma, chemotherapy

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-024 EFFICACY OF CARBOPLATIN-VINORELBINE IN ADVANCED NSCLC PATIENTS AT PERSAHABATAN HOSPITAL, JAKARTA - INDONESIA

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Background: Combination of platinum-based and third generation drugs such as vinorelbine chemotherapy are frequently used as paliative chemotherapy for Non-small cell lung cancer (NSCLC) patients in Indonesia especially in Persahabatan Hospital. But there is still no data about the efficacy and tolerability of carboplatin-vinorelbine regimen. This study was conducted to evaluate the efficacy and toxicity of this regimen as first line chemotherapy for advanced NSCLC patients in Persahabatan Hospital. **Method:** This study was an observational study in advanced NSCLC patients who receive carboplatin-vinorelbine regimen as first line chemotherapy. subjects were recruited between 1st January 2015 to 30th March 2017. Clinical data regarding the histological type, staging, side effect of chemotherapy, RECIST and survival were recorded. **Result:** Thirty eight subjects were recruited in this study of which carboplatin 5 AUC on day 1 and vinorelbine 30mg/m^2 on day 1 and 8 were administered as a combination therapy. This regimen has a good efficacy with overall response rate (ORR) 12,5% and clinical benefit rate (CBR) 87,5%. The overall survival (OS) 34,2% with median of survival time 387 days (12,9 moths) and progression free survival (PFS) 323 days (10,7 months). We found grade 1 anemia (38,4%) and grade 2 nausea vomiting (57,9%) as hematological and non-hematological toxicity that frequently occured in this study. Two cases of grade 2 gastrointestinal bleeding were observed but the subjects still be able to continue the chemotherapy soon after recovery. Mild phlebitis were observed in 65.7% cases (24 subjects) and moderate phlebitis in 2.6% (1 subject) as procedural complication of this chemotherapy regimen. **Conclusion:** Combination of carboplatin and vinorelbine as first line chemotherapy has a good efficacy and tolerability for advanced NSCLC subjects.

Keywords: carboplatin and vinorelbine combination, tolerability, advanced NSCLC

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-025 COMBINATION THERAPY WITH CARBOPLATIN AND HYPEROXIA SYNERGISTICALLY ENHANCES SUPPRESSION OF BENZO[A]PYRENE INDUCED LUNG CANCER

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Background: We explored the effects of intermittent normobaric hyperoxia alone or combined with chemotherapy on the growth, general morphology, oxidative stress, and apoptosis of benzo[a]pyrene (B[a]P)-induced lung tumors in mice. **Method:** Female A/J mice were given a single dose of B[a]P and randomized into four groups: (1) control, (2) carboplatin (50 mg/kg intraperitoneally), (3) hyperoxia (95% fraction of inspired oxygen), and (4) carboplatin and hyperoxia. Normobaric hyperoxia (95%) was applied for 3 h each day from weeks 21 to 28. Tumor load was determined as the average total tumor numbers and volumes. Several markers of oxidative stress and apoptosis were evaluated. **Result:** Intermittent normobaric hyperoxia combined with chemotherapy reduced the tumor number by 59% and the load by 72% compared with the control B[a]P group. Intermittent normobaric hyperoxia, either alone or combined with chemotherapy, decreased the levels of superoxide dismutase (SOD) and glutathione (GSH) and increased the levels of catalase and 8-hydroxydeoxyguanosine (8-OHdG). The Bax/Bcl-2 mRNA ratio, caspase-3 level, and number of transferase-mediated dUTP nick end-labeling (TUNEL)-positive cells increased following treatment with hyperoxia with or without chemotherapy. **Conclusion:** Intermittent normobaric hyperoxia was found to be tumoricidal and thus may serve as an adjuvant therapy for lung cancer. Oxidative stress and its effects on DNA are increased following exposure to hyperoxia and even more with chemotherapy, and this may lead to apoptosis of lung tumors.

Keywords: carboplatin, lung cancer, hyperoxia

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-026 INTERIM RESULTS OF A PHASE I STUDY OF NIVOLUMAB PLUS NAB-PACLITAXEL/CARBOPLATIN IN PATIENTS WITH NSCLC

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Background: Chemotherapy, including taxanes, may augment the effects of immune checkpoint inhibitors through tumor cell lysis and subsequent antigen release. This phase I trial is evaluating safety and efficacy of nivolumab plus *nab*-paclitaxel in NSCLC (+ carboplatin), pancreatic cancer (± gemcitabine), and metastatic breast cancer. Interim results for Arm C, in which patients with NSCLC were treated with nivolumab starting in cycle 1, are presented. **Method:** Potential dose-limiting toxicities (DLTs) were evaluated in Part 1 before Part 2 expansion. Chemotherapy-naive patients with histologically/cytologically confirmed stage IIIB/IV NSCLC received 4 cycles of *nab*-paclitaxel 100 mg/m^2 days 1, 8, 15 plus carboplatin AUC 6 day 1 plus nivolumab 5 mg/kg day 15 of each 21-day cycle. In cycles ≥ 5, single-agent nivolumab was continued as maintenance therapy. Primary endpoints are number of patients with DLTs (Part 1) and percentage of patients with grade 3/4 treatment-emergent adverse events (TEAEs) or treatment discontinuation due to TEAEs (Parts 1/2). DLT-evaluable patients were those who received ≥ 2 complete nivolumab cycles and remained on study for 14 days after the last nivolumab dose in cycle 2, received ≥ 1 nivolumab dose and discontinued due to DLT before completing 2 nivolumab cycles, or experienced an equivocal DLT after ≥ 1 nivolumab dose. Secondary endpoints included PFS, DCR, ORR, DOR (all by RECIST v1.1), OS, and safety. **Result:** All patients (N = 22) received *nab*-paclitaxel/carboplatin; results for those who received *nab*-paclitaxel/carboplatin plus nivolumab (n = 20) are presented. The median age was 65.5 years (55% ≥ 65 years), 70% had ECOG PS 1, 75% were female, and 80% were white. More patients had adenocarcinoma (50%) than squamous cell carcinoma (35%; adenosquamous carcinoma, atypical, and data pending, 5% each). No DLTs were reported among 6 DLT-evaluable patients (Part 1). The most common grade 3/4 TEAEs were neutropenia (45%) and anemia (40%). No grade 3/4 colitis or pneumonitis was reported. Best ORR was 50% (1 CR [5%] and 9 PRs [45%]; 10 patients [50%] had SD); ORR was 43% (3 PRs among 7 patients) and 54% (1 CR and 6 PRs among 13 patients) in those with squamous and nonsquamous histologies, respectively. Median PFS was 10.5 months (95% CI, 4.9-18.1 months); 10.5 and

10.2 months for those with squamous and nonsquamous histologies, respectively. **Conclusion:** These results suggest that *nab*-paclitaxel/carboplatin plus nivolumab is tolerable for patients with NSCLC. Preliminary efficacy findings indicate promising antitumor activity across histologies. (NCT02309177)

Keywords: nab-paclitaxel, non-small cell lung cancer, Nivolumab

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-027 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: The study objective was to compare efficacy and safety of CBDCA+PTX+BEV and CDDP+PEM+BEV in non-squamous (non-Sq) NSCLC patients. **Method:** Treatment-naïve patients aged 20-74 with advanced or recurrent EGFR/ALK-negative non-Sq NSCLC were randomly assigned at 1:2 ratio to either treatment A (4 cycles of CBDCA [AUC 6] + PTX [200mg/m^2] + BEV [15mg/kg] q3wk, and maintenance therapy with BEV q3wk until progression) or treatment B (4 cycles of CDDP [75mg/m^2] + PEM [500mg/m^2] + BEV q3wk, and maintenance therapy with PEM + BEV until progression). The primary endpoint was PFS by central review. The secondary endpoints included OS and safety profile. Target enrollment number was 210. **Result:** A total of 55 sites across Japan enrolled 199 patients: 67/132 (A/B). The median age was 67/66 years, 70%/74% were male, 54%/52% were PS 0, 75%/73% were stage IV and 93%/98% had adenocarcinomas. As of April 14, 2017, patients had completed a median of 7/8 treatment cycles, while 94%/80% had discontinued treatment. The most common ≥G3 adverse events were neutropenia (75%/24%), and hyponatraemia (6%/10%). The most common BEV-related adverse events (≥G1) were hypertension (44%/58%), proteinuria (52%/43%) and epistaxis (26%/14%). Dose reduction was necessary due to an adverse event in 31%/22% patients. Treatment-related death (pulmonary infection) was reported in 1 patient receiving treatment B. **Conclusion:** CBDCA+PTX+BEV and CDDP+PEM+BEV had different safety profiles. Efficacy results including the primary endpoints will be presented in 2018.

Keywords: NSCLC, chemotherapy, bevacizumab

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-028 A PHASE II TRIAL OF ALBUMIN-BOUND PACLITAXEL AND GEMCITABINE IN PATIENTS WITH UNTREATED STAGE IV SQUAMOUS CELL LUNG CANCERS

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Background: Therapeutic options for squamous cell lung cancer (SQCLC) patients remain limited. Platinum-based chemotherapies, which have been the standard first-line treatments for nearly 20 years, are associated with ORR=30-40%, median PFS=4-5.7mo, and median OS=9-11.5mo. We previously reported the results of a phase 1/2 trial of albumin-bound paclitaxel (ABP) in 40 patients with untreated stage IV NSCLC, noting an ORR of 30%, median PFS of 5mo, and median OS of 11mo (Rizvi JCO 2008). These data suggest that platinum adds little when coupled to ABP. Conversely, compelling evidence of anti-tumor synergy between gemcitabine and ABP was recently demonstrated by Frese et al. who showed that ABP downregulates cytidine deaminase (which inactivates gemcitabine), 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 is a phase II trial of ABP (100mg/m^2) + gemcitabine (1000mg/m^2) given on D1, D8, D15 of an every 4 week cycle (A1) in patients with untreated stage IV SQCLC. Patients received up to 6 cycles and were followed thereafter (A1). The primary endpoint is best objective response (RECIST 1.1). The study utilizes a Simon two-stage design with H0=25% (6/17 responses) and H1=45% (16/41 responses). After clearing the first stage, the study was amended to a 3 week cycle (D1, D8 treatment); to allow ABP + gemcitabine until progression; and to allow maintenance ABP to begin after C4 for tolerability (A2). PFS, TTP, and OS were calculated using the Kaplan-Meier method. Patients underwent NGS by MSK-IMPACT for genotype-phenotype correlation. **Result:** N=17 patients (14 evaluable) were treated on A1 and, to date, N=3 patients (2 evaluable) have been treated on A2. Median age=70, female=30%, median KPS=90%, smokers=90%, median pack years=32. Median cycles of therapy in A1=4. Grade ≥3 related AEs included: peripheral neuropathy (5%); diarrhea (5%); elevated ALT (5%); anemia (15%); and decreased neutrophils (25%). Three patients (15%) experienced a related SAE including G3 decreased WBC, G3 diarrhea, and G3 lung infection. There was 1 unrelated death as a result of complications from a G3 mechanical fall. ORR in A1=50% (7/14 PRs). ORR in A2=100% (2/2 PRs). ORR in A1+A2=56% (9/16 PRs). SD=6 (38%) and PD=1 (6%). Median PFS=5.8mo; TTP=6.9mo; OS=13.3mo. **Conclusion:** ABP + gemcitabine has promising efficacy and is relatively well-tolerated, particularly when compared to platinum regimens. Accrual to the study is ongoing and updated data, including NGS correlates, will be presented.

Keywords: squamous, abraxane, gemcitabine

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-029 STUDY OF PLASMA HOMOCYSTEINE AS A MARKER OF TOXICITY AND DEPRESSION IN PATIENTS TREATED WITH PEMETREXED-BASED CHEMOTHERAPY

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Background: Vitamin supplementation reduces pemetrexed toxicity. Raised plasma homocysteine levels reflect folate deficiency and are suppressed by supplementation. Depression is common in lung cancer patients. Elevated homocysteine levels are linked to neurotoxicity; its association with depression is less clear. **Method:** This prospective observational study of 112 lung cancer patients receiving pemetexed-based chemotherapy assessed homocysteine level after 3 weeks of vitamin B12 and folate supplementation, hypothesizing that high levels reflect an ongoing deficiency and would correlate with increased chemotherapy toxicity and depression. All patients received B12 and folate supplementation and had a homocysteine level checked 3 weeks later. The primary objective was proportion of patients with a treatment delay/ dose reduction/ drug change or hospitalisation during the first six weeks of chemotherapy, between patients showing normal plasma homocysteine (i.e. successfully supplemented, SS group) and patients showing high levels (i.e. unsuccessfully supplemented, US group). Secondary objectives included grade 3-4 toxicity, overall survival and exploratory analyses for depression. **Result:** 100 patients were included in the primary end-point analysis. 84% of patients demonstrated appropriate supplementation (SS group). The proportion of patients undergoing a treatment delay/ dose reduction/ drug change or hospitalisation in the SS group was 44.0% (37/84) (95% confidence interval [CI] 33.2% to 55.3%) and in the US group was 18.8% (3/16) (95% CI 4.0% to 45.6%) (p=0.093). Proportion of patients experiencing grade 3-4 toxicity in SS group was 14.5% (95% CI 7.7% to 23.9%) and in US group was 18.8% (95% CI 4.0% to 45.6%) (p=0.705). The proportion of patients with a Hospital Anxiety and Depression (HAD) score >7 (indicative of depression) in the SS group was 63.9% (95% CI 46.2% to 79.2%) and in the US group was 75% (95% CI 34.9% to 96.8%) (p=0.695). Median overall survival was 11.8 months (95% CI 8.6 – 16.5 months) in the SS group and 8.8 months (95% CI 6.6 – 16.2 months) US group (Log Rank test; p-value = 0.484). **Conclusion:** Standard vitamin supplementation was adequate in the majority of patients and thus our US population was small. Homocysteine levels at 3 weeks did not correlate with increased toxicity or overall survival and is unlikely to be useful to identify patients at an increased risk of toxicity, though analysis was limited by the smaller than expected number of patients in the US group. Depression is very common in this population, and HAD score is a feasible assessment tool in this patient group.

Keywords: lung cancer, chemotherapy, Homocysteine

P1.03: CHEMOTHERAPY/TARGETED THERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-030 PROGNOSTIC IMPACT OF THE PRESENCE OF COPD IN PATIENTS WITH NSCLC UNDER CONVENTIONAL SYSTEMIC CHEMOTHERAPY

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Background: Effects of the presence of COPD on clinical outcomes in patient with advanced stage NSCLC cancer were inconclusive. Aim of our study is to evaluate the effects of COPD on overall survival of NSCLC patients who undergo conventional chemotherapy as 1st line treatment. **Method:** Advanced NSCLC (stage IIIB and IV) received first-line chemotherapy from January of 2008 to December 2015 were enrolled from 6 university hospitals. Patients who underwent pretreatment pulmonary function test were selected in the analyses, and COPD was defined according to GOLD guideline: FEV1/ FVC < 0.7. Primary endpoint was the overall survival according to the patients' clinicopathological characteristics. **Result:** A total of 197 patients comprised of 92 patients (46.7%) in the COPD group and 105 (53.3%) in the non-COPD group were enrolled in the analysis. The median duration of follow-up for survived patients was 23.9 months. The presence of COPD was a significant risk factor for mortality in the univariate analysis (HR, 1.402; p = 0.037), however not in the multivariate analysis (HR, 1.275; p = 0.144). The patients with COPD have poor clinical outcomes in subgroups of smokers and stage IV cancer, significantly. **Conclusion:** COPD does not have clinical impact of overall survival of

advanced NSCLC patients who undergo conventional chemotherapy. However COPD was a poor prognostic factor in terms of overall survival of in smokes and stage IV NSCLC patients. Further studies which evaluate clinical effects of airflow obstruction management on lung cancer patients can elucidate the clinical impact of COPD.

Keywords: copd, systemic chemotherapy, NSCLC

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-031 ADHERENCE AND FEASIBILITY OF 2 TREATMENT SCHEDULES OF S-1 AS ADJUVANT CHEMOTHERAPY IN COMPLETELY RESECTED LUNG CANCER

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Background: S-1 is one of the key-drugs as chemotherapy for the non-small cell lung cancer (NSCLC). We conducted a multicenter randomized study of adjuvant S-1 administration schedules for surgically treated pathological stage IB-IIIA NSCLC patients. **Method:** Patients receiving curative surgical resection were centrally randomized to arm A (4 weeks of oral S-1 and a 2-week rest over 12 months) or arm B (2 weeks of S-1 and a 1-week rest over 12 months). The primary endpoints were total days of administration, and the secondary endpoints were relative total administration dose (relative dose intensity), toxicity, and 3-year disease-free survival. Total days of administration were evaluated according to the cumulative rates of total S-1 administration days within 224 days, at the end of 12 months. Relative dose intensity was defined as (the actual total dose administered divided by the planned total administered dose) × 100. **Result:** From April 2005 to January 2012, 80 patients were enrolled, of whom 78 patients were eligible and assessable. The cumulative rates of total S-1 administration days at the end of 12 months, were 81.3% for arm A (38 cases) and 60.2% for arm B patients (40 cases, p = 0.04). The relative dose intensity was 77.2% for arm A and 58.4% for arm B (p = 0.01). Drug-related grade 3 adverse events were recorded for 11% of arm A and 5% of arm B (p = 0.43). The 3-year disease-free survival rate was 79.0% for arm A and 79.3% for arm B (p = 0.94). Toxicity showed no significant difference among the shorter schedule and the conventional schedule, except for grade 1-3 elevation of bilirubin. **Conclusion:** The superiority of feasibility of the shorter schedule was not recognized in the present study. The conventional schedule showed higher cumulative rates of total S-1 administration days at the end of 12 months (p = 0.04) and relative dose intensity of S-1 (p = 0.01).

Keywords: lung cancer, adjuvant chemotherapy, S-1

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-032 OBSERVATION OF DURATIVE INFUSION ENDOSTAR COMBINED WITH CHEMOTHERAPY WITHIN VASCULAR NORMALIZATION PERIOD IN ADVANCED NSCLC

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Background: To investigate the safety and efficacy of recombinant human endostatin (endostar) administrated by durative infusion combined with chemotherapy within the vascular normalization period in treating advanced non-small cell lung cancer (NSCLC). **Method:** From February 2012 to December 2013, 34 cases of IIIB-IV NSCLC patients were treated with endostar (15mg/m2) durative infusion combined with chemotherapy within vascular normalization time. Endostar was durative infusion every 24 hour for 7 days, and in the fourth day of the normalization time patients were received combined chemotherapy based on platinum, 21 days per cycle. All patients received 2-6 cycles; efficacy was evaluated every two cycles, and side effects were recorded every cycle. **Result:** Every patient was received at least 2 cycles, one patient achieved CR, 14 patients were PR and 8 patients were SD. Eleven patients were PD. The overall response rate (ORR) of 34 patients was 44.1%, and non-squamous NSCLC was 38.9%, squamous NSCLC was 50.0%. First-line treatment of patient showed higher ORR, 53.9%. Major toxicities related to endostar were sinus tachycardia in one case, and one case hypertension. No serious side effects such as bleeding were observed. **Conclusion:** Endostar (15mg/m2) durative infusion combined with normalization period chemotherapy for NSCLC was an efficacy and safe regimen. A larger prospective randomized controlled clinical study is worth to carry out in future.

Keywords: Durative infusion, Endostar, NSCLC

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-033 LONG-TERM OUTCOME OF HISTOCULTURE DRUG RESPONSE ASSAY GUIDED ADJUVANT CHEMOTHERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Histoculture Drug Response Assay (HDRA) is a representative in vitro drug response assay used for anticancer agents. Several papers reported that HDRA was useful to predict chemosensitivities in non-small cell lung cancer (NSCLC). However, it is unknown that whether HDRA truly predict clinical outcome and associate with other predictive markers, such as ERCC1 and class III beta-tubulin (TUBB3). **Method:** Between August 2007 to July 2009, 46 patients with non-small cell lung cancer who underwent surgical treatment were enrolled. HDRA technique was the same as we previously reported (JTCVS 133: 303-8, 2007). Chemosensitivities of cisplatin (CDDP), paclitaxel (PTX), docetaxel (DTX), and vinorelbine (VNR) were evaluated. Immunohistochemical staining for ERCC1 and TUBB3 were done using monoclonal antibody clone 8F1 and TUJ1. The H-score was adopted for the evaluation of ERCC1 and TUBB3 expression. Adjuvant therapy was selected for each patient based on HDRA within the standard treatment. Median follow up period was 117 months. **Result:** ERCC1 was positive in 38 specimens and negative 6 specimens. Inhibition rate for CDDP in HDRA was significantly lower (p=0.02) in ERCC1-positive specimens (41±16)% than in ERCC1-negative specimens (58±8%). TUBB3 was positive in 12 specimens and negative 32 specimens. Inhibition rate for VNR in HDRA was significantly higher (p=0.01) in TUBB3-positive specimens (38±17)% than in TUBB3-negative specimens (23±15%).However, inhibition rate for PTX and DTX were not significantly correlated with TUBB3 status (p=0.39, 0.94). Disease -free survival(DFS) in patients from IB to IIIA with HDRA guided therapy tended to be longer than those without HDRA (p=0.083). Overall survival (OS) in patients from IB to IIIA with HDRA guided therapy were not to be longer than those without HDRA (p=0.77). **Conclusion:** Tumors with low ERCC1 levels exhibited greater chemosensitivity to CDDP than tumors with high ERCC1 levels. Tumors with high TUBB3 levels exhibited greater chemosensitivity to VNR than tumors with low TUBB3 levels. HDRA-guided adjuvant chemotherapy may prolonged RFS, but not affect to OS.

Keywords: chemotherapy, ERCC1, Histoculture Drug Response Assay

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-034 THERAPEUTIC EFFECT OF NOVEL LEUCYL-TRNA SYNTHETASE INHIBITOR, B1206, IN NON-SMALL CELL LUNG CANCER

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Background: Among the aminoacyl-tRNA synthetases (ARSs) which catalyze ligation of amino acids to their cognate tRNAs, leucyl-tRNA synthetase (LRS) involves in amino acid-induced mammalian target of rapamycin (mTOR) complex 1 (mTORC1) activation by sensing intracellular leucine concentration. Because mTORC1 regulates cell growth and proliferation by coordination upstream signals such as growth factor and amino acid availability, we hypothesized that inhibition of LRS inhibits cell growth and proliferation and synergize in cell death when combined with cytotoxic agents. **Method:** Expression of LRS and pS6 was observed by immunochemical staining of NSCLC tissue from 117 patients. The effect of B1206 on mTORC1 signaling was analyzed by immunoblotting and confocal imaging and its cytotoxic effect was measured by flow cytometer after annexin V-propidium iodide staining. In vivo effect of B1206 was evaluated by microCT in LSL-Kras G12D mouse lung cancer model. **Result:** Among 117 human NSCLC tissues, LRS was overexpressed in the 52 (44.4%) cases of cytoplasm and 14 cases (11.2%) of nucleus and the expression of pS6(Ser235/236) in the serial tissue section from matched lung cancer patient showed significant correlation with that of LRS expression (Pearson's correlation coefficiency=0.315, p-value<0.001). Treatment of B1206 inhibited phosphorylation of pp70S6K(T389), pS6(S235/236), and p4EBP1(T36/45) in a dose dependent manner, which is more prominent in 6 Hr after treatment. On the other hand, it did not influence phosphorylation of pAKT(S473) and pGSK(S9), which are signaling markers of mTORC2. There was a significant change in the cell size by treatment of sublethal dose of B1206, which is additional finding suggesting B1206 possesses mTORC1 inhibitory effect. Among the 10 cell lines tested, B1206 treatment could not induce cell death in 6 cell lines up to 30 uM of concentration. But H2009, H460, and H358 cells were sensitive to B1206 and most cell death occurred at concentrations below 10 uM and H1703 showed moderate sensitivity to B1206. Treatment of B1206, cisplatin, and combination of both drugs significantly reduced tumor size when compared with that of vehicle treated group and the anti-tumor effect of B1206 and cisplatin was comparable. However, combination of B1206 and cisplatin did not show significant difference in tumor size when compared with single drug treatment. **Conclusion:** This study suggests that B1206 could be used as a new concept of therapy for NSCLC by inhibiting the non-canonical function of LRS and that continuous efforts are required on exploring non-canonical function of ARS as well as its inherent function for protein synthesis.

Keywords: Leucyl-tRNA synthetase (LRS), B1206, non-small cell lung cancer (NSCLC)

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-035 EFFICACY OF NINTEDANIB AND DOCETAXEL IN COMBINATION WITH THE NUTRACEUTICAL USE OF SILIBININ IN ADVANCED NSCLC

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Background: 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. The bioactive flavonolignan silibinin, the main component of standardized extracts from the seeds of the milk thistle herb *Silybum marianum*, has been shown to exert significant anti-cancer effects in pre-clinical models. The oral use of the silibinin-containing nutraceutical Legasil® could represent the first silibinin formulation with proven clinical benefit as an adjunct cancer treatment. **Method:** Patients with stage IV NSCLC who failed ≥1 prior treatment were eligible for nintedanib/docetaxel combination. We present data of patients that received nintedanib plus docetaxel with or without combination with up to 5 capsules/day of Legasil®, which equated to a 630 mg/ day dose silibinin regimen, as complementary treatment. The nature of the interaction between nintedanib and silibinin was explored in a broad panel of human NSCLC cell lines. **Result:** Twenty-two patients were enrolled in the study: median age 63y (range: 44–74); male: 14. All the cases were non-squamous NSCLC. All patients had received first line therapy; 3 patients had ≥2 prior lines of treatment. The mean PFS was 1.82 months (95% confidence interval [CI] 1.39–2.26) for the nintedanib plus docetaxel combination (n=7) *versus* 4.97 (95%CI 2.87–7.07) for the nintedanib, docetaxel and Legasil® triple combination (n=15) (p=0.02). No statistically significant differences in mean OS were observed between the two arms: 4.88 (95%CI 3.26–6.48) for nintedanib plus docetaxel *versus* 10.3 (95%CI 5.85–14.76) for nintedanib plus docetaxel plus Legasil® (p=0.534). At the data cutoff in June 2017, 9 (41%) patients remained alive. A significant inverse correlation was found between nintedanib and silibinin sensitivity among NSCLC cell lines. The combined treatment of nintedanib and silibinin produced unanticipated, synergistic cytotoxic effects in nintedanib-unresponsive NSCLC cells. **Conclusion:** There is a clinical and biological rationale for combining nintedanib and docetaxel with the silibinin-containing nutraceutical Legasil® in patients with advanced NSCLC, where few effective second-line treatment options are available.

Keywords: silibinin, nintedanib, docetaxel

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-036 ADJUVANT CHEMOTHERAPY WITH URACIL-TEGAFUR FOR PATHOLOGICAL T1AN0M0 LUNG ADENOCARCINOMA WITH LYMPHATIC VESSEL INVASION

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Background: The aim of this retrospective study was to investigate the efficacy of adjuvant chemotherapy for patients in pathological T1aN0M0 lung adenocarcinoma with lymphatic vessel invasion. **Method:** We retrospectively collected data on 72 consecutive patients with pathological T1aN0M0 (the 7th edition of the UICC TNM stating system) lung adenocarcinoma with lymphatic or/and vessel invasion from January 2001 to December 2013. Adjuvant uracil-tegafur group were compared with control group. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method and differences compared using log-rank test. Prognostic factors were evaluated using a Cox proportional hazard model. **Result:** Among the 72 patients, 21 patients (29.1%) were treated with adjuvant chemotherapy with uracil–tegafur. No significant difference was found in patient characteristics between the two groups. In the 21 adjuvant chemotherapy and 51 control groups, the 5-year OS rates were 100% versus 80.8%, respectively; and the 5-year DFS rates were 88.2% versus 65.1% (p=0.0138), respectively. Multivariate analysis revealed that adjuvant chemotherapy was only independent predictor of OS and DFS (p = 0.014, 0.013, respectively). **Conclusion:** Adjuvant chemotherapy with uracil–tegafur improves survival among patients with completely resected pathological T1aN0M0 lung adenocarcinoma with lymphatic vessel invasion. Our study suggests that pathological T1aN0M0 lung adenocarcinoma with lymphatic vessel invasion potentially benefits from adjuvant chemotherapy.

Keywords: non-small cell lung cancer, adjuvant chemotherapy, Lymphatic vessel invasion

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-037 A PHASE II STUDY OF ADJUVANT CHEMOTHERAPY WITH DOCETAXEL PLUS NEDAPLATIN FOR COMPLETELY RESECTED NON-SMALL CELL LUNG CANCER

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Background: Nedaplatin, a cisplatin derivative, has similar activity to cisplatin for non-small-cell lung cancer (NSCLC). We previous reported that the combination chemotherapy of docetaxel plus nedaplatin was well tolerated in patients with advanced NSCLC. The purpose of this phase II study was to evaluate the feasibility of combination chemotherapy of docetaxel plus nedaplatin as an adjuvant chemotherapy in patients with completely resected stage IB-IIIA NSCLC. **Method:** Following a radical surgery, patients were treated with docetaxel (60 mg/m^2) and nedaplatin (80 mg/m^2) on day 1 every four weeks up to four cycles. The primary endpoint was feasibility, determined by the proportion of patients who completed four cycles of the combination chemotherapy. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (version 4.0). Median relapse-free survival time after surgery was calculated by analyzed by Kaplan-Meier analysis. **Result:** From December 2010 and April 2016, 34 patients with median age of 64.5 years (range, 36–77 years) were enrolled in this study. The patients consisted of 30 males and four females. Histological types were adenocarcinomas in 20 patients, squamous cell carcinomas in 12, and others in 2. Pathological stages were IB in 2 patients, II in 21, and IIIA in 11. Concerning the feasibility of the combination adjuvant chemotherapy, twenty-six patients (76.5%) completed four cycles of the combination chemotherapy. In 11 of those patients (42.3%), doses of the agents were decreased from the initial doses due to toxicities. Grade 3 or 4 toxicities included leukopenia (36.4%), neutropenia (69.5), anemia (1.7%), thrombocytopenia (0.8%), anorexia (7.6%), and nausea (3.4%). There were no treatment-related deaths. Median relapse-free survival time after the surgery was not reached, and 5-year survival rate was 65.8%. **Conclusion:** Given high completion rate of adjuvant chemotherapy with docetaxel plus nedaplatin, we conclude that the adjuvant chemotherapy is feasible and tolerable in patients with completely resected NSCLC.

Keywords: adjuvant chemotherapy, Nedaplatin, docetaxel

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-038 A PHASE I TRIAL OF AFATINIB AND BEVACIZUMAB IN UNTREATED PATIENTS WITH ADVANCED NSCLC HARBORING EGFR-MUTATIONS: OLCSG1404

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Background: In advanced EGFR-mutant NSCLC, afatinib, a second-generation EGFR-tyrosine kinase inhibitor (EGFR-TKI) has demonstrated a significant survival benefit over platinum-based chemotherapy (Lancet Oncol. 2015) and the combination therapies of EGFR-TKI and bevacizumab showed favorable PFS data (J Thorac Oncol. 2015 and Lancet Oncol. 2014). Also, our preclinical study revealed the synergistic effect of afatinib and bevacizumab (Mol Cancer Ther. 2013). We hypothesized afatinib and bevacizumab potentially yields further efficacy and conducted a phase I trial. **Method:** Untreated patients with advanced EGFR-mutant NSCLC were enrolled. The primary endpoint was set as safety. The first 6 patients received afatinib at 40 mg/body daily and bevacizumab intravenously at 15 mg/kg every 3 weeks until PD or unacceptable toxicity (level 0). If 2 or fewer patients experienced DLT, we repeated at the same dose to additional 6 patients. When 2 or fewer patients experienced DLT in the both sets, we concluded this dose was feasible. Otherwise, we repeated the same method at the level -1 (afatinib 30 mg/body, bevacizumab 15 mg/kg). If the dose was feasible, the level was recommended. **Result:** Nineteen patients were enrolled (level 0: 5 and level -1: 14). Three patients at level 0 experienced DLT, which concluded level 0 was unfeasible. At level -1, 3 patients developed DLT. All of the DLT soon recovered. Severe adverse events were shown in Table. Three patients at level 0 and 5 at level -1 required dose reduction for toxicity, respectively. Two patients at level 0 stopped protocol therapy for toxicity, whereas 2 at level -1 for wish of patients. Among 16 evaluable patients, the best response was CR / PR (81.3%) and SD (18.8%). **Conclusion:** Dose level -1 was well tolerated and had evidence of disease control. There was no refractory patient as well as other trials of EGFR-TKI plus bevacizumab.

		Level 0 (n=5)	Level -1 (n=14)
Grade 4		0	0
Grade 3		5	4
Grade 3 (* DLT)	Diarrhea	2*	2*
	Skin rash	1	1
	Hypoxia	1*	0
	Anorexia	0	1*
	Paronychia	1	0

Keywords: Bevcizumab, Phase 1 trial, afatinib

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-039 THERAPEUTIC INHIBITION OF THE CANCER STEM CELL MARKER, ALDH1, A PROMISING MECHANISM BY WHICH CISPLATIN SENSITIVITY CAN BE RESTORED IN NSCLC

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Background: Cisplatin remains the cornerstone of current chemotherapeutic combination startegies in the treatment of NSCLC. Despite initial cisplatin sensitivity tumours develop resistance, which in turn undermines the efficacy of cisplatin as a therapuetic agent. Numerous mechanisms, signalling pathways and theories have been suggested and elucidated in terms of cisplatin resistance and in the development of it, however, to date the clinical issue of resistance has not been overcome. A current avenue of interest is the cancer stem cell (CSC) hypothesis, in which the survival and expansion of highly resistant CSCs during chemotherapeutic treatment are thought to be a contributing factor of resistance and recurrence. Specific inhibition of key CSC markers in combination with chemotherapy may undermine the inherent resistance of the CSC population and sensitise these cells to the cytotoxic effects of therapy. One such CSC marker observed across numerous tumours is aldehyde dehydrogenase 1 (ALDH1), our hypothesis suggests that inhibition of the ALDH1-positive CSC population within cisplatin resistant NSCLC will resensitise the cellls to the cytotoxic effects of cisplatin. **Method:** Using an isogenic panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines ALDH1 was identified as a CSC marker present within the CisR sublines of each NSCLC histology and characterised as CSCs. ALDH1 was inhibited using two pharmacological ALDH1 inhibitors, diethlylaminobenzaldehyde (DEAB) and disulfiram (commercially known as Antabuse used in the treatment of alcoholism). ALDH1 inhibition was confirmed by flow cytometry. PT and CisR cell lines were treated with inhibitor alone and in combination with cisplatin and assessed in terms of proliferation, clonogenic survival and apoptosis relative to cisplatin-only treatment. **Result:** Both DEAB and the FDA-approved disulfiram significantly decreased the presence of the ALDH1-positive CSC subpopulation across all CisR cell lines. DEAB and disulfiram in combination with cisplatin induced a significant decrease in proliferation and clonogenic survival as well as significant increases in cisplatin-induced apoptosis across CisR sublines when compared to cisplatin alone. **Conclusion:** DEAB and disulfiram significantly reduced the presence of the highly resistant ALDH1-positive CSC subpopulation. This pharmacological CSC depletion in conjunction with cisplatin was associated with the resensitisation of cisplatin resistant cells to the cytotoxic effects of cisplatin, thus restoring cytotoxic efficacy. The resensitisation effect of the disulfiram-based combination strategy, as well as its FDA-approval and extentsive safety profile highlights this strategy as one of great promise. In summary, these data suggest a role for ALDH1 inhibition in the resensitisation and possible circumvention of cisplatin resistance.

Keywords: Cancer Stem Cells, aldehyde dehydrogenase 1, Cisplatin resistance

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-040 SMOKERS HAVING ACTIVATING EGFR MUTANT NON-SMALL CELL LUNG CANCER MIGHT BENEFIT FROM EGFR-TKI TREATMENT - SINGLE CENTER EXPERIENCE

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Background: Epidermal growth factor receptor (EGFR) mutation is seen 15-20% in non-small cell lung carcinomas (NSCLC), more common in non-smokers, female sex and Asian population. Treating NSCLC patients having activating EGFR mutations with tyrosine kinase inhibitor (TKI) significantly prolongs progression-free survival compared to standard chemotherapy and is a more tolerable. Our aim is to evaluate clinicopathologic features of patients using EGFR directed therapies (erlotinib or gefitinib) longer than 1 year. **Method:** Files of 46 patients with metastatic NSCLC having activating EGFR mutations and treated with EGFR TKI between 2012-2017 were retrospectively evaluated. Statistical analysis was done by SPSS 16. **Result:** Median age was 61 (30-80), and 56.5% (26/46) was female. Mean follow-up was 38 months.The rate of smoking was 41% (19/46). LDH elevation was found in 67% and CEA elevation was found in 50% of the patients at presentation. Median progression-free survival time (mPFS) was 21 months (range 2-58). mPFS is 21 months (2-35) for patients using erlotinib in first line (35 patients), and 13 months (5-30) in second line setting (11 patients). Sixty four percent of patients had exon 19 deletion, 28% had exon 21 mutation, and 8% had activating exon 18 mutations. There were 27 patients with PFS 12 months or more and 9 patients with less than 12 months. No statistically significant difference was found for PFS when clinicopathologic features (age, gender, 1st or 2nd line usage, LDH or CEA levels, ECOG PS, smoking, weight loss, mutation status) of these patients were compared. Median overall survival time (mOS) for metastatic disease was 39 months (range 4-65). The negative effect of ECOG-PS on OS was shown by univariate and multivariate analysis. Skin toxicity was observed in 18 patients (43%), while treatment was interupted and dose was reduced in 6 patients (14%) due to side effects. **Conclusion:** Activating mutation in EGFR is the most important marker that predicts response to EGFR-TKIs in NSCLC. Smokers should be tested for EGFR mutations, as some patients may benefit from EGFR-TKI treatment for longer than reported in the literature.

Keywords: metastatic non-small cell lung cancer, EGFR-TKI, smoking

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-041 EXPLOITATION OF THE CANCER STEM CELL MARKER ALDH1 WITHIN THE VITAMIN A/RETINOIC ACID AXIS PROMOTES RE-SENSITISATION OF CISPLATIN RESISTANT NSCLC

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Background: Despite significant advances in personalised medicine in recent decades, cisplatin remains the mainstay chemotherapy in the treatment of NSCLC. The major clinical challenge facing NSCLC today is the development of pan-resistance to platinum agents. Novel drug design, preclinical and clinical trials working toward the approval of new drugs is a lengthy and costly process and in the interim of the drug indentifcation and commercialisation research has turned its focus to two avenues of interest; overcoming cisplatin resistance and the repurposing of approved therapeutics with new indications. Cancer stem cells (CSCs) have been hypothesised to be the initiating cells of therapeutic resistance and tumour recurrence. An ALDH1-positive cell subset has been identified as a key CSC subpopulation present within cisplatin resistant NSCLC sublines. ALDH1 is involved in the metabolism of retinol (vitamin A) and the catalytic conversion of retinal to retinoic acid, where retinoic acid induces cell differentiation. All-trans retinoic acid (ATRA) is a well-established chemotherapeutic agent in the treatment of acute promyelocytic leukaemia; it induces the terminal differentiation of immature cells. We hypothesise that treatment of the cisplatin resistant NSCLC sublines with retinol or ATRA will deplete the ALDH1-positive population and subsequently increase or restore cisplatin sensitivity. **Method:** Flow cytometry on a panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines revealed the greater presence of ALDH1-positive CSC subpopulations within the CisR sublines of each NSCLC histology relative to PT lines. Cells were treated with retinol (substrate of the retinoic acid pathway) or ATRA (product of the retinoic acid pathway) and the presence of the ALDH1-positive CSC subset reanalysed by flow cytometry. Following treatment of the PT and CisR cells with retinol or ATRA alone and in combination with cisplatin the functional parameters of proliferation, clonogenic survival and apoptosis were reassessed relative to cisplatin alone. **Result:** Treatment of the CisR sublines with retinol (1μM) or ATRA (5μM) significantly reduced the presence of the ALDH1-positive CSC subset across CisR sublines. Both retinol and ATRA when used in combination with cisplatin significantly reduced the proliferative and survival capacity of each CisR subline while significantly increasing apoptotic cell death compared to cisplatin alone. **Conclusion:** Exploitation of the vitamin A/retinoic acid pathway in combination with cisplatin re-sensitised resistant cells to the cytotoxic effects of cisplatin. These data suggest vitamin A supplementation or the addition of FDA-approved ATRA to the cisplatin-based chemotherapeutic regimen may be of clinical benefit in overcoming tumour recurrence and cisplatin resistance.

Keywords: Cancer Stem Cells, Aldehyde Dehydrogenase 1 (ALDH1), Retinoic Acid Pathway

P1.03-042 BBI608, A SMALL MOLECULE STEMNESS INHIBITOR, CIRCUMVENTS CISPLATIN RESISTANCE IN NSCLC

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Background: The cancer stem cell (CSC) hypothesis is now a well-established and widely investigated field within oncology. It hypothesises that there is a robustly resistant stem-like population of cells that survive and thrive initial chemotherapeutic treatment. These surviving CSCs contribute to the recapitulation of a heterogeneous tumour via a combination of asymmetric and symmetric cell division, subsequently resulting in relapse and therapeutic resistance. BBI608 is a small molecule inhibitor of cancer stemness; it targets STAT3, leading to the inhibition of critical genes required for the maintenance of cancer stemness. Following initial *in vitro* and *in vivo* preclinical promise of BBI608 reported in the literature, phase II and III clinical trials are underway and are at various stages of recruitment, progress and completion to investigate BBI608 across a number of advanced malignancies and in combination with numerous chemotherapeutic agents. **Method:** Aldefluor (Stemcell Technologies) staining and flow cytometry analysis of a panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines identified the ALDH1-positive (ALDH1+ve) subpopulation of cells as an omnipresent CSC subset across cisplatin resistant NSCLC sublines. PT and CisR cell lines were treated with BBI608 (1μM) and the presence of the ALDH1+ve CSC population was reassessed by flow cytometry and expression of stemness factors (Nanog, Oct-4, Sox-2, Klf4 and cMyc) were examined by reverse transcriptase PCR. The functional parameters of proliferation, clonogenic survival and apoptosis were investigated with increasing concentrations of cisplatin in the presence and absence of 1μM BBI608. **Result:** The NSCLC CisR sublines showed a significantly greater ALDH1+ve CSC population relative to their PT counterparts. Treatment of the CisR sublines with 1μM BBI608 significantly depleted the ALDH1+ve CSC population and decreased gene expression of stemness markers. BBI608 significantly decreased the proliferative capacity and clonogenic survival of the CisR sublines when in combination with cisplatin relative to cisplatin alone. Cisplatin in combination with BBI608 significantly increased cisplatin-induced apoptosis in the CisR sublines indicating restoration of cisplatin sensitivity. **Conclusion:** To date, BBI608 has not been investigated in terms of a cisplatin resistant ALDH1+ve CSC population in lung cancer. BBI608, via the inhibition of STAT3, pharmacologically depleted the CSC subpopulation and stemness expression while simultaneously restoring cisplatin sensitivity. There are currently a number of clinical trials in various stages of completion to further investigate BBI608. These data suggest a promising role for BBI608 in the treatment of non-responsive or recurrent NSCLC.

Keywords: Cancer stemness, Cisplatin resistance, BBI608

P1.03-043 30-DAY MORTALITY FOLLOWING SYSTEMIC ANTI-CANCER TREATMENT FOR NSCLC AT A SINGLE CANADIAN CANCER CENTRE

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Background: Systemic Anti-Cancer Therapies (SACT) are frequently employed as either curative or palliative treatments in patients with lung cancer, but the benefits of SACT take time and may not always render immediate benefit. Death within 30 days of receiving SACT suggests that treatments were futile since these patients did not live long enough to derive direct therapeutic benefit. This study aimed to identify clinical factors associated with the risk of 30-day mortality among patients with advanced non-small cell lung cancer (NSCLC) at the Tom Baker Cancer Center (TBCC) in Calgary, Canada. **Method:** A retrospective review of NSCLC patients receiving SACT between January 2010 and December 2014, and captured in the Glans-Look Lung Cancer Database was conducted. We identified patients with a regimen start or change of SACT in the last 30 days of life. Mortality rates were calculated, and multivariable logistic regression was used to identify demographic, tumor or treatment-related factors that correlated with 30-day mortality risk. **Result:** Of 573 NSCLC patients receiving SACT between January 2010 and December 2014, 119 patients were identified as dying ≤ 30 days following SACT, yielding a 22% 30-day mortality rate. Of these 119 patients, 47% had a change or initiation of SACT within the last 30 days of life, and 54% received treatment within the last 14 days of life. Of patients dying within 30 days, 50% received cytotoxic chemotherapy, and 48% received anaplastic lymphoma kinase/tyrosine kinase inhibitors (ALK/TKI) as compared to 79% and 20% of surviving patients, respectively. This resulted in a 30-day mortality rate of 10.6% for cytotoxic chemotherapy and 10.3% for ALK/TKI therapy. Ongoing analysis will elucidate predictive factors that are associated with increased risk of 30-day post-SACT mortality. **Conclusion:** A number of NSCLC patients are at increased risk of dying within 30 days of SACT receipt. Efforts to determine the clinical characteristics of patients dying within 30 days of SACT, and to ascertain potential indicators of poor outcome following SACT can reduce avoidable harm. Data from a diverse and representative patient population such as this can provide real world evidence and serve as a means of informing best practices in palliative and end-of-life care for cancer patients.

Keywords: Systemic anti-cancer therapy, 30-day mortality, non-small cell lung cancer

P1.03-044 EXPLORATORY ANALYSIS OF LUNG CANCER PATIENTS IN A PHASE IB/II TRIAL OF NC-6004 (NANOPARTICLE CISPLATIN) PLUS GEMCITABINE

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Background: NC-6004 is a polymeric micelle exhibiting sustained release of cisplatin and selective distribution to tumors, reducing plasma C_{max} and increasing AUC. Preclinical data showed less neuro- and nephrotoxicity with greater anti-tumor activity versus cisplatin. A previous trial evaluated NC-6004 and gemcitabine defining a recommended phase 2 dose of 90 mg/m^2. A Bayesian continual reassessment method (N-CRM) design evaluated escalating doses of NC-6004 in combination with gemcitabine at 1250 mg/m^2. **Method:** Patients with refractory solid tumors were enrolled at four US sites. NC-6004 was administered intravenously (IV) at 60-180 mg/m^2 over 1 hour on Day 1 with gemcitabine at 1250 mg/m^2 IV over 30 mins on Day 1 and Day 8 every 3 weeks. All patients were administered a hydration regimen. Escalation of NC-6004 began with a single patient run-in, escalating by 15 mg/m^2 until a dose limiting toxicity (DLT) occurred at 180 mg/m^2. Cohorts of four patients were then enrolled at each dose predicted by the N-CRM design. The maximum tolerated dose (MTD) was defined as the dose with the greatest posterior probability of target toxicity < 25%. **Result:** Among 22 patients enrolled in Phase 1b, 11 patients (six male, five female) had lung cancer. Non-squamous non-small cell lung cancer (NSCLC) was the most common subtype in 8/11 (72%) followed by squamous NSCLC, SCLC and large cell neuroendocrine histology in 1/11 (9%) of each type. Patients received a mean of 1.7 (range, 1-5) prior lines of therapy with 82% receiving a prior platinum agent. Common Grade 3/4 hematologic adverse events (AEs) among all patients were leukopenia (27%), thrombocytopenia (27%), anemia (18%) and neutropenia (18%). All AEs/DLTs were manageable and resolved. Of the four lung cancer patients treated at the MTD (135 mg/m^2), the mean number of cycles received was 6 (range, 2-17). The total cumulative doses were 120-2340 mg/m^2. Of ten patients evaluable, partial response was observed in 2/10 and stable disease in 7/10. Tumor shrinkage was observed in 6/10. **Conclusion:** The nanoparticle formulation allowed greater cisplatin equivalent doses with no clinically significant neuro-, oto- or nephrotoxicity allowing patients to receive treatment for a longer duration. Activity was observed in heavily pretreated platinum exposed lung cancer patients with a majority of patients exhibiting tumor regression or stable disease. NC-6004 with gemcitabine demonstrated promising activity and tolerability in heavily pretreated lung cancer patients in this trial and warrants further investigation.

Keywords: Cisplatin, lung cancer, nanoparticle

P1.03-045 HER-2 MUTATION IS NOT A PROGNOSTIC FACTOR TREATED WITH FIRST-LINE CHEMOTHERAPY IN NSCLC PATIENTS

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Background: *Human epidermal growth fator2 (HER-2)* is a driver gene in non-small cell lung cancer (NSCLC), however, the effect of chemotherapy in patients with *HER-2* mutation has not been studied. **Method:** *HER-2* mutation was detected in 1041 EGFR/ALK/ROS1/KRAS/BRAF wild type NSCLC patient samples in Shanghai Pulmonary Hospital using ARMS method, and the mutation positive samples were confirmed by DNA sequencing. The clinicopathologic features and prognosis of the *HER-2* mutation patients were analyzed. **Result:** 63 samples (6.1%) were *HER-2* mutation positive, and 53 samples (84.1%) were confirmed by DNA sequencing. 5(7.9%) were point mutation and 58(92.1%) were insertion mutations with 33 (52.4%) A775_G776insYVMA. Patients with A775_G776insYVMA mutation had no association with other mutations in sex, age, smoking status, and pathological types, as well as in objective response rate (ORR, 40.0% vs 28.6%, p=1.000) and progression-free survival (PFS, p=0.069). Patients with six gene wild type were matched with the 63 *HER-2* mutation patients in clinicopathologic features. We found that there was no significant difference between *HER-2* mutation and wild type patients in ORR (30.4% vs 29.3%, p=0.157) and PFS (7.0month vs 4.5month, p=0.086), although the PFS was longer in *HER-2* mutation patients. **Conclusion:** *HER-2* mutation was 6.1% in EGFR/ALK/ROS1/KRAS/BRAF wild type NSCLC patients. There was no significant difference between *HER-2* mutation and wild type patients in ORR and PFS treated with first-line chemotherapy. Target therapy maybe needed to treat these patients.

Keywords: EGFR, non-small cell lung caner, HER-2

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-046 A RETROSPECTIVE ANALYSIS OF CORRELATION BETWEEN CYTOKINES IN TME AND THERAPEUTIC EFFECT OF ADVANCED LUNG CANCER CHEMOTHERAPY IN CHINA

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Background: Chemotherapy plays an important role in the treatment of lung cancer in the world as well as in China. Studies showed that chemotherapeutic drugs may change the interactions of cancer cells and TME. A number of international studies have changed the treatment paradigm of advanced lung cancer. Since we already entered into a new era of immunotherapy, positive reactions of immunotherapy usually related to the changes of TME. This retrospective study was designed to evaluate relationship between immune-related cytokines in TME and chemotherapy in advanced lung cancer. **Method:** A total of 728 patients with advanced lung carcinoma diagnosed and treated in Shanghai pulmonary hospital from June 2010 to June 2015 were included. IL-1, IL-2R, IL-5, IL-6, IFN-γ,TNF and different cut off values of the 6 cytokines (25%, 50%, 75%, 90%, median level) as well as proportion and ratio of CD4+T lymphocytes and CD8+T lymphocytes were analyzed by Flow Cytometry before and after chemotherapy. **Result:** Median age at diagnosis was 61 (19-83 years), and median OS was 435 days. Our results suggested that IFN-γ(cut off value 25%) had significant correlation with OS after first-line chemotherapy (OS:below 25% vs above 25% 406 vs 463 days, log-rank p=0.049). Other factors such as IL-1, IL-2R, IL-5, IL-6, TNF, did not showed statistically significant with the chemotherapy and PFS or OS (log-rank p>0.05 for all). **Conclusion:** IFN-γ is a predictive and prognostic factor of advanced NSCLC independent of chemotherapy. The results of our study may be expected to serve as useful information of influence by chemotherapy on TME and may indicate treatment sequence in the near future.

Keywords: lung cancer, TME, chemotherapy

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-047 CARBOPLATIN/ WEEKLY NAB-PTX IN ELDERLY PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED SQUAMOUS NSCLC SELECTED BASED ON MNA-SF

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Background: This multicenter, single-arm, open-label, phase 2 study assessed the efficacy and safety of carboplatin plus weekly nanoparticle albumin-bound paclitaxel in elderly patients with previously untreated advanced squamous non-small-cell lung cancer, selected based on the Mini Nutritional Assessment short-form scores (MNA-SF). **Method:** Patients received carboplatin (area under the curve: 6) on Day 1, and nanoparticle albumin-bound paclitaxel (100 mg/m^2) on Days 1, 8, and 15, every 28 days for ≤4 cycles. Eligibility criteria included an MNA-SF score of ≥8 points. The primary endpoint was the objective response rate. **Result:** Thirty patients with a median age of 76 (range, 70–83) years were enrolled. The objective response rate was 50.0% (95% confidence interval: 31.3–68.7%), which met the primary objective of this study. The disease control rate was 73.3% (95% confidence interval: 54.1–87.7%). At a median follow-up of 15.0 months, the median progression-free and overall survival was 7.1 and 19.1 months, respectively. The most common treatment-related adverse event of Grade ≥3 was neutropenia (66.7%). Non-hematological adverse events of Grade ≥3 were minor. Well-nourished patients, based on the MNA-SF, experienced fewer adverse events of Grade ≥3 compared to patients at risk of malnutrition. All treatment-related adverse events were tolerable and reversible. There were no treatment-related deaths. **Conclusion:** Carboplatin plus weekly nanoparticle albumin-bound paclitaxel is effective and well tolerated as a first-line treatment for elderly patients with advanced squamous non-small-cell lung cancer. Eligibility based on MNA-SF screening may be useful in determining acceptable toxicity.

Keywords: elderly, Squamous cell carcinoma, Mini Nutritional Assessment short-form

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-048 MIR-34A AND THE MICROMANAGEMENT OF CANCER STEMNESS AND RESISTANCE IN NSCLC. DOES IT HOLD THERAPEUTIC BENEFIT?

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Background: The capacity of microRNAs to post-transcriptionally regulate a myriad of genes has extended their remit into the realm of stemness and furthermore cancer stemness regulation. Disruption of *Dicer-1*, a crucial component of microRNA biogenesis, has been shown to completely deplete the stem cell pool in early development, indicating a potential role for microRNAs in the maintenance of stem cells. Such logic has led microRNAs to be investigated in the context of cancer stem cells (CSCs). Studies have revealed that microRNAs play a role in CSC self-renewal, differentiation, drug resistance and metastasis. With this, our hypothesis suggests that microRNAs associated with cisplatin resistance and CSC maintenance may be a key target by which the CSC root of cisplatin resistance could be overcome. **Method:** MicroRNA expression within a panel of age-matched parent (PT) and cisplatin resistant (CisR) NSCLC sublines was profiled using the 7th generation miRCURY LNA arrays (Exiqon) and validated by qPCR. Cell lines were stained for the presence of the CSC marker, aldehyde dehydrogenase 1 (ALDH1) and FACS was used to isolate the ALDH1-positive CSC population from the ALDH1-negative bulk cell population. Expression of the panel of cisplatin resistance-associated microRNAs was investigated within the ALDH1-positive CSC population relative to their negative counterparts by qPCR. Significantly altered miRNAs were inhibited in the CisR subline using antagomirs (Exiqon) and the presence of the ALDH1-positive subset reassessed by flow cytometry and expression of stemness genes (Nanog, Oct-4, Sox-2, Klf4, cMyc) determined. The presence of the cisplatin-associated miRNAs was investigated in FFPE murine tumours within a xenograft model of CSCs, in which 1x10^3 ALDH1-positive and negative subsets were injected into NOD/SCID mice. **Result:** Upon validation, a 5-miR signature was identified across NSCLC histologies to be associated with cisplatin resistance. When this panel was further investigated within the ALDH1-positive CSC subpopulation, it was observed that there was a significant up-regulation of miR-34a-5p relative to corresponding ALDH1-negative populations. Interestingly, the ALDH1-positive subpopulations showed significantly greater miR-34a-5p expression when compared to the CisR sublines from which they were isolated. This up-regulation was also observed within the FFPE xenograft tumours. However, inhibition of miR-34a-5p with antagomiRs did not significantly alter the presence of the ALDH1-positive CSC population, or the expression of stemness-associated genes. **Conclusion:** These data suggest that miR-34a-5p while significantly up-regulated in cisplatin resistance and CSCs may not play a functional role in CSC maintenance and further investigation is required to fully elucidate the role of miR-34a-5p in cancer stemness.

Keywords: Cisplatin resistance, microRNA, Cancer Stem Cells

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-049 PHASE II STUDY OF S-1 PLUS BEVACIZUMAB COMBINATION THERAPY FOR PATIENTS PREVIOUSLY TREATED FOR NON-SQUAMOUS NON–SMALL CELL LUNG CANCER

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Background: The combination of platinum plus third-generation cytotoxic drugs has been the gold standard first-line chemotherapy for patients with advanced NSCLC. However, most patients experience disease progression during or after first-line treatment. The survival benefit of S-1 monotherapy as second-line therapy is not satisfactory. Bevacizumab conferred a survival benefit when combined with carboplatin and paclitaxel as first-line treatment in non-squamous NSCLC. The benefit of adding bevacizumab to non-platinum cytotoxic monotherapy such as S-1 is not clear as subsequent treatment. Therefore, we conducted a multi-center, a single-arm phase II study to evaluate the safety and efficacy of combination therapy of tailored-dose S-1 plus bevacizumab in patients with recurrent non-squamous NSCLC. **Method:** This was a prospective, multi-center, single-arm phase II study. Patients with non-squamous NSCLC who had experienced progression after cytotoxic chemotherapy were enrolled. Oral S-1 was administered on days 1–14 of a 21-day cycle, and bevacizumab (15 mg/kg) was given intravenously on day 1. Patients received S-1 adjusted on the basis of their creatinine clearance and body surface area. The primary endpoint was response rate (RR); secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. **Result:** We enrolled 30 patients. One patient had never received platinum-based therapy. Five patients had activating mutations of the epidermal growth factor receptor gene, of whom four had received tyrosine kinase inhibitors before this study. The RR was 6.7% (95% confidence interval (CI) 1.8–21.3%), and the disease control rate (DCR) was 80% (95% CI 62.7–90.5%). Median PFS was 4.8 months (95% CI 2.7–6.4 months], and median OS was 13.8 months (95% CI 8.4 months – not applicable). Patients did not experience any Grade 4 toxicity or treatment-related death. Grade 3 hematologic toxicity (anemia) occurred in one patient (3.3%). The main Grade 3 non-hematologic toxicities were anorexia (10%), infection (10%), and diarrhea (6.7%). **Conclusion:** The addition of bevacizumab to S-1 was tolerable, but not beneficial for patients with previously treated non-squamous NSCLC. We do not recommend further study of this regimen.

Keywords: S-1, bevacizumab, non-squamous non–small cell lung cancer

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-050 CLINICAL CONSEQUENCES, QUALITY OF LIFE, AND MANAGEMENT OF NEUTROPENIC NSCLC PATIENTS IN THE REVEL TRIAL

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Background: Ramucirumab is a human IgG1 monoclonal antibody antagonist of VEGFR-2 approved as a post-platinum progression therapy in non-small cell lung cancer (NSCLC). Chemotherapy-induced neutropenia is a major risk during cancer treatment and can be potentially dose-limiting, as well as play a significant role in infection-related morbidity and mortality. In the REVEL phase 3 global, placebo-controlled study of Stage IV NSCLC patients (NCT01168973), ramucirumab plus docetaxel treatment improved patient survival versus docetaxel monotherapy independent of histology; however, all grade and high-grade (Grade ≥3) neutropenia was numerically increased with ramucirumab versus placebo (Table 1). A post-hoc analysis was performed on the REVEL data to characterize neutropenia: clinical consequences, quality of life (QoL), and clinical management. **Method:** The duration of neutropenia, as well as the course and incidence of complications and their severity and related consequences associated with neutropenia were summarized. Time to deterioration in ECOG performance status (PS) was analyzed using Kaplan-Meier method, and stratified hazard ratios and 95% confidence intervals (CI, Wald) were estimated for average symptom burden index and lung cancer symptom scale items using Cox model. Clinical management summary data will be presented at the meeting. **Result:** Neutropenia events from the REVEL trial are summarized in terms of duration, course, incidence of complications, severity and resolution status in Table 1. All-grade neutropenia risk ratio is 1.197 (95% CI 1.072, 1.338) and Grade ≥3 is 1.226 (95% CI 1.081, 1.390).

Table 1. Summary of Treatment-Emergent Neutropenia in the REVEL Safety Population

Parameters	Ramucirumab + Docetaxel (*N* = 627)		Placebo + Docetaxel (*N* = 618)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Incidence of neutropenia, *n* (%)	345 (55.0)	306 (48.8)	284 (46.0)	246 (39.8)
Neutropenia leading to any study drug dose modification, *n* (%)	77 (12.3)	71 (11.3)	55 (8.9)	50 (8.1)
Neutropenia leading to ramucirumab/ placebo drug dose modification, *n* (%)	25 (4.0)*	18 (2.9)*	10 (1.6)	7 (1.1)
Neutropenia leading to docetaxel drug dose modification, *n* (%)	75 (12.0)	70 (11.2)	54 (8.7)	49 (7.9)
Deaths due to neutropenia (Grade 5 events)	0	N/A	0	N/A
In patients with Neutropenia	***n* = 345**	***n* = 306**	***n* = 284**	***n* = 246**
Neutropenia cases leading to hospitalization, *n* (%)	31 (9.0)	31 (10.1)	27 (9.5)	26 (10.6)
Duration of hospitalization (days) Median (Range)	8.0 (1.0 – 103)	6.0 (1.0 – 103)	5.0 (2.0 – 32)	5.0 (2.0 – 32)
Neutropenia cases leading to antibiotic use, *n* (%)	25 (7.2)	25 (8.2)	14 (4.9)	14 (5.7)
Neutropenia patients with infections of Common Toxicity Criteria toxicity, *n* (%)	170 (49.3)	55 (18.0)	102 (35.9)	41 (16.7)
Number of episodes of neutropenia, *n*	863	677	640	487
Resolved, *n* (%)	846 (98.0)	664 (98.1)	626 (97.8)	476 (97.7)
Unresolved, *n* (%)	17 (2.0)	13 (1.9)	14 (2.2)	11 (2.3)
Duration of neutropenia (weeks)				
Median (Min – Max)	1.29 (0.14-24.43)	1.14 (0.14-18.86)	1.29 (0.14-24.71)	1.14 (0.14-12.14)
Quality of Life (in patients with all grade neutropenia)	**Ramucirumab + Docetaxel (*n* = 345)**	**Placebo + Docetaxel (*n* = 284)**	**Stratified HR (95% CI)**	
Median Time to Deterioration (TtD, months) to ECOG PS ≥2, (95% CI)	10.05 (8.54, NE)	13.37 (9.03, NE)	1.160 (0.873, 1.542)	
Average Symptom Burden Index (ASBI, from the LCSS), # events	108	82	1.030 (0.768, 1.382)	
Total Lung Cancer Symptom Scale (LCSS), # events	119	82	1.120 (0.840, 1.493)	

* = *P*<0.05 comparison between treatment groups based on Fisher's exact test

Conclusion: Despite numerically increased rates of neutropenia observed in the ramucirumab plus docetaxel arm of the REVEL trial, the clinical consequences (resolution) of neutropenia, rate of hospitalization, and duration/incidence of Grade ≥3 infection were similar to placebo. In addition, the quality of life results do not indicate any significant differences between placebo and ramucirumab. Therefore, neutropenia in the NSCLC population is considered to be manageable during ramucirumab treatment.

Keywords: quality of life, ramucirumab, Neutropenia

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-051 DEVELOPMENT OF A NOVEL MICROFLUIDIC DEVICE FOR STUDYING THE CHEMOTAXIS MECHANISM OF BACTERIAL CANCER TARGETING

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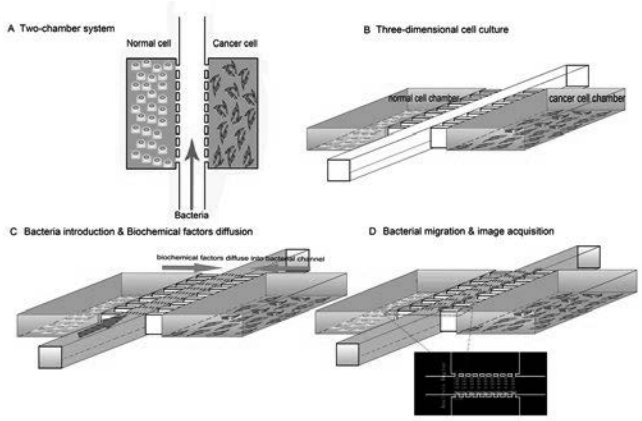
Background: The increasing prevalence of cancer cases worldwide and shortcomings of existing treatment methods including chemotherapy, radiation therapy, surgery and transplantation call for the immediate development of novel cancer therapies. Due to the non-specificity of current therapies, recognition between cancer cells and normal cells is a challenging dilemma in cancer therapeutics. Bacterial-mediated cancer therapy is a novel alternative treatment currently under intensive study. However, the exact mechanism of tumor degradation in bacterial-mediated cancer therapy is not fully understood and remains a challenging question for cancer therapeutics. **Method:** To characterize the mechanism of bacterial chemotactic preference towards cancer cells, we developed a novel microfluidic device for *in vitro* applications. The device, when used as model for lung cancer, provides simultaneous three-dimensional co-culture of multiple cell lines in separate culturing chambers and establishes constant concentration gradients of biochemical compounds in a central channel by diffusion through micro-channels. The quantification of preferential accumulation of bacteria towards a particular cell type was determined against established chemotactic gradient. Bacterial taxis behavior towards cancer and normal cells was measured in the two-chamber system using the fluorescence intensity of green fluorescence protein (GFP)-encoding bacteria. Furthermore, secretome and bioinformatic analysis of the cancer cells determined significant factors in bacterial cancer targeting.



Result: Using the microfluidic platform, *E. coli* clearly illustrated the preference for lung cancer cells (NCI-H460) which was attributed to biochemical factors secreted by carcinoma cells. Furthermore, secretome and bioinformatic analysis of the cancer cells determined CLU, SRGN and TGFβ2 as significant factors in bacterial cancer targeting. By validation test, clusterin (CLU) was found as a key chemo attractants for *E. coli* to target lung cancer. **Conclusion:** CLU, which released by lung cancer cells, was found as a key regulator for the chemotaxis of *E. coli* in targeting lung cancer.

Keywords: microfluidic platform, CLU, bacterial cancer targeting

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-052 COMPARING EGFR-TKI WITH EGFR-TKI PLUS CHEMOTHERAPY AS 1ST LINE TREATMENT IN ADVANCED NSCLC PATIENTS WITH BOTH MUTATED EGFR AND BIM POLYMORPHISM

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Background: Not all advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) activating mutations could get benefit from 1st line treatment of *EGFR* tyrosine kinase inhibitors (TKIs). Our previous study indicated that B-cell chronic lymphocytic leukemia/lymphoma-like 11 (Bim) deletion polymorphism was about 10% and was significantly associated with a poor clinical response to *EGFR*-TKIs in *EGFR* mutation-positive NSCLC. This retrospective study compared efficacy and tolerability of the *EGFR*-TKI alone versus *EGFR*-TKI plus chemotherapy as the 1st line treatment in advanced NSCLC patients with both activated *EGFR* mutation and Bim polymorphism. **Method:** Main included criterias were patients older than 18 years, histologically confirmed stage IIIB or IV NSCLC, *EGFR* mutation-positive (exon 19 deletion or 21 L858R mutation) and Bim polymorphism. Patients received gefitinib 250mg orally a day or gefitinib together with up to 4 cycles of pemetrexed/gemcitabine and platinum until disease progression

or unacceptable toxic effects. The primary endpoint was progression-free survival (PFS); the second endpoint included objective response rate (ORR), overall survival (OS) and toxicity. **Result:** From June 2014 to September 2016, 65 patients were enrolled into this trial. 36 of them received gefitinib, and 29 received gefitinib plus pemetrexed/gemcitabine and platinum. Median PFS was significantly longer in *EGFR*-TKI plus chemotherapy-treated patients than in *EGFR*-TKI (7.2 [95% CI 5.35-9.05] vs 4.6 [4.01-5.19] months; p=0.008). The ORR was significantly lower in *EGFR*-TKI than in *EGFR*-TKI plus chemotherapy-treated patients (38.9% vs. 65.5% p=0.046). *EGF*R-TKI plus chemotherapy was associated with more grade 3 or 4 hematological toxic effects than *EGFR*-TKI (8 neutropenia, 4 thrombocytopenia vs. no any event).

Table 1. Compare EGFR-TKI plus chemotherapy with EGFR-TKI alone as 1st line setting in advanced NSCLC patients with both mutated EGFR and Bim deletion polymorphism

	EGFR-TKI (n=36)	EGFR-TKI plus chemotherapy (n=29)	p-value
Efficacy			
PFS, median, months	4.6 [95% CI 4.01-5.19]	7.2 [95% CI 5.35-9.05]	0.008
ORR, %	38.9%	65.5%	0.046
Treatment-related AEs (≥3 grade), %			
neutropenia	0	2.8%	0.001
thrombocytopenia	0	1.4%	0.035
rash	16.7%	0	0.029
diarrhea	16.7%	3.4%	0.120

Conclusion: Compared with *EGFR*-TKI, *EGFR*-TKI plus chemotherapy conferred a significant higher ORR and longer PFS in advanced NSCLC patients with both activated *EGFR* mutation and Bim polymorphism. An open-label, multicenter, randomized, phase 2 study is ongoing to validate these results in our institute (NCT03002844).

Keywords: EGFR mutation, BIM polymorphism, NSCLC

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-053 TAIWAN REAL WORD EFFICACY OF 1ST LINE EGFR TKIS TREATMENT IN EGFR MUTATION POSITIVE ADVANCED NON SMALL CELL LUNG CANCER

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Background: Previous studies have shown EGFR TKIs provided superior 1st line efficacy to chemotherapy for advanced non-small cell lung cancer (NSCLC) patients harboring activating EGFR mutation. LUX-Lung7, a phase IIB randomized head-to-head study, showed afatinib significantly improved PFS, TTF, and ORR compared with gefitinib. However, it is still unclear how to choose among these three EGFR TKIs in clinical setting, especially for uncommon mutation, which was excluded in most studies. This retrospective study is aimed to evaluate the treatment pattern in our hospital and efficacy of three EGFR TKI for patients with common mutations and uncommon mutations. **Method:** Patients with advanced NSCLC were retrospectively reviewed in a university hospital in central Taiwan from Jan 2013 to Mar 2017. In this population, patients with EGFR mutations and have to be taking EGFR TKIs as 1st line treatment more than 30 days were recorded for analysis. **Result:** 1,951 patients with advanced lung cancer were reviewed. About 75% of lung cancer were adenocarcinomas and 55% were EGFR mutation rate. Clinical data of 467 patients with advanced EGFR mutation lung adenocarcinomas were extracted, 95.7% of them used EGFR TKI as 1st line therapy including gefitinib (n=210), erlotinib (n=147), and afatinib (n=110). The median age was 64 years old. More female was included in the gefitinib cohort and afatinib cohort tended to have higher component of uncommon mutations. The TTF among gefitinib (G), erlotinib (E) and afatinib (A) were 9.8 vs 11.4 vs 12.2 months (p=0.094). Patients treated with afatinib had improved TTF compared with gefitinib (HR= 0.72, 95% CI: 0.54-0.97, p=0.035) and showed a trend compared with erlotinib without significantly difference. In del 19, TTF among G, E and A were 9.4 vs 12.0 vs 12.2 months (p=0.074). In L858R, TTF among G, E and A were 10.4 vs 10.9 vs 11.7 months (p=0.721). Intriguingly, afatinib showed excellent TTF in uncommon mutations (median TTF G vs E vs A: 7.5 vs 7.0 vs 19.7 months, p=0.506). Afatinib dose reduction didn't have impact TTF (median TTF 30 mg vs 40 mg: 16.1 vs 10.3 months. p=0.923) **Conclusion:** Consistently, our findings supported improved efficacy as observed from LUX-Lung7. In more resistance mutation type such as uncommon mutation, afatinib tended to have better efficacies. Due to insufficient sample size and the retrospective study design, further confirmatory study is warranted.

Keywords: EGFR-TKI, lung cancer

P1.03: CHEMOTHERAPY/TARGETED THERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.03-054 A PHASE II RANDOMIZED TRIAL OF GEFITINIB ALONE VS OLAPARIB PLUS GEGITINIB IN ADVANCED NSCLC EGFRMUT + GOAL TRIAL SPANISH LUNG CANCER GROUP

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Background: EGFR tyrosine kinase inhibitors (TKI) are considered the treatment of choice for p harboring EGFR mutations with higher response rate (RR) and longer progression free survival (PFS) than chemotherapy. Nevertheless, resistance to TKIs is developed in the majority of cases and several resistance mechanism are involved. In EURTAC trial patients treated with Erlotinib, with high BRCA1 mRNA expression levels shorter PFS was observed. Olaparib, a PARP-inhibitor can reduce BRCA1 expression and could achieve an improvement in PFS in this subset of P when added to EGFR TKI. In a previous Phase IB for this association we have confirmed activity and tolerance in absence of pharmacokinetic interactions. Recommended dose for combination was Gefitinib 250 mg daily + Olaparib 200 mg TDS **Method:** P with Stage IV NSCLC with centrally confirmed EGFR mutations, without previous treatment for metastatic disease and with PS 0-2 and evaluable disease (RECIST criteria) are randomly assigned in 1:1 ratio to Gefitinib single agent or Gefitinib+Olaparib. Planned end-points: Primary Endpoint: PFS; Secondary Endpoints: overall survival (OS); RR; Safety, Initial presence of T790M; Influence of BRCA1, EGFR mutations on PFS; parallel analysis of EGFR mutations in serum and Ancillary molecular analysis. Statistical hypothesis: Median PFS 10 months (m) in Gefinitib group could be increased to 16 m in Combination Group; with alpha error = 0.05 and potency 80% number of events 116 needed to test the superiority hypothesis. Total planned number of inclusions: 186 P. Interim analysis pre-planned at 58 events (progression or death) **Result:** From July/2013 to July/2016, 186 patients were included in 35 centers in Spain and Mexico. There were no major disbalances for major prognostic factors between arms at the inclusion. Toxicity profile was collected according CTCAE v4 . Patients were assessed every 4 weeks and imaging assessment of response was performed every 8 weeks. Patients continue on the assigned treatment until progression or excessive toxicity. **Conclusion:** The first analysis for safety, response and primary end-point PFS will be presented with a cut-off at July 15th after pre-planned events have occurred (NCT=1513174/GECP-GOAL 10-03)

Keywords: PARP inhibitors, EGFR mutation, gefitinib

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-001 OSIMERTINIB WITH RAMUCIRUMAB OR NECITUMUMAB IN ADVANCED T790M-POSITIVE EGFR-MUTANT NSCLC: PRELIMINARY PH1 STUDY RESULTS

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Background: Combination studies of a first- or second-generation EGFR tyrosine kinase inhibitor (TKI) and either a VEGF or EGFR-targeting monoclonal antibody have recently shown promising clinical results in *EGFR*-mutant non-small cell lung cancer (NSCLC) patients. The preliminary safety results from the phase 1 study JVDL (NCT02789345), combining third-generation EGFR TKI osimertinib (Osi) with human IgG1 monoclonal antibodies ramucirumab (Ram) or necitumumab (Neci), are reported. **Method:** Eligible pts naïve to third-generation EGFR TKI therapy with advanced *EGFR* T790M-positive NSCLC who progressed after initial EGFR TKI therapy were enrolled. In the dose-finding portion, following a dose de-escalation 3+3 design, patients received daily oral Osi (80 mg) and either 10 mg/kg intravenous (IV) Ram on day 1 (D1) every two weeks (Q2W), or 800 mg (IV) Neci on D1 and D8 Q3W. Primary objective of the study is to assess the safety and tolerability of Ram or Neci combined with Osi, and secondary objectives include preliminary evaluation of efficacy. **Result:** As of data cutoff on 09-May-2017, 7 pts were treated in the completed dose-finding portion: 3 pts with Ram+Osi (Arm A) and 4 pts (1 non-evaluable and replaced) with Neci+Osi (Arm B). No DLTs were observed in either arm, and the initial dose level became the recommended dose for expansion cohort. After the DLT observation period was complete, the only Grade ≥3 (Gr≥3) treatment-related adverse

event (TRAE) was dermatitis acneiform (Arm B), with one unrelated Gr≥3 treatment-emergent AE (TEAE) of increased lipase (Arm B) and one serious AE of Gr2 diverticulitis (unrelated to study treatment) (Arm A). Expansion cohort A of Ram+Osi is fully enrolled with 22 pts. Safety data were available for 18 out of 22 cohort A patients. Gr≥3 TEAEs were reported in 4 patients, including dyspnea (unrelated [n=1]), decreased appetite (unrelated [n=1]), and hypertension (related [n=2]). Three patients reported serious adverse events (none related to study treatment): Gr3 dyspnea and Gr2 pyrexia, Gr2 dyspnea, and Gr2 urinary tract infection. No death was reported in patients in the dose-finding portion, and one death unrelated to study treatment was reported in the expansion cohort. **Conclusion:** No DLTs were observed and no unexpected safety signals were seen to date. The recommended dose for expansion cohort was the initial dose level of 10 mg/kg ramucirumab IV Q2W with oral 80 mg osimertinib. Additional safety and efficacy observation for the combination of Ram+Osi is ongoing, and will be presented at the meeting.

Keywords: ramucirumab, osimertinib, Necitumumab

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-002 TOLERABILITY OF OSIMERTINIB AND ITS IMPACT ON QUALITY OF LIFE IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS: THE ARPA STUDY

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Background: Osimertinib is a potent Epidermal Growth Factor Receptor (EGFR) inhibitor, conferring a longer survival if compared to platinum-pemetrexed chemotherapy in Non-Small Cell Lung Cancer (NSCLC) EGFR mutated patients who have progressed after first-line Tyrosine Kinase Inhibitor (TKI), with the aquired resistance mutation T790M. The ARPA study is a phase II, single institution observational study aiming to evaluate the tolerability of Osimertinib in a real world population of EGFR-T790M+ NSCLC patients, with special attention to patients' perception of symptomatic Adverse Events (AEs), their impact on health-related quality of life (HRQoL) and psychological issues. **Method:** Before entry into the study, patients have been requested to perform a new tissue or liquid biopsy to confirm the T790M+ status of their tumours. Multiple previous oncologic treatments and asymptomatic brain metastases at baseline were allowed. Patients' perception of symptomatic AEs and the matched medical evaluation were performed every 21 days under continuous treatment with dedicated questionnaires which mainly evaluated the HRQoL, until discontinuation. The psychological assessments include changes in domains related to physical, mental, emotional and social functioning, depression, sleep quality and distress. In case of documented clinical benefit, the study allows to patients to remain on treatment beyond progression. **Result:** From February 2016, a total of 34 patients have been evaluated: 2 of them were registered as screening failures for symptomatic brain metastases and lack of compliance, respectively. The 32 patients enrolled have a median age of 67,6 years (range 40-84 years), are predominantly female (65,6%), with ECOG performance status 0 (68,7%) and a non-smoking history (75,0%). Activating EGFR mutation at diagnosis have been described on exon 19 and 21 in 62,5% and 28,1% of cases, respectively. Only four patients had brain metastases at study entry. Osimertinib has been used as second-line treatment, after failure of first-line TKI, in 78,1% of cases. On the date of 1 June 2017, ten patients have interrupted the treatment for disease progression, with a median duration of therapy equal to 6,69 months (range 2,80-11,20 months). **Conclusion:** Data concerning the tolerability of treatment with Osimertinib in EGFR-T790M+ NSCLC patients, their perception of symptomatic AEs together with the psychological issues evaluated in the ARPA study, are not mature. Great expectations come from this study which reflects a real world population, and the hope of the investigators is to highlight the critical aspects for patients in order to better manage their treatment and the psychological issues.

Keywords: non-small cell lung cancer, Osimertinb, quality of life

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-003 THE INTERNATIONAL LUNG SCREEN TRIAL: A MULTI-CENTRE STUDY TO EVALUATE LDCT SCREENING SELECTION CRITERIA AND NODULE MANAGEMENT

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Background: There remain important knowledge gaps surrounding the optimal selection criteria of high-risk individuals for low-dose CT (LDCT) screening for lung cancer and the optimal management of screening-detected pulmonary nodules. The International Lung Screen Trial (ILST) is an international, multi-centre prospective cohort study with recruitment sites in Canada and Australia. The rationale and design for the study are presented here. The $PLCO_{m2012}$ risk prediction model[1] may have higher sensitivity and positive predictive value in identifying individuals who develop lung cancer compared to the United States Preventive Services Task Force (USPSTF) criteria. The PanCan model[2] calculates malignancy probability in screen-detected nodules and provides a risk-based approach to managing pulmonary nodules. Both models will be prospectively tested in this study. Primary aims: (a) to define the optimal selection criteria for LDCT screening, (b) to evaluate pulmonary nodule management using the PanCan nodule risk calculator. **Method:** We aim to recruit 4,000 high-risk individuals with 5 years follow up. Eligible participants are current or former smokers, aged 55-80 years, with a $PLCO_{m2012}$ lung cancer risk of ≥1.51% over 6 years or USPSTF criteria (age as above, plus ≥30 pack year history of smoking and smoking cessation <15 years ago). Exclusion criteria include: symptoms suspicious of lung cancer, severe co-morbidity, previous lung cancer and chest CT within the last 2 years. Baseline assessment includes interview, smoking status assessment and pulmonary function testing. Eligible individuals are offered a baseline screening LDCT and subsequent interval surveillance LDCTs dependent on the PanCan risk score. Participants with no nodules or nodule risk score of <1.5% will have biennial LDCT screening. Participants with nodule malignancy risk score ≥10%, or significant growth in subsequent scan will be considered suspicious for lung cancer and undergo clinical review for further investigation. The primary outcome is the proportion of lung cancers detected by either selection criteria. Secondary outcomes include: number needed to screen, cancer detection rate, lung cancer mortality, cancer stage distribution, resection rate, number of interval cancers, recall rate, invasive procedure rate, benign biopsy/surgery rate, screening-related adverse events and comprehensive healthcare economic evaluation. **Result:** This study is currently in its recruitment phase. Results will be reported in future conferences and peer-reviewed publications. **Conclusion:** The ILST trial will provide a clearer understanding on the optimum selection criteria for LDCT screening for lung cancer and prospective validation of the PanCan model. *ClinicalTrials.gov number: NCT02871856* References: Tammemägi MC *et al* (2013). *NEJM*; 368:728-736. McWilliams A *et al* (2013). *NEJM*; 369:910-919.

Keywords: CT, Screening, nodules

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-004 PHASE I/IB STUDY OF NIVOLUMAB AND VELIPARIB IN ADVANCED SOLID TUMORS AND LYMPHOMA WITH AND WITHOUT ALTERATIONS IN SELECTED DNA REPAIR GENES

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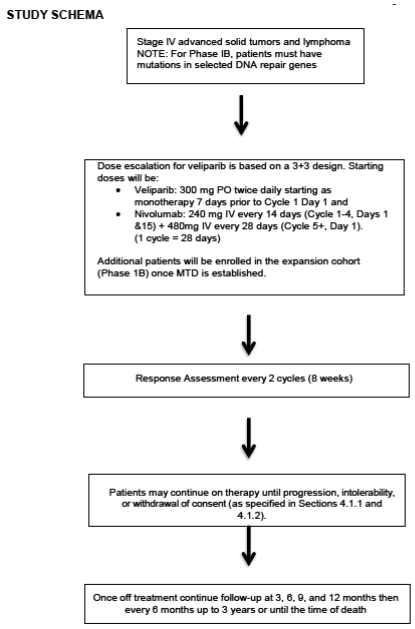
Background: Inhibition of the PD-1/PD-L1 axis with nivolumab has been a successful treatment strategy in a minority of patients with many different tumor histologies (non-small cell lung cancer, squamous cell head and neck cancer, melanoma, Hodgkin lymphoma, renal cell carcinoma, urothelial carcinoma). An increase in the proportion of patients that benefit from this emerging mechanism is needed. Veliparib is an inhibitor of poly (ADP-ribose) polymerase (PARP), and it has been shown in preclinical models and in patients with *BRCA* mutant ovarian cancer to exert anti-tumor effects through lethal exacerbation of DNA repair defects. Extensive genomic sequencing of tumors of varying histologies has revealed that approximately 5% of all tumors harbor defects in DNA repair genes such as *BRCA1/2, RAD51, CHEK1, ATM, ATR, CHEK2, FANCD2, FANCA*. We propose combining PD-1 inhibition with nivolumab with PARP inhibition with veliparib in patients with DNA repair gene defects in order to maximize the proportion of patients with clinical responses to these novel treatment strategies. **Method:** We are currently enrolling patients on this phase I/Ib clinical trial at the Northwestern Medicine Developmental Therapeutics Institute. The study schema is shown below.



Result: Section not applicable **Conclusion:** Section not applicable

Keywords: Phase I/Ib, Nivolumab, veliparib

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-005 PHASE 2 STUDY OF NIVOLUMAB AND METFORMIN IN ADVANCED NON-SMALL CELL LUNG CANCER WITH AND WITHOUT PRIOR TREATMENT WITH PD-1/PD-L1 INHIBITORS

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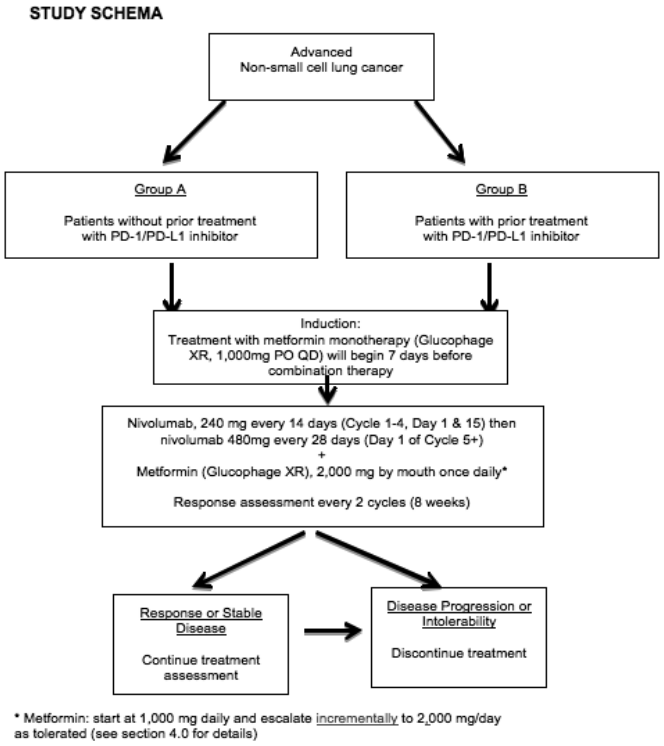
Background: Inhibition of the PD-1/PD-L1 axis with nivolumab has been proven to be a successful treatment strategy in a minority of patients with non-small cell lung cancer. An increase in the proportion of patients that benefit from this emerging mechanism is needed, and many novel combination therapies are being tested. Furthermore, many patients with non-small cell lung cancer are excluded from further clinical trials if they have received prior checkpoint inhibitor therapy, so this trial provides for this additional unmet need. Epidemiologic studies have consistently demonstrated an association between decreased cancer incidence and mortality in patient treated with metformin. Preclinical models have demonstrated that this anti-cancer effect is potentially mediated by inhibition of insulin like growth factor-1 (IGF-1) and mTOR, as well as activation of AMPK and tuberous sclerosis complex (TSC1, TSC2). Also, metformin has recently been found to exert immunomodulatory functions, inhibiting the exhaustion of CD8+ tumor infiltrating lymphocyte (TIL) function, thereby upregulating tumor-specific immune function. It accomplishes this by preventing apoptosis of CD8+ TILs and converting CD8+ TILs from quiescient central memory T cells to effector memory T cells with active anti-tumor effects. In vivo, the addition of metformin to vaccination enhances the generation of effector memory T cells, congruent with the overall hypothesis. We propose a proof-of-concept parallel phase 2 trial using the combination regimen of nivolumab and metformin. We hypothesize that the combination of nivolumab and metformin will be synergistic and can overcome resistance to single agent PD-1/PD-L1 inhibitors. **Method:** We are currently enrolling patients in this phase II clinical trial at the Northwestern Medicine Developmental Therapeutics Institute.



Result: Section not applicable **Conclusion:** Section not applicable

Keywords: Nivolumab, metformin, phase II

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-006 ROVALPITUZUMAB TESIRINE VS TOPOTECAN IN PATIENTS WITH ADVANCED SMALL CELL LUNG CANCER FOLLOWING 1ST LINE CHEMOTHERAPY

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Abbvie Inc., North Chicago/US

Background: Small cell lung cancer (SCLC) represents ~15% of lung cancers. Patients (pts) are staged with limited or extensive stage disease (ES). ES standard therapy consists of a platinum-based therapy + a second agent (etoposide). Initial response rates are high but not durable. Treatment for relapsed pts 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 ES SCLC pts, 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 pts 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. Pt 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. Primary objectives: to determine if Rova-T improves objective response rate and overall survival vs topotecan. Secondary objectives: to assess if Rova-T improves progression-free survival vs topotecan; to compare duration of objective response between arms; and to assess effect on patient-reported outcomes. 1. Rudin et al., Lancet Oncol, 2016. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Phase 3, topotecan, Rovalpituzumab tesirine

P1.04-007 ROVALPITUZUMAB TESIRINE MAINTENANCE THERAPY FOLLOWING 1ST LINE PLATINUM-BASED CHEMOTHERAPY SMALL CELL LUNG CANCER

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Background: SCLC embodies 15-20% of lung cancers. Patients (pts) are staged with either limited or extensive disease; 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 pts enrolled yet as of 7 February 2017). Approximately 740 ED SCLC pts will be enrolled to include ~480 pts with high DLL3 expression. Eligibility: pts ≥ 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. Pts 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 pt 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

P1.04-008 POSEIDON: A PHASE 3 STUDY OF FIRST-LINE DURVALUMAB ± TREMELIMUMAB + CHEMOTHERAPY VS CHEMOTHERAPY ALONE IN METASTATIC NSCLC

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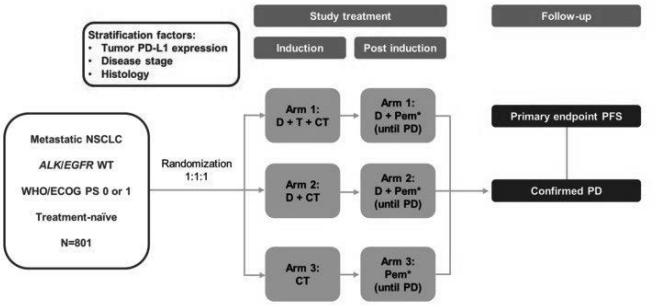
Background: Immunotherapy is an important new treatment modality for NSCLC. Dual blockade of the non-redundant PD-1/PD-L1 and CTLA-4 pathways may provide additive or synergistic effects. Durvalumab is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Tremelimumab is a selective human IgG2 mAb against CTLA-4. A combination regimen of immunotherapy with chemotherapy may further enhance clinical benefit. In a Phase 1b study (NCT02537418), durvalumab ± tremelimumab combined with chemotherapy demonstrated manageable tolerability and preliminary signs of clinical activity in patients with solid tumors, including NSCLC. **Method:** POSEIDON (NCT03164616) is a Phase 3, randomized, multicenter, open-label, global study to investigate durvalumab ± tremelimumab + platinum-based chemotherapy vs platinum-based chemotherapy alone as first-line treatment in metastatic NSCLC. Patients must be immunotherapy- and chemotherapy-naïve with *EGFR/ALK* wild-type metastatic NSCLC, and have confirmed tumor PD-L1 expression status, and a WHO/ECOG performance status of 0/1. Approximately 801 patients will be randomized 1:1:1 to receive durvalumab + tremelimumab + chemotherapy (Arm 1); durvalumab + chemotherapy (Arm 2); or chemotherapy alone (Arm 3). After induction, patients in the immunotherapy arms will receive durvalumab monotherapy, and non-squamous patients who initially received pemetrexed during induction will receive it as maintenance therapy if eligible. Treatment will continue until disease progression or another discontinuation criterion has been met. The primary endpoint is PFS according to blinded independent central review (RECIST v1.1). Secondary endpoints include OS; ORR; duration of response; best overall response; proportion of patients alive and progression-free at 12 months; disease-related symptoms and HRQoL; and safety and tolerability. Recruitment is ongoing.



*Patients with non-squamous histology who initially received pemetrexed during induction will receive pemetrexed maintenance therapy in the post induction phase if eligible. CT, chemotherapy; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; OS, overall survival; PD, progressive disease; Pem, pemetrexed; PFS, progression-free survival; PS, performance status; T, tremelimumab; WHO, World Health Organization; WT, wild-type

Result: Section not applicable **Conclusion:** Section not applicable

Keywords: durvalumab, NSCLC, tremelimumab

P1.04-009 THE FIRST STUDY OF BBSKE IN HEAVY TREATED ADVANCED EGFR WILD TYPE AND ALK NEGATIVE, TRXR1 HIGH EXPRESSION NSCLC PATIENTS.

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Background: Thioredoxin reductase plays a critical role in cell metabolism. According to our previous study, The expression of TrxR1 was significantly higher in serum of tumor patients than in heathy volunteers and approximately 50% of non-small cell lung cancer patients harbored high thioredoxin reductase expression. EGFR and ALK negative patients with high expression of TrxR1 responded poorer to chemotherapy. Ethaselen, a potent mammalian thioredoxin reductase 1 inhibitor was applied to address the heavy treated EGFR and ALK negative NSCLC with high thioredoxin reductase expression. **Method:** We plan to recruit 40 EGFR wild type and ALK negative metastatic non small cell lung cancer patients who have received at least 2 lines of standard therapy, performance status as 0-2 and with high TrxR1 IHC expression. It is a single arm project and all patients receive the treatment of BBSKE 1200mg PO QD until disease progression according the Response Evaluation Criteria in Solid Tumor 1.1(RECIST 1.1) or intolerable toxicity or withdraw from the study. The primary endpoint is 8 weeks Disease Control Rate and the anticipated rate is over 20%. Test of TrxR1 Serum activity is mandatory and performed by a central laboratory at the Medical Center of Casis. There will be several times of dynamic testing, from baseline to parallelly go along with each RECIST Evaluation, so as to draw some correlation between the change of TrxR1 expression and imaging. This program has been registered at clinicaltrials.gov and the number is NCT02166242. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: BBSKE, EGFR wildtype and ALK negative NSCLC, TrxR1 High Expression

P1.04-010 CHECKMATE 870: AN OPEN-LABEL SAFETY STUDY OF NIVOLUMAB IN PREVIOUSLY TREATED PATIENTS WITH NON-SMALL CELL LUNG CANCER IN ASIA

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Background: Programmed death-1 (PD-1) is an immune checkpoint receptor that attenuates T-cell activation by binding to its ligands, PD-L1 and PD-L2, which are expressed on tumor cells. Nivolumab, an anti–PD-1 antibody, showed durable antitumor activity and a favorable safety profile compared with docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC) in 2 global phase 3 studies (CheckMate 017 and CheckMate 057). Data from these trials led to the approval of weight-based nivolumab 3 mg/kg administered as a 60-minute infusion every 2 weeks (Q2W) in previously treated patients with NSCLC. Data from exposure-response simulations indicated that flat-dose nivolumab 240 mg Q2W has comparable pharmacokinetic, safety, and efficacy profiles to the weight-based dose, and data from CheckMate 153 demonstrated that nivolumab 3 mg/kg can be safely infused over 30 minutes. CheckMate 078 is an ongoing phase 3 registrational trial evaluating second-line nivolumab 3 mg/kg as 60-minute infusions Q2W versus docetaxel in patients with advanced NSCLC in a predominantly Chinese population. CheckMate 078

excludes patients with hepatitis B virus (HBV) infection, which represent a clinically relevant subgroup of patients in Asia; approximately 15% of patients with lung cancer in China are seropositive for HBV surface antigens. CheckMate 870 is an open-label, single-arm phase 3b study evaluating the safety and tolerability of flat-dose nivolumab 240 mg infused over 30 minutes Q2W in Asian patients with advanced or metastatic NSCLC, with or without HBV infection. **Method:** Approximately 400 patients in Asia with advanced or metastatic NSCLC and disease progression during or after 1 prior systemic platinum-based therapy will be enrolled; those with *EGFR* mutations (maximum of 40 patients) or *ALK* translocations should have received 2 prior systemic treatments including a tyrosine kinase inhibitor and chemotherapy. Nivolumab will be administered 240 mg over 30 minutes Q2W until disease progression or unacceptable toxicity, for a maximum of 24 months. Nivolumab may be reinitiated for subsequent disease progression and administered for up to 1 additional year. The primary objective is to evaluate the safety and tolerability of nivolumab in non–HBV-infected patients with NSCLC. The secondary objective is to assess safety and tolerability in all patients and in HBV-infected patients. Exploratory objectives include efficacy, patient-reported outcomes, health care resource utilization and direct medical costs, biomarker characterization in all patients, and viral load change and HBV reactivation rate in HBV-infected patients. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Nivolumab, non-small cell lung cancer

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-011 DEVELOPMENT OF NOVEL BLOOD-BASED BIOMARKER ASSAYS IN 1L ADVANCED/ METASTATIC NSCLC: BLOOD FIRST ASSAY SCREENING TRIAL (BFAST)

T. Mok[1], R. Dziadziuszko[2], S. Peters[3], X. He[4], T. Riehl[4], E. Schleifman[4], S. Paul[4], S. Mocci[4], D. Shames[4], M. Mathisen[4], S. Gadgeel[5]

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Background: Worldwide it is estimated that 20%-30% of advanced NSCLC patients do not receive a complete molecular diagnosis at baseline and are ineligible for targeted therapies due to tissue biopsy limitations. Blood-based, multiplex testing that analyzes circulating tumor DNA (ctDNA) by targeted next-generation sequencing offers a minimally invasive testing method, but clinical utility has yet to be established. High tumor mutational burden (TMB) measured in tissue is associated with atezolizumab (anti–PD-L1) clinical activity in several tumor types, including NSCLC. Alectinib, a potent, selective ALK/RET kinase inhibitor, has shown activity in 1L and is approved as 2L therapy in patients with ALK- or *RET*-positive advanced NSCLC but requires tissue for analysis. Here we present an umbrella trial that aims to clinically validate novel blood-based diagnostic assays that measure TMB in the blood (bTMB) and somatic mutations (e.g., *ALK*/*RET*), and to determine the efficacy and safety of 1L atezolizumab or alectinib in biomarker-selected NSCLC patients. **Method:** BFAST is a Phase II/III global, multicenter, open-label, multi-cohort screening and interventional umbrella trial designed to evaluate the safety and efficacy of targeted therapies in patients with unresectable, advanced or metastatic NSCLC selected based on the presence of oncogenic somatic mutations or a positive bTMB score. Key eligibility criteria include previously untreated, stage IIIB-IVB NSCLC of any histology and measurable disease per RECIST v1.1. Pre-enrollment blood-based screening will identify patients whose tumors harbor oncogenic somatic mutations (*ALK*/*RET*) or a positive bTMB score (above a pre-specified cutoff); patients will be assigned to the appropriate cohort based on the screening results. Study treatment will continue until disease progression (all cohorts) or loss of clinical benefit (atezolizumab only) (Table). The modular trial design allows for additional biomarker-driven BFAST cohorts with distinct screening and treatment requirements, and endpoints such as ORR with highly active drugs.

Table. BFAST Study Details

Cohort	Treatment	Planned Enrollment, n	Primary Endpoints	Key Secondary Endpoints
Cohort A ALK+	Alectinib 600 mg PO bid	78	ORR per RECIST v1.1 (INV-assessed)	DOR, CBR[c] and PFS per RECIST v1.1 (INV-assessed) ORR, DOR, CBR and PFS per RECIST v1.1 (IRF-assessed) OS
Cohort B RET+	Alectinib 900 and 1200 mg dose escalation	52-62	ORR per RECIST v1.1 (INV-assessed)	DOR, CBR and PFS per RECIST v1.1 (INV-assessed) ORR, DOR, CBR and PFS per RECIST v1.1 (IRF-assessed) OS
Cohort C bTMB+	Atezolizumab 1200 mg IV q3w or platinum-based chemotherapy[a]	≈440 (R, 1:1)[b]	PFS per RECIST v1.1 (INV-assessed)	OS PFS, ORR and DOR per RECIST v1.1 (IRF-assessed) ORR and DOR per RECIST v1.1 (INV-assessed) 6- and 12-month PFS rates

[a]Cisplatin or carboplatin + pemetrexed for non-squamous histology, and cisplatin or carboplatin + gemcitabine for squamous histology. Administered per standard of care. [b]Stratification factors include tissue availability, ECOG performance status, bTMB level and tumor histology. [c]CBR is defined as the rate of patients with confirmed CR or PR or stable disease that has been maintained for ≥ 24 weeks. bid, twice a day; bTMB, blood tumor mutational burden; CBR, clinical benefit rate; INV, investigator; IRF, independent review facility; IV, intravenously; PO, orally; q3w, every 3 weeks; R, randomized.

Result: Section not applicable **Conclusion:** Section not applicable

Keywords: Alectinib, Biomarkers, atezolizumab

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-012 A PHASE 1B DOSE-ESCALATION STUDY OF TRC105 IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Nivolumab (N) has demonstrated clinical benefit in advanced non-small cell lung cancer (NSCLC) patients (PTS) who have progressed to platinum-based chemotherapy: improved overall survival (OS) versus (Vs) docetaxel in squamous NSCLC (median OS of 9.2 months [mo} Vs 6 mo) and in non-squamous NSCLC (median OS of 12.2 mo Vs 9.4 mo). TRC105 is an antibody to endoglin, a receptor expressed on proliferating endothelial cells and myeloid derived suppressor cell (MDSCs). MDSCs also inhibit anti-cancer immunity, but by a mechanism of action that is distinct from that inhibited by N. TRC105 inhibits tumor growth in preclinical models and complements the activity of antibodies that target the programmed death receptor (PD-1). Its toxicity profile is distinct from that of N. By targeting MDSCs, TRC105 has the potential to complement N and improve clinical efficacy over that seen with single agent N. **Method:** This is a phase 1b,dose-finding (3+3 design) study of TRC105 in combination with standard dose (240mg) of N in pts with advanced NSCLC with disease progression to platinum-containig doublet chemotherapy.The primary objective is to evaluate safety and tolerability and determine a recommended phase 2 dose of TRC105 in combination with standard dose of N. Secondary objectives include: preliminary evidence of antitumor activity by assessing response rate and progression-free survival; characterize the pharmacokinetic profile of TRC105 when given in combination with N; and to explore biologic effects of TRC105 and N on circulating immune cells. Two dose levels of TRC105 are initially considered: Dose Level I: 8mg/kg intravenously (IV) weekly for 4 weeks 15mg/kg every 2 weeks; Level II: 10mg/kg (iv) for 4 weeks 15mg/kg every 2 weeks. N will be administered IV every 2 weeks in both cohorts of pts.Toxicity and efficacy assessments will be determine using NCI-CTCAE(V 4) and RECIST (V 1.1),respectively. The dose-limiting toxicity (DLT) evaluation period will be the first 4 weeks of the first cycle of treatment. It is anticipated that up to 18 pts will be enrolled in the study,and up to 12 pts at the maximum tolerated dose(MTD). Main criteria for inclusion are: confirmed stage 4 NSCLC,prior platinum-based doublets,measurable disease,ECOG PS 0-1,PD-L1 expression >/ 1%,adequate organ function,and no prior therapy with an immuno check point inhibitor. Descriptive statistics will be used to summarize pt characteristics,safety/efficacy/pharmacokinetic parameters ,and immunologic biomarkers. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: non-small cell lung cancer, phase I study, Immunotherapy

P1.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.04-013 PHASE 1B MULTI-INDICATION STUDY OF THE ANTIBODY DRUG CONJUGATE ANETUMAB RAVTANSINE IN PATIENTS WITH MESOTHELIN-EXPRESSING ADVANCED OR RECURRENT MALIGNANCIES

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[1]Mayo Clinic, Rochester/US, [2]Bayer AG, Berlin/DE, [3]Bayer Healthcare Pharmaceuticals, Whippany/US

Background: Mesothelin is expressed in a wide variety of tumors, including mesothelioma, ovarian, pancreatic, gastric/GEJ, NSCLC, triple-negative breast cancer, cholangiocarcinoma, and thymic carcinomas. Anetumab ravtansine (BAY 94-9343), is a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4 and has shown encouraging anti-tumor activity in mesothelioma and ovarian cancer patients in a phase I study. We will therefore conduct a signal

generating study with anetumab ravtansine in six additional high unmet medical need malignancies with mesothelin expression (NCT03102320). **Method:** Eligibility criteria include: ≥18 years, unresectable locally advanced or metastatic recurrent or relapsing disease, one or more prior lines of therapy, and availability of tumor tissue for mesothelin expression testing. Mesothelin-positive patients with selected adenocarcinomas (NSCLC, triple negative breast, gastric including gastroesophageal junction) and thymic carcinoma will receive anetumab ravtansine as monotherapy at 6.5 mg/kg IV on a 21-day cycle. Patients with cholangiocarcinoma will receive anetumab ravtansine in combination with cisplatin (25 mg/m2 IV day 1 and 8 on a 21-day cycle for up to 6 cycles) and patients with pancreatic adenocarcinoma will receive anetumab ravtansine in combination with gemcitabine (1000 mg/m2 IV day 1 and 8 on a 21-day cycle). A safety run-in phase (18-24 patients each) will be conducted for the combination regimens prior to enrolling patients in the main study phase. The primary objective of the main phase of the study is objective response rate (ORR) of anetumab ravtansine as monotherapy or combination therapy in patients with either of two mesothelin expression levels: high (≥30% positive tumor cells with moderate and stronger membrane staining intensity) and low-mid (≥5% all intensities and <30% positive tumor cells with moderate and stronger membrane staining intensity). Secondary objectives include safety, disease control rate, duration of response, durable response rate, and progression-free survival. Approximately 348 patients will be enrolled. **Result:** Section not applicable **Conclusion:** Section not applicable

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-001 MICROWAVE ABLATION PLUS RECOMBINANT HUMAN ENDOSTATIN (ENDOSTAR) VERSUS MICROWAVE ABLATION ALONE IN INOPERABLE STAGE I NON SMALL CELL LUNG CANCER

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Background: Previous studies showed that inoperable stage I non small cell lung cancer (NSCLC) benefited from microwave ablation (MWA) alone. This prospective, randomized, control, single-center clinical trial aimed to determining the survival benefit of MWA plus recombinant human endostatin (endostar) compared with MWA alone. **Method:** Patients with untreated, inoperable, stage I NSCLC were recruited. They were divided into MWA/ endostar group and MWA group, the former received MWA in the primary tumor sites, followed by 2 to 4 cycles of endostar and the latter treated with MWA only. The primary endpoint was overall survival (OS), the second endpoint included disease-free survival (DFS) , and adverse events (AE). **Result:** A total of 183 patients were enrolled, involved 92 cases in the MWA/ endostar group and 91 cases in the MWA group. Up to the latest follow-up , there were 24 cases of disease progression and 6 deaths in the MWA/ endostar group, versus 49 cases of disease progression and 9 deaths in the MWA group. DFS in the MWA/ endostar group (30.0 months, 95% CI, 27.1-32.9) was significantly better than MWA group (21.3 months, 95% CI, 19.5-23.1, p = 0.000). But there was no significant difference (p = 0.471) in OS between the MWA/ endostar group (31.6 months ,95% CI, 28.3-35.0) and MWA group (30.0 months, 95% CI, 27.2-36.5). The 1, 2 and 3 year survival rates in the MWA/ endostar group were 94%, 82% and 82%, respectively, while those in the MWA group were 94%, 89% and 89%, respectively. There was no significant difference between the two groups (p=0.982, p=0.924, p=0.924). AEs of MWA were observed in 63.7 % patients. Endostar -associated AEs were not observed in the MWA/ endostar group. **Conclusion:** MWA was a safe and effective alternative treatment for patients with inoperable stage I non small cell lung cancer. MWA combined with endostar significantly improved DFS compared to MWA alone, while not increased the MWA-related complications.

Keywords: microwave ablation, non small cell lung cancer, Endostar

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-002 CHARACTERISTICS AND PROGNOSIS OF GROUND GLASS OPACITY PREDOMINANT PRIMARY LUNG CANCER LARGER THAN 3.0 CM ON THIN-SECTION COMPUTED TOMOGRAPHY

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Background: The solid component size of lung cancer showing ground glass opacity (GGO) on thin-section computed tomography (TSCT) has been regarded as a more important preoperative prognostic indicator than the whole tumor size. Moreover, previous study revealed that radiological early lung adenocarcinoma which has an excellent prognosis could be defined as an adenocarcinoma 3.0 cm or less with consolidation to tumor ratio (CTR) of 0.5 or less on TSCT. However, the characteristics and the prognosis of lung cancer larger than 3.0 cm showing GGO remain unclear. **Method:** From January 2002 through June 2012, we retrospectively reviewed 3,735 consecutive patients with primary lung cancer, which underwent complete resection at our institution. We extracted 686 (18.4%) patients with lung cancer larger than 3.0 cm in diameter and evaluated their preoperative TSCT findings. In total, 160 (4.3%) lung cancers larger than 3.0 cm showing GGO were eligible for this analysis. We divided the 160 lesions into three types based on CTR; type A: 0<CTR≦0.25, type B: 0.25<CTR≦0.5, and type C: 0.5<CTR<1.0. **Result:** Type A, type B, and type C were found in 16 (10%), 37 (23%), and 107 (67%) lesions, respectively. Regarding the operative mode, all patients except for two patients underwent lobectomy. All patients except for one patient was diagnosed as having adenocarcinoma. Lymph node metastasis was seen in none of types A and B, in 34 (32%) lesions of type C. Lymphovascular invasion was seen in 73(68%) lesions of type C, 6 (16%) lesions of type B but not in type A. The median follow-up period was 68 (2-162) months. Recurrence was not observed in patients with type A and type B. The 5-year overall survival (OS) and disease free survival (DFS) rates were both 100% in type A, both 97.2% in type B, and 88.4%, 66.7% in type C, respectively. Patients with type C had a significantly worse prognosis than did those with the other types with respect to OS (p = 0.033) and DFS (p < 0.001). **Conclusion:** Tumors with type A and type B on TSCT showed an excellent prognosis with no lymph node metastasis. Therefore, GGO predominant lung cancer could be considered "early" lung cancer even if tumor size was larger than 3.0 cm in diameter.

Keywords: Consolidation to tumor ratio, Thin-section computed tomography, Ground glass opacity

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-003 IMPACT OF COEXISTING PULMONARY DISEASES ON ONCOLOGICAL OUTCOMES OF PATIENTS WITH PSTAGE I NON-SMALL CELL LUNG CANCER

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Background: Cigarette smoking is a well-known cause of interstitial lung diseases (ILDs), pulmonary emphysema, and lung cancer. Coexisting pulmonary diseases can affect outcomes of patients with early-stage lung cancer. The aim of this study was to analyze the influence of pulmonary diseases upon oncological outcomes of patients with smoking history who underwent surgery for pStage I non-small cell lung cancer (NSCLC). **Method:** Medical records of a total of 227 patients with smoking history (current/former) who underwent anatomical lung resections (200 lobectomies and 27 segmentectomies) for pStage I NSCLC between June 2009 and December 2014 were reviewed. Coexisting ILDs were evaluated on high-resolution computed-tomography (HRCT). The degree of pulmonary emphysema was determined using image analysis software, applying Goddard classification. The impact of clinicopathologic factors including pulmonary diseases on oncological outcome was evaluated. **Result:** Among the 227 patients, ILDs on HRCT were detected in 47 (20.7%) patients; of those, UIP pattern and non-UIP pattern were seen in 19 (8.4%) and 28 (12.3%) patients, respectively. The degree of pulmonary emphysema was classified into normal, mild and moderate, including 44 (19.4%), 146 (64.3%) and 37 (16.3%) patients, respectively. Pathological stages were IA in 131 patients and IB in 96. The 5-year overall survival (OS) and cancer-specific survival (CSS) were 81.2% and 88.2%, respectively. Univariate analysis showed that UIP-pattern on HRCT, moderate pulmonary emphysema, vascular invasion, visceral pleural invasion (VPI), and pStage IB were correlated with poor CSS. Cox proportional hazards models revealed that the presence of UIP-pattern and VPI were independent risk factors for poor CSS. During a median follow-up period of 42.7 months, recurrent diseases were seen in 41 (18.1%) patients. Multiple logistic regression analysis showed that the presence of UIP-pattern and VPI were significantly related with tumor recurrence. **Conclusion:** The coexistence of UIP-pattern ILD on HRCT was shown to negatively affect the oncological outcome of patients with smoking history who underwent surgery for pStage I NSCLC.

Keywords: non-small cell lung cancer, interstitial lung disease, Surgery

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-004 ADENOCARCINOMA SUBTYPING OF EARLY STAGE LUNG CANCER IN A DANISH COHORT

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Background: The incidence of lung cancer in Denmark is approximately 4600/year. Adenocarcinoma is the most common histologic subtype, and standard treatment for early stage disease is radical surgical resection. According to the latest World Health Organisation (WHO) classification the histological subtyping of adenocarcinomas as well as visceral pleural invasion (VPI) are prognostic factors. Vascular invasion (VI) have also been associated with poor survival. This study aimed to validate the revised WHO classification on completely resected stage-I lung adenocarcinomas and investigate the prognostic significance of VPI and VI. **Method:** During a 9-year period (2004-2012) 367 consecutive patients with stage-I adenocarcinoma underwent surgical resection at a university based thoracic surgical centre. An average of 4 HE slides of tumour per case (range 2-10) were analysed microscopically by two dedicated pathology specialists. The predominant growth pattern was classified according to the revised WHO-classification and presences of subtypes. VPI and VI were included when evident from the primary pathology records and clinical data were retrieved from recorded electronic patient files. Survival was recorded from

the National Civil Registry. We used a Cox proportional hazard regression model for all statistical analysis. **Result:** The 5-year overall survival (OS) for stage-I lung adenocarcinomas was 67%. Stratified by predominant histological subtypes univariate analysis showed OS was 72,7% for lepidic, 71,5% for acinar, 51,9% for papillary, 54,5% for solid, and 52,5% for micropapillary. However, multivariate analysis did not show any significant correlation between OS and predominant subtype (p=0.127). VI was highly predictive of OS (p=0.002) but VPI involvement was not (p=1,020). When analysing data for presence of subtypes we found that the papillary subtype was the only significant predictor (p=0.002). Age (p<0.001) and gender (p<0.001) were significant predictors for survival. **Conclusion:** Data from a consecutive Danish cohort of stage-I adenocarcinoma could not confirm the prognostic significance of the adenocarcinoma subtyping suggested by the WHO, but papillary subtype was associated with poor survival. Our data confirm that VI is a poor prognostic factor suggesting that VI should be included in the TNM classification.

Keywords: lung adenocarcinoma, adenocarcinoma subtypes, early stage NSCLC

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-005 PERCUTANEOUS CRYOABLATION FOR LUNG CANCER PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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Background: Lung cancer patients concomitant with interstitial pulmonary fibrosis (IPF) sometimes develop a life-threatening acute exacerbation after surgery or radiotherapy. Percutaneous cryoablation is evolving as a potentially less invasive local treatment for lung cancer. The purpose of this study is to retrospectively analyze the outcomes of cryoablation for clinical T1N0M0 non-small cell lung cancer (NSCLC) patients for whom surgery or radiotherapy is contraindicated because of IPF. **Method:** Between December 2003 and June 2017, 215 patients underwent computer tomography guided percutaneous cryoablation for lung tumors at our institution. Of these, 11 histologically proven clinical T1N0M0 NSCLC patients, for whom surgery or radiotherapy was considered contraindicated because of severe IPF, were retrospectively reviewed. Complications, local progression-free survival and clinicopathological factors were evaluated. **Result:** The cohort was composed of 11 men with a mean age of 74 years (range: 68 to 82). The median follow-up time was 24 months (range: 15 to 65 months). The mean Krebs von den Lungen-6 (KL-6) level was 1608 ±1025 U/mL. The mean tumor size was 24 ± 7mm. The mean percentage of predicted diffusing capacity for carbon monoxide (DLCO) was 37±27%. Thirty and 90-day mortality was 0 and 18%, respectively. Two patients required chest tube drainage because of severe pneumothorax. Acute exacerbation of IPF occurred in two patients (18%). The use of oral steroids and need for chest tube drainage were predictors of higher mortality ($p < 0.05$) and higher incidence of acute exacerbation of IPF ($p < 0.05$). However, higher level of KL-6 and low percentage of DLCO were not significant risk factors of mortality or acute exacerbation of IPF. Local progression-free survival at 1, 2 and 3 year was 51, 41 and 31%, respectively. **Conclusion:** Percutaneous cryoablation for lung cancer patients with IPF provoked acute exacerbation of IPF in 18% of patients. The use of oral steroids and need for chest tube drainage were predictors of higher mortality and higher incidence of acute exacerbation of IPF.

Keywords: cryoablation, interstitial pulmonary fibrosis, lung cancer

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-006 CLINICOPATHOLOGICAL FEATURES OF SMALL-SIZED PERIPHERAL SQUAMOUS CELL LUNG CANCER

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Background: Recent advances in imaging technology have enhanced the detection rate of small-sized peripheral lung cancers. While squamous cell carcinoma (SCC) had previously been regarded as a representative histological type of centrally-located lung cancer, recent studies have reported an increase in peripheral SCC. In order to reveal the malignancy of such peripheral lung cancer, we retrospectively compared the clinicopathological features of small-sized peripheral SCC with that of adenocarcinoma (ADC) in surgically resected cases. **Method:** We retrospectively analyzed lung cancer patients who underwent radical surgical resections at Gunma University Hospital between July 2007 and October 2011. We included all 26 patients diagnosed with SCC and 214 patients diagnosed with ADC who had tumors smaller than 2 cm in pathological size. **Result:** Patients with SCC were significantly older than those with ADC. In SCC patients, 80% of patients were male and almost all patients were smoker, whereas in ADC patients, only half of patients were male and smoker. For pathological stage, only 62% of SCC were staged IA whereas 85% of ADC were staged IA. On the other hand, 16% of SCC were staged IIA to IIIA whereas only 8% of ADC were staged IIA to IIIA. SCC patients tended to have higher rate of lymph node metastasis compared to ADC patients, although there was no significant difference (16% vs. 8%; $p = 0.25$). The incidences of pleural invasion (31% vs. 12%; $p < 0.01$), vascular invasion (50% vs. 19%; $p < 0.01$), and lymphatic invasion (50% vs. 15%; $p < 0.01$) were significantly higher in SCC than in ADC. Rate of postoperative recurrence was higher in SCC patients compared to ADC patients (23% vs. 10%; $p = 0.04$), although there was no significant difference in pattern of recurrence. Five-year survival rate of SCC was significantly shorter compared to that of ADC (60% vs. 94%; $p < 0.01$). **Conclusion:** SCC patients had worse prognosis compared to ADC patients, although there was no difference in lymph node metastasis. Adjuvant chemotherapy should be considered in SCC patients in order to improve treatment outcome.

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-007 A RETROSPECTIVE STUDY TO COMPARE RESECTION RATE AND SURVIVAL RATE IN OPERABLE STAGE I TO III NSCLC AFTER INTRODUCTION OF LUNG CANCER MDT

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Background: Multidisciplinary team (MDT) has emerged as the standard of care for lung cancer management in the past two decades.Lung cancer MDT Hospital Umum Sarawak was established in June 2013. It is a collaboration of healthcare professionals involving in lung cancer management comprising of oncologists, cardiothoracic surgeons, pulmonologists, radiologists and pathologists. Although MDT approach is widely accepted, it is poorly evaluated with limited observational data available especially in developing countries. While some studies had proven a significant benefit from MDT approach to the management of inoperable non small-cell lung carcinoma (NSCLC), comparison of resection rate in operable NSCLC is scarcely done. **Method:** Data was retrieved from Hospital Umum Sarawak lung cancer registry and individual patient's case note. Subjects were recruited according to inclusion criteria: operable newly diagnosed histologically proven Stage I to III NSCLC, from July 2012 to June 2013 (non-MDT group), January to December 2014 and 2015 (MDT group). **Result:**

Table 1 illustrates the patients' characteristics before and after introduction of MDT

	Non-MDT Group	MDT Group	
Variables	July 2012 to June 2013, n (%)	January to December 2014, n (%)	January to December 2015, n (%)
Age at Diagnosis <40 41 – 50 51 – 60 61 – 70 71 – 80 >80	0 (0.00) 4 (13.33) 6 (20.00) 10 (33.33) 6 (20.00 4 (13.33)	1 (6.67) 1 (6.67) 3 (20.00) 7 (46.67) 3 (20.0) 0 (0.00)	0 (0.00) 3 (13.00) 4 (17.40) 7 (30.40) 8 (34.80) 1 (4.40)
Gender Male Female	11 (36.67) 19 (63.33)	6 (40.00) 9 (60.00)	5 (21.74) 18 (78.26)
Histology Adenocarcinoma Squamous Cell Carcinoma Adeno-squamous Carcinoma Large Cell Carcinoma Others Unsure	17 (56.67) 8 (26.67) 0 (0.00) 1 (3.33) 0 (0.00) 4 (13.33)	10 (66.67) 2 (13.33) 0 (0.00) 1 (6.67) 2 (13.33) 0 (0.00)	15 (62.22) 7 (30.43) 1 (4.35) 0 (0.00) 0 (0.00) 0 (0.00)
Stage I II III Unsure	2 (6.67) 3 (10.00) 21 (70.00) 4 (13.33)	2 (13.33) 3 (20.00) 7 (46.67) 3 (20.00)	3 (13.04) 2 (8.70) 14 (60.87) 4 (17.39)

Table 2 illustrates the comparison of resection rates and 2-year survival rates before and after introduction of MDT

	Non-MDT Group	MDT Group	
	July 2012 to June 2013	January to December 2014	January to December 2015
Number of patients with Stage I to III NSCLC (n)	30	15	23
Number of patients with resection done (n)	10	7	9
Resection rate (%)	33.3	46.7	39.1
Total number of traceable patients (n)	30	15	18
Missing data (n)	0	0	5
Number of patients survived ≥2 years (n)	10	9	12
Two-year survival rate (%)	33.3	60.0	66.7

Conclusion: This single-centre study demonstrates a marked increase of resection rates and two-year survival rates in operable stage I to III NSCLC after introduction of lung cancer MDT. More quality evidence is yet to be explored to confirm the association between MDT approach and improvement in lung cancer outcomes.

Keywords: lung cancer multidisciplinary team, resection rate, two-year survival rate

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-008 A COMPARISON OF THE IMAGING FEATURES OF EARLY STAGE PRIMARY LUNG CANCER IN PATIENTS TREATED WITH SURGERY, SABR AND MICROWAVE ABLATION

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Background: Stereotactic Ablative Radiotherapy (SABR) and percutaneous microwave ablation (PMWA) are now being performed in patients deemed "medically inoperable" with non-small cell lung cancer (NSCLC). The majority of these patients are treated without ground truth histology, relying on imaging to establish the diagnosis. The purpose of this study was to investigate whether there were differences in the visible imaging features including CT Texture Analysis (CTTA) between patients referred for surgery, SABR and PMWA, which might suggest differences in underlying diagnosis. **Method:** A retrospective analysis of 92 patients with one pulmonary nodule (PN) suspected as T1N0M0 to T2AN0M0 NSCLC on imaging were treated either with SABR (22 patients), PMWA (25) or Video-assisted thorascopic surgery (45) of which 23 had NSCLC (SURG M) and 22 had benign disease (SURG B). Patient characteristics, CT nodule morphology, presence of emphysema and percentage emphysema score, FDG avidity and CT textural features were compared. Twenty texture features previously used in combination to predict nodule probability of malignancy were extracted from each automatic contoured region surrounding the PN. The Kruskal-Wallis test was used to compare texture features between the 4 patient groups (SABR, PMWA, SURG M and SURG B). **Result:** There was no significant difference in nodule morphology, volume at presentation (p=0.280) or nodule volume doubling times (p=0.149), and presence of emphysema (p= 0.348) or emphysema score (p= 0.367) between the 4 groups. There was no statistical difference in CTTA malignancy prediction score between the SABR, PMWA and SURG M groups (p>0.05). The probability of malignancy score was significantly lower (p-value < 0.01) for SURG B (0.58 mean ± 0.19 sd) vs. SABR (0.79 ± 0.15) treatment groups. In post-hoc analysis, 6 out of 20 texture features showed significant differences that were driven by the SURG B group. **Conclusion:** This is the first study to our knowledge to evaluate the radiological differences between patient groups referred for surgical and non-surgical treatments for NSCLC. On this small study, the results support the hypothesis that the non-operative patient groups comprise the same proportion of benign and malignant as those in the operative group. The results also demonstrate the potential clinical utility of CTTA in patient selection when histology is not obtainable. CTTA does not require volumetry detectable growth to detect change, and therefore may be a useful biomarker of malignancy at first diagnosis.

Keywords: NSCLC, SABR, CT Texture Analysis

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-009 ANALYSIS OF POSTOPERATIVE PROGNOSIS IN TERMS OF THE DIFFERENCE BETWEEN THE INVASIVE GROWTH AREA AND THE TOTAL TUMOR DIAMETER

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Background: In the 8th edition of the TNM classification of lung cancer, the T descriptor reflects the invasive growth area, which is not always equal to the total tumor diameter. In this study, we analyzed the difference in postoperative prognosis between tumors for which the invasive growth area was equal to the total tumor diameter and those for which the invasive growth area was smaller than the total tumor diameter. **Method:** One hundred forty-two patients with pathological stage I lung adenocarcinoma that was completely resected in our institute were enrolled. Adenocarcinoma in situ and minimally invasive adenocarcinoma were excluded. The average age at operation was 67.8±9.7 years, 87 patients were male, the average total tumor diameter was 1.9±0.6 cm, and the average invasive growth area was 1.6±0.6 cm. In 61 patients, the invasive growth area was smaller than the total tumor diameter (Group A), and in the remaining 81, the invasive growth area was equal to the total tumor diameter (Group B). The postoperative prognosis was compared between Groups A and B. **Result:** The estimated 5-year recurrence-free survival (RFS) probabilities by the Kaplan-Meier method in Groups A and B were 94.4% and 70.1%, respectively (p = 0.002, log-rank test). By a log-rank test, T factor (p < 0.001) and lymphatic permeation (p = 0.031) were also significantly associated with RFS. By a multivariate COX proportional hazards model, Group B (p = 0.045) and a pathological T descriptor of T1c or more (p = 0.001) were independently associated with RFS. Group B had a higher percentage of smokers (p = 0.004) and a higher percentage of cases in which the predominant histological subtype was other than a lepidic pattern (p < 0.001). **Conclusion:** Tumors for which the invasive growth area is equal to the total tumor diameter are associated with smoking and a predominant subtype of other than a lepidic pattern, and have a worse prognosis than tumors for which the invasive growth area is smaller than the total tumor diameter.

Keywords: TNM classification, Surgery, Early-stage lung cancer

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-010 CURATIVE TREATMENT RATES FOR PATIENTS DIAGNOSED WITH EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC) IN ENGLAND

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Background: Overall survival for lung cancer in England has previously been shown to be improving year on year and to correlate with surgical resection rates (National Lung Cancer Audit (NLCA) 2016 report). Recently the NLCA switched to use anonymised data collected and processed by the National Cancer Registration and Analysis Service (NCRAS) which has allowed linkage of the dataset to other national datasets including the radiotherapy dataset (RTDS), not previously reported. The main aim of this study was to identify a national curative treatment rate for early stage NSCLC and to identify which patient features influence whether a patient receives surgery, radical radiotherapy (RT) or no active treatment. **Method:** A cross-sectional analysis was conducted on all English patients diagnosed with stage I-II lung cancer between January 2015 and December 2015. Types of surgery and radical radiotherapy were identified from NCRAS databases including Cancer Outcomes and Services Dataset (COSD), Hospital Episode Statistics (HES) and RTDS databases. Survival was defined from time from treatment until death and Cox regression analysis was used to determine factors associated with survival. **Result:** 36025 cases of lung cancer were identified in 2015 with 8841 (28%) cases of stage IA-IIB proven or presumed NSCLC. 4560 (51.6%) cases received surgery and 1437 (16.2%) received radical RT creating a combined total of 5997 (67.8%) cases receiving treatment with curative intent. Curative intent treatment varied across cancer networks from 61.6% to 74.4%. Stereotactic Ablative Radiotherapy (SABR) was delivered in 750/1437 (52.2%) radical RT cases, generally for stage I disease, 60/1437 (4.1%) cases received Continuous Hyper-fractionated Accelerated RT (CHART) and 486/1437 (33.8%) cases received 55Gy/20 fractions, a commonly prescribed hypo-fractionated radical RT regime in England. Notably, 2844 (32.2%) patients did not receive treatment with curative intent, receiving either palliative therapy or supportive care only. Lack of treatment with curative intent was associated with increasing age and worsening performance status and varied across networks (25.6% - 38.4%). Updated survival data will be presented. **Conclusion:** In England for 2015, the curative treatment rate for stage I and II NSCLC was 67.8%. This means that almost one third of patients did not receive definitive treatment for their early stage lung cancer, ranging from 25.6% to 38.4 % across networks. A NLCA deep dive spotlight audit to identify more details about why these patients did not receive definitive treatment is planned for later this year.

Keywords: Surgery, early stage NSCLC, Radiotherapy

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-011 COMPARISON OF TUMOR MEASUREMENT METHODS IN PATIENTS WITH CLINICAL STAGE IA NON-SMALL CELL LUNG CANCER

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Background: The consolidation size of tumor in early lung cancer is related to prognosis. However, the tumor area and volume can show the amount of tumor more precisely. The purpose of this study was to compare the prognostic impact of the tumor size, the area, and the volume in whole tumor and consolidation of it. **Method:** We retrospectively reviewed the clinicopathological characteristics of 160 patients with clinical stage IA NSCLC who received curative pulmonary lobectomy and mediastinal lymph node dissection between January 2008 and June 2011. We measured the size, the area and the volume in whole tumor and consolidation part respectively by using the volume analyzer SYNAPSE VINCENT by Fujifilm. We evaluated the relationships between these measurement methods and pathological upstage, tumor recurrence with receiver operating characteristics curve. **Result:** The median duration of follow up was 64.9 months. Thirty four percent of patients (n=55) were pathologically upstaged. Twenty three patients developed recurrence (14%). The mean whole tumor size, the area and the volume were 21 mm, 264

mm², 3741 mm³, respectively. The mean consolidation tumor size, the area and the volume were 17 mm, 156 mm², 1861 mm³, respectively. The receiver operating area under the curve for the consolidation tumor size, the area, and the volume used to predicting pathological upstage were 0.686, 0.692 and 0.687 respectively, and they all had significant correlations. The receiver operating area under the curve for the consolidation tumor size, the area, and the volume used to predicting tumor recurrence were 0.626, 0.649 and 0.623 respectively. The tumor area had significant correlation and the others had marginally significant correlations. On the other hand, there was no significant correlation between the whole tumor measurements and either pathological upstage or tumor recurrence. **Conclusion:** Each measurement method in consolidation of the tumor can be useful for predicting prognosis.

Keywords: lung cancer, Tumor size, Tumor volume

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-012 TREATMENT PLANNING IN NON-SMALL CELL LUNG CANCER SHOWS VARIABLE UTILIZATION OF MULTIDISCIPLINARY TUMOR BOARD

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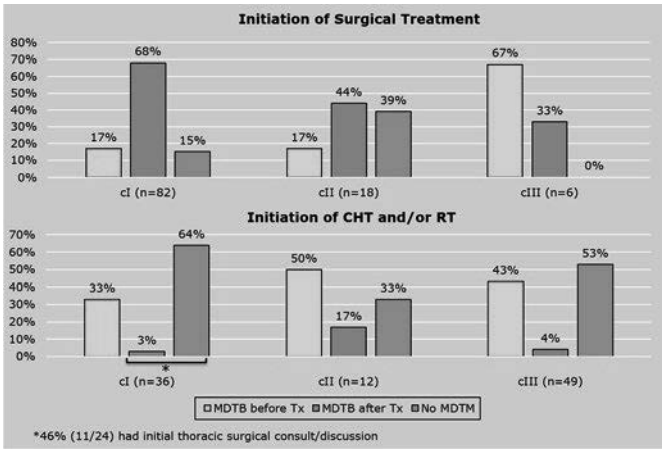
Background: With competing treatment options for early stage non-small cell lung cancer (NSCLC), and controversies over patient selection and management of later stage disease, multidisciplinary tumor board (MDTB) is a critical decision-making forum for management plans. Studies encompassing several cancer domains have shown the benefit of MDTBs on operative mortality, 5-year survival, and patient satisfaction. We aimed to determine the timing and utilization of MDTBs, relative to the initiation of treatment, for patients with NSCLC within a large community healthcare system. **Method:** We reviewed cI-III patients who underwent work-up for primary NSCLC during 6/2013-6/2015 in a hospital network of 7 institutions. This network offers mature multidisciplinary care with dedicated thoracic oncologic services collaborating for formal, weekly MDTBs. Only patients who underwent oncologic treatment were included, and were stratified based on initial treatment type: surgical versus chemotherapy (CHT) and/or radiation therapy (RT). Stage was defined as clinical stage established prior to MDTB, or treatment initiation. **Result:** We identified 203 patients; the figure depicts MDTB timing and utilization stratified by stage for each initial treatment type. Sixty seven percent (24/36) of cI patients did not have a MDTB prior to receiving stereotactic ablative radiotherapy (SABR). In addition, 33% (2/6) of the cIII patients did not receive a MDTB prior to surgical resection.



Conclusion: Variable utilization of MDTB was demonstrated for all clinical stages of NSCLC. In cI NSCLC where competing treatment options of surgery and SABR exist, less than half of the patients received multidisciplinary discussion. MDTB was also underutilized in cIII where treatment controversy exists. Although time constraints, referral patterns and provider bias challenge clinical practice, greater study and quality initiatives are necessary to ensure patients have access to MDTB discussion in the rapidly evolving landscape of NSCLC care.

Keywords: Multidisciplinary Team Meeting, multidisciplinary, tumor board

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-013 INDUCTION CHEMORADIATION IS ASSOCIATED WITH IMPROVED SURVIVAL IN RESECTED NON-PANCOAST LUNG CANCER WITH CHEST WALL INVASION

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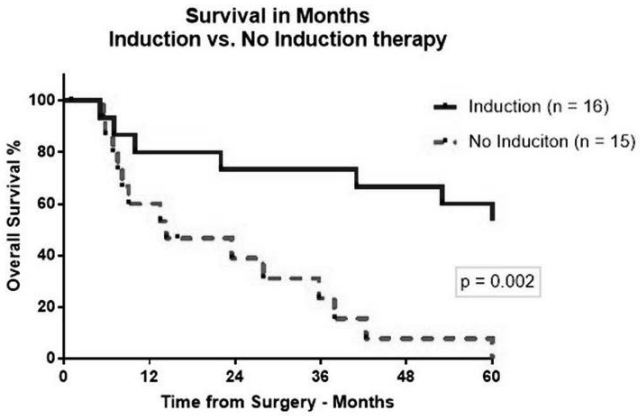
Background: Induction chemo-radiation therapy has shown an increase in 5-year survival in patients with superior sulcus tumors and complete surgical resection. We hypothesized that induction chemo-radiation therapy followed by surgical resection is associated with improved survival in patients with non-superior sulcus lung cancer with chest wall invasion. **Method:** We performed a retrospective review of a single institution database (1/1/1992-1/31/17) of T3 (chest wall invasion) N0/N1 patients with non-small cell lung cancer who underwent surgical resection. Exclusion criteria included 1) superior sulcus tumors and 2) resection performed for palliation or recurrence. Statistical analysis was performed using Kruskal-Wallis test (disease free times), and Kaplan-Meier curves. **Result:** Thirty-four patients were included in the analysis. Median age was 63.5 (range 37-84). By clinical stage, 31(91%) were IIB(T3N0) and 3(9%) were IIIA(T3N1). By histology, 15 were adenocarcinomas, 11 squamous and 8 large cell. Five-year overall survival (OS) was 30% for the entire cohort. Of the 34 patients, 16(47%) received induction chemo-radiation (platinum-based doublet and radiation dose 59-61 Gy) before surgery, and the remaining 18(53%) underwent surgery as the first treatment. Three patients belonging to the no-induction group died within 30 days after initial surgical treatment and were excluded from analysis. In the remaining 31 patients, induction chemo-radiation was associated with improved 5-year OS (53% for induction group vs 7% for no-induction group; p<0.01; Figure). Disease recurrence was evident in 10 cases, 3 in the induction group and 7 in the no-induction group (median disease-free time 94.6 months vs. 14.0 among the no-induction group; p<0.01). R1 resection status was observed in 6 patients, 5 of them in the no-induction group.



Conclusion: In patients with non-superior sulcus lung cancers with chest wall invasion, induction chemo-radiation therapy followed by surgical resection is associated with decreased recurrence. More importantly, induction chemo-radiation is associated with improved overall survival in this population.

Keywords: Induction Chemo-radiation Therapy, Non-superior Sulcus Lung Cancer with Chest Wall Invasion, survival

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-014 EFFICACY OF ADJUVANT CHEMOTHERAPY FOR COMPLETELY RESECTED STAGE IB NON-SMALL CELL LUNG CANCER

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Background: This study aimed to identify the predictive factors for prognosis of stage IB NSCLC and determine the efficacy of adjuvant chemotherapy on recurrence and survival. **Method:** This is a retrospective study with reviewing the electronic medical records. We enrolled 89 patients with stage IB NSCLC who underwent complete resection surgery at Gangnam Severance Hospital from Jan 2008 to Dec 2014. As per the National Comprehensive Cancer Network guidelines, patients were considered to be at high risk when they showed poorly differentiated tumors, lymphovascular invasion, tumor size > 4 cm, and visceral pleural invasion (VPI). We evaluated disease-free survival and overall survival. **Result:** Among the 89 patients, 62 underwent adjuvant chemotherapy. Young patients or patients with squamous cell lung cancer received adjuvant chemotherapy frequently. Adjuvant chemotherapy was not a significant factor for disease-free survival and overall survival. Adjuvant chemotherapy did not show a significant protective effect for survival, even for high-risk patients. However, VPI was a significant risk factor for disease-free survival (hazard ratio [HR]: 7.051; 95% confidence interval [CI]: 1.570–31.659; *P*-value = 0.011) and overall survival (HR: 8.289; 95% CI: 1.036–66.307; *P*-value = 0.046), even after adjustment for various factors. **Conclusion:** Adjuvant chemotherapy does not affect the prognosis of stage IB NSCLC, even in high-risk patients. Additionally, VPI is a strong prognostic factor of stage IB NSCLC.

Keywords: lung cancer, early stage, adjuvant chemotherapy

P1.05-015 MAJOR PATHOLOGICAL RESPONSE AS A PREDICTIVE VALUE OF SURVIVAL IN EARLY-STAGE NSCLC AFTER CHEMOTHERAPY: COHORT OF NATCH PHASE III TRIAL

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Background: In early-stage non-small cell lung cancer (NSCLC) patients, randomized phase III NATCH trial reported no statistically differences in disease-free survival (DFS) or overall survival (OS) with the addition of preoperative or adjuvant chemotherapy to surgery. In pre-operative arm, those patients who achieved a complete response obtained a benefit in 5-year DFS rate (59% *vs.* 38%). Recently, major pathological response (MPR) to preoperative therapy (10% or less of residual viable tumor after preoperative chemotherapy) has reported as surrogate marker of OS. We assess to validate this prognostic factor in a cohort of patients included the NATCH trial. **Method:** Retrospectively MPR was collected in a cohort of 57 early-stage NSCLC patients treated in the preoperative arm into NATCH trial from 2 institutions. OS according to MPR was analysed (long-rank test) in the whole population and by histologic subtype **Result:** In this cohort, median age was 67 years (47-78), 48 (84%) were males, 26 (46%) squamous subtype. By stage according to 6th TNM: 9 (16%) stage IA, 35 (61%) stage IB, 12 (21%) stage IIB and 1 (2%) stage IIIA. All except 3 completed 3 cycles of preoperative treatment. Surgical procedures: 81% lobectomies or bi-lobectomies, 14% pneumonectomies, 5% no surgery. In the whole population, there was a trend toward 5-year OS benefit among those patients with MPR (84.6% vs. 58.5%, p=0.106). According to histologic subtype, squamous tumours with MPR had significantly better 5-year OS (100% *vs.* 47.1%, p=0.026), but not in adenocarcinoma subtype (66.7% *vs.* 66.7%, p=0.586). **Conclusion:** MPR is a prognostic value in squamous NSCLC patients who receive preoperative chemotherapy. Validation in extended cohort merits further evaluation.

Keywords: preoperative chemotherapy, Early-stage, pathological response

P1.05-016 THE PROGNOSTICATOR IN SYNCHRONOUS MULTIPLE PRIMARY LUNG CANCER: A COMPREHENSIVE ANALYSIS OF 438 CASES

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Background: Synchronous multiple primary lung cancers (sMPLC) demonstrate good outcome if metastatic disease was absent. However, the prognostic factors vary across published reports. **Method:** Patients who met Martini & Melamed criteria of sMPLC were included for this study. Patients with small cell lung cancer, carcinoid tumor, neuroendocrine, incomplete resection or insufficient follow-up were excluded. Overall survival (OS) was estimated using the Kaplan-Meier method, cause-specific mortality analysis was performed with competing risks analysis; factors associated with survival outcome were evaluated using log-rank test and Cox proportional hazards models. Propensity score was taken to match the variables between sMPLC and sPLC with a ratio of 1:4. **Result:** A total of 438 patients met inclusion criteria for the study. The mean follow-up time was 6.3 years (1-22.9), with a 5-year OS rate of 59.48%. Squamous cell carcinoma (SQC) was a sole histology in 50 patients (Pure SQC group); SQC with other cell type in 59 patients (SQC-other group); no SQC in 329 patients (Non-SQC group). The 5-year OS rate of pure SQC group, SQC-other groups and Non-SQC group were 44.7%, 33.0% and 66.8% (p<0. 001) in univariate analyses. In multivariable analyses the SQC present as an independent poor predictor, the hazard ratio (HR) for pure SQC group was 1.39 (95% CI, 0.97-2.0, P=0.004) and SQC-other group was 1.82, (95% CI, 1.27-2.61, P=0.004) compared to Non-SQC group. Pure SQC group and SQC-other group were both with poorer survival than Non-SQC group in cause-specific mortality analysis. The sublobe resection (n=233) and pneumonectomy (n=14) shows worse outcome than pure lobectomy (n=174) with 5-year OS rate were 53.8%, 45.9% and 70.5%. The HR for sublobe resection and pneumonectomy in multivariate analyses were 1.41 (95% CI, 1.07-1.89, P=0.002) and 1.91 (95% CI, 1.0-3.7). The outcome of surgical T1-4N0M0 sMPLC with solo cell type (n=339) was worse than well-matched sPLC (n=1356), with a 5-year OS rate were 65% and 68.2% (P=0.05); the 5-year OS rate of sMPLC with different cell type and well-matched sPLC (cell type match to more aggressive one) were similar (41.7 vs. 52.7, P=0.36). The other significant prognostic factors include sex, age, highest tumor stage, highest lymph node stage and smoke status. **Conclusion:** The presence of SQC in sMPLC represents the poor outcome; The sublobe resection and pneumonectomy decease the survival of sMPLC patients; For those surgical T1-4N0M0 patients, the outcome was similar with well-matched sPLC; Studies with bigger size were needed to further confirm the findings.

Keywords: Synchronous multiple primary lung cancers, Matching, Prognosis

P1.05-017 PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE PLASMA D-DIMER LEVEL IN PATIENTS WITH SURGICALLY RESECTED CLINICAL STAGE I NON-SMALL CELL LUNG CANCER

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Background: The plasma D-dimer (D-dimer) level, a marker of hypercoagulation, has been reported to be associated with survival in several types of cancers. The aim of this study was to evaluate the prognostic significance of the preoperative D-dimer level in patients with surgically resected clinical stage I non-small cell lung cancer (NSCLC). **Method:** A total of 237 surgically resected NSCLC patients were included in this study. In addition to age, sex, the smoking status, etc., the association between the preoperative D-dimer level and survival was explored. **Result:** The patients were divided into two groups according to the D-dimer level: group A (≤ 1.0 μg/ml, n = 170) and group B (> 1.0 μg/ml, n = 67). The 5-year overall survival rate was 89.0 % (95 % confidence interval [CI] 77.7–95.3) for group A, 78.2 % (95 % CI 62.3–83.6) for group B (p = 0.015). A multivariate survival analysis showed that the D-dimer level was an independent significant prognostic factor, in addition to age and SUVmax of the tumor. **Conclusion:** The preoperative D-dimer level is an independent prognostic factor in patients with surgically resected clinical stage I NSCLC.

Keywords: non-small cell lung cancer, Prognosis, plasma D-dimer level

P1.05-018 PROGNOSTIC IMPACT OF TUMOR SHADOW DISAPPEARANCE RATE IN PATIENTS WITH CLINICAL IA LUNG ADENOCARCINOMA

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Background: The aim of this study was to clarify whether tumor shadow disappearance rate (TDR) or consolidation to tumor diameter ratio (CTR) predict outcomes in patients with clinical stage IA lung adenocarcinoma. **Method:** We reviewed 250 patients with completely resected clinical stage IA lung adenocarcinoma between 2007 and 2014 and examined the prognostic impact of TDR and CTR. We classified all tumors into each two groups based on the TDR and CTR on high-resolution computed tomography: TDR >50% (Group A, n=77), TDR ≤50% (Group B, n=173), CTR <0.5 (Group C, n=33), and CTR ≥0.5 (Group D, n=217). TDR and CTR were calculated using the following formulas: TDR = 100 – (tumor size on mediastinal window/tumor size on lung window) ´ 100 and CTR = maximum diameter of consolidation/maximum tumor diameter. **Result:** The study group comprised 117 men (47%) and 133 women (53%), with a median age of 66 years (range, 36-83 years). The median follow-up was 50 months (range, 1 to 110 months). The disease-free survival rate at 5 years was 100%, 78.2%, 100%, and 82.5% in Groups A, B, C, and D, respectively. The lung cancer-specific survival rate at 5 years was 100%, 94.8%, 100%, and 95.9% in Groups A, B, C, and D, respectively. Multivariate analysis showed that the following factors were significant predictors of recurrence: lymph-node metastasis, lymphatic vessel invasion, blood vessel invasion, and TDR (TDR: hazard ratio=3.61, 95% confidence interval: 1.01-12.8, p=0.048). On the other hand, multivariate analysis revealed that lymph-node metastasis and TDR were significant predictors of lung cancer-specific mortality (TDR: hazard ratio=23.85, 95% confidence interval: 1.22-466.5, p=0.037). **Conclusion:** TDR is a significant predictor of not only recurrence but also lung cancer-specific mortality in patients with clinical stage IA lung adenocarcinoma.

Keywords: Tumor Shadow Disappearance Rate, Adenocarcinoma, consolidation to tumor diameter ratio

P1.05-019 EFFECTS OF TUMOR STROMA AND INFLAMMATION ON SURVIVAL OF STAGE I-IIP LUNG CANCER

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Background: In lung cancer (LC) TNM classification allows an estimation of patient prognosis, but a third of patients with initial stages will relapse within three years. Molecular markers may increase prognostic accuracy and identify subgroups with high risk of progression. **Method:** Stromal (fibrous stroma and α-actin) and inflammation markers (IL1β, TNF-α and COX-2) were examined by immunohistochemistry in tumor tissue from a cohort of 222 patients with early-stage (I-IIp) LC recruited in Spain for the International Association for the Study of Lung Cancer TNM-16 staging project. **Result:** The diagnosis was non-small cell lung carcinoma (NSCLC) in 199 patients (106 adenocarcinoma and 93 squamous cell carcinoma) who were the target for this study. The participants had a mean age of 69 (SD 9) years, frequent respiratory (108, 54.3%) and cardiac (84, 42.2%) comorbidities, and were staged as IA (53, 26.5%); IB (56, 28.1%); IIA (41, 20.6%); IIB (40, 20.1%) or ≥III (9, 4.5%). After three years 94 patients had died (47.2%). In the bivariate analysis, 3-year mortality showed statistically significant associations with more advanced stage (p <0.001) and a higher proportion of fibrous stroma in the tumor (p = 0.014); and a marginal relationship with cardiac comorbidity (p= 0.07) and higher IL1β levels (p = 0.098). Sensitivity and specificity of fibrous stroma and IL1β were calculated and optimal cut-off points established according to Youden's index. Using these cut-offs, fibrous stroma in >8% of the tumor sample and IL1β H-score levels above 1356 were significantly related to mortality. In Cox proportional hazards models, adjusting by stage and cardiac morbidity, patients with fibrous stroma levels above 8% had higher 3 year-mortality [HR= 2.03, 95% CI (1.1-3.7), p= 0.021]; and similar results were obtained in patients with IL1β levels above 1356 [HR= 2.05, 95% CI (1.1-3.7), p= 0.019]. Combining both markers, patients with both markers above their established cut-offs had a significantly higher risk of 3 year mortality [HR= 2.95% CI (1.1-3.6), p= 0.022]. **Conclusion:** An overrepresentation of fibrous stroma and IL1β in the tumor sample is independently associated with 3 year mortality in NSCLC, confirming that the tumor stroma influences survival in LC. Funded by PII Oncology SEPAR and FIS 12-02040

Keywords: tumor stroma, inflammation, NSCLC

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-020 CLUES OF STROMAL INVASION OF PULMONARY ADENOCARCINOMA ON CT, FOCUSING ON CICATRICIAL CHANGE

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Background: To investigate whether a cicatricial change of adenocarcinoma appearing as pure ground glass opacity nodule (GGN) on CT correlate with stromal invasion. **Method:** From June 2013 to December 2016, 425 adenocarcinomas were pathologically confirmed in our institution. With a retrospective investigation of CT images and pathologic reports, we found 37 surgically resected pure GGNs. Then, we analyzed the statistical difference of the presence of cicatricial changes (traction bronchiectasis and cystic airspace dilatation) on CT between two groups according to the presence of stromal invasion (Adenocarcinoma in situ vs Invasive pulmonary adenocarcinoma). **Result:** Among the 37 pure GGNs, there were 17 adenocarcinoma in situ and 20 invasive pulmonary adenocarcinomas (13 minimally invasive adenocarcinomas and 7 adenocarcinomas). The frequencies of traction bronchiectasis (12 % vs 70 %, p<0.001) and cystic airspace dilatation (24% vs 55%, p=0.052) were higher in invasive pulmonary adenocarcinoma with or without statistical significance. The presence of either traction bronchiectasis or cystic airspace dilatation (35% vs 80%, p=0.006) was also more frequently found in the invasive pulmonary adenocarcinoma.

Fig 1. A 3.0cm sized pure ground-glass opacity nodule proven to be minimally invasive adenocarcinoma with surgical resection in 80-year-old woman. There are internal cystic air space dilatation (arrow head) and traction bronchiectasis (arrows).

Fig 2. A 1.3cm sized pure ground-glass opacity nodule proven to be adenocarcinoma in situ with surgical resection in 77-year-old woman. There is no evidence of cicatricial change including traction bronchiectasis or cystic air space dilatation.

Conclusion: Cicatricial changes in adenocarcinoma presenting pure GGN may be a finding suggesting stromal invasion.

Keywords: pure ground-glass opacity lung nodule, Cicatricial change, early stage NSCLC

P1.05: EARLY STAGE NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.05-021 ARE PROGNOSTIC FACTORS DIFFERENT FROM THAT WHICH PREDICTS RECURRENCE IN COMPLETELY RESECTED PATHOLOGICAL STAGE IB ADENOCARCINOMA?

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Background: The 5-year survival rate of pathologic stage IB stage lung adenocarcinoma is reported to be 73%, and adjuvant chemotherapy is expected to improve prognosis about 10%. In Japan, UFT is the standard regimen as adjuvant chemotherapy for completely resected pathological stage IB. In addition to conventional clinicopathological factors, adenocarcinoma tissue subtype, EGFR mutation status and maxSUV of primary tumor like have also been found to have a large Impact as a recurrence / prognostic predictor. The purpose of this study is to investigate the factors which affect recurrence and prognosis in stage IB lung adenocarcinoma **Method:** From 2008 to 2015 lung, completely resected 218 cases that undergo lobectomy with mediastinal lymph node dissection and diagnosed as pathological stage IB (7th UICC) . We examined the relationship between clinical pathologic factors including postoperative adjuvant therapy and, recurrence and prognosis. **Result:** Median follow-up period was 45.4 months. There were 122 male and 96 female. Mean age was 69.4 years old, BMI 22.2, smoking 122 cases (56.0%). CEA elevation was noted in 63 cases (28.9%). Median value of max SUV was 2.96. Median operative time was 166 minutes and blood loss was 45.7 g. Histological adenocarcinoma subtypes were followed; MIA 6, Lepidic 62, Acinar 79, Papillary 27, Solid 40 and Micopapillary 4. Lymph vessel invasion was noted in 35 (16.0%) and vascular vessel invasion was in 72 (33.0%) and pleural invasion was in 102 (46.8%), EGFR mutation was noted in 62 among 150 examined cases (41.3%). Mean tumor diameter was 3.33 cm, collapse-fibrosis size was 2.18 cm. Adjuvant chemotherapy was performed in 90 cases (41.3%). The relapse-free survival rate (RFS) at 5-year was 77.1%, the factors influencing RFS were lymph vessel invasion, vascular vessel invasion, pleural invasion, histological adenocarcinoma subtypes, blood loss and maxSUV. In multivariate analysis, RFS was significantly affected by pleural invasion (HR=3.141 (95% CI 1.122 - 8.798)), blood loss (HR = 1.004 (1.000 - 1.007)) and maxSUV (HR = 1.083 (1.004 - 1.169)). However, the presence or absence of EGFR mutation did not contribute to relapse (p = 0.208). The overall survival rate (OS) at 5-year was 88.3%, the histological subtype and BMI statistically affected OS. In multivariate analysis, only histological subtype (lepidic vs. non-lepidic) (HR = 4.710 (95% CI = 1.097-20.218) was left, it was an independent prognostic factor. After matching the distribution of histological subtype to examine the effect of adjuvant chemotherapy, but no significant difference was observed. On the other hand, when focusing on prognosis based on the presence or absence of EGRF mutation in recurred cases (35 cases), the 5-year OS was 58.8% in wild type and 90.0% in mutant; it was not statistically significant difference (p = 0.165), but the mutant case seemed to have a high probability of long-term survival after relapse. **Conclusion:** Factors that contribute to recurrence were pathological malignancy (vascular invasion, histological subtype) and biological malignancy (high value of maxSUV). On the other hand, only histological subtypes contributed to prognosis. In addition, lepidic predominant was almost free from relapse and survived. Even if lepidic subtype was excluded, the effect of adjuvant UFT administration was not observed. Cytotoxic agent or EGFR-TKI should be examined in the future. On the other hand, the presence or absence of EGFR mutation seems to be an important OS predictor after recurrence.

Keywords: Pathological stage IB, Adenocarcinoma, Adjuvant therapy

P1.05-022 ASSOCIATION BETWEEN NEUTROPHIL/LYMPHOCYTE RATIO AND LYMPHOCYTE/MONOCYTE RATIO WITH DISEASE FREE SURVIVAL IN OPERATED NSCLC PATIENTS IN PERU

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Background: Tumor recurrence after surgical resection is the main obstacle for long term survival in patients with NSCLC. The identification of factors related to recurrence may help to determine new risk predictors and guide different forms of treatment. An elevated neutrophil to lymphocyte ratio (NLR) and a low lymphocyte to monocyte ratio (MNR) have been reported to be poor predictors of disease free survival (DFS) in patients with NSCLC. There is a lack of evidence on the association of these ratios in early stages of lung cancer. **Method:** Data of NSCLC patients who were lobectomized at Edgardo Rebagliati Hospital between years 2008-2014 were retrospectively reviewed. Patients with incomplete data were excluded. NLR and LMR were calculated before surgery. DFS was determinate according to Kaplan-Meier method, the comparison of the survival curves was made by Logrank test or Cox model. **Result:** Forty patients were included. The median age was 68.5 years old, 52.5% were men and 92% had an ECOG scale 1. The 32.5% were asymptomatic at the time of diagnosis and 22.5% were in pre-surgical evaluation for different diseases. The 57.5%, 32.5% and 10% of patients had clinical stage I, II and IIIA, respectively. The 80% of patients had adenocarcinoma and the 20% had a squamous subtype. The 36.1% and 63.9% of the patients had NLR < 1.5 and >1.5, meanwhile 8.6% and 91.4% of the patients had LMR < 2.3 and >2.3, respectively. The median follow-up was 4.4 years, in which the 40% of patients died. The DFS rate at 4-years was 40.5%. Three patients had LMR < 2.3, all of them have died during follow up. The variables associated to DFS were lymphatic permeation (HR: 3.2, p=0.011), tumor size > 5 cm (HR: 1.2, p=0.028) and NLR (HR: 3.5, p=0.136). DFS rate at 4-years was 75% in patients with NLR < 1.5 and 28.5% in those with NLR >1.5. **Conclusion:** A NLR > 1.5 before surgery is associated with a worse DFS than patients who had a NLR < 1.5. Studies with a bigger number of patients are needed to determine the importance of NLR and LMR as recurrence predictors in operated patients with NSCLC. This result encourages further investigation about available and inexpensive biomarkers as predictors of disease recurrence in early stages of lung cancer.

Keywords: Neutrophil/lymphocyte ratio, disease free survival, operated lung cancer

P1.06-001 DOES ACCESS TO PRIVATE HEALTH CARE INFLUENCE POTENTIAL LUNG CANCER CURE RATES?

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Background: Numerous studies show a link between poor socioeconomic status (SES) and late stage cancer diagnosis. This however has not been consistently shown looking at non-small cell lung cancer (NSCLC) in isolation. Despite the extremely high prevalence of lung cancer as well as disparities in access to healthcare based on health insurance in South Africa, there is a paucity of data looking at the influence of health insurance (as a surrogate for SES) on stage at presentation of NSCLC. We aimed to study the relationship between health insurance status (and invariably SES) and staging of patients (and by virtue, resectability) with primary non-small cell lung carcinoma at the time of initial presentation. **Method:** We retrospectively compared privately health insured patients (n=55) to those with no health insurance (n=610) with regard to demographics, tumour node metastasis staging and cell type at initial presentation. **Result:** Those with no health insurance were younger (59.9±10.1 years) than those with private health insurance (64.15±9.6 years, p = 0.03). Poorly differentiated NSCLC was significantly more common in the privately health insured group (23.6%) compared to those with no health insurance (4.6%; p < 0.01). Six of 51 NSCLC patients (11.8%) with private health insurance presented with early stage, potentially curable disease (up to stage IIIA) compared to 55 patients (10.3%) in the uninsured group (p = 0.75). **Conclusion:** We found that access to private health insurance did not have a significant impact on stage at initial presentation. The only significant differences were the relatively advanced age at presentation and relatively higher percentage of poorly differentiated NSCLC seen in private practice.

Keywords: medical aid, NSCLC

P1.06-002 THE ROLE OF COMORBIDITY IN THE MANAGEMENT AND PROGNOSIS IN NONSMALL CELL LUNG CANCER: A POPULATION-BASED STUDY

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Background: Coexisting disease constitutes a challenge for the provision of optimal cancer care. The influence of comorbidity on lung cancer management and prognosis remains incompletely understood. We assessed the influence of comorbidity on treatment intensity and prognosis in a population-based setting in patients with nonsmall cell lung cancer. **Method:** Our study was based on information available in Lung Cancer Data Base Sweden (LcBaSe), a database generated by record linkage between the National Lung Cancer Register (NLCR) and several other population-based registers in Sweden. The NLCR includes data on clinical characteristics on 95% of all patients with lung cancer in Sweden since 2002. Comorbidity was assessed using the Charlson Comorbidity Index. Logistic regression and time to event analysis was used to address the association between comorbidity and treatment and prognosis. **Result:** In adjusted analyses encompassing 19,587 patients with a NSCLC diagnosis and WHO Performance Status 0-2 between 2002 and 2011, those with stage-IA-IIB disease and severe comorbidity were less likely to be offered surgery (OR: 0.45; 95% CI: 0.36-0.57). In late-stage disease (IIIB-IV), severe comorbidity was also associated with lower chemotherapy treatment intensity (OR: 0.76; 95% CI: 0.65-0.89). In patients with early, but not late-stage disease, severe comorbidity in adjusted analyses was associated with an increased all-cause mortality, while lung cancer-specific mortality was largely unaffected by comorbidity burden. **Conclusion:** Comorbidity contributes to the poor prognosis in NSCLC patients. Routinely published lung cancer survival statistics not considering coexisting disease conveys a too pessimistic picture of prognosis. Optimized management of comorbid conditions pre- and post-NSCLC-specific treatment is likely to improve outcomes.

Keywords: Comorbidity, Prognosis, lung cancer

P1.06-003 PREOPERATIVE PHYSICAL FUNCTION AND ACTIVITY IN ELDERLY LUNG CANCER PATIENTS COMPARED TO GENERAL ELDERLY

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Background: An increasing interest is seen in the role of preoperative physical function and activity in enhancing postoperative recovery. But, the short-term effect of preoperative physical activity (PA) on recovery after lung cancer surgery is unknown. The purpose of this study was to compare the difference of physical function and activity between General elderly and lung cancer patients before surgery. Also, we compared post-operative Cardiorespiratory fitness (CRF) according to preoperative PA level. **Method:** Lung cancer patients of this study consisted of patients who were registered for lung cancer cohort. Patients of cohort included were those scheduled to undergo lung cancer surgery, at participating hospitals in the Seoul of South Korea. We are selected a total 69 elderly lung cancer patients in cohort patients. Exclusion criteria of a cohorts of lung cancer study included ECOG PS >1 and neoadjuvant therapy, Multiple cancer, recurrent lung cancer. Patients planned for lung cancer surgery filled out a questionnaire and perform before, as well as at 3 weeks after the operation. Also, we selected 69 general elderly by matching the gender and age, at users of Seniors Welfare Center in Seoul of South Korea. The physical function test included muscle strength, gait ability, and cardiorespiratory fitness (6-minute walk test). PA was assessed using the self-reported short form IPAQ questionnaires. **Result:** Preoperatively, No difference was seen CRF and PA between General elderly and lung cancer patients before surgery. More active lung cancer patients (MVPA>150min) had higher CRF at 3 weeks after surgery (p<.002*) than inactivity lung cancer patients. Table 1. Differences of physical function and activity by PA level

	General elderly (n=69)		P	Elderly Lung Cancer Patientsn(n=69)		P
	Inactive	active		Inactive	active	
6MWT(m)	466.7±2.9	508.2±3.1	0.350	484.5±10.6	544±28.3	0.144
Hand grip strength (kg)	27.2±0.1	27.1±0.1	0.971	24.4±0.7	30.1±1.4	0.000*
10m gait maximum speed (sec)	6.7±0.0	6.4±0.0	0.853	5.9±0.1	5.4±0.1	0.049*
Rate of MVPA>150min/ week	55.1%	44.9%		85.3 %	14.7 %	-

Conclusion: The preoperative physical function of elderly lung cancer patients is not different from general elderly, but physical activity is very low. Also, Regular and increase physical activity before surgery with elderly lung cancer has been associated with CRF after surgery.

Keywords: Eldelry lung cancer patients, Physical function and activity, Cardiorespiratory fitness

P1.06-004 OCCURRENCE OF LUNG CANCER AMONG YOUNG PATIENTS BELOW THE AGE OF 50 – A RETROSPECTIVE ANALYSIS

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Background: Lung cancer is the leading cause of death worldwide in both women and men. According to the guidelines of the Polish National Cancer Registry in 2013, it is estimated that lung cancer had first place in oncological morbidity of men and third of women. The aim of the study was to evaluate the occurrence of lung cancer retrospective analysis in a group of patients before the age of 50. Patients had confirmed lung cancer diagnosis and were hospitalized in Center for Pulmonary Disease in Olsztyn between October 2014 and March 2017. **Method:** A retrospective analysis of 1,622 medical history patients who were hospitalized in the center at that time with histopathologically confirmed diagnosis of lung cancer. We selected only the patients who were diagnosed before the age of 50. The inclusion criteria were met by 23 patients: 7 women and 16 men. We analyzed: age, gender, symptoms, risk factors, including family history and additional diseases, type, stage, and survival. **Result:** We identified 23 cases of lung cancer before the age of 50, which was 1.41% of all patients diagnosed with lung cancer. There were 12 cases of small cell carcinoma, 6 cases of adenocarcinoma, 4 cases of squamous cell carcinoma and 1 case of NOS (Not Otherwise Specified). The majority (78%) of the respondents had a positive history of smoking - 2 of them quit smoking, the average pack-years was 31 (SD 13.72). A positive family history was reported in 11 individuals, while exposure to harmful environmental factors at work in 12 subjects. Prior to the diagnosis of cancer, 15 out of 24 patients had reported respiratory symptoms such as dyspnoea, cough, hemoptysis, or weight loss. Out of these 23 patients: 12 have died - their average lifetime from the moment of diagnosis till death was 6.45 months (SD 2.98) **Conclusion:** 1. The incidence of lung cancer below the age of 50 years is 1.41% of all patients hospitalized with the diagnosed of lung cancer at that time. 2. Most common, in patients diagnosed with lung cancer below the age of 50, is small cell carcinoma 52.17%. 3. Most of the patients had a positive history of smoking (78%) and often additional factors such as family history (47%) or workplace exposure (52%); the total percentage was 91%. 4. Most (78%) of lung cancers were diagnosed in an advanced non-operative stage. 5. The average lifetime from the moment of diagnosis till death was 6.45 months.

Keywords: below the age of 50, lung cancer, retrospective analysis

P1.06-005 SEX-BASED DISPARITIES IN NSCLC: AN EVIDENCE-BASED STUDY

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Background: Previous studies report intrinsic sex differences among lung cancer patients; however, current epidemiological data remains inconclusive as to the existence and impact of inherent sex differences. This study aimed to perform a descriptive evidence-based study of the literature to identify and quantify sex-associated characteristics among non-small lung cancer (NSCLC) patients. **Method:** We retrieved all potentially relevant articles published in English by searching Medline between 1996 and 2016, worldwide. Using a systematic review protocol, all abstracts were reviewed for eligibility, and studies meeting inclusion criteria retained. We identified eligible studies on NSCLC and its subtypes, with the inclusion of both men and women of age over 45 in the study population. Pooled data was analyzed using a semi-parametric longitudinal regression model and an ANOVA Two-way test. A data-visualization tool was used to demonstrate global NSCLC incidence distribution and sex-based disparities. **Result:** Of 1405 articles identified on Medline, 46 studies met eligibility requirements; 36 were included in statistical analyses, and 10 underwent descriptive-systematic review. We found that disparities between the sexes are significant (p=0.01). Among men, we found a significant effect of race on age-standardized incidence rates (ASR) in this subset (p <0.001). Among women, the incidence of NSCLC was found to increase over time, irrespective of race. For adenocarcinoma (ADC), a significant interaction between sex and race was found (p=0.02), with women showing higher rates of ADC than men. Asians, however, had the highest rates of ADC among other races. For squamous cell histology (SCC), no interaction between sex and race was found (p=0.7); however, a significant difference in SCC incidence rates was found between the sexes (p= 0.01). Analyzing SCC data shows significant effect over time by gender (p=0.02), with ASR values in males decreasing by -0.31 units per year. Conversely, the data-visualizing tool showed an increase in incidence rates of SCC among Canadian women. **Conclusion:** Our findings demonstrate that NSCLC trends vary by sex, and both race and sex have a significant affect on incidence rates. However, the inclusion of women in clinical studies is increasing over time, and women often express ADC. This histology is also predominant among all Asians. Findings also illustrated that global trends do not always align with regional trends. Our study serve as a basis to begin to resolve the inherent controversies in the research, and highlight the importance of the inclusion of sex as a risk modifier in the development of screening initiatives and therapies in NSCLC.

Keywords: race, Sex-based disparities, NSCLC

P1.06-006 SURVIVAL BENEFITS AND ASSOCIATED PROGNOSTIC FACTORS AMONG YOUNG NSCLC PATIENTS

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Background: Lung cancer is rare in young patients. The aim of this study was to determine the incidence of non-small cell lung cancer (NSCLC) among young patients (YP) versus older patients (OP) at our tertiary cancer centre. Additionally, associated prognostic factors, survival outcomes, and adherence to guideline-recommended treatment based on age were described. **Method:** All NSCLC patients initially diagnosed through the Tom Baker Cancer Centre (TBCC), in Calgary, Alberta, Canada between January 1999 and December 2013 were included. Patient data was retrospectively collected from electronic and paper charts as part of an institutional research program (Glans-Look Lung Cancer Database). YP were defined as ≤47 years, or two standard deviations below the mean. Chi-square tests were used to analyze categorical clinical and demographic factors among the age groups (≤47 versus >47), and overall survival (OS) was determined using Kaplan-Meier. The Cox proportional hazard model was applied to calculate the hazard ratio (HR) and its 95% confidence intervals (CI). **Result:** A total of 6,899 cases were examined. YP represented 3% (n=197) of incident NSCLC from 1999-2013: 1999-2004 (4.1%), 2005-2009 (2.8%), and 2010-2013 (1.8%). Compared to OP, YP tend to be female (54.8% vs. 47.9%, p=0.062) and never-smokers (25.4% vs. 7.7%, p<0.001). Additionally, most present with stage IV disease (61.4% vs. 54.1%, p=0.279), and adenocarcinoma (57.4% vs. 42.4%, p<0.001). YP demonstrated better median OS (13.5 months, 95% CI: 10.8-16.2) compared to OP (9.4 months, 95% CI: 9.0-9.9, p<0.001). Positive independent prognostic factors were early stage disease (IB-IIIA) (HR, 0.544; CI: 0.392-0.753, p=0.002), female sex (HR, 0.880; CI: 0.836-0.927, p<0.001), never-smoker (HR, 0.714, CI: 0.654-0.779, p<0.001), and former smoker (HR, 0.735; CI: 0.671-0.806, p<0.001). Non-adenocarcinoma subtypes were negative prognostic predictors of survival (HR, 1.648; CI: 1.416-1.919, p<0.001). Compared to OP, YP were more likely to receive guideline treatment according to disease stage. Among stage IV patients, YP were 30% more likely to receive chemotherapy (p<0.001). YP with stage III were twice as likely to receive concurrent chemo-radiation (p=0.007). Lastly, 90% of YP with stage I and II (A and B) received surgery, compared to half of OP (p<0.001). **Conclusion:** The incidence of NSCLC diagnoses among YP has been decreasing at the TBCC since 1999. In our cohort of NSCLC patients, YP demonstrated better overall survival; possibly due to a higher likelihood of receiving guideline-recommended therapy. Additionally, clinical characteristics of YP NSCLC patients differ from those observed in OP.

Keywords: age, NSCLC, outcomes

P1.06-007 EGFR STATUS EVALUATION AND EPIDEMIOLOGICAL PROFILE IN PATIENTS WITH NSCLC IN A BRAZILIAN PUBLIC HEALTH INSTITUITION

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Background: Therapies targeting genetic alterations have improved response rates and overall survival for some patients with NSCLC (non small cell lung cancer) as agents against EGFR (epidermal growth factor receptor) actionable mutations. Is recommended to test all patients with advanced/metastatic non squamous NSCLC, but the rates of patients actually tested vary in different institiutions.The prevalence of EGFR mutations in non-squamous NSCLC population range from 15% to 40%. There is few data about EGFR mutations in the Brazilian population, which is known for ethnic heterogeneity. This study intends to report the rates of EGFR evaluation in advanced non-squamous NSCLC, as the prevalence and the profile of such mutations in a south brazilian public health instituition. **Method:** We performed an observational retrospective study including patients diagnosed with advanced non-squamous NSCLC between January 2011 to December 2016 at CEPON (Centro de Pesquisas Oncológicas). Their medical record have been reviewed and information regarding epidemiological profile as well as EGFR testing was retrieved. **Result:** 345 patients were accrued. Targetable genetic alterations in EGFR were assessed in 74% (255/345) along the years and has a incremental pattern rising from only 22% of patients tested in 2011, 60% in 2012, 72% in 2013, 85% in 2014, to 100% of patients tested in 2015 and 2016. EGFR mutations were found in 18,03% (46/255) using the PCR COBAS method in tumoral tissue. EGFR mutations were more prevalent in women (30.09% vs. 9.60%; p < 0.001); and in never-smokers (49.12 vs. 9.58%; p < 0.001), but no significant difference was found regarding age under 50 year-old (27.66 vs. 17.28%; p = 0.159). The mean age of the mutated patients was 59 years (SD 11.82) with female predominance (74% vs. 26%). The most frequent genetic alteration

detected was exon 19 deletion (50%), followed by L858R mutation (36%). Among the 46 patients with targetable EGFR mutation, 32 received getitinib or erlotinib in first or second line. **Conclusion:** Our findings show that nowadays we have a good rate of screening of EGFR in advanced NSCLC. This improved over the years, reflecting the test availability, medical education with subespecialization, and easier acess to TKIs in CEPON. The prevalence of EGFR mutations in our population (18,03%) is slightly lower than the prevalence founded in other studies with brazilian patients (around 20%), maybe reflecting the european immigration in south of Brazil. Epidemiological profile is similar to previous studies showing EGFR mutation rates higher in female and non smokers patients.

Keywords: EGFR, epidemiology, Brazil

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-008 PREVALENCE OF LUNG CANCER IN PATIENTS WITH INTERSTITIAL LUNG DISEASE IS HIGHER THAN IN THOSE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: Lung cancer epidemiology related to interstitial lung disease (ILD) with or without connective tissue disease (CTD) and idiopathic pulmonary fibrosis (IPF) is not yet established. ILD potentially develops into scar lung cancer. We aimed to explore lung cancer prevalence in ILD patients with or without CTD and IPF in comparison with chronic obstructive pulmonary disorder (COPD). **Method:** We evaluated lung cancer prevalence associated with ILD and IPF using Korean Health Insurance Review and Assessment Service (HIRA) data from January to December 2011. This database (HIRA-NPS-2011-0001) was created using random sampling of outpatients; 1,375,842 sample cases were collected, and 670,258 (age ^{3} 40) were evaluated. Patients with ILDs, IPF, CTD, or COPD were identified using the International Classification of Disease-10 diagnostic codes. **Result:** Lung cancer prevalence rates per 100,000 person for the study population and those with ILD, IPF, CTD-ILD, and COPD were 420, 7334, 7404, 7272, and 4721, respectively. Lung cancer prevalence was significantly higher in those with ILD than in those with COPD. **Conclusion:** More attention must be paid to lung cancer development in those with ILD as well as COPD.

Keywords: lung cancer, interstitial lung disease, PREVALENCE

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-009 BARRIERS TO CLINICAL TRIAL PARTICIPATION IN LUNG CANCER PATIENTS, A SINGLE INSTITUTION EXPERIENCE

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Background: Multiple previous studies have revealed disparities in clinical trial (CT) participation among oncology patients. In this study, we examined the factors that affect CT participation for lung cancer (LC) patients at the University of Washington (UW). Specifically, we hypothesized that patients who spoke a primary language other than English had significantly lower CT participation. **Method:** We analyzed data from patients with stage IV LC evaluated at UW from 2004-2015. We examined patient and disease characteristics such as histologic subtype, molecular status, ECOG performance status (PS) and total lines of therapy. We analyzed multiple demographic factors including age, self-reported race, primary language and gender, as well as socioeconomic factors including marital status, employment, insurance status, zip code, distance to clinic, and presence of email address and phone number. We performed multiple logistic regression analyses to evaluate the association between the primary language and CT participation and also examined other factors independently affecting CT enrollment in this patient population. **Result:** 654 patients were included in our study. 73% did not participate in clinical trials, while 27% enrolled in at least one trial. The median age was 63 and 50% were female. 69% patients self-identified as Caucasian, 11% Asian, 5% African-American and the remainder as other or unknown. 94% of patients named English as their primary language. 90% had non-small cell histology, 73% had ECOG PS score of 0 or 1 and patients had received a median of 2 prior lines of therapy. In the multiple logistic regression model, we did not observe an association between the primary language and CT participation (OR 0.96, 95% CI 0.43 – 2.14). However, factors independently associated with a greater likelihood of CT participation were: an active email address (p = 0.01), better ECOG PS at diagnosis (0-1) (p=0.001), non-adenocarcinoma histology (p = 0.02), and increased number of lines of therapy (p<0.0001). **Conclusion:** We did not find that patients with non-English primary language had lower rates of CT participation. Our findings replicate the nationally low level of CT participation and identified surrogates for socioeconomic status as being important. Continued efforts to understand the barriers and factors affecting CT participation will be necessary to help increase access and enrollment.

Keywords: barriers affecting clinical trial participation, metastatic lung cancer, socioeconomic and demographic factors

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-010 INTERACTION BETWEEN TREATMENT DELIVERY DELAY AND STAGE ON THE MORTALITY FROM NON-SMALL CELL LUNG CANCER

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Background: Objective: The aim of this study is to evaluate the effect on the mortality of a delay of more than 2 months in treatment delivery after the diagnosis of non small cell lung cancer (NSCLC). **Method:** We performed a retrospective review of records form patients registered in a prospectively keep database on lung câncer. patients with malignant lung neoplasms, admitted at a single reference oncology center of public-system health between July 2008 and December 2014. Patients were considered eligible for this study if they were older than 18 years and had not undergone any previous oncology treatment when they were admitted at the institution. The following data were collected from all patients: age, gender, smoking status, histological type, surgical treatment, tumor staging and time from the date when the patient was diagnosed with cancer to the starting date of effective treatment. **Result:** We identified 359 elegible patients. Of these, 278 (77.4%) died during follow-up while 81 (22.6%) were censored. Age, sex and smoking status were not statistically significant predictors of mortality and were not considered for multivariate analysis. Stage of disease, surgical treatment and histological type of lung cancer were predictor of mortality (p< 0.05)). Besides that, in both the crude and adjusted analysis, delayed delivery of treatment was protective for the risk of death, with a crude HR= .75 (.59 - .97; p= .02) and an adjusted HR= .59 (.46 - .77; p<.001). A statistically significant interaction for mortality was observed between timely delivery of treatment and tumor stage (p=.01). The HR for mortality of getting delayed access to treatment according to stage are described: stages I and III, mortality was not significantly different between those that got treatment before or after 2 months from diagnosis (Stage I: HR= 1.24 (.39 – 3.98; p=.71); Stage III: HR= .65 (.38 – 1.1; p=.11)). However, patients with stage II disease who received delayed treatment had a mortality 3 times higher than those that received timely treatment delivery (HR= 3.08 (1.05 – 9.0; p=.04)). On the other hand, stage IV patients that received delayed treatment had a 52% reduction in mortality. **Conclusion:** There was influence of stage at the association between time to start treatment and mortality. About this influence, only the subgroup of stage II NSCLC patients appears to benefit of early treatment.

Keywords: public health, mortality, Lung Neoplsams

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-011 HYPONATREMIA - EVALUATION OF PREVALENCE IN HOSPITALIZED LUNG CANCER PATIENTS AND ITS PROGNOSTIC SIGNIFICANCE

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Background: Hyponatremia is an underestimated hazardous complication; which goes side by side since diagnosis till terminal outcome of carcinoma lung patients. The aim of study is to evaluate the prevalence of hyponatremia in hospitalized lung cancer patients and influence of hyponatremia on prognosis in same group of patients. **Method:** Observational study was conducted between July, 2015 to November, 2016 in United Hospital Cancer Care Centre. A total 200 hospitalized patients were analyzed with diagnosed carcinoma lung. These subjects were free from gross liver diseases; kidney diseases and brain metastasis. Prevalence of hyponatremia including severity (mild, moderate and severe) was evaluated. The role of hyponatremia with lung cancer was also evaluated in hospital mortality. Hyponatremia was treated with oral salt, NaCl tablets along with fluid restriction to 500 mL per day. In some cases hypertonic saline was also used. In the present study we were not assessing the prevalence of SIADH but only hyponatraemia. **Result:** Among 200 patients; NSCLC were 79.5 %(n=159) and SCLC were 20.5% (n=41). Various degree of hyponatremia was found in 63.52 % (n=101) NSCLC patients and 56.09 %(n=23) SCLC patients. There was no statistical significance in prevalence of hyponatremia between histological types of lung cancer. Out of 200 patients, 124 patients had mild, moderate and sever hyponatremia which was 61.29 %(n=76), 27.42 %(n=34) and 11.29 %(n=14) respectively. Among 124 hyponatremic patients 23.38% (n=29) died and 76.61 %(n=95) survived. And remaining 76 normo-natremic patients 10.53% (n=8) died of their illness and 89.47 %(n=68) survived. In patients with lung cancer with hyponatremia compared to patient with lung cancer without hyponatremia; a significant increase in hospital mortality was found. (23.38% Vs 10.53%) (p <0.001) **Conclusion:** Hyponatremia is common abnormality found in approximately 62% of lung cancer patients. It is also considered as a significant prognostic factor associated with mortality of lung cancer patient. In future large prospective multicenter study is needed to better understand the relation of hyponatremia in lung cancer patient for both management and outcome.

Keywords: Hyponatremia, lung cancer, prognostic significance

P1.06-012 NON-SMALL CELL LUNG CANCER (NSCLC) PATIENT CHARACTERISTICS AND CLINICAL CARE INSIGHTS IN SWEDEN: THE SCAN-LEAF STUDY

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Background: Understanding non-small cell lung cancer (NSCLC) epidemiology and outcomes is fundamental for clinical decision-making. SCAN-LEAF is a retrospective longitudinal cohort study that aims to describe NSCLC epidemiology, clinical care, and outcomes of patients in Scandinavia. The present analyses examine clinical characteristics and disease management of a subset of these patients. **Method:** Cohort 2 (EMR data from Uppsala, Stockholm sites, extracted using the Pygargus Customized Extraction Platform (CXP 3.0) and linked to registry data) consisted of NSCLC patients diagnosed 2005-2013 (follow-up until 2014). Co-morbidity burden was calculated with the Charlson Co-morbidity Index (CCI). Descriptive statistics were calculated, stratified by disease stage at diagnosis [resectable: I-IIIA; locally advanced: IIIA-B (radiation therapy within 3 months); advanced: IIIB (no radiation therapy within 3 months)-IV]. **Result:** 48.4% of the 3984 patients were male. At diagnosis, mean age was 68.4 years with disease stage distribution: resectable (30.4%), locally advanced (10.5%), advanced (56.3%), not specified (2.7%). CCI distribution was similar between stages, as was BMI. Smoking status: never (7.4%), former smoker (34.7%), current smoker (25.6%), unknown (32.4%). Histology: adenocarcinoma (63.3%), squamous (20.5%), NSCLC NOS (Not Otherwise Specified) (16.2%). ECOG: 0/1 (48.4%), 2/3 (13.2%), 4 (2.2%), unknown (36.2%). Metastases at diagnosis were reported for 42.4% patients. 829 patients were tested for molecular sub-type EGFR (of which 751 had a valid test result, of which 14.6% were positive for the mutation) and 267 for ALK (of which 247 had a valid test result, of which 14.6% were positive for the rearrangement). More patients with locally advanced disease were treated with radiation than patients with resectable or advanced disease [(68.8%, n=289) vs (35.9%, n=436) and (47.4%, n=1064), respectively], and a greater proportion of locally advanced patients received systemic therapy [(72.1%, n=303) vs (39.4%, n=478) and (67.1%, n=1505), respectively]. The proportion of patients not treated with surgery, radiation, or systemic therapy (based on pre-selected procedure lists) was higher for advanced (22.3%, n=500) vs resectable (6.5%, n=79) and locally advanced disease (11.9%, n=50). **Conclusion:** SCAN-LEAF EMR data provides unique insights into Scandinavian NSCLC patient populations and treatments. These data suggest unmet medical need based on majority of patients being diagnosed at advanced stage and low numbers tested for molecular subtype mutation but we expect these dynamics to change over time. Additionally, our data suggest unmet treatment need in patients with advanced disease based on a high proportion receiving no surgery, radiation, or systemic therapy, whilst acknowledging potential for misclassification and/or missing treatment data.

Keywords: NSCLC, Patient characteristics, disease management

P1.06-013 LATENT TUBERCULOSIS IN NEWLY DIAGNOSED LUNG CANCER PATIENTS. AN SPANISH PROSPECTIVE STUDY

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Background: Lung cancer and tuberculosis (TB) share common risk factors and are associated with high morbidity and mortality. Coexistence of lung cancer and TB were reported in previous studies, with uncertain pathogenesis. The association between lung cancer and latent TB infection (LTBI) remains to be explored. In Spain the prevalence is higher compared to other European countries and there are a high emigration rates. The key objetive is to place value on the need to detect LTBI for assesment for prophylaxis in patients at risk of reactivation due to cancer and cancer treatments. **Method:** Newly diagnosed , treatment-naïve advanced lung cancer patients from October-December 2015 and from October-December 2016 were prospectively enrolled .The presence of LTBI was determined by QuantiFERON-TB Gold In-Tube (QFT-GIT). Demographic characteristics and cancer-related factors associated with LTBI were investigated. **Result:** A total of 67 lung cancer patients were enrolled. The patients demographics were: median age 64 years, 10 (15%) female and 58 (85%) male. Adenocarcinoma 50% (n=34) , 23% (n=16) squamous-cell carcinoma and small cell lung cancer 26% (n= 18) The stage was IV in 71%(n=53) and III in 29% (n=20) These patients come from urban area in 16% of cases and rural areas in the 83% and the 82% (n=56) had history of smoking. The 79,4% % (n= 54) of patients received chemotherapy and 16% (n= 11) inunotherapy with Nivolumab. Among these patients including 23 % (n=16) LTBI,65% (n=44) non-LTBI, and 12% (n=8) QFT-GIT results-indeterminate cases. Out of these LTBI patients received Isoniazid chemoprophylaxis only 60% because of poor performance status. Adenocarcinoma had higher proportion of LTBI 64% vs 18 % for epidermoid and 18% for oat-cell At the time of database lock, the median of overall survival was only 6 months. **Conclusion:** Nearly a quarter of newly diagnosed advanced lung cancer patients in Toledo (Spain) have LTBI. There is a lack of widely acceptable and established standards for screening for latent TB in patients undergoing treatment for active solid-organ malignancy. Perhaps is recommended screening all patients born in countries with endemic TB before beginning radiotherapy or chemotherapy to avoid TB reactivation.

P1.06-014 HIGHER BODY MASS INDEX PROLONGS SURVIVAL TIME IN NON-SMALL CELL LUNG CANCER WITH GOOD PERFORMANCE STATUS

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Background: Obesity is the accumulation of body fat that has a harmful effect on health and has been increased the risk and mortality of multiple diseases, such as cardiovascular diseases and diabetes. Obesity has been associated with increased risk and mortality of most cancers. On the other hand, obesity is associated with decreased risk of a part of lung cancer. The mechanism to decrease risk of lung cancer in obese individuals is not clear. **Method:** In our hospital, we retrospectively assessed 675 lung cancer patients who were hospitalized for the first time from April 2012 to July 2015. We collected patient data of baseline characteristics, histology, performance status (PS), body mass index (BMI), stage, smoking history, molecular profiling for *EGFR, ALK*. Patients were stratified into 3 BMI groups based on the WHO classification: underweight (< 18.5 kg/m^2), normal weight (18.5 to < 25 kg/m^2), and overweight (≥ 25 kg/m^2). The classification of obese (≥ 30 kg/m^2) was included in the overweight group in this study. Overall survival was calculated using the Kaplan-Meier method. We compared overall survival between BMI groups using log rank test. **Result:** In this retrospective cohort study, we assessed 566 patients with non-small cell lung cancer (NSCLC) and 109 patients with small cell lung cancer (SCLC). There were no significant differences in patient characteristics except for smoking history. In SCLC patients, there was no significant difference in overall survival by each BMI group (good PS [0 – 1] group, p = 0.186; poor PS [2 – 4] group, p = 0.809). In NSCLC patients with good PS, overall survival was prolonged in the order of the standard group and the overweight group, in comparison with the underweight group (p = 0.031). In NSCLC patients with poor PS, there was no significant difference in overall survival by each BMI group (p = 0.401). In NSCLC patients with good PS, higher BMI and activating *EGFR* mutation were associated with longer overall survival in a multivariate analysis (BMI: hazard ratio 0.468, 95% CI 0.253 – 0.855, p = 0.0136; *EGFR* mutation: hazard ratio 0.476, 95% CI 0.279 – 0.796, p = 0.0044). In SCLC patients with good PS, there was a tendency of longer overall survival in the overweight group than in the underweight group. **Conclusion:** Overweight in NSCLC patients with good PS had significantly improved overall survival.

Keywords: Body mass index, Obesity, lung cancer

P1.06-015 ANALYSIS OF RELATIONSHIP BETWEEN NON-SMALL CELL LUNG CANCER AND NICOTINE DEPENDENCE

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Background: Approximately 80% of non-small cell lung cancers (NSCLC) are related to smoking, and smokers are 10-20 times more likely to have NSCLC than non-smokers. Nicotine has a 1.5 times higher rate of post-exposure dependence than other drugs, making it very difficult to stop. Thus, the aim of this study is to clarify the association between NSCLC and nicotine dependence.Approximately 80% of non-small cell lung cancers (NSCLC) are related to smoking, and smokers are 10-20 times more likely to have NSCLC than non-smokers. Nicotine has a 1.5 times higher rate of post-exposure dependence than other drugs, making it very difficult to stop. Thus, the aim of this study is to clarify the association between NSCLC and nicotine dependence. **Method:** We investigated the prevalence of nicotine dependence in NSCLC patients and analyzed the clinical characteristics of nicotine dependent NSCLC patients. Smoking information was assessed via questionnaires and personal interview in a cohort of 120 patients from four hospitals of the Catholic Medical Center between 2016 and 2017. Tobacco Use Disorder criteria of DSM-V, DSM-IV nicotine dependence criteria, and Fagerstrom Test for Nicotine Dependence (FNTD) were used to define nicotine dependence. Urine cotinine test was also performed to validate tobacco use. **Result:** Most of them were male (93.3%) and the average smoking amount was 40 pack years. At the time of diagnosis of NSCLC, 71.7% were current smoking status. The prevalence of nicotine dependence was 77-92% according to the diagnostic tool, DSM-V (92%), DSM-IV (78%) and FNTD (77%), which is expected to be higher in the NSCLC group compared to the general smoking population. Based on FTND scores, patients were divided into mild, moderate, and severe groups. Smoking amount was significantly higher in severe

group than the others. In addition, although drinking habit scores were higher in the severe nicotine dependent group, there were no significant differences among the groups in the other parameters, such as number of attempts to quit smoking, smoking cessation success, urine cotinine test results, depression, anxiety, and quality of life. **Conclusion:** These preliminary results of the prevalence of nicotine dependence in NSCLC patients may provide medical evidence for development of intensive smoking-cessation program in NSCLC patients.

Keywords: nicotine dependence, non-small cell lung cancer, PREVALENCE

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-016 ROUTE TO LUNG CANCER DIAGNOSIS IN THE UK: HOW DOES THIS AFFECT PATIENT OUTCOME?

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Background: The commonest route to lung cancer diagnosis in the United Kingdom (UK) is via emergency presentations (EP), with 35% of lung cancer diagnoses being made via this route. We aim to study the outcome of patients diagnosed with lung cancer via all routes of presentation and its contributing factors in a UK district general hospital. **Method:** Data was collected retrospectively from a non-teaching hospital over the period of January to June 2015. Only patients with a confirmed diagnosis (clinical or histological) of lung cancer were included. The following categories were analysed: -Demographics -Histological subtype of lung carcinoma -Performance Status -Stage of disease at presentation -Proportion offered treatment -Survival data (overall and at 1-year) **Result:** 94 patients were identified over this period. 35% (n = 33) presented via the EP route, while 51% (n=48) presented via the elective (2 week wait) route. The remaining 14% (n = 13) presented via other routes.

Category	Elective (2-week wait)	Emergency	Other routes
Age at presentation (median)	72 years	74 years	73 years
Proportion of patients in <50% most deprived areas in the UK	66.7%	69.7%	53.8%
Proportion of males	60.4%	54.5%	61.5%
Proportion of non small cell lung carcinomas (excluding large cell neuroendocrine tumours)	60.4%	60.6%	69.2%
Proportion of small cell lung carcinomas	8.3%	12.1%	7.7%
Performance status	1.25*	2.5*	2.5*
Proportion with stage 4 disease at presentation	33.3%	60.6%	0%
Proportion offered active treatment	79.1%	36.3%	61.5%
Proportion alive at 1-year	58.3%	21.2%	53.8%
Overall survival rate (to date)	41.7%	9.09%	38.5%

A higher proportion of patients presenting via the EP route have more extensive disease and a poorer performance status. A significantly lower proportion of patients in the EP subgroup were offered treatment. A substantial difference in overall survival between the EP and elective subgroups was also noted. **Conclusion:** Patients diagnosed via the EP route have a poorer performance status at presentation and are less likely to receive treatment or be alive at 1-year. Non-small cell lung carcinomas form the majority subtype of lung carcinoma in all routes of presentation. The demographics between the three subgroups are comparable, with a significant proportion of patients from the most deprived areas in the UK. This study suggests earlier diagnosis of lung cancer is crucial to improve outcomes. Due to strong associations between smoking and social deprivation with lung cancer, this study supports a risk-based screening programme utilising low-dose computerised tomography (LDCT).

Keywords: Screening, outcome, Emergency

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-017 LUNG CANCER DETECTION RATES FOR NATIONAL COMPREHENSIVE CANCER NETWORK GROUP 2 HIGH RISK INDIVIDUALS

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Background: Lung cancer screening with LDCT scan is covered by private insurance and Medicare for current and former smokers quit within the last 15 years, age 55 to 77 (55-80 for private insurance), with a 30 or greater pack year smoking history. However, it is not covered for National Comprehensive Cancer Network (NCCN) Group 2; a group of slightly younger, lighter smokers with no limit on quit duration but at least one additional risk factor. Our previous study on 1328 patients demonstrated NCCN Group 2 (Cohort A) to be at equivalent risk for lung cancer as the covered group (Cohort B). The objective of this study is to statistically evaluate the potential difference in lung cancer prevalence between Cohorts A and B. Towards that end we are compiling a large sample set (1563 Cohort A, 4000 Cohort B) with 80% power that can detect a minimum of 1% difference in lung cancer prevalence between the two groups. **Method:** A REDCap data registry was created to retrospectively collect LDCT scan data on high-risk individuals from two historical cohorts who underwent lung cancer screening at three institutions between January 1, 2012 and May 31, 2017. **Result:** To date, 804 Cohort A and 2712 Cohort B individuals have been entered into the data registry. Data entry is expected to be complete by the end of 2017 with follow-up through end of May 2019 to ensure a minimum follow up period of two years for each patient. A preliminary analysis is planned with 3 month minimum follow-up. A separate analysis of overall cancer detection rates (CDR) with a smaller sample at one of the study institutions shows CDR are not statistically different between the two cohorts (Pearson's Chi-Square). The CDR for Cohort A, the NCCN Group 2 patients, was 3.98% (28 lung cancers in 704 patients) and in Cohort B, the covered group, was 3.92% (91 lung cancers in 2319 patients; p=0.95). Average time in the program was 2.5 years for Cohort A and 2.4 years for the Cohort B (p=0.18). Maximum time in the program was 5.4 years for both groups; minimum follow-up time was 3 months. **Conclusion:** Using an expanded data set, NCCN Group 2 CDR continue to be the same as the group covered by Medicare and insurance. At this point, there is no statistical difference in lung cancer risks between the two groups.

Keywords: lung cancer screening, NCCN Group 2, LDCT

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-018 EGFR MUTATIONS AND ALK GENE REARRANGEMENTS: CHANGING PATTERNS OF MOLECULAR TESTING IN BRAZIL

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Background: Lung cancer is the leading cause of cancer death worldwide. In Brazil, cancer is the second most common cause of death and there were an estimated 27,330 new cases of lung cancer in 2014. Targeted therapies have changed disease prognosis and current clinical guidelines advocate for testing all patients with advanced disease for EGFR mutations and ALK gene rearrangements. Access to this testing is often limited in the developing world. In the case of Brazil, there is limited data regarding the frequency of testing and the changes in patterns of testing overtime. **Method:** Observational, retrospective study involving practice patterns of over 2000 cancer physicians in Brazil. We obtained de-identified data from a commercial database which included 11,684 patients with non-small cell lung cancer treated between 2011 and 2016. We analyzed the frequency of EGFR mutation testing and ALK rearrangement testing. **Result:** 11,684 patients were analyzed, of which all had stage IV lung adenocarcinoma. In the years ranging from 2011 to 2016 there was a significant increase in the frequency of testing for EGFR mutations overtime; from 13% in 2011 (287/2228) to 34% in 2012 (738/2142), 39% in 2013 (822/2092), 44% in 2014 (866/1972) to 53% in 2015 (1165/2184) and 58% in 2016 (626/1066). Testing for ALK rearrangements over that same time period also increased noticeably from no patients tested in 2011 and 2012, to 0.9% in 2013 (19/2092) 3% in 2014 (59/1972), 5% in 2015 (121/2184), 5% in 2016 (52/1066). **Conclusion:** To our knowledge this is the largest data analysis regarding changing practice patterns of molecular testing for lung adenocarcinoma over time in Brazil and Latin America. The frequency of testing for EGFR mutations and ALK gene rearrangement has increased over the last 5 years but is still below the current guidelines recommending that all patients with advanced disease be tested. Further understanding of the barriers to testing, will hopefully lead to national strategies for universal implementation of molecular testing.

Keywords: EGFR mutations, ALK rearrangements, Brazil

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-019 THE ASSOCIATION BETWEEN HPV PRESENCE AND EGFR MUTATIONS IN ASIAN PATIENTS WITH NSCLC: A META-ANALYSIS

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Background: The etiology of non-smoking NSCLC remains largely unknown. It has been widely proved that human papillomavirus (HPV) participate in the development of various cancers unrelated to smoking. Epidermal growth factor receptor (EGFR) mutation patients represent a large part of non-smokers with NSCLC. We performed this meta-analysis to evaluate whether HPV infection in NSCLC tissue is associated with EGFR mutation compared with HPV negative controls. **Method:** MEDLINE, EMBASE, PubMed and Web of Science were searched through June 2017, using the search terms "lung cancer", "human papillomavirus", "HPV", "epidermal growth factor receptor", "EGFR" and their combinations. We included studies in which HPV detection was based on PCR methods. Association was tested using odds ratio (OR) with 95% confidence intervals (95%CI). Heterogeneity was assessed using Q and I^2 statistic. **Result:** Finally, three studies with a total of 288 patients from Asian countries were identified as eligible publications. The presence of EGFR mutation was significantly related to HPV DNA compared with HPV negative controls (57% vs. 27%,OR 3.91, 95% CI 1.85 to 5.50; p<0.001), with no statistical heterogeneity among

studies (I^2=0; p=0.525). **Conclusion:** Our results suggest that HPV may contribute in part to EGFR mutations in non-small cell lung cancer, at least in Asian population.

Keywords: HPV, EGFR, NSCLC

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-020 UNEQUAL ACCESS TO HEALTH CARE SYSTEM HAVE A HIGHER IMPACT IN UPGRADING STAGING FOR 8TH TNM ED

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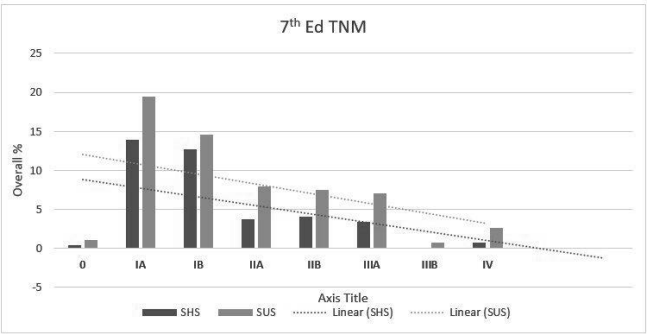
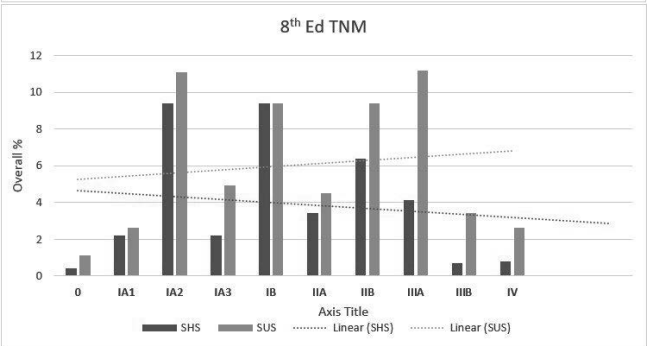
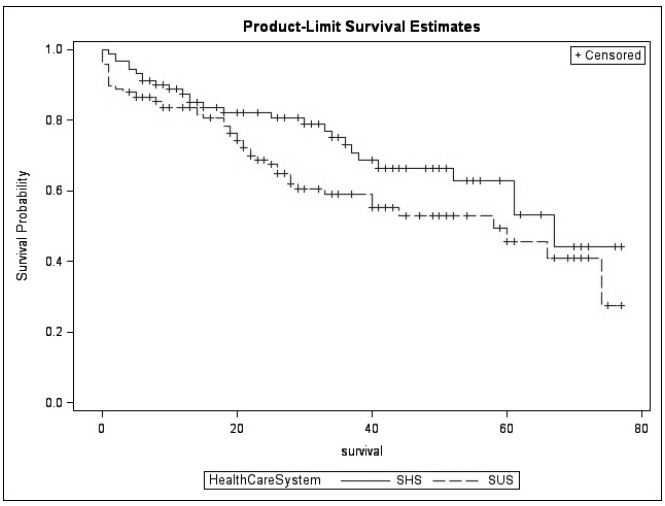
Background: Lung cancer is the leading worldwide cancer related death. Recently, 8thedTNM lung cancer was published, changing prognosis. Brazil provides free public healthcare system (SUS); however, we believe access is unequal. 25% of population has private healthcare insurance (SHS). Our objective was to evaluate the impact of the new staging and overall survival comparing patients from SUS and SHS. **Method:** Restrospective analysis of primary lung cancer patients resected between 2011 and 2016. Pathological was classificated according to 8thed TNM. Proportional odds model was used to compare staging and healthcare system, Kaplan-Meier and Log-Rank test for survival analysis. **Result:** 267 patients underwent surgery for lung cancer. 52.6% (139) were females, 64.5yo (SD=10.06), adenocarcinoma (60.7%) and 61%(163) from SUS. The upgrade in staging for the current system (8th) was significantly higher for SUS (graphic 1) (OD1.55– 95%CI1.00-2.39). Overall median survival was 61 months regardless staging, with SHS better survival (p=0.080) graphic 2







Conclusion: Lung cancer new staging is more precise predicting prognosis. An upstaging was expected with new TNM classification. However, a patient from SUS has a 55% higher chance than private care patients of being upstaged not only in T descriptor but also in final staging TNM. Also, SUS had a lower survival tendency. We need to review and address our unequal healthcare system in order better assist our patients.

Keywords: Staging, lung cancer, public health

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-021 LUNG CANCER AMONG WOMEN ASSISTED IN AN ARGENTINEAN UNIVERSITY INSTITUTION

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Background: Lung cancer remains the leading cause of cancer death worldwide and is responsible for 20,000 deaths yearly in Argentinean women. Despite prevention strategies the incidence of lung cancer in women in our population has not been decreasing. We described the clinicopathological and epidemiological profile of women diagnosed with lung cancer in our institution in the last seven years **Method:** A retrospective cohort of women with lung cancer diagnosis from the data base of the Thoracic Oncology Unit was reviewed **Result:** From 2010 to 2017, a total of 185 women with lung cancer were included. Median age was 61 (30-92). Distribution by age group was: ≤30: 1 (0.5%), 31-39:6 (3.2%), 40-49: 17 (9.2%), 50-64: 87 (47%), ≥65: 74 (40%).Histologic subtypes were: adenocarcinoma (77.3%, n=143), squamous cell carcinoma (13%, n=24), small cell lung cancer (5.9%,n=11), NOS (2.2%, n=4), large cell carcinoma (1.1%, n=2), and large cell neuroendocrine cancer (0.5%, n=1). Most women were smokers (70.8%, n=131)(mean 24.52±29.84 pack/year) and presented with and advanced disease (III-IV)(75%, n=139). Twenty eight women (15%) had history of other cancer (36% breast cancer and 21% cervix cancer).EGFR mutationand ALK rearrengements were identified in 26(14%) and 8 (4.3%)patients, respectively. Uncommon EGFR mutations like G719X in exon 18 (4/12, 33%) were observed in smokers (46%, 12/26). We also detected compound mutation patterns in 2 cases (1.9%)(G719X+L861Q and del19+T790M). Median OS for all patients was 25 months (95% CI 21.53-28.46), whereas for patients at stage III-IV was 20 months (95% CI 21.53-28.46). The independent factors associated with the OS were the ECOG PS, disease stage and the presence of symptoms at diagnosis. **Conclusion:** Women with lung cancer assisted in our institution showclinical and epidemiologic characteristics previously described in western population. However, we observed a relatively high proportion of EGFR mutations in smokers. Prospectively collected data will explore molecular and epidemiologic items in this subgroup of patients.

P1.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.06-022 PROGNOSTIC VALUE OF NLR IN OVERALL SURVIVAL OF PATIENTS WITH ADVANCED LUNG CANCER

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Background: Lung cancer remains as the principal death cause in many regions around the world. Unfortunately, between 60-70% of patients are diagnosed with advanced disease (clinical stage IIIB-IV), that determinate the prognosis of patients. The high mortality rates of advanced lung cancer (ALC) are partly due to the lack of effective prognostic biomarkers. Recent investigations suggest that neutrophils-to-lymphocyte ratio (NLR) play an important role in the immune response to lung cancer, high value is considered as a prognostic indicator. We evaluated the prognostic value of NLR in overall survival (OS) of patients with ALC treated at a private institution (Oncosalud – AUNA). **Method:** We analyzed data of 75 patients with advanced lung cancer, treated at Oncosalud-AUNA between 2013 - 2014. The clinical-pathological data were collected from digital medical records. The laboratory data (hemoglobin, leukocytes, neutrophil, lymphocyte, and monocyte) were collected from blood routine test. Optimal cutoff value of NLR (<3.6 and >3.6) and LMR (<4.7 and >4.7) were calculated using the maximally selected rank statistics. OS was determinate using Kaplan-Meier method and survival curves comparison were performed using log-rank test or Breslow. Cox model was used to estimate the effect of NLR on overall survival. **Result:** The median age was 70 years (range: 39-91) and 49% of patients were women. The metastatic sites were brain (28%), osseous (18%), cervical and supraclavicular (14%). The 66.7% of patients received chemotherapy with/without radiotherapy, 9% radiotherapy only and 24% non-treatment. In patients previously treated with chemotherapy, 52% received targeted therapy. The median follow-up was 23 months (CI95%: 17-29), median survival was 9.6 months (CI95%. 5.6-13.5) and, 1 and 2 years survival rate were 38% and 23%, respectively. The survival rate at 1 and 2 years in those receiving targeted therapy were 65% and 43%, and those who did not receive were 35% and 10%. In univariate analysis, ECOG scale 2-4 (p = 0.001), leukocytes > 10,000 cell/uL (p = 0.031), neutrophil > 7500 cell/mL (p = 0.021), monocytes > 800 cell/mL (p = 0.027), NLR >3.6 (p = 0.001), LMR>4.7 (0.036) and CYFRA 21.2 > 3.3 ng/mL (p = 0.033) were associated with poor survival. However, in the Cox model only NLR was associated with poor prognosis (HR: 3.2, CI95%: 1.6-6.3) **Conclusion:** Overall survival for our patients is similar to other series. Patients under NLR e <3.6 had a relatively better prognostic.

P1.06-023 SPATIO-TEMPORAL DISTRIBUTION OF LUNG CANCER MORTALITY RATE IN PERU: 2005-2014

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Background: Lung cancer still remains as the principal death cause in many regions around the world. Its mortality varies according to the regions and study periods. In Peru it represents the sixth most frequent malignant neoplasm and the fourth cause of cancer related death. We reported the spatial autocorrelation and the temporal variation in lung cancer mortality rate in Peru. **Method:** Data of lung cancer mortality in Peru between 2005-2014 was obtained from the Ministry of Health. Information on the number of inhabitants was obtained from National Institute of Statistics and Informatics. Age standardized mortality rate (ASMR) was calculated based on the 2011 world standard population. Spatial autocorrelation was determined according to Moran's Index and the Local G Cluster Map to explore the cluster patterns between regions. **Result:** During the study period 16,839 deaths due to lung cancer were reported. The lung cancer mortality rate in Peru increased from an ASMR of 12.8 (95% CI: 11.9-13.7) by 100,000 persons in 2005 to 13.4 (95% CI: 12.5-14.3) in 2014. According to the quartiles, the ASMR was higher in the north, south and east, and lowest in others regions. The spatial distribution of the ASMR showed a significant spatial autocorrelation (Moran´s I: p = 0.025). Also, during the study period, the ASMR showed a significant increase and decrease in some regions and in others it was constant. **Conclusion:** In Peru, lung cancer mortality rate showed a spatial and temporal variation in different regions. The increase in mortality rate in some regions requires identification of risk factors in order to establish public measures to reduce the risk of lung cancer mortality.

Keywords: Lung cancer, mortality rate, spatio-temporal distribution

P1.06-024 OUTCOME OF NON-SMALL CELL LUNG CANCER PATIENTS TREATED IN THE PRIVATE HEALTH CARE IN BRAZIL

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Background: Developing countries often present a dichotomous health care system, where patients may be treated in either public or private institutions that differ substantially in terms of level of access to diagnostic and therapeutics procedures. Herein, we present the first report of this comprehensive study to assess real-world data in non-small cell lung cancer (NSCLC) patients treated in the private health care in Brazil. **Method:** This is a prospective study of lung cancer patients treated in a private health care institution, comprising six unities in Rio de Janeiro and surroundings. Eligible patients were at least 18 years old and had a histology-proven diagnosis of lung cancer between July 2012 and February 2017. For this analysis, only NSCLC patients with an invasive component were included. Patients or relatives were contacted by telephone to ensure that all information was annotated. Data quality was certified by regular monitoring. This study was approved by the local Research Ethics Committee. **Result:** Six hundred twenty-eight patients were enrolled. Eighty-three were excluded in this analysis due to small-cell (57), carcinoid (5), *in situ* carcinoma (5), and other histological subtypes (16). The final report comprises 545 NSCLC patients, predominantly of non-squamous histology (76.5%). Median age was 68 years (range 21-93), and most cases were males (54.3%). Most patients were current (28.3%) or former (49.7%) smokers, diagnosed in advanced stages (stage III in 20.7% and stage IV in 57.2%). Treatment had a curative intent in 38.9% of times, and included surgery in 29.4%. Palliative chemotherapy was delivered in 64.5% of times, while adjuvant and neoadjuvant chemotherapy was used in 10.2% and 5.4%, respectively. Radiotherapy was used in 53.9% of cases. Molecular testing was available for 49.3% of cases, mostly in non-squamous histology (92.8%) and in advanced stages (stages III/IV in 74.8%). Median overall survival was 25.3 months (95% CI 22.0-28.6). Factors significantly correlated to OS were disease stage, *performance status*, tumor grade, gender, and weight loss (p<0.01 in all). Among patients with metastatic or recurrent disease, OS was significantly longer in those with a molecular testing (p<0.01). **Conclusion:** To our knowledge, this is the most comprehensive and best-annotated study in this scenario. Outcomes were favorably similar to the current literature from developed countries in all stages, which suggest that data generated from international clinical trials should be reproducible locally. Our dataset may serve as a foundation to guide resource allocation in the years to come.

Keywords: Lung neoplasms, developing countries, survival

P1.07-001 CLINICAL VALUE OF EXPRESSION OF PD-L1 AND CD8 OF 58 CASES WITH NSCLC

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Background: The aim of this study was to classify non-small cell lung cancer (NSCLC) based on the tumor microenvironment (TME) immune status according to the expression of PD-L1(5H1) and infiltration of CD8+ T-cells. To provide effective guidance for patients with NSCLC to use immunotherapy. **Method:** Fifty-eight patients with NSCLC were enrolled, most of whom are stage I adenocarcinoma. Analyse the expression of PD-L1 and CD8 by immunohistochemistry. According to the tumor microenvironment immune status , we classify the patients into four types: type I (PD-L1+ CD8+), type II (PD-L1-CD8-), type III (PD-L1+CD8-), and type IV (PD-L1-CD8+). Analyze the relationship between the characteristics of patients and the immune status. **Result:** The positive rate of PD-L1 expressing on the tumor cell is 74.14%(43/58) in 58 cases of NSCLC patients. Whereas the rate of CD8 positive lightly is 60.34%(35/58), the rate of CD8 positive mediately is 29.31%(17/58), and the rate of CD8 positive heavely is 1.72%(1/58). And the rate of type I is 72.41%(42/58), the rate of type II is 6.90%(4/58), the rate of type III is 1.72%(1/58) ,and the rate of type IV is 18.97%(11/58) . **Conclusion:** The major type of the tumor microenvironment immune status is type I, while the slightest type is type III. Except for the pathological classification (adenocarcinoma, squamous carcinoma, or others) (P < 0.05), we cannot relate the expression of PD - L1 (especially the tumor cell surface expression) to patients' gender, age, and tumor stage (P > 0.05).We conclude the expression of PD-L1 in squamous cell carcinoma is more than that in adenocarinoma ; we also cannot relate tumor infiltration of CD8 + T lymphocytes (none, mild, moderate, severe) with patients' gender, age, pathological classification, and stage (P > 0.05). So we would better test the the expression of the immune bio-marker like PD-L1 which express in the early stage of NSCLC and CD8+ T cell infliction before PD-1 antibody curing in patients of NSCLC to promote the cure rate.

Keywords: NSCLC; PD-L1; CD8

P1.07-002 THE EXPRESSION OF PD-L1 PROTEIN AS A PROGNOSTIC FACTOR IN LUNG SQUAMOUS CELL CARCINOMA

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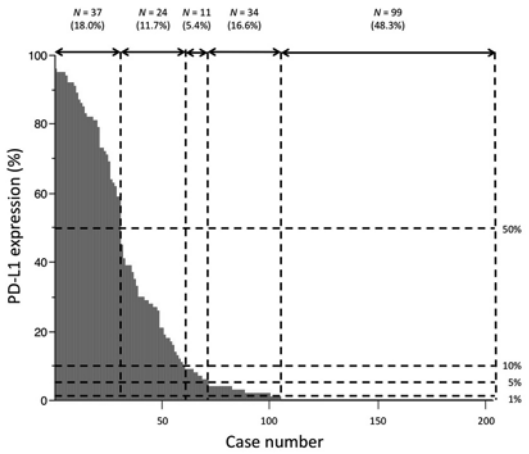
Background: Programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway-targeted immunotherapy has become the standard option of care in the management of lung cancer. The expression of the PD-L1 protein in lung cancer is expected to be a prognostic factor or to predict the response to PD-1-blocking antibodies. However, the association between PD-L1 positivity and the clinicopathological features and patient outcomes in lung squamous cell carcinoma (SCC) remains unclear because the definitive cut-off value for the expression of PD-L1 protein remains to be established. **Method:** The expression of PD-L1 protein in 205 surgically resected primary lung SCC patients was evaluated by immunohistochemistry with the antibody clone SP142. We generated a histogram to show the proportion of PD-L1-positive carcinoma cells as described in the figure below, and set the cut-off values as 1%, 5%, 10% and 50%. Moreover, we examined the proliferative capacity of these tumors using Ki-67 immunohistochemistry.



Result: The samples from 106 (51.7%), 72 (35.1%), 61 (29.7%) and 37 (18.0%) patients

were positive for the expression of PD-L1 protein at cut-off values of 1%, 5%, 10% and 50%, respectively. Fisher's exact test showed that, for almost all of the factors, PD-L1 positivity was not associated with the clinicopathological features with any of the four cut-off values. Univariate and multivariate survival analyses revealed that the PD-L1-positive patients only had a poorer prognosis than the PD-L1-negative patients at the 1% cut-off value. The Ki-67 labeling index in the PD-L1-positive patients was higher than that in the PD-L1-negative patients. **Conclusion:** The expression of PD-L1 protein was associated with a poor prognosis in lung SCC patients. The 1% cut-off value for PD-L1 might become a better predictive marker than the other cut-off values, and notably, even minimal expression of PD-L1 protein may have a negative prognostic significance.

Keywords: Squamous cell carcinoma, PD-L1, lung

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P1.07-003 CYTOLITIC TESTS WITH HYPERIMMUNE PATIENT SERA IS A GOOD PROGNOSTIC TOOL IN RACOTUMOMAB IMMUNOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The preferential accumulation of NeuGcGm3 in a variety of malignant tumors, compared with healthy tissues, made this molecule as an attractive target for cancer immunotherapy. 14F7 monoclonal antibody is a highly specific IgG1 against NeuGcGM3 gangliosid. The immunohistochemical detection of NeuGcGM3 allow the potential selection of patients for specific therapy with anti-idiotype racotumomab cancer vaccine. Racotumomab is an anti-idiotype vaccine, mimics this ganglioside and triggers an immune response. Antibodies reactive to NeuGcGM3 ganglioside in the vaccinated patient's sera have cytotoxic anti-tumor properties which can be assessed in L1210 cell line, expressing this ganglioside. **Method:** 12 patients with advanced stage NSCLC, whose tumor tissue expressed NeuGcGM3 with 14F7 monoclonal antibody included in the study. Progressing patients, unresponsive to the 1.st line platinum doublets excluded from the study. 10 Patients received racotumomab as switch maintanance following the 1st.line chemotherapy, whereas 2 patients in Stage IIIA received Racotumomab as adjuvant. Antibodies to NeuGcGM3 have been detected with ELISA test,and cytotoxic tests was performed with hyperimmune patient's sera in the L1210 cancer cell line expressing N-Glycol GM3, at the time of initiation, and at the 3rd,6th,9th, and 12th months of vaccination. Results of cytotoxic tests as a prognostic tool and clinical outcome of the patiens were compared. The assesment of the potential predictive value of NeuGcGM3 expressions in the tumor tissue for efficacy outcomes was also investigated. **Result:** Out of 12 patients, 11 patient's sera showed positive cytotoxic activity over cut off value, in NueGcGM expressing L1210 cell line. Mean PFS for these patients was 13.8(8-21) months. One patient's PFS lasted as long as 21 months whose initial stage was IIIB. In 9 patients cytototoxic activity was progressively incresed at consecutive vaccinations on the 3rd, 6th, 9th and 12th months . There was no significant difference in between IHC staining intensities with 14F monoclonal antibody in terms of cytotoxicity results. **Conclusion:** As a result, we can assume that cytotoxic tests may predict prognosis in the vaccinated patients. When percentage of cytotoxicity progresivelly increase in consecutive assays, we can predict a better outcome, looking to the longer PFS of these patients.In this study we could not assess the potential predictive value of NeuGcGM3 expression in the tumor tissue for efficacy outcome, since there was no significant difference in between IHC staining intensities with 14F monoclonal antibody in terms of cytotoxicity results. However, the issue of NeuGcGM3 expression in the tumor tissue as a biomarker deserve further investigation.

Keywords: Racotumomab, cytotoxic tests with hyperimmune sera, non-small cell lung cancer vaccine

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P1.07-004 PREDICTIVE BIOMARKERS OF RESPONSE TO NIVOLUMAB IN NON–SMALL CELL LUNG CANCER: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Background: It is important to seek predictive factors for the efficient use of immune check point inhibitors in non-small-cell lung cancer (NSCLC), because of the lack of a definitive predictive biomarker. **Method:** Study design for the analysis: A multicenter retrospective cohort study. Patient eligibility criteria: Consecutive patients treated with nivolumab between January 2016 and October 2016 after the second line systemic chemotherapy outside of a clinical trial. Definition of exposures: Variables were retrieved from the medical records before the administration of nivolumab. All variables were dichotomized based on previous study or median. Definition of study endpoint: Progression free survival (PFS) defined by response evaluation criteria in solid tumours (RECIST) 1.1. Two researchers evaluated the endpoint independently. Any disagreements were resolved by discussion. Statistical methods: Cox proportional hazards models were used to assess the impact of pretreatment markers on PFS. Missing values were imputed by multiple imputations. **Result:** A total of 189 patients were included in the study. Median follow-up time was 5.5 months. Fourty six (24%) patients were censored. Median age was 69 (range, 38–88); 26% were female. 64% had received ≧2 prior systemic therapies. In multivariate analyses, worse performance status, higher lactate dehydrogenase, and higher carcinoembryonic antigen,were independently associated with inferior PFS (Table 1)

Table 1 unadjusted and adjusted hazard ratio for progression free survival

Characteristics	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Histology		
non Sq vs Sq	0.72 (0.48 to 1.08)	0.91 (0.59 to 1.42)
ECOG PS		
0,1 vs ≧2	2.00 (1.34 to 2.98)	1.94 (1.29 to 2.92)
smoke		
current vs light or never	0.87 (0.59 to 1.27)	1.13 (0.71 to 1.80)
targetable driver mutation		
absent vs present	1.48 (0.96 to 2.27)	1.67 (0.98 to 2.84)
Neutrophil-to-Lymphocyte Ratio		
5> vs 5≧	1.12 (0.79 to 1.60)	1.00 (0.99 to 1.01)
LD		
217> vs 217≦	1.60 (1.15 to 2.23)	1.60 (1.12 to 2.30)
CEA		
13.8> vs 13.8≧	2.02 (1.40 to 2.90)	1.72 (1.17 to 2.53)
CYFRA 21-1		
5.05> vs 5.05≦	1.29 (0.87 to 1.92)	1.19 (0.82 to 1.73)

Abbreviations: CEA: Carcinoembryonic Antigen, CI: confidence interal, CYFRA 21-1: Fragments of cytokeratin-19, ECOG PS: Eastern Cooperative Oncology Group Performance Status, LD: Lactate Dehydrogenase, Sq: squamous cell carcinoma.

Conclusion: Our study indicated that patients with NSCLC treated with nivolumab in routine practice, pretreatment performance status ≧2, carcinoembryonic antigen ≦13.8, and Lactate Dehydrogenase ≧217 were associated with inferior PFS. Another study is warranted to determine the precise utility of each marker take account of the programmed death-ligand 1.

Keywords: immunetherapy, NSCLC, biomarker

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-005 A SYSTEMATIC AND GENOME-WIDE CORRELATION ANALYSIS OF PD-L1 EXPRESSION AND COMMON NSCLC DRIVER GENES

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Background: Programmed cell death ligand 1(PD-L1) targeted immunotherapy is emerging as a promising therapeutic strategy for non-small-cell lung cancer (NSCLC). However, the association of PD-L1 and EGFR, KRAS, and ALK and other driver genes in NSCLC are not well known. To explore the potential association, we systematically integrated published articles and analyzed RNA-seq dataset from The Cancer Genome Atlas project (TCGA) in order to comprehensively investigate the association between PD-L1 and the mutation and expression of these common driver mutations. **Method:** The relevant articles published in English were searched by using the database of PubMed, Web of science and Embase up to September 2016. The effect sizes were estimated by odds ratio with a correspondent 95% confident interval (CI), which were pooled by random effect or fixed effect models. Subgroup and sensitivity analysis were performed and the Begg's test was used to analysis the potential publication bias. We further applied the Pearson correlation analysis to investigate the association of PD-L1 and the expression of driver genes. Wilcoxon rank sum was used to evaluate the expression difference of PD-L1 among population. **Result:** A total of 9934 lung cancer cases were collected from 34 published studies. Patients with EGFR wild type (OR 0.68, 95% CI 0.48 to 0.96; P = 0.03), KRAS mutation positivity (OR 1.27, 95% CI 1.02 to 1.58; P=0.03) or non-adenocarcinoma histology (OR 0.68, 95% CI 0.47 to 0.98; P =0.04) were associated with high PD-L1 expression rate. However, PD-L1 expression was not associated with the status of ALK. Complementary to the findings of the meta-analysis, results from the TCGA project indicated that the expression of PD-L1 was significantly higher for patients with squamous cell carcinoma than adanocarcinoma (p=0.023) while the expression of common driver genes including EGFR, KRAS, ALK, MET, ROS1, PIK3CA, RET, HER2, NRAS and BRAF do not correlate with PD-L1 expression in NSCLC. **Conclusion:** High expression of PD-L1 was associated with the presence of EGFR wild-type, KRAS mutations or non-adenocarcinoma histology in NSCLC patients. Our results provide evidences for screening candidates for anti-PD-1/PD-L1 treatments.

Keywords: driver gene, PD-L1, NSCLC

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P1.07-006 ALTERED EXPRESSION OF PROGRAMMED DEATH-1 RECEPTOR (PD-1) AND ITS LIGAND PD-L1, PD-L2 AFTER NEO-ADJUVANT CHEMOTHERAPY IN LUNG CANCER

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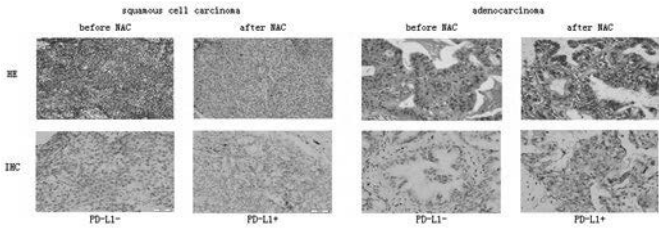
Background: Immunotherapy is a new research direction in the treatment of lung cancer. PD1/PD-L1, PD-L2 pathway as representative of the immune checkpoint, play critical roles in the development and progression of cancer. And the expression of PD-1, PD-L1, PD-L2 were associated with therapeutic effect. Many studys have shown that many factors may effect the expression of PD1, PD-L1, PD-L2, such as chemotherapy. The present study aims to examine the impact of neo-adjuvant chemotherapy (NAC) on PD-1, PD-L1, PD-L2 expression in lung cancer. **Method:** In this study, tumor samples were obtained from 26 patients who confirmed primary lung cancer prior to and after NAC (platinum-based)from June, 2009 to May, 2016 in the First Hospital of Jilin University. Expression of PD-1, PD-L1, PD-L2 in lung cancer tumor specimens were assessed by immunohistochemistry (IHC). Using 5%, 10%, 20%, 30%, 50% expression threshold to define PD-1, PD-L1, PD-L2 positive status, respectively. The variation of PD-1, PD-L1, PD-L2 in prior to and after NAC were evaluated by Matching chi-square test. Besides that, Spearman's rank correlation and non-parametric test were used to calculate the relationship between the changes of PD-1, PD-L1, PD-L2 and tumor shrinkage rate, interval from the end of NAC to operation, pathological type, gender, smoking or not. P value < 0.05 was considered statistically significant. **Result:** Using 5%, 10%, 20% expression threshold to define PD-L1 positive status, 65.4%(17/26), 53.8%(14/26), 42.3%(11/26) were found to be PD-L1 positive prior to NAC, and 92.3% (24/26), 80.8%(21/26), 69.2%(18/26) expressed positively after NAC, PD-L1 was up-regulated after NAC (p=0.003, p=0.016, p=0.016), however, there were no obviously statistical significance about the expression of PD-L1 (p>0.05)when using 30%, 50% expression threshold. The expression of PD1, PD-L2 were not show any statistical significance before and after NAC (p>0.05). Furthermore, there were no relationship between the changes of PD-1, PD-L1, PD-L2 and pathological type, interval from the end of NAC to operation, gender, smoking or not (p>0.05).



Conclusion: The expression of PD-L1 was up-regulated after NAC when using 5%, 10%, 20% expression threshold, there were obviously statistical significance. No correlations existed between the variation of PD-1, PD-L1, PD-L2 and tumor shrinkage rate, interval from the end of NAC to operation, pathological type, gender, smoking or not.

Keywords: Programmed death-ligand 1, neo-adjuvant chemotherapy, lung cancer

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-007 INTERLEUKIN-17A PROMOTES LUNG TUMOR PROGRESSION THROUGH NEUTROPHIL ATTRACTION TO TUMOR SITES AND MEDIATING RESISTANCE TO PD-1 BLOCKADE.

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Background: Proinflammatory cytokine Interleukin (IL)-17A (IL-17A) is the prototypical member of the IL-17 family of pro-inflammatory cytokines. It is produced by Th17 cells, CD8 T cells, γδT cells, and Natural Killer (NK) cells in the tumor microenvironment. The inflammatory milieu can contribute to lung cancer growth by further production of tumor promoting cytokines, reduction in cytotoxic T cells, and development of myeloid derived suppressor cells. IL-17A and its receptors are expressed across different tumor types; however, their exact role in tumor development, progression, and response to therapeutic regimens is unclear. IL-17A is overexpressed in a subset of patients with lung cancer. We hypothesized that IL-17A promotes a pro-tumorigenic inflammatory phenotype, and inhibits anti-tumor immune responses. **Method:** IL-17A is expressed at high levels in a subset of lung cancers. Interestingly, we observed that IL-17A could not be detected in Bronchoalveolar lavage fluids (BALFs) from immunocompetent mouse lung cancer models. To characterize the role of IL-17A in *Kras* mutant lung tumors, we developed a mouse model of chronic inflammation that more closely resembles human *KRAS* mutant lung cancer through expressing IL-17A constitutively in the lung epithelium and then introducing this allele into lox-stop-lox Kras G12D mutant mice. We performed immune phenotyping of mouse lungs, survival analysis, and treatment studies with antibodies either blocking PD-1 or IL6, or depleting neutrophils. To support preclinical findings, we analyzed human gene expression datasets and immune profiled patient lung tumors. **Result:** Tumors in IL-17:Kras G12Dmice grew more rapidly, resulting in a significantly shorter survival as compared to Kras G12D. IL-6, G-CSF, MFG-E8, and CXCL1 were increased in the lungs of IL17:Kras mice. Time course analysis revealed that tumor-associated neutrophils were significantly elevated, and lymphocyte recruitment was significantly reduced in IL17:Kras G12D mice as compared to Kras G12D. In therapeutic studies PD-1 blockade was not effective in treating IL-17:Kras G12D tumors. In contrast, blocking IL-6 or depleting neutrophils with an anti-Ly-6G antibody in the IL17:Kras G12D tumors resulted in a clinical response associated with T cell activation. In tumors from lung cancer patients with *KRAS* mutation we found a correlation among higher levels of *IL-17A* and the colony stimulating factor (*CSF3)*, and a significant correlation among high neutrophil and lower T cell numbers. **Conclusion:** Here we show that an increase in a single cytokine, IL-17A, without additional mutations, can promote lung cancer growth by promoting inflammation, which contributes to resistance to PD-1 blockade and sensitizes tumors to cytokine/neutrophil depletion.

Keywords: IL-17, neutrophils, Checkpoint blockade

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-008 MICROBIOME & IMMUNOTHERAPY: ANTIBIOTIC USE IS ASSOCIATED WITH INFERIOR SURVIVAL FOR LUNG CANCER PATIENTS RECEIVING PD-1 INHIBITORS

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Background: Mounting evidence suggests the gut microbiome influences response to cancer immunotherapy. Antibiotic exposure (ATB+) alters the gut microbiome, and limited clinical data demonstrate ATB may negatively impact cancer immunotherapy response and survival outcomes. This study evaluates the impact of ATB+ on response and survival outcomes in patients with metastatic non-small-cell lung cancer (NSCLC) treated with programmed death-1 (PD-1) inhibitors. **Method:** We performed a retrospective review of all metastatic NSCLC patients treated with PD-1 inhibitors at our institution. A patient was considered to be in the ATB+ group if exposed to ATB within 6 weeks of initiating PD-1 inhibitors. All other patients were included in the antibiotic unexposed (ATB-) group. The primary outcome of interest was overall survival (OS), and secondary outcomes included overall response rate (ORR) and progression-free survival (PFS). ORR was compared between ATB+ and ATB- utilizing logistic regression modeling. The Kaplan-Meier method and Cox regression model were utilized to compare PFS and OS between ATB+ and ATB- groups. **Result:** A total of 74 patients met study eligibility criteria. The median age was 66 years old (range 33-88 years old). The majority of patients were male (55%), Caucasian (65%), and had adenocarcinoma histology (57%). A minority had brain metastases (15%) and radiation (38%) prior to receiving a PD-1 inhibitor. Most received nivolumab (95%). A total of 18 patients (24%) received antibiotics prior to initiating a PD-1 inhibitor, and most received fluoroquinolones (50%) for mild respiratory infections (72%). Antibiotic exposure did not impact ORR in our study. The ORR was 23% in ATB- and 25% in ATB+ patients (adjusted OR 1.2, p=0.20). ATB+ patients had inferior PFS compared to ATB- patients (median PFS 2.0 vs 3.8 months, p<0.001). Likewise, ATB+ patients had worse OS compared with ATB- (median OS 4.0 months vs 12.6 months, p=0.005). The association between ATB+ and inferior PFS (HR 2.5, p=0.02) and OS (HR 3.5, p=0.004) remained significant when controlling for age, sex, race, tobacco history, tumor histology, presence of brain metastases and previous radiation. **Conclusion:** To our knowledge, this is the first study evaluating the impact of ATB on survival outcomes with immunotherapy in metastatic NSCLC. ATB+ was associated with inferior PFS and OS, suggesting a link between antibiotic-induced alteration of the gut microbiome and efficacy of immunotherapy. While this is a relatively small retrospective study, it does generate justification for further investigation into the interaction between the gut microbiome and cancer immunotherapy.

Keywords: Immunotherapy, Antibiotics, microbiome

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-009 PD-L1 EXPRESSION IN CIRCULATING TUMOR CELLS AND RESPONSE TO PD-1 INHIBITOR TREATMENT IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Inhibitors of the immune checkpoint PD-1/PD-L1 (ICI) have become a standard of care in non-small cell lung cancer (NSCLC). The outcomes, although very promising, remain inconstant. Patient selection, currently based on PD-L1 expression in tumor tissue, must be improved, through more dynamic and non-invasive tests. PD-L1 staining of circulating tumor cells (CTCs) could represent such a valuable predictive biomarker. **Method:** Blood samples were prospectively collected from patients with advanced NSCLC before their first infusion of nivolumab. Ten ml of blood were collected and CTCs were isolated on cell size-based technology (ISET, Rarecells). PD-L1 expression was assessed by immunofluroescence (IF) on CTCs and immunochemistry (IHC). **Result:** 60 advanced NSCLC patients were included. 45 tissue biopsies were available for PD-L1 expression analysis of: 31.4 (68.9%) and 9 (20%) of biopsies were positive, respectively, using a 5% and a 50% cut-off for tumor cell PD-L1 expression. 56 ISET filters were analyzed. The number of PD-L1(+)

CTCs ranged from 1.5 to 47.5 per 7.5mL of blood (median 8.5, 12.5% of CTCs). No correlation between tissue and CTC staining of PD-L1 was observed. A optimal cutoff of 30/7.5mL number of CTCs was determined. Patients with elevated CTCs (>30/7.5mL) experienced a decrease of overall and progression-free survival (p=0.04 and p<0.0001 respectively). PD-L1 expression on CTCs at baseline was not predictive of outcome in the global population but significantly increased in "non-responders" group (PFS <6 months) in comparison with the "responder" group (PFS>6 months) (p=0.02).

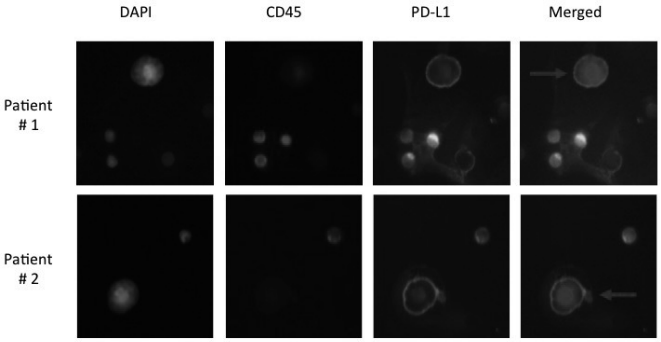

Figure 1: PD-L1 analysis by immunofluorescence on CTCs (high nucleocytoplasmic ratio, no CD45 staining) from 2 patients showing strong PD-L1 membranous expression

Conclusion: We demonstrated the feasibility of PD-L1 detection in CTCs in patients with advanced NSCLC. In our cohort, PD-L1(+) CTCs are associated with a worse outcome. This can be partly explained by the pejorative impact of the number of CTCs that may outweigh its possible predictive value. The interest of PD-L1 assessment on CTC will be likely reinforced by integrating other biomarkers.

Keywords: PD1 inhibitors, Circulating tumor cells, PD-L1 expression

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-010 PERIPHERAL BLOOD BIOMARKERS ASSOCIATED WITH CLINICAL OUTCOME IN NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH NIVOLUMAB

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Background: Targeting of the immune system has been found to confer clinical benefit for patients with some types of advanced solid tumor. Given that only a limited number of patients experience a durable response, whereas all those treated are at risk for specific immune side effects, the identification of individuals who are most likely to benefit from nivolumab and similar agents is an important clinical goal. We have now examined the possible impact of clinical parameters determined in the routine laboratory setting—including peripheral blood cell counts such as ANC, absolute lymphocyte count (ALC), absolute monocyte count (AMC), and absolute eosinophil count (AEC)—on outcome in patients with advanced or recurrent NSCLC treated with nivolumab. **Method:** A total of 134 patients with advanced or recurrent NSCLC treated with nivolumab was analyzed retrospectively. Univariable and multivariable analyses were performed to evaluate the relation between survival and peripheral blood parameters measured before treatment initiation, including absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count, and absolute eosinophil count (AEC) as well as serum C-reactive protein and lactate dehydrogenase levels. Progression-free survival (PFS), overall survival (OS), and response rate were determined. We further evaluated the association of these factors and the expression level of PD-L1 of tumor tissue. **Result:** Among variables selected by univariable analysis, a low ANC, high ALC, and high AEC were significantly and independently associated with both better PFS ($P = 0.001$, $P = 0.04$, and $P = 0.02$, respectively) and better OS ($P = 0.02$, $P = 0.04$, and $P = 0.003$, respectively) in multivariable analysis. Categorization of patients according to the number of favorable factors revealed that those with only one factor had a significantly worse outcome compared with those with two or three factors. Median PFS was 209, 87, and 42 days and the response rate was 43.5%, 27.1%, and 5.9% in patients with three, two, or one of the three favorable factors, respectively. The association between survival factors and the expresssion of PD-L1 in tumor tissue will be presented at the conference as well. **Conclusion:** A baseline signature of a low ANC, high ALC, and high AEC was associated with a better outcome of nivolumab treatment, with the number of favorable factors identifying subgroups of patients differing in survival and response rate.

Keywords: non–small cell lung cancer, peripheral blood biomarker, Nivolumab

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-011 PD-L1 EXPRESSION AND CD8+ T CELL INFILTRATION ASSOCIATE WITH THE PROGNOSIS OF PULMONARY NEUROENDOCRINE TUMOR

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Background: For the past few years, the predictive role of programmed death-ligand 1 (PD-L1) for anti-PD1 immunotherapy in advance NSCLC has raised People's attention. Tumor–infiltrating lymphocytes (TILs) are often observed in resected cancer tissue and anticipated in the host adaptive immune response against tumor cells as well. However, expression and the prognostic value of PD-L1 as well as CD8+ TILs in pulmonary neuroendocrine tumors (PNETs) have not been fully studied. The aim of our research is to investigate the status of PD-L1 expression and CD8+ TILs and to measure the prognostic value of PD-L1 and CD8+ TILs in different types of PNETs. **Method:** Totally 168 specimens of PNETs (36 TC, 7 AC, 100 SCLC, 25 LCNEC) were involved in this study. Immunohistochemistry (IHC) was used to detect the expression of PD-L1 on these cases. Cases demonstrating ≥ 5% tumor cell expression or any expression (>1%) of PD-L1 on TILs were considered positive. CD8+ TILs both within stroma and tumor areas of invasive carcinoma were analyzed using whole slide digital imaging. For each case, manual regional annotation and machine cell counts were taken. The number of positive cells has been evaluated by counting them in 4 peritumoral and 6 intratumoral non-overlapping fields using the fixed areas of 1.44 square milimeter. **Result:** PD-L1 was expressed on the membrane of tumor cells or immune cells of 72 cases (42.9%). Significant correlation was observed between CD8+ TILs and PD-L1 expression (P<0.001). For overall survival (OS) and progression free survival (PFS) analysis of PD-L1 as well as CD8+ TILs, there was no association between PD-L1 expression with OS and PFS, however, higher CD8+ TIL levels in stroma was demonstrated to have significant correlations with better OS (P=0.000) and PFS (P=0.020). Importantly, multivariate analysis revealed that CD8+ TILs in stroma was an independent prognostic factor for better OS (p=0.045) and PFS (p=0.006). In high grade NECs, similar analysis was performed and the result showed that positive expression of PD-L1 was associated with better OS (P=0.011) but not with PFS (P=0.383), in contrast, CD8+ TILs in stroma was proved to be an independent prognostic factor for both of OS (p=0.035) and PFS (p=0.005) as well. **Conclusion:** We found that PD-L1 was expressed in about half of PNETs and correlated with better OS in NECs. Higher CD8+ TIL levels within stroma was positively associated with PD-L1 expression and proved to be an independent prognostic factor for favorable OS and PFS in PNETs and NECs.

Keywords: Pulmonary Neuroendocrine tumors, programmed death-ligand 1 (PD-L1), CD8+ T cell density

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-012 PREDICTION SENSITIVITY OF PD-1 CHECKPOINT BLOCKADE USING PATHOLOGICAL TISSUES SPECIMENS BY NOVEL COMPUTERIZED ANALYSIS SYSTEM

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Background: Recent development of immune checkpoint blockade such as anti-PD-1 antibody brought great benefits to non-small cell lung cancer (NSCLC) patients. However, some population of NSCLC showed resistance and pseudo-progressions against anti-PD-1 checkpoint blockade. Thus, it is very important for developing biomarkers which predict of efficacy of PD-1 checkpoint blockade. In this background, we developed novel digital pathology system that predict for response to anti-PD-1 checkpoint blockade using H&E staining sections and technology of AI. **Method:** In this study, we extract 361 ROIs(Region of Interest) and 254,205 nuclei were measured from NSCLC cases that treated with anti-PD-1 antibody. We used ilastik for nuclei image segmentation, CellProfiler and our CFLCM tool for features measurement, 992 features are evaluated for each ROI. At first, we analyzed by step-wise discriminant analysis for select the effective features, and using canonical discriminant analysis and SVM (Support vector Machine) RBF kernel model discrimination, we analyzed morphological data based PD-1 blockade response on statistical platform R. **Result:** Except undeterminable cases, we got the more than 95% accuracy level discrimination results. The mapping the discriminant scores, SD cases were mapped in the middle of PR and PD. Only using the average and standard deviation of ROIs' nuclei shape features (size, roundness, perimeter, etc.) and inside nuclei features (mainly chromatin texture) more than 90% discrimination results were obtained. This means the nuclei morphological data is more important than CFLCM (pleomorphism and heterogeneity measurement data). We challenged the prediction for undeterminable cases by using canonical discriminant and SVM. **Conclusion:** This time analysis is small number samples, so the results application robustness may be limited. But our results show the possibility for clinical response prediction even on the pre-treatment pathological tissues specimens.

Keywords: prediction of sensitivity, PD-1 checkpoint blockade, computerized analysis system

P1.07-013 DETECTION OF GENOMIC ALTERATIONS IN PLASMA CIRCULATING TUMOR DNA IN PATIENTS WITH METABOLICALLY ACTIVE LUNG CANCERS

Z. Yuan[1], C. Zhou[2], L. Qi[3], A. Mahavongtrakul[4], Y. Li[5], D. Yan[5], Y. Rong[5], W. Ma[5], J. Gong[5], J. Li[3], M. Molmen[6], T.A. Clark[6], G.M. Frampton[6], M. Cooke[6], E.H. Moore[7], D.K. Shelton[2], R.D. Badawi[2], J.P. Gregg[8], P.J. Stephens[6], T. Li[9]

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Background: Targeted exome sequencing (TES) using plasma ctDNA has been used in complementing tissue-based genomic assay for matching targeted molecular therapy for individuals with advanced solid tumors. However, concordance varies significantly in reported studies. Unlike tissue-based genomic assays, plasma ctDNA assays are more dependent on viable tumors producing sufficient ctDNA. The objective of this study was to explore successful detection of genomic alterations (GAs) and tumor metabolic activity by FDG PET/CT scan. **Method:** Plasma ctDNA samples extracted from frozen plasma (Group A) or fresh whole blood (Group B) samples were subjected to a 62-gene panel TES assay (FoundationACT™). The fraction of ctDNA in the blood was estimated using the maximum somatic allele frequency (MSAF) for each sample. Tumor load, assessed by RECIST V1.1, and tumor metabolic activity, assessed by SUVmax, were correlated with ctDNA GAs detected by FoundationACT™. **Result:** Patient characteristics are summarized in Table. MSAF was significantly higher in fresh blood than frozen plasma specimens. GAs (≥1) were detected in 50 cases (77%). Various tumor features contributing to undetectable GAs include low tumor burden, indolent growth, and tumor regression. Tumor metabolic activity (i.e., viable tumor burden) measured by SUVmax on FDG-PET scan correlated better with the detection of GAs in plasma ctDNA than tumor radiographic burden measured by RECIST V1.1 on CT scan (Table).

FoundationACT	Group A (N=14)	Group B (N=51)	Total (N=65)
Specimen Type	Frozen plasma	Fresh whole blood	All samples
Volume (mL)	~3.0	8.5 (6.0-11.0)	-
Age: median (range)	66 (44-74)	68 (50-93)	67 (44-93)
Gender: Female (N, %)	7 (50%)	32 (63%)	39 (60%)
Race/Ethnicity (N, %)			
Hispanic	2 (14%)	6 (12%)	8 (12%)
Caucasian	10 (71%)	33(65%)	43 (66%)
Asian	2 (14%)	10 (20%)	12(18%)
African American	0	2(3%)	2 (4%)
Histology:			
Lung adenocarcinoma	3 (21%)	40 (78%)	43 (66%)
Lung squamous cell carcinoma	11 (79%)	8 (16%)	19 (29%)
Others*	0	3 (6%)	63(5%)
GA ≥1	10 (71%)	40 (78%)	50 (77%)
MSAF (mean± SD); (GA ≥1 vs GA = 0)	0.122 ±0.250 vs 0.008±0.009 (P=0.185)	0.163±0.256 vs 0.002±0.004 **(P=0.0003)**	0.155±0.253 vs 0.004±0.006 **(P=0.0001)**
Tumor burden by RECIST V1.1 (GA ≥1 vs GA = 0) (mean ± SD)	7.1±6.2 vs 12.8±7.4 (P=0.182)	10.0±6.2 vs 6.9±3.6 (P=0.145)	9.4±6.2 vs 8.6±5.4 (P=0.682)
Tumor metabolic activity by SUVmax (GA ≥1 vs GA = 0) (mean ± SD)	47.6±30.9 vs 39.0±23.2 (P=0. 637)	48.3±30.9 vs 20.2±12.5 **(P=0.003)**	48.1±30.5 vs 25.6±17.6 (P=0.002)

*Other tumor types include lung small cell carcinoma (n=2); Lung large cell neuroendocrine (n=1). *P-values in abstract are calculated using unpaired t-test. **Conclusion:** Our study supports the clinical utility of plasma ctDNA genomic profiling in patients with metabolically active tumors that are measurable by SUVmax on PET/CT scan. Further study is needed to understand the biology of plasma ctDNA and to optimize imaging tools for quantifying tumor metabolism and guiding clinical use of plasma ctDNA assay.

Keywords: plasma ctDNA, FDG PET/CT

P1.07-014 ASSOCIATION OF PREOPERATIVE SERUM CRP WITH PD-L1 EXPRESSION IN NSCLC: A COMPREHENSIVE ANALYSIS OF SYSTEMIC INFLAMMATORY MARKERS

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Background: Programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors have been approved as a standard therapy for metastatic non-small cell lung cancer (NSCLC). Although PD-L1 expression serves as a predictive biomarker for the efficacy of immunotherapy, there are no established biomarkers to predict the expression of PD-L1. The inflammatory markers C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR) were recently shown to predict the efficacy of nivolumab for NSCLC patients. Therefore, here we investigated the potential association of PD-L1 expression with systemic inflammatory markers, including CRP, NLR, lymphocyte-monocyte ratio and platelet-lymphocyte ratio. **Method:** We retrospectively examined tumor PD-L1 expression in 508 surgically resected primary NSCLC cases by immunohistochemical analysis (cut-off value: 1%). The association of PD-L1 expression with preoperative systemic inflammatory markers was assessed by univariate and multivariate analyses. We generated a PD-L1 association score (A-score) from serum CRP level (cut-off value: 0.3 mg/dl) and smoking status to predict PD-L1 expression. **Result:** Among the total 508 patients, 188 (37.0%) patients were positive for PD-L1 expression at the 1% cut-off value and 90 (17.5%) had elevated serum CRP level. Multivariate logistic regression revealed that that PD-L1 positivity was significantly associated with advanced stage, the presence of vascular invasion and high serum CRP level (P=0.0336, 0.0106 and 0.0018, respectively). Though not significant, smoking history tended to be associated with PD-L1 protein expression (P=0.0717). There was no correlation with other inflammatory markers. Smoking history with elevated CRP level (A-score: 2) was strongly associated with PD-L1 protein expression (odds ratio: 5.18, P<0.0001), while it was inversely associated with *EGFR* mutation (odds ratio: 0.11, P<0.0001). **Conclusion:** Our results indicate that among all systemic inflammatory markers examined, serum CRP level could be a helpful biomarker for PD-L1 expression that is easily determined and available worldwide.

Keywords: programmed death-ligand 1 (PD-L1), C-reactive protein (CRP), Systemic inflammatory marker

P1.07-015 INTERFERON-GAMMA (INFG) AS A BIOMARKER TO GUIDE IMMUNE CHECKPOINT BLOCKADE (ICB) IN CANCER THERAPY

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Background: PD-L1 is induced by oncogenic signals or via INFG. STAT3, through DNMT1, epigenetically silences STAT1 and RIG-I and opposes INFG signaling. TET1 is a DNA demethylase. I kappa B kinase epsilon (IKBKE), a noncanonical I-kappa-B kinase, is essential for INFG induction, but can also promote NFATc1 phosphorylation and T cell response inhibition. Eomesodermin (Eomes) regulates T cell exhaustion. CCL5 (or Rantes), dependent on STAT3, causes myeloid-derived suppressor cell (MDSC) recruitment. YAP1 can also drive MDSC recruitment via CXCL5 signaling. We have explored whether the expression of genes related to INFG signaling, T cell exhaustion and MDSC recruitment is associated with response to ICB. **Method:** Total RNA from pre-treatment tissue samples of 17 NSCLC and 21 melanoma patients treated with nivolumab and pembrolizumab respectively, was analyzed by qRT-PCR. INFG, STAT3, IKBKE, STAT1, RIG-I and PD-L1 mRNA were examined. CCL5, YAP1, CXCL5, NFATC1, EOMES and TET1 expression was additionally assessed. Gene expression was categorized with respect to tertiles and patients were divided into two risk groups (low and intermediate/high). $CD8^+$ tumor-infiltrating lymphocytes (TILs) and PD-L1 protein expression in tumor and $CD8^+$ TILs were examined by immunohistochemistry (SP57 and SP142 assay, respectively). Progression free survival (PFS), overall survival (OS) and Disease Control Rate (DCR) were estimated. **Result:** Seventeen NSCLC patients, previously treated with one or more prior systemic therapies, received nivolumab. IKBKE was positively correlated with INFG (r=0.65, p=0.0124) and PD-L1 (r=0.58, p=0.0225) expression. RIG-I was loosely

anticorrelated with NFATc1 (r=-0.55, p=0.0518). Among all biomarkers explored, only INFG was associated with PFS, OS and DCR. Specifically, PFS was significantly longer for nivolumab-treated patients with intermediate/high versus low INFG expression (5.1 versus 2.0 months, p=0.0124). OS was longer (though not statistically significant) for patients with intermediate/high versus low INFG expression (10.2 versus 4.9 months, p=0.0687). DCR to nivolumab was 71.43% for patients with intermediate/high INFG versus 0% for patients with low INFG expression. Neither PD-L1 immunohistochemistry expression nor $CD8^+$ TILs were related to nivolumab outcome. The same results were observed for 21 melanoma patients treated with pembrolizumab. **Conclusion:** IFNG production by T-cells plays critical roles in anti-cancer immune responses by augmentation of MHC Class I expression, growth arrest, post-proteasomal trimming of antigen epitopes, recruitment of effector cells, induction of T-regs fragility and PD-L1 expression. Further research is warranted in order to validate whether INFG is more accurate than PD-L1.

Keywords: Interferon-gamma (INFG), PD-L1, immune checkpoint blockade (ICB)

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-016 COMPARISON OF PD-L1 IMMUNOHISTOCHEMICAL STAINING BETWEEN EBUS-TBNA AND RESECTED NON-SMALL CELL LUNG CANCER SPECIMENS

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Background: PD-L1 can be detected by immunohistochemical (IHC) analysis and has emerged as a biomarker that predicts which patients are more likely to respond to anti-PD-L1/PD-1 immunotherapies in non-small cell lung cancer (NSCLC)(1, 2). To date, there is no evidence to support or refute PD-L1 IHC staining on endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) samples. Our study aimed to establish the sensitivity, specificity, positive predictive value, and negative predictive value of PD-L1 IHC staining reliability on EBUS-TBNA samples, when compared to resected tumor specimens. **Method:** A retrospective review was performed on all patients who underwent an EBUS-TBNA of either a lymph node(s) or the tumor itself, who subsequently had surgical resection of their tumor between July 2006 through September 2016. Patients who had a concordant NSCLC EBUS-TBNA diagnosis with their resected tumor were included. Patients with small cell lung cancer were excluded. All EBUS-TBNA samples were obtained using Olympus EBUS bronchoscopes and a 22-gauge ViziShot needle (Olympus Medical Systems Corp., Tokyo, Japan). The Dako PD-L1 IHC 22C3 (Agilent Pathology Solutions) assay was used. A positive PD-L1 stain was defined as ≥1% of tumor cell positivity. EBUS-TBNA aspirates were compared with the surgically resected specimen to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). **Result:** We performed 5448 EBUS-TBNA procedures for lung cancer. Seventy patients were included in our analysis. To date, 23 cases have been stained and reviewed (Table). The sensitivity and specificity was 71% and 100%, respectively. The PPV and NPV were 100% and 69%, respectively. We expect to complete our analysis of all patients prior to the IASLC World Conference.

Comparison of PD-L1 IHC stain between EBUS-TBNA samples and resected tumor specimen.

	Resected tumor PD-L1 positive	Resected tumor PD-L1 negative
EBUS-TBNA PD-L1 positive	10	0
EBUS-TBNA PD-L1 negative	4	9

Conclusion: Positive PD-L1 IHC staining on EBUS-TBNA aspirates appears to have a strong correlation with resected tumor specimen. When EBUS-TBNA aspirates are negative for PD-L1 staining, additional tumor specimens are required to confirm the PD-L1 status.

Keywords: Non-small cell lung cancer, PD-L1, immunotherapy

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-017 ASSESSMENT OF CANCER IMMUNITY STATUS IN EACH PATIENT USING IMMUNOGRAM

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Background: For successful cancer immunotherapy, comprehensive profiling of cancer-immune system interaction is required for each individual patient. To this end, we developed an immunogram reflecting the cancer immunity cycle and applied it to real patients with lung cancer. **Method:** Whole-exome sequencing and RNA-Seq were performed in 25 non-small cell lung cancer patients (13 adenocarcinoma, 11 squamous cell carcinoma, and 1 large cell neuroendocrine carcinoma). The number of somatic mutations and the expression of genes related to cancer-immunity were assessed and normalized using TCGA-LUAD and LUSC data (n=1035). Immunogram of each patient was drawn in a radar chart composed of 9 axes reflecting 7 steps of cancer-immunity cycle. **Result:** Various patterns of immunogram were observed in all 25 lung cancer patients, suggesting that each patient has their own pattern of immunosuppressive microenvironment (Figure 1). The hierarchical clustering using each scores of immunogram showed four clusters of patients characterized by T cell phenotype (inflamed vs non-inflamed) and tumor antigenicity (high vs low) (Figure 2). T cell-inflamed tumors (Clusters 3&4) had gene signatures of abundant T cells and interferon gamma (IFNG) response, as well as inhibitory cells and checkpoint molecules, suggesting the presence of counter regulatory immunosuppressive microenvironment. Unleashing of counter regulations by checkpoint inhibitors, for example, may be indicated for these patients. Each scores of immunogram had no correlation with histology. This result was consistent with previous studies of checkpoint blockade that clinical responses were not easily predicted solely by the histology. Patient age, gender and TNM stage also did not correlate with each immunogram scores.

Figure 1.
Immunogram for the Cancer-Immunity Cycle

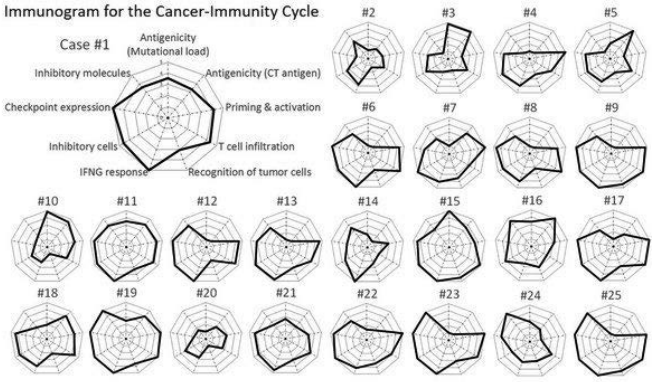
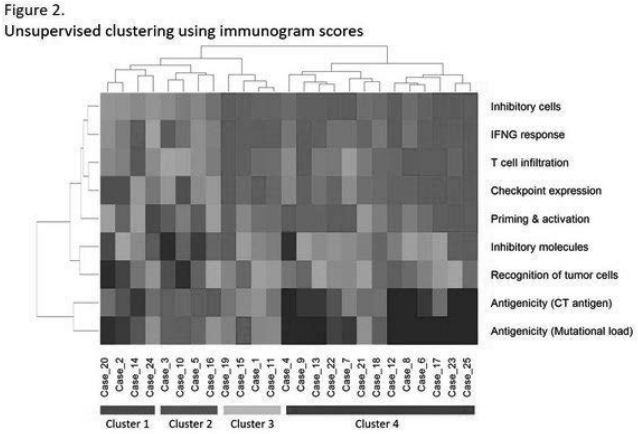


Figure 2.
Unsupervised clustering using immunogram scores



Conclusion: The landscape of the tumor microenvironment in each patient can be appreciated by utilizing immunogram. Immunogram for the cancer-immunity cycle can be used for the assessment and visualization of cancer immunity status in each patient, and thus may become a helpful resource toward optimal personalized immunotherapy.

Keywords: cancer-immunity cycle, immunogram, TCGA

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-018 A META-ANALYSIS OF PD-L1 EXPRESSION AS A BIOMARKER OF PD-1 BLOCKADE IN ADVANCED NON SMALL CELL LUNG CANCER

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Background: The recognition of programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) as key therapeutic targets has led to the clinical development of several PD-1 and PD-L1 inhibitors as breakthrough treatments in advanced non small cell lung cancer. Although some patients experience durable tumour response, many do not derive any clinical benefit, therefore highlighting the importance of identifying methods to improve patient selection. PD-L1 expression on tumour cells with or without immune cells is the most reported association with anti-tumour activity of PD-1 blockade. Despite multiple publications, the use of different assays and cutpoints make it difficult to know if PD-L1 is a reliable biomarker for predicting

outcomes to anti PD-1/PD-L1 treatment. **Method:** We performed a systematic search of MEDLINE, EMBASE, PubMed and conference proceedings up to 20 June 2017 and identified all clinical trials of anti PD-1 or PD-L1 monotherapy in advanced non-small cell lung cancer. We retrieved data regarding outcomes of 1 year overall survival (1yr OS), 1 year progression free survival (1yr PFS) and overall response rate (ORR), including 95% confidence intervals, in subgroups of varying PD-L1 tumour expression with cutpoints of 1%, 5%, 10%, 25%, 50% and 90%. Results were pooled and analysed based on different cutpoints. As PD-L1 expression is a continuum, we also tested for a correlation between outcomes and increasing cut-points of PD-L1 expression. **Result:** Of sixteen included studies with a total of 4,452 patients who received PD-1/PD-L1 inhibitor monotherapy, eight trials (n=821) reported on PD-1 blockade as first-line (1L) therapy and thirteen trials (n= 3,631) reported on treatment as second-line or beyond (>2L). Using 1% cutpoint, PD-L1 positivity was associated with higher ORR in 1L and >2L and 1yr PFS in >2L. Using a high cutpoint of 50%, PD-L1 positivity was associated with higher ORR in 1L and >2L, and higher PFS in 1L. Comparison of increasing cutpoints of PD-L1 expression and outcomes showed a positive correlation with 1yr PFS in 1L, a modest correlation with 1yr PFS in >2L and ORR in 1L and >2L, and little correlation with 1yr OS in 1L and >2L. Sensitivity analysis revealed no difference when excluding studies using the SP142 assay with weaker tumour staining. **Conclusion:** Within the limitations of current data, there is a positive correlation between increasing cutpoints of PD-L1 expression and ORR and 1yr PFS, but little correlation with 1yr OS in treatment naive and pretreated patients.

Keywords: Programmed cell death ligand 1, Checkpoint Inhibitor, Predictive biomarker

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-019 IMMUNE CELL INFILTRATES IN NON-SMALL CELL LUNG CANCER AND INTERLEUKIN-22 EXPRESSION

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Background: In non-small cell lung cancer (NSCLC) the TNM staging remains standard for prognostic assessment and therapy decisions. Nevertheless, stage-specific outcomes vary significantly, indicating a need for additional prognosticators. Lymphocytic infiltrates are found in 6-11% of NSCLC patients and associated with a significant increase in disease-free and overall survival (OS). We now want to assess T cells and PD-L1$^+$ cells in tissue microarrays (TMAs) cored at the invasive margin (IM) and tumor center (CT) via multispectral imaging. We asked the question of their link to interleukin-22 (IL-22). Furthermore, we want to elucidate the role of IL-22 in prognosis, therapy response and recurrence. **Method:** TMAs were generated from formalin-fixed paraffin embedded tissue of 89 curatively resected patients with stage IA-IIIA NSCLC. TMAs included each 3 cores from CT and IM, selected from areas with the most dense lymphocytic infiltrates. Immunolabelling followed mIHC technique for PD-L1, CD8, CD3, FoxP3, CD163 and Cytokeratin. IL-22 expression was analyzed by immunohistochemistry (double-staining: IL-22, CD3). **Result:** We could show that the ratio of CD8$^+$ cells in CT compared to IM is significantly higher in stage I than stage II/III NSCLC. A similar pattern was seen for CD3$^+$, but not for ratios of PD-L1$^+$, FoxP3$^+$ or CD163$^+$. Based on the CT/IM ratios of CD8$^+$ and PD-L1$^+$ we established an ‹Invasive Score› ranging from 0–2. A Score of 0 (low CD8, low PD-L1) had a median OS of 45 months. A score of 1 (high CD8 or PD-L1) had a median OS of 53 months. A score of 2 (high CD8 and PD-L1) had a 62% survival rate at 72-months: Combining the rate of CD8 T cell infiltrates with PD-L1 positivity in the tumor is a stronger predictor for survival than one based only on CD8 CT/IM ratio. We will now combine these results with the IL-22 expression and present the respective progression free and OS data. **Conclusion:** Multispectral assessment of CD8 and PD-L1 performed on "hot-spots" NSCLC does show a clear correlation with clinical outcome: A tumor-controlling immune response appears to be associated with the permeability of the tumor to CD8 cells. This is consistent with other reports that immune infiltrates are associated with improved outcome. Current studies are seeking to verify these findings in a larger cohort of patients with NSCLC. *Authors Stump and Reu contributed equally to this study. Supported by the Harder Family, Lynn and Jack Loacker, Robert W. Franz, Wes and Nancy Lematta, the Murdock Trust and Providence Medical Foundation.

Keywords: NSCLC, imaging, Immune Infiltrates

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-020 AUTOANTIBODY PROFILES OF CANCER-TESTIS GENES IN NON-SMALL CELL LUNG CANCER

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Background: Cancer testis (CT) genes are expressed in various types of cancer but otherwise restricted to normal tissues of testis and placenta. Several CT genes have shown to encode immunogenic proteins that are able to induce an anti-tumour response in cancer patients. The presence of autoantibodies towards expressed CT proteins could indicate which CT proteins that are more suitable for immunotherapeutic interventions, as these are recognized by the patient´s immune system. **Method:** Suspension bead arrays (Luminex) were used to analyse the presence of autoantibodies towards expressed CT proteins in plasma samples from patients with non-small cell lung cancer (NSCLC). The technology enables to screen for autoantibodies in minute amount of patient plasma. Protein fragments with an average length of 80 amino acids, produced within the Human Protein Atlas, were coupled to unique beads, allowing multiplex analysis of 244 different autoantibodies towards antigens representing 198 unique genes in each sample. The primary sample set included 51 samples from 34 individuals taken before radiation therapy and 17 samples taken after radiation therapy. Longitudinal plasma samples taken during radiation therapy were available for most individuals resulting in a total of 89 samples. **Result:** Of 198 analysed CT genes, autoantibodies against antigens representing 25 genes were detected in at least one of the 51 samples from the primary study set. The autoantibody detection ranged from five different autoantibodies in two individuals to no detected autoantibodies in seven individuals. Among those individuals with samples available both before and after radiation therapy (n=13), the autoantibody profiles were not altered by the treatment. Three individuals however showed autoantibodies towards one additional protein in the sample taken after radiation therapy compared to the sample before radiation. In two individuals, autoantibodies detected towards one protein in the sample taken before radiation were not detected in the sample taken after radiation. Unsupervised hierarchical clustering with 25 detected autoantibodies and all 89 samples showed that samples from the same individual cluster based on the autoantibodies´ profile. There was no apparent association of autoantibody profiles with clinical parameters (histology, gender, age, stage). However, patients with detected autoantibodies showed a longer overall survival than patients without autoantibodies. **Conclusion:** This study provides a first comprehensive analysis of autoantibody detection against antigens representing 198 CT genes. Among the identified autoantibodies only AKAP4 has been reported previously in NSCLC. The individual autoantibody profiles showed only minor differences between samples taken before, during and after radiation therapy.

Keywords: autoantibodies, cancer-testis genes, Immunotherapy

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-021 MULTIPLEX IMMUNE PROFILING IDENTIFIES PROGNOSTIC IMPORTANCE OF THE SPATIAL CO-LOCALIZATION OF IMMUNE CELLS IN NSCLC

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Background: There is an increasing impact of the immunotherapy in the treatment of NSCLC. The accurate characterization of immune cell infiltrates in the *in situ* environment of cancer is regarded to be of major importance to predict prognosis and to guide therapy. The aim of this study was to perform a multi-marker characterization of immune cells and to evaluate their spatial distribution patterns with regard to patient survival. **Method:** A tissue microarray including 55 cases of non-small cell lung cancer (NSCLC) was used to perform multiplex immuno-fluorescent staining with antibodies against CD8, CD20, CD4, FoxP3, CD45RO and pan-cytokeratin (Opal, Perkin Elmer). The staining was digitalized by a multispectral imaging system (Vectra 3, PerkinElmer). Single cell marker expression profiles and their tissue coordinates were used to evaluate cell quantity and spatial distribution patterns. The data were validated with conventional immunohistochemical staining on consecutive sections. **Result:** Based on the co-expression of single immune markers we determined eight different classes of immune cells. While CD8+ single positive cells are evenly distributed in the stroma and tumor cell compartment, CD20+ and CD4+ cells were predominantly located in the stroma. Based on the immune cell subtypes we could define patients with a predominant B-cell response and patient with dominating T-cell infiltrates. No statistically significant impact on survival was found with regard to the abundance of immune cell subpopulations. When the spatial relation of stromal CD8+ regulatory T cells (CD8+FoxP3+) was considered, the shorter distance (< 20 µm) between CD8+FoxP3+ cells and tumor cells was associated with shorter survival (median 34 vs. 76 month, HR=2.6, 95%CI 1.3-6.8, log-rank p<0.01). **Conclusion:** The fluorescence multiplexed IHC technique provides a multi-marker characterization and spatial information for single cell-level analysis of immune infiltration patterns. Spatial localization of CD8+ regulatory T lymphocytes in relation to cancer cells is associated with overall survival in NSCLC.

Keywords: Digital Pathology, Tumor immunology, multiplex microscopy

P1.07-022 ROUTINE PD-L1 IMMUNOHISTOCHEMISTRY TESTING BY 22C3 IN A CANADIAN REFERENCE TESTING CENTRE

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Background: Immunohistochemical testing for PD-L1 expression is increasingly used as a predictive biomarker for anti PD-1/PD-L1 immunotherapies in non-small cell lung cancer (NSCLC). We report here the experience of population-based PD-L1 testing using the 22C3 antibody in the routine clinical practice of a large regional reference pathology laboratory. **Method:** PD-L1 testing was performed by the PD-L1 immunohistochemistry (IHC) 22C3 PharmDx assay (Agilent) using a Dako Link48 autostainer, according to the manufacturer's instructions. Testing was performed on (1) all biopsies and resections for NSCLC performed at University Health Network (UHN) and partner hospitals between August 1, 2016 and March 31, 2017; (2) all cases of NSCLC referred from external sources for EGFR/ALK testing; and (3) cases of pulmonary squamous cell carcinoma referred in specifically for PD-L1 testing. PD-L1 IHC was also performed retroactively on archived UHN cases upon request by oncologists, dating from January 1, 2013. Tumour Proportion Scores (TPS) were reported in three categories (no expression, <1%; low expression, 1-49%; and high expression, ≥50%). **Result:** A total of 2027 PD-L1 IHC were performed on specimens from 1814 patients, of which 110 (5.4%) were reported as indeterminate, mostly due to insufficient tumor cellularity. Indeterminate results were more frequent in biopsy (6.4%) vs. resection (2.7%) specimens. For the remaining 1917 evaluable tests, proportions in each TPS category were: <1% (42.3%); 1-49% (28.5%); ≥50% (29.3%). In 1482 tests with known *EGFR* mutation status, *EGFR*-mutated tumors (n=296) demonstrated lower rates of PD-L1 expression [TPS <1% (51.7%); 1-49% (29.4%); ≥50% (18.9%); P<0.01]. No statistically significant difference in PD-L1 expression was detected in *ALK*-rearranged tumors (n=29). Of 100 patients with successful PD-L1 staining in both a biopsy and paired resection specimen, 57/100 (57%) demonstrated concordant TPS categories in both specimens. Only 22/49 (44.9%) biopsies with TPS<1% showed TPS<1% in the resection, while 26/49 (53.1%) and 1/49 (2.0%) showed TPS 1-49% and ≥50%, respectively. Of biopsies with TPS 1-49%, 17/29 (58.6%) were concordant in the resection, while 5/29 (17.2%) and 7/29 (24.1%) showed TPS <1% and ≥50%, respectively. Among biopsies with TPS≥50%, 18/22 (81.8%) were concordant in the resection, while 4/22 (18.2%) showed TPS 1-49% in the resection. **Conclusion:** In our population-based study, PD-L1 expression in NSCLC using the 22C3 antibody demonstrated similar prevalence as reported in clinical trials. *EGFR* mutated but not *ALK* rearranged tumors were associated with lower PD-L1 expression. Intra-tumoral heterogeneity of PD-L1 expression may result in its under-estimation in biopsy specimens compared to paired resection specimens.

Keywords: PD-L1, Immunotherapy, NSCLC

P1.07-023 THE CORRELATION BETWEEN B7-H4 EXPRESSION AND SURVIVAL OF NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH NIVOLUMAB

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Background: In spite of the results achieved by nivolumab in advanced non-small cell lung cancer (NSCLC), reliable predictive factors are still needed, and even the expression of the programmed death protein 1 ligand (PD-L1) has a limited role in predicting benefit from this agent. Our aim was to determine whether the expression of other molecules involved in immune response might be associated with outcomes of NSCLC patients receiving nivolumab. **Method:** This retrospective study included patients treated with nivolumab for advanced NSCLC (Nivolumab Cohort). Response rate (RR) and progression-free survival (PFS) were assessed by response evaluation criteria in solid tumors (RECIST) v 1.1 and immune-related response criteria (irRC). Available tumor specimens were analyzed by immunohistochemistry (IHC) in order to determine the expression of PD-L1, PD-1 ligand 2 (PD-L2), PD-1, B7-H3, and B7-H4. The possible correlations between IHC findings and clinical outcomes were explored. Additionally, the meaningful biomarkers observed in the Nivolumab Cohort were assessed in a population of NSCLC patients treated with platinum-based chemotherapy (Chemotherapy Cohort) and the results from the two cohorts were compared in order to determine whether the administered treatment played a role in our observations. **Result:** The Nivolumab Cohort included 46 evaluable patients. The following proportions of positive IHC samples were observed: PD-L1=15.22%; PD-L2= 17.39; PD-1= 67.39%; B7-H3= 13.04%; B7-H4= 36.96%. At univariate analysis, patients expressing B7-H4 ≥1% had significantly lower PFS compared to those patients with B7-H4 <1% according to RECIST (1.67 vs. 2.00 months; p= 0.026) and irRC (1.73 vs. 2.17 months; p= 0.039), as well as a numerically lower overall survival (OS; 4.37 vs. 9.83 months; p= 0.064). At multivariate analysis for OS, PD-L1 ≥1% had favorable effect (HR= 0.29; p= 0.027), while B7-H4 ≥1% had unfavorable effect (HR= 2.98; p= 0.006). No other correlation was observed in this cohort. Within the Chemotherapy Cohort (n=27), no significant correlation between IHC findings and response or survival was observed. At the multivariate analysis including both cohorts, a statistically significant interaction was observed between OS and the combined effect of B7-H4 expression and treatment (p= 0.048), favoring nivolumab in B7-H4 <1% patients (HR= 0.60) and chemotherapy in B7-H4 ≥1% patients (HR= 0.67). **Conclusion:** A meaningful negative correlation between B7-H4 expression and outcomes was observed with nivolumab, but not with chemotherapy. In spite of a relatively small patient population, our results strongly encourage further studies exploring the potential role of B7-H4 as predictor of outcomes during treatment with nivolumab.

Keywords: survival, B7-H4, Nivolumab

P1.07-024 ISEND MAY PREDICT CLINICAL OUTCOMES FOR ADVANCED NSCLC PATIENTS ON PD-1/PD-L1 INHIBITORS BUT

Not Chemotherapies or Targeted Kinase Inhibitors

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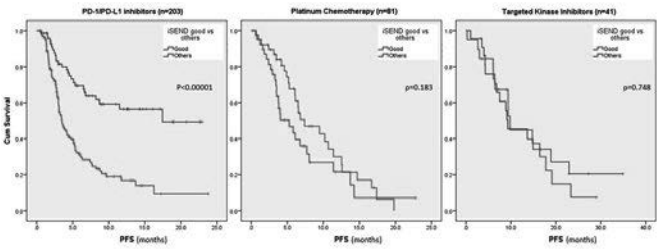
Background: We have shown that the iSEND model may be predictive of clinical outcomes for advanced NSCLC (aNSCLC) patients receiving nivolumab but little is known of its potential performance for patients on other PD-1/PD-L1 inhibitors (PD-1/PD-L1i), chemotherapies (Chemo) or Targeted Kinase Inhibitors (TKIs). **Method:** We evaluated clinical outcomes of 325 aNSCLC patients who received second-line PD-1/PD-L1i (nivolumab, pembrolizumab, or atezolizumb, n=203), first-line platinum followed by maintenance (Chemo, n=81), and TKIs (erlotinib, afatinib, or crizotinib, n=41). As described in our previous reports, the iSEND model (Sex, ECOG [Performance status], NLR [Neutrophil-to-Lymphocyte Ratio] & DNLR [Delta NLR = NLR after treatment - pretreatment NLR]) was developed. We stratified each treatment group by iSEND and compared progression free survivals (PFS) and clinical benefit rates (CBR) at 12+/-2 weeks in the iSEND Good vs. the iSEND Others (Intermediate and Poor). **Result:** Median follow-up was 9.5 (95% CI: 7.1-11.9), 11.7 (95% CI: 4.5-18.9) and 9.3 months (95% CI: 4.5-14.2), respectively for PD-1/PD-L1i, Chemo, and TKIs groups. In the PD-1/PD-L1i group, PFS was better in the iSEND Good than the iSEND Others with a median of 17.4 vs. 5.1 months, (HR: 0.32, 95% CI, [0.20-0.50], p<0.0001) (Figure 1). In contrast, PFS was not better in the iSEND Good in Chemo (HR, 0.69, 95% CI, [0.42-1.20], p=0.19) or TKIs (HR, 0.89, 95% CI, [0.43-1.84], p=0.75). The area under the curves (AUC) of the iSEND for CBR at 12+/-2 weeks for aNSCLC patients treated with PD-1/PD-L1i was 0.72, (95% CI: 0.65-0.79, p<0.0001). The AUCs of iSEND for CBR in Chemo and TKIs were not significant.
Figure 1. Kaplan-Meier curves for PFS in PD-1/PD-L1i, Chemo, and TKIs stratified by iSEND Good vs. Others



Conclusion: In our single-institution retrospective cohort, the iSEND model showed a predictive potential for advanced NSCLC patients treated with PD-1/PD-L1i but not for those treated with Chemo or TKIs

Keywords: Predictive, PD-1 inhibitor, Clinical outcome

P1.07-025 CORRELATING ISEND AND TUMOR MUTATION BURDEN (TMB) WITH CLINICAL OUTCOMES OF ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) PATIENTS ON NIVOLUMAB

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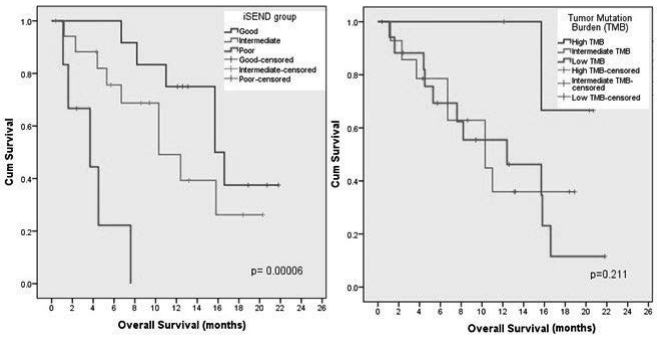
Background: We developed an algorithmic model namely, the iSEND (Sex, ECOG performance status, NLR [Neutrophil-to-Lymphocyte Ratio] & DNLR [Delta NLR =NLR posttreatment - pretreatment NLR]) to predict the clinical outcomes of aNSCLC patients receiving nivolumab. Performance of the iSEND has not been compared with other potential immunotherapy biomarkers like TMB. **Method:** We identified 36 aNSCLC patients who received nivolumab after platinum with commercial TMB reports. As described in our previous reports, the iSEND was used to categorize patients into good, intermediate, and poor groups. 36 matched patients were also categorized into high TMB: ≥ 20 m/Mb (mutations per megabase), intermediate TMB: 6-19 m/Mb, and low TMB: ≤5 m/Mb. We evaluated progression free survival (PFS), and overall survival (OS). Performances of the iSEND and TMB were correlated with clinical benefit at 12+/-2 weeks by receiver operating characteristic (ROC) curves. **Result:** The median follow-up was 18.4 months (95% CI: 10.1-26.7). There were 16 deaths. The number of patients from iSEND good, intermediate, and poor groups were 12 (33%), 18 (50%), and 6 patients (16%), respectively. The median overall survivals of iSEND good, intermediate, and poor groups were 15.7 (10.8-20.58), 10.3 (4.8-15.7), and 3.7 (0-7.8) months, respectively (p=0.00006). The median overall survivals for high, intermediate, and low TMB groups were unreached, 10.3 (4.7-15.9), and 12.4 (7.1-17.7) months, respectively. (p=0.211, Figure 1) The area under ROC curve of the iSEND for clinical benefit at 12+/-2 weeks was 0.733 (p=0.025, 95% C.I.: 0.56-0.90). Four intermediate iSEND patients who had OS less than 6 months had low TMBs.
Figure 1. Kaplan-Meier curves for Overall Survival by iSEND model and TMB



Conclusion: From a limited retrospective single institutional database, iSEND characterized the clinical outcomes of aNSCLC patients on nivolumab well and high TMB correlated with better outcomes. A larger cohort validation is encouraged to explore the mutual supplementary benefit for improved performance.

Keywords: Tumor mutation burden, biomarker, Nivolumab

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-026 PREDICTING TUMOR MUTATIONAL BURDEN (TMB) AND TUMOR NEOANTIGEN BURDEN (TNB) OF EAST ASIAN ANSCLC PATIENTS BY A TARGETED GENOMIC PROFILING

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Background: High tumor mutational burden (TMB) and High tumor neoantigen burden (TNB)is an emerging biomarker of sensitivity to immune checkpoint inhibitors. However, analysis of TMB and TNB by Whole Exome Sequencing (WES) is complicated and highly cost. Recent studies have also shown that TMB can be accurately measured in smaller gene assays. We aim to find and validate such a panel of genes to predict both TMB and TNB, as well as benefit to anti-PD-(L)1 blockade in East Asian aNSCLC patients. **Method:** We compare TMB and TNB measured by a Targeted Genomic Profiling (TGP, targeting 811 genes) assay and by WES using the data from previously publication including efficacy data of patients treated with Pembrolizumab. Then, we validated this 811 gene panel in Chinese aNSCLC patients (n=27), and analysis the correlation between TMB and TNB. Comparisons of TMB were also made to a cohort of eight aNSCLC patients obtained from tumor tissue and ctDNA. **Result:** We first sought to determine whether TMB, as measured by a TGP assay targeting 811 genes could provide an accurate assessment of whole exome. We performed targeted TGP and WES on the same biopsy specimen for a cohort of 27 NSCLC patients. In this cohort, median TMB was 5.3/Mb and median TNB was 2.7/Mb. We found that the tumor mutation burden calculated by these two methods was highly correlated (R2=0.71, p<0.05). We use the cutoff point of 11/Mb of TMB and 3/Mb of TNB respectively, 5/27(18.5%) and 8/27(29.6%) patients were identified with high TMB and high TNB, respectively. MMR genes were mutated only in high TMB patients (one in MSH2 and another in PMS2). Then, using the efficacy data from previous publication, including aNSCLC patients (n=34) treated with pembrolizumab, the AUC estimate for response was 0·80 of TGP and 0.84 of WES, respectively. For eight patients with paired tumor tissue and ctDNA, the TMB calculated from tumor tissue and ctDNA was also highly correlated (R2=0.80, p<0.05). Further analyses of ctDNA analyses in context of patient and trial outcomes are in progress.

Conclusion: These results show that TGP (targeting 811 genes)can accurately assess TMB compared with sequencing the whole exome and this finding will be clinically actionable. Using this targeted NGS panel, we find TMB is highly correlation with TNB, which also imply the accuracy of this panel. Finally, We may also use ctDNA to evaluate TMB by a non-invasive method.

Keywords: tumor mutational burden (TMB), tumor neoantigen burden (TNB), a Targeted Genomic Profiling (TGP, targeting 811 genes)

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-027 PD-L1 EXPRESSION ANALYSIS IN AFRICAN AMERICAN (AA) AND HISPANIC LUNG CANCER PATIENTS AT A MINORITY-BASED ACADEMIC CANCER CENTER

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Background: PD-L1 testing has been incorporated into the standard treatment paradigm given recent immunotherapy approvals for metastatic lung cancer (LC). Minority populations are notoriously under-represented in large immunotherapy clinical trials. Thus, we examined PD-L1 expression profiles in a minority-based academic cancer center. Among 989 patients with newly diagnosed LC at Montefiore Medical Center (MMC) from 2014-2015, 330 (33%) were AA and 195 (20%) were Hispanic. **Method:** Retrospective chart review was conducted to determine PD-L1 expression patterns between 1/1/14-6/19/17 at MMC. PD-L1 testing was performed using 22C3pharmDx IHC and positivity was defined as >/=1%. Chi-squared statistical analysis was performed with SPSS. All statistical tests were two-sided. **Result:** We identified 92 patients who had PD-L1 testing, with a median age of 66. Based on race, 43 (46.7%) were AA, 20 (21.7%) were White, 20 (21.8%) were Other and 9 (9.8%) were race unknown. Based on ethnicity, 27 (29.3%) were Hispanic, 54 (58.7%) were non-Hispanic and 11 (12%) were ethnicity unknown. Adenocarcinoma was the dominant histology (61%). Nine (9.8%) were EGFR mutant and 1 (1.1%) had an ALK rearrangement. Fresh tissue was used in 50% of cases. PD-L1 TPS >50% was found in 30 (33%), 1-49% in 22 (24%) and <1% in 39 (42%). At time of this analysis, 29 (32%) had received immunotherapy. In the racial analysis, 9 were excluded due to unknown race. Amongst the 43 AA patients, 28 (65%) were PD-L1 positive, and 15 (35%) were negative compared to the 40 non-AA patients which were PD-L1 positive in 20 (50%) and negative in 20 (50%). AAs trended toward increased PD-L1 positivity compared to non-AAs although it was not significant (p=0.163). In the ethnicity analysis, 11 were excluded due to unknown ethnicity. Amongst the 27 Hispanic patients, 11 (40.7%) were PD-L1 positive and 16 (59.3%) were negative compared to the 54 non-Hispanic patients who were PD-L1 positive in 37 (68.5%) and 17 (31.5%) were negative. Analysis suggests there is a negative association between Hispanic ethnicity and positive PD-L1 testing (p=0.016). **Conclusion:** This is the first known report on PD-L1 expression in AA and Hispanic patient populations. We found that Hispanics had significantly more PD-L1 negative cases compared to non-Hispanics. Correlation with response to immunotherapy is ongoing. Continued research and focus on minority populations will further help to narrow known health disparities based on race and ethnicity.

Keywords: PD-L1, race and ethnicity, Immunotherapy

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-028 DETERMINATION OF SOLUBLE PD-L1 AS A POTENTIAL BIOMAKER FOR ANTI-PD(L)1 THERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: PD-L1 has been established as a predictive marker for anti-PD(L)1 treatment, although patients negative for PD-L1 may also respond to those treatments. Soluble PD-L1 (sPD-L1) in blood has been described as prognostic factor in advanced NSCLC. To date, no evidence of efficacy of anti-PD(L)1 treatment according to sPD-L1 has been reported. The objective of this study is the correlate the efficacy of anti-PD(L)1 treatment according to sPD-L1 in our patients. **Method:** Baseline sPL-L1 levels were prospectively determined in pretreated advanced NSCLC patients receiving anti-PD(L)1 treatment. sPD-L1 levels (high (H) and low (L)), were calculated based on the median value of sPD-L1, and those values were correlated with OS and PFS for all patients and for according to histology. sPD-L1 levels were also correlated with leucocyte and platelet count and PD-L1 expression in tumor. **Result:**

	sPD-L1			
	OS (m)		PFS (m)	
	H	L	H	L
Adenocarcinoma (n: 19)	10.3 (5.3-17.4)	14.3 (10.1-18.5)	5.8 (0.9-10.7)	8.7 (4.0-13.4)
	P 0.7		P: 0.7	
Squamous cell carcinoma (n: 11)	16.1 (7.5-24.8)	14.7 (9.4-20.0)	11.4 (2.5-20.3)	6.9 (3.2-10.7)
	P: 0.8		P:0.7	
All (n:30)	13.2 (9.2-17.2)	15.4 (12.0-18.9)	4.2 (0.4-7.9)	6.0 (0.6-11.3)
	P: 0.2		P: 0.5	

In patients with adenocarcinoma, a positive correlation was observed between sPD-L1 levels and monocyte count (R^2:0.44; *p: 0.0008*), and with the ratio platelet/lymphocyte (R^2:0.55; *p<0.0001*). In all NSCLC patients and squamous cell carcinoma, a positive correlation was observed between sPD-L1 levels and neutrophil count (R^2:0.42; *p: 0.002* and R^2:0.59; *p: 0.0025* respectively). No correlation between sPD-L1 level and PD-L1 expression in tumor was observed (n: 22 patients; p: 0.9065) **Conclusion:** Although no significant differences in OS or PFS were observed according to sPD-L1, a trend to a better OS was seen in NSCLC patients with low sPD-L1, especially in patients with adenocarcinoma. Prospective studies analyzing sPD-L1 levels and other PD-L1 variants are needed to find possible new biomarkers for anti-PD(L)1 treatments in NSCLC.

Keywords: Immunotherapy, Biomarkers, NSCLC

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-029 CORRELATION STUDY BETWEEN PLASMA SPD-L1 AND THE EFFICACY AND PROGNOSIS OF PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: To investigate the relationship between the expression of soluble programmed death-ligand 1(sPD-L1) and the clinical features of patients with non-small cell lung cancer (NSCLC). To observe whether the dynamic changes of soluble PD-L1 before and after treatment is related to the clinical efficacy and EGFR gene status. **Method:** 176 patients who were newly diagnosed as NSCLC by pathology in Shanxi Cancer Hospital from April 2014 to January 2017 were enrolled, 12 cases of benign lung lesions.There were 73 healthy people selected as control group. The levels of soluble PD-L1 in plasma of three groups were detected by ELISA, the expression of sPD-L1 before and after treatment was measured and EGFR gene was detected by ARMS in lung cancer group,observing the correlation between the changes of sPD-L1 and clinical efficacy and EGFR gene status. The patients were followed up to analyze the relationship between sPD-L1 expression and prognosis. **Result:** The expression of soluble PD-L1 in plasma for patients with non-small cell lung cancer was higher than that in benign lung disease group and healthy control group (3.18±2.04ng/ml, 1.36±1.02ng/ml and 1.67±0.38ng/ml respectively. P<0.05). The expression of sPD-L1 was not correlated with gender, age, smoking status, pathological type, tumor stage and metastasis (P>0.05).The level of soluble PD-L1 in patients with disease controlled after 2, 4 cycles treatment was lower than that before (P<0.05). The expression of soluble PD-L1 in progression disease group is higher than that in disease controlled group with no statistically significant (P>0.05). The level of soluble PD-L1 in patients with EGFR mutation was significantly higher than that in wild type (P=0.001). The level of soluble PD-L1 was lower than that before treatment for patients with EGFR mutation (2.46ng/ml vs1.69ng/ml,P=0.028), but not for wild type. The OS was higher in the low expression of soluble PD-L1 group (28.0m vs 12.0m, P <0.001), but there was no significant difference in PFS. **Conclusion:** The expression of plasma soluble PD-L1 in patients with NSCLC was higher than that in healthy and benign lung disease patients, the dynamic changes of soluble PD-L1 were related to the clinical efficacy, the mutation status of EGFR affected the expression of soluble PD-L1 in patients with NSCLC, patients with high expression of soluble PD-L1 may have a poor prognosis, indicating that soluble PD-L1 may be used as a molecular marker for predicting the efficacy and prognosis of patients with NSCLC.

Keywords: non-small cell lung cancer, EGFR, Soluble programmed death-ligand 1

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-030 PROGNOSTIC IMPACT OF PD-L1 EXPRESSION IN CORRELATION WITH HLA CLASS I EXPRESSION STATUS IN ADENOCARCINOMA OF THE LUNG

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Background: Programmed death-ligand 1 (PD-L1) and human leukocyte antigen (HLA) class I, expressed on tumor cells are important roles in cancer immunity. The current study was conducted to assess prognostic impact of PD-L1 status in correlation with HLA class I status in lung adenocarcinoma. **Method:** A total of 166 patients with completely resected lung adenocarcinoma were retrospectively reviewed. PD-L1 expression on tumor cells was evaluated with immunohistochemistry, in correlation with several clinicopathological and molecular features including HLA class I expression on tumor cells. **Result:** Twenty-one patients (12.7%) had tumor with positive PD-L1 expression (percentage of tumor cells expressing PD-L1, ≥ 5%), and the incidence was higher in smokers with higher smoking index and in poorly differentiated tumor. There was no significant correlation between HLA class I expression and PD-L1 expression. PD-L1 positivity provided no prognostic impact for all patients, but seemed to be correlated with a poor prognosis among patients with normal HLA class I expression (p=0.145). When only p-stage I patients were analyzed, PD-L1 positivity was a significant factor to predict a poor survival (5-year survival rate, 66.7% versus 85.9%; P=0.049), which was enhanced in tumor with normal HLA class-I expression (P=0.029) but was not evident in tumor with reduced HLA class I expression (P=0.552) **Conclusion:** The prognostic impact of PD-L1 expression on tumor cells in resectable lung adenocarcinoma was distinct according to HLA class I expression on tumor cells.

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-031 AUTOANTIBODIES ASSOCIATED WITH RISK OF SUBCLINICAL AUTOIMMUNITY AND IMMUNE-RELATED ADVERSE EVENTS FROM CHECKPOINT INHIBITOR THERAPY

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Background: Immune checkpoint inhibitors have emerged as a highly promising treatment option for advanced lung cancer. However, a minority of patients develop unpredictable, potentially severe, and possibly permanent immune-related adverse events. We hypothesized that pre-existing subclinical autoimmunity predisposes patients to these toxicities. **Method:** We collected serum from patients treated with immune checkpoint inhibitors at multiple time-points: pre-treatment, 2-3 weeks, 6 weeks, 12 weeks, every 12 weeks thereafter, and at time of toxicity. We determined baseline and dynamic autoantibody profiles associated using an array panel of 125 antigens including nuclear, cytosolic, and tissue-specific antigens. Autoantibody levels between toxicity and no toxicity groups were compared using the quasi likelihood F test. **Result:** A total of 29 subjects were enrolled. Mean age was 69 years, 55% were women, and 83% had lung cancer. Immune-related adverse events occurred in 31% of cases as follows: pneumonitis (n=6), endocrinopathy (n=2), dermatitis (n=1). We also enrolled 11 healthy controls who underwent two blood draws 2-3 weeks apart. Across the entire cohort, there was substantial variation in baseline autoantibody levels. Patients receiving immunotherapy demonstrated a trend toward greater increase in autoantibody levels over time compared to the control group (*P*=0.23). In general, the greatest increases in autoantibody levels were noted among individuals with the highest baseline autoantibody levels. Broadly, elevated baseline levels of autoantibodies were associated with the development of immune-related adverse events, with 4 individual antibodies classically associated with systemic autoimmunity having significantly higher levels in the toxicity group (*P*<0.05). Immune-related adverse events were also more common among cases with greater post-treatment increase in antibody levels, with 10 individual antibodies having significant increases in the toxicity group (*P*<0.05). **Conclusion:** Subclinical autoimmunity occurs in a substantial proportion of patients with lung cancer and other malignancies. These clinically silent auto-antibodies may be associated with increased risk of immune-related adverse events from immune checkpoint inhibitor therapy.

Keywords: biomarker, immune-related adverse events, Immunotherapy

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-032 28-COLOR, 30 PARAMETER FLOW CYTOMETRY TO DISSECT THE COMPLEX HETEROGENEITY OF TUMOR INFILTRATING T CELLS IN LUNG CANCER

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Background: Defining the phenotypic, molecular and functional characteristics of tumor infiltrating leukocytes advances our understanding of how the immune system is defective in fighting cancer and may thus lead to the identification of new therapeutic targets to be exploited in the clinic. Considerable heterogeneity is found at the tumor site in terms of leukocyte populations and cellular subsets which may retain pro- or anti-cancer potential. Such heterogeneity can only be addressed by more powerful single cell technologies. **Method:** We used 30-parameter single cell

flow cytometry to define the memory differentiation, activation, tissue-residency, exhaustion and transcription factor profile of millions of single T cells infiltrating human lung adenocarcinomas. **Result:** We revealed that PD-1^{high} exhausted T cells were enriched at the tumor site compared to the peripheral blood or to the non-tumoral portion of the lung from the same patient, were mainly confined to the CD69+ tissue-resident memory compartment and expressed high levels of the transcription factor T-bet and the activation marker HLA-DR. Conversely, these PD-1^{high} cells were nearly absent from the early-differentiated, circulating memory compartment identified by CCR7+ expression. Bona fide naïve T cells, as identified by the simultaneous expression of 5 markers, were virtually absent at the tumor site. The exhausted T cells also lacked markers of terminally-differentiated senescent T cells, which in turn are CD57+ T-bet^{low}Eomes^{high}, thereby suggesting that exhaustion and senescence are divergent differentiation states. **Conclusion:** We anticipate that such high-content single cell profiling will identify patient-specific subpopulations capable to correlate with disease progression and clinical/metabolic parameters.

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-033 DIFFERENTIAL EXPRESSION OF IMMUNE INHIBITORY MARKERS IN ASSOCIATION WITH THE IMMUNE MICROENVIRONMENT IN RESECTED LUNG ADENOCARCINOMAS

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Background: Similar to programed death ligand 1 (PD-L1), indoleamine 2,3-Dioxygenase 1 (IDO1) is known to exert immunosuppressive effects and be variably expressed in human lung cancer. However, IDO1 expression has not been well-studied in lung adenocarcinoma (ADC). **Method:** PD-L1 and IDO1 expression were evaluated in 261 resected ADC using tissue microarrays and H-scores (cutoff 5). We compared IDO1 with PD-L1 expression in association with clinical features, tumor-infiltrating lymphocytes (TILs), HLA class I (β-2 microglobulin; B2M) expression, molecular alterations, and patient outcomes. **Result:** There was expression of PD-L1 in 89 (34.1%) and IDO1 in 74 (28.5%) cases, with co-expression in 49 (18.8%). Both PD-L1 and IDO1 were significantly associated with smoking, aggressive pathologic features, and abundant CD8+ and T-bet+ (Th1 marker) TILs. PD-L1 expression and abundant CD8+ were inversely associated with a loss of B2M membranous expression (p=0.002 and p<0.001, respectively). Compared to PD-L1+/IDO1+ and PD-L1+ only cases, significantly fewer IDO1+ only cases had abundant CD8+ and T-bet+ TILs (p<0.001, respectively). PD-L1 expression was significantly associated with EGFR wild-type (p<0.001) and KRAS mutants (p=0.021), whereas there was no difference in IDO1 expression between different molecular alterations. As for survival, PD-L1 was significantly associated with decreased progression-free (PFS) and overall survival (OS), while IDO1 was associated only with decreased OS. Interestingly, there was a significant difference in the 5-year PFS and OS (p=0.004 and 0.038, respectively), where cases without PD-L1 or IDO1 expression had the longest survival, and those with PD-L1 alone had the shortest survival. **Conclusion:** While PD-L1 +/- IDO1 expression is observed in association with B2M expression, CTL/Th1 microenvironments, EGFR wild-type, and KRAS mutations, isolated IDO1 expression does not demonstrate these associations. These results suggest that IDO1 may serve a distinct immunosuppressive role in ADC. Thus, blockade of IDO1 may represent an alternative and/or complementary therapeutic strategy to reactivate anti-tumor immunity. Additional study to examine a larger number of immunoregulatory markers is ongoing.

Keywords: PDL1, Tumor immunology, lung cancer

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-034 PRETREATMENT NEUTROPHIL & PLATELET COUNT AS A PREDICTOR FOR UNFAVORABLE CLINICAL OUTCOME IN NON-SMALL CELL LUNG CANCER (NSCLC)

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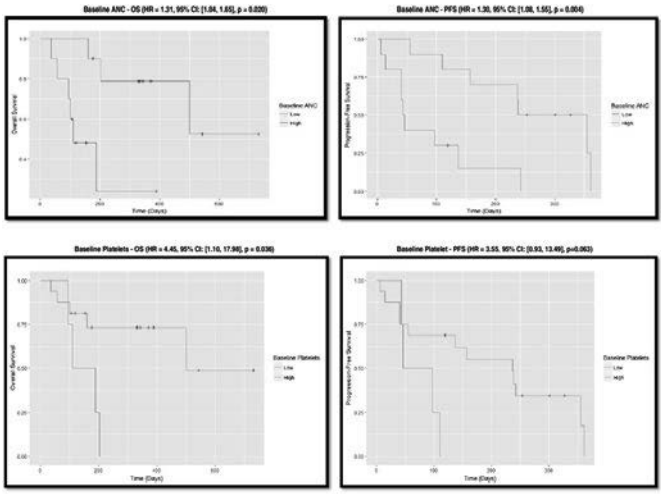
Background: The importance of tumor immune microenvironment in disease outcomes has already been established. We can speculate that markers present in patients' complete blood count (CBC) such as absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and absolute monocyte count (AMC) could potentially help predict clinical benefit. In addition, given the recently discovered T cell inhibitory role of platelets, we hypothesized that increased platelet counts may lower the efficacy of T cell mediated immune checkpoint inhibitors. Here, we explored how well the information obtained from the simple non-invasive peripheral blood CBC can predict clinical outcome to immunotherapy in NSCLC. **Method:** ANC, ALC, AMC, neutrophil lymphocyte ratio (NLR) and platelet values were collected for twenty NSCLC patients at two times points; pretreatment (t1) & approximately 2-3 weeks after first treatment (t2). Response to immune checkpoint inhibitors based on RECIST criteria (response rate (RR) and clinical benefit rate (CBR)), progression-free survival (PFS) and overall survival (OS) were examined. Cox regression analyses were performed for baseline and delta (t2-t1) CBC values while controlling for various other clinical variables. **Result:** Baseline ANC and AMC were significantly associated with both worse PFS and OS, respectively (ANC; HR= 1.30, p=0.004 & HR= 1.31, p=0.020, AMC; HR= 13.75, p=0.030 & HR= 38.14, p=0.042). Platelets showed significance for only worse OS (HR= 4.45, p=0.036). Delta hematological profiles did not show any significant differences in clinical outcome. In multivariate analyses adjusting for clinical variables, ANC remained as an independent predictor of unfavorable PFS. None of the above variables examined were predictive of RR or CBR.



Conclusion: Elevated pretreatment ANC appears to strongly predict shorter PFS and OS in patients with NSCLC treated with immunotherapy. Pretreatment platelets greater than 400K was linked with poor survival outcome. Further studies with a larger cohort and serial CBC collection during treatment are warranted to validate this study.

Keywords: ANC, platelets, immunotherapy

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-035 LYMPHOCYTES AND NEUTROPHILS COUNT AFTER TWO CYCLES AND TTF1 EXPRESSION AS EARLY OUTCOME PREDICTORS DURING IMMUNOTHERAPY

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Background: Non-small cell lung cancer (NSCLC) therapeutic paradigm has dramatically changed with immune checkpoint blockers. The unconventional response patterns seen in patients treated with immunotherapy (IT) make it difficult to differentiate patients who respond from non-responders early on in treatment; and biomarkers predicting clinical benefit are still lacking. As previously shown in melanoma, changes in absolute lymphocytes and neutrophils count (ALC and ANC) during IT (PD-1/PD-L1 inhibitors) may be related to response in NSCLC (Nakamuta *et al*, *Oncotarget* 2016). TTF1 expression has been associated with PD-L1 expression (Vieira *et al*, *Lung Cancer* 2016). We aimed to investigate TTF1 expression and changes in ALC and ANC after 2 cycles and their potential association with clinical outcomes to IT. **Method:** We enrolled 32 consecutive patients with advanced NSCLC treated with IT at Clínica Universidad de Navarra (Spain) since 2015. Radiological response was evaluated according to RECIST v1.1. The potential correlation between ALC and ANC changes during the first two cycles and response to treatment [disease control rate (DCR) vs progression] was evaluated using Student's T-test. Fisher's exact test was used to study the association between changes in ALC (<1,000 vs ≥1,000) and ANC (<4,000 vs ≥4,000) after 2 cycles and response to IT. TTF1 expression was correlated with IT response. Overall survival (OS) was assessed with Kaplan-Meier analysis and Log-rank test according to ALC and ANC. **Result:** TTF1 tumor expression in adenocarcinoma histology (n= 18) was significantly associated with response to IT (88% vs 45%, p= 0.03). Patients with ANC <4,000 after two cycles showed a longer median OS (NR vs 4.9 months; p=0.02). An ALC increase after 2 cycles was associated with DCR compared to progression (147 vs -155; p=0.05). ALC ≥1,000 after 2 cycles seemed to be more frequent among patients with TTF1+ tumors (82% vs 45%; p= 0.05) and among those experiencing DCR compared to progression (73% vs 58%; p=0.30). **Conclusion:** Our results show that ALC and ANC changes during IT and TTF1 expression may act as early predictors of clinical benefit in stage IV NSCLC patients treated with PD1/PD-L1 blockers. Our results warrant further investigation in larger series.

Keywords: lymphocytes, Immunotherapy, biomarker

P1.07-036 LC-HRMS METABOLOMICS PROFILING IN ADVANCED NSCLC TREATED WITH ANTI PD-1 AGENTS. METABOLIC FEATURES AT DIAGNOSIS AND AT RESPONSE EVALUATION

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Background: Non-small cell lung cancer (NSCLC) is one of the most common cancer types wolrldwide. In the metastatic setting, palliative approaches include chemotherapy and immunotherapy, including anti PD-1 agents, that have become a standard approach in second line, but unfortunately, except for immunohistochemistry of PD-L1, any markers have been established to predict which patients can benefit from anti PD-1 agents. Metabolomics, which is the profiling of metabolites in biofluids, cells and tissues, is applied as a tool for biomarker discovery. The platform more used nowadays is liquid chromatography-mass spectrometry (LC-MS). Our objective is to study blood metabolites of advanced NSCLC patients to establish a profile to differentiate patients with clinical benefit (B-P) or without benefit (NB-P, that is, progressive disease) to anti PD-1 therapy. **Method:** We have analysed by LC-HRMS of serum samples, performing an untargeted metabolomic analysis from advanced NSCLC before immunotherapy (n= 11 patients, vs 10 healthy controls), at the first radiological evaluation and at the progression. Reverse phase and HILIC chromatographic modes were applied to deal with highly polar as well as hydrophobic as required for untargeted metabolomics. For identification of potential biomarkers, we used in combination two independent variable selection techniques: principal component analysis and Student t test. **Result:** From the total of 11 patients, 6 had some clinical benefit (partial response or stable disease) and 5 experienced as best response a progressive disease. We observed differences in metabolic profile between patients with NSCLC & healthy controls and B-P & NB-P to anti PD-1 therapy. Six identified metabolites contributed most to the differentiating between B-P and NB-P **Conclusion:** There are different metabolomic phenotypes among patients B-P and NB-P to anti PD-1 therapy, so our data demonstrates the potential of metabolimics in identifying biomarkers of response to anti PD-1 agents in NSCLC. Further studies may validate a metabolomic signature to allow a prediction of clinical benefit in patients treated with anti PD-1 agents.

Keywords: metabolomics, anti PD-1, biomarker

P1.07-037 TESTING THE POSITIVE AND NEGATIVE IMMUNE CHECKPOINT ON PBMCS OF PATIENTS FROM INITIATORY TO TERMINATIVE TREATMENT OF ANTI PD-1 ANTIBODY

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Background: Recent approaches to malignant tumor have turned to immunotherapy which shows outstanding clinical efficacy, especially the agents of programmed death 1(PD-1) pathway. In this study, we try to find the relationshi between the clinical benefit and the change of immune biomarkers in peripheral blood monocular cells(PBMCs) by continuous testing. **Method:** Nineteen patients diagnosed with medium and advanced cancer received nivolumab 3mg/kg or pembrolizumab 2mg/kg intravenously, combined with chemotherapy in some cases, every two or three weeks until the disease is progression or the treatment is suspended due to unacceptable toxicity. We performed flow cytometry analysis of peripheral blood samples to test negative immune checkpoint molecules: PD-1, CTLA-4, TIM-3, LAG-3, BTLA, 2B4, VISTA, CD160, CD107a, Ki-67 and positive molecules: OX40, GITR, ICOS, CD137. Blood was collected before, during and after treatment. **Result:** Between Dec 22, 2016 and Jun 14, 2017, we collected blood samples from 19 patients and evaluated them every two cycles by RECICST 1.1. The objective responses rate(ORR) was 3/19(15.8%). Progressive disease(PD) was observed in two of these patients after two cycles of treatment. The rate of grade 3-4 adverse events related to anti-PD-1 agents was 2/19(10.5%), including interstitial pneumonia. Immune biomarker analysis demonstrated that negative biomarkers including LAG-3(P=0.027), 2B4(P=0.049), VISTA(P=0.035), CD160(P=0.037), and the positive one ICOS(P=0.030) showed variation before and after treatment. After immunotherapy, such inhibited molecules as BTLA and CD160 obviously higher expressions than others. Additionally, the proportions of CD4+T, CD8+T and NK might have been effects to the response of immunotherapy. **Conclusion:** The clinical benefit after the treatment with anti-PD-1 agents might be related to the change of expressions of other immune checkpoints, which may suggest the next therapy when patients get progressed. The low expressions of LAG-3, 2B4, VISTA, CD160 and the high expression of ICOS may be a good signal of the response of immunotherapy. Our study is ongoing and we still need a large amount of sample analysis and in-depth profiling.

Keywords: immune biomarkers, Immunotherapy, malignant tumor

P1.07-038 THE POTENTIAL CLINICAL APPLICATION OF COMPREHENSIVE GENOMIC PROFILING IN TARGETED THERAPY AND IMMUNOTHERAPY OF LUNG CANCER

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Background: The comprehensive genomic profiling (CGP) diagnosis initially designed for targeted therapy is finding its way in cancer therapy with immune checkpoint inhibitors. Besides the utility of identifying targets for precision therapy, CGP also measures the tumor mutational burden (TMB) and the microsatellite instability status (MSI), which both are associated with the response to PD-1 blockade immunotherapy. **Method:** Totally FFPE samples from 147 lung cancer patients (median age=58, male vs. female = 80 vs. 67) were subjected to comprehensive genomic profiling (CGP) assay consisting of 450 gene full exons and selected introns. We measured the mutational atlas of cancer related driver genes and calculated the tumor mutational burden (TMB) of total somatic substitutions and indels per megabase after filtering know driver mutations. The MSI status is determined by identifying and scoring multiple mononucleotide repeats which are instable comparing to matched normal control. **Result:** The oncogenic mutation profile of this cohort is consistent as reported with *EGFR* mutation (N=70, 47.6%), *KRAS* mutation (N=14, 9.5%), tyrosine kinase fusions (N=8, 5.4%) and *EGFR*/*KRAS* wildtype (N=55, 37.4%). We find that the patients with *KRAS* mutations have significantly high TMB values (median TMB = 10.6) compared to *EGFR* mutant patients (median TMB = 4.6; p=0.027). The *EGFR* mutation subset also showed statistically different TMBs comparing to *EGFR*/*KRAS* wildtype (median TMB = 8.4; p=0.034). The TK gene fusion subgroup displays intermediate TMB level at 6.5 with no significant difference to other groups. We also found that about 15% of *EGFR* wildtype lung patients have high TMB (>20) while only around 6% of *EGFR* mutation cohort exhibits high TMB. Approcimately 10% of the lung patients exhibits MSI-H status. In this cohort, three lung cancer patients with higher TMB showed good responses to PD1/PDL1 inhibitors, and consistently responded in multiple cycles. **Conclusion:** These results show that a comprehensive gene profiling (GCP) assay is informative for assisting two pillar cancer treatments targeted therapy and immunotherapy. We find that a sizable portion of lung cancer patients with *KRAS* mutation have higher TMB, which indicated the patients previously lack effective treatments might benefit from cancer immunotherapy. In addition, about 6% of the *EGFR* mt lung cancer patients might be alternatively treated with immune checkpoint blockade even after the failure of TKI targeted therapy. 10% of lung patients who possesses high MSI score might also suitable for immune checkpoint blockade treatment. However, more samples and investigations are under way.

Keywords: TMB, PD-1 blockade immunotherapy, MSI

P1.07-039 BLOOD BIOMARKERS CORRELATE WITH OUTCOME IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH ANTI PD-1 ANTIBODIES

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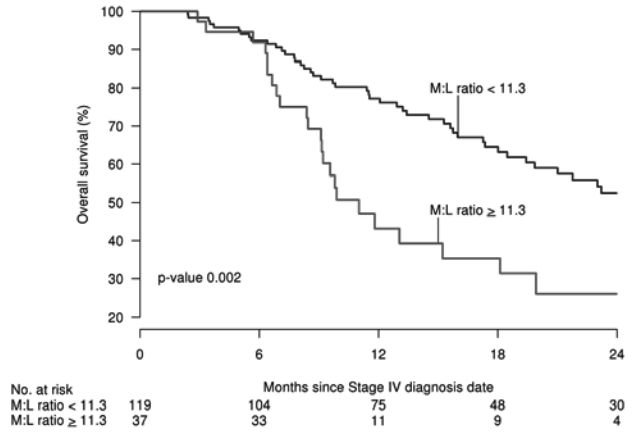
Background: Anti-PD-1 antibodies have demonstrated improved overall survival (OS) and progression free survival (PFS) in a subset of patients with metastatic or locally advanced non-small cell lung cancer (NSCLC). Currently, no blood biomarkers in NSCLC predict clinical outcome to anti-PD-1 antibodies. **Method:** A retrospective analysis of locally advanced or metastatic NSCLC patients treated with anti-PD-1 antibodies at Mayo Clinic was performed. White blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute neutrophil to lymphocyte count ratio (ANC/ALC), absolute eosinophil count (AEC), platelet counts and myeloid to lymphoid ratio (M:L) at baseline and throughout treatment were assessed. Kaplan–Meier and Cox regression analysis were performed. **Result:** 157 patients were treated with nivolumab or pembrolizumab between 1/2015 and 4/2017. At median follow-up of 20 months, median OS and PFS were 13.4 and 2.6 months respectively. Higher baseline ANC, AMC, ANC/ALC ratio and M:L ratio significantly correlated with worse clinical outcomes. A baseline ANC/ALC ratio ≥ 5.9 had a significantly increased risk of death [hazard ratio (HR) = 1.65; 95% CI 1.06–2.56, p 0.027] and disease progression [HR = 1.65; 95% CI 1.17–2.34, p 0.005] compared with patients with ANC/ALC ratio <5.9. A baseline M:L ratio ≥ 11.3 had significantly increased risk of death [HR = 2.13; 95% CI 1.32–3.44, p 0.002] even after a multivariate analysis [HR = 1.89, p 0.015] compared to those with lower ratio. An increase from baseline values at 8 weeks for ANC [HR 1.10, p 0.006] and WBC [HR 1.11, p 0.004] was significantly associated with worse OS.



Conclusion: Increased baseline ANC/ALC ratio and M:L ratio were associated with poor PFS and OS in NSCLC patients treated with anti-PD-1 antibodies. The potential predictive value of these biomarkers might help with risk stratification, treatment strategies and warrant further investigation in a larger, prospective study.

Keywords: non small cell lung cancer, Anti-PD-1, blood predictive biomarkers

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-040 PROGNOSIS-RELEVANT SUBGROUPS IN NSCLC ACCORDING TO GRANULOCYTIC MYELOID-DERIVED SUPPRESSOR CELL FREQUENCY AND CYTOKINE LEVELS

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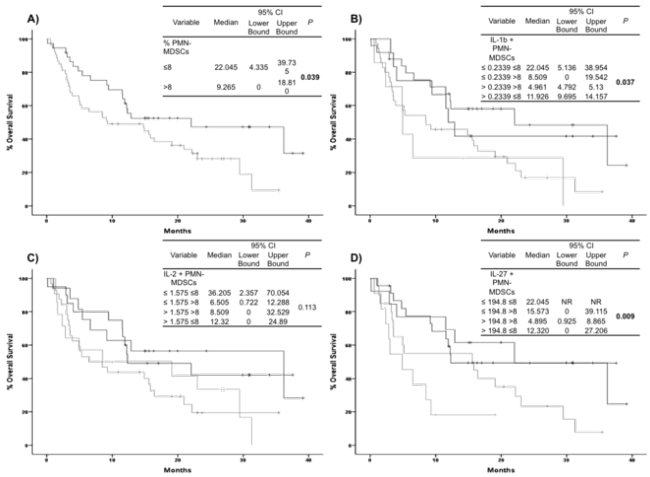
Background: The percentage of Polymorphonuclear-MDSCs (PMN-MDSCs) has emerged as an independent prognostic factor for survival in Non-small cell lung cancer (NSCLC) patients. Similarly, cytokine profiles have been used to identify subgroups of NSCLC patients with different clinical outcomes. This prospective study investigated whether the percentage of circulating PMN-MDSC, in conjunction with the levels of plasma cytokines, was more informative of disease progression than the analysis of either factor alone. **Method:** We analyzed the phenotypic and functional profile of peripheral blood T-cell subsets ($CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$), neutrophils ($CD66b^+$) and polymorphonuclear-MDSCs (PMN-MDSCs; $CD66b^+CD11b^+CD15^+CD14^-$) as well as the concentration of 14 plasma cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p70, IL-17A, IL-27, IL-29, IL-31, and IL-33, TNF-α, IFN-γ) in 90 treatment-naïve NSCLC patients and 25 healthy subjects (HS). **Result:** In contrast to HS, NSCLC patients had a higher percentage of PMN-MDSCs and neutrophils ($P<0.0001$) but a lower percentage of $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ cells. PMN-MDSCs% negatively correlated with the levels of IL1-β, IL-2, IL-27 and IL-29. Two groups of patients were identified according to the percentage of circulating PMN-MDSCs. Patients with low PMN-MDSCs (≤8 %) had a better OS (22.045 months [95% CI: 4.335-739.735]) than patients with high PMN-MDSCs (9.265 months [95% CI: 0-18.810]). OS was significantly different among groups of patients stratified by both PMN-MDSC% and cytokine levels.



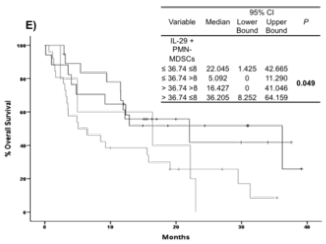


Figure 1. ***Kaplan-Meier curves of OS by PMN-MDSC% and Cytokine levels.***
A) ***OS of patients dichotomized by PMN-MDSC percentage alone.*** High PMN-MDSC% patients (N=53): OS=9.265 months (95% CI: 0 - 18.810) Low PMN-MDSC% patients (N=37) OS = 22.045 months (95% CI: 4.335-739.735); **B)** ***OS in subgroups stratified by PMN-MDSCs% and IL-1β levels***. Patients with a high percentage of PMN-MDCS (>8%) and high levels of IL-1β (>0.2339 pg/ml), had a dramatically poor OS (4.961 months); **C)** ***OS in subgroups stratified by PMN-MDSCs% and IL-2 levels***. Low PMN-MDSCs% patients with low levels of IL-2 (≤1.575 pg/ml) had the best OS (36.205 months). Low PMN-MDSCs% patients and high IL-2 (>1.575 pg/ml), OS= 12.320 months. In contrast, patients with high PMN-MDSCs% and low IL-2 had a worse OS (6.505 months) than patients with high PMN-MDSCs% and high IL-2 (8.088 months); **D)** ***OS in subgroups stratified by PMN-MDSCs% and IL-27 levels.*** Patients with low PMN-MDSC% and low levels of IL-27 (≤194.8 pg/ml) had a higher OS (22.045 months) than those with low PMN-MDSC% and high IL-27 (>194.8 pg/ml), whose OS was 12.32 months ; **E)** ***OS in subgroups stratified by PMN-MDSCs% and IL-29 levels.*** Patients with high PMN-MDCS% and low levels of IL-29 (≤36.74 pg/ml) had a worse OS (5.092 months) than patients with high PMN-MDSCs% and high IL-29 (>36.74 pg/ml), whose OS was 16.427 months .

Conclusion: Our findings provide evidence suggesting that PMN-MDSC% in conjunction with the levels IL-1β, IL-27, and IL-29 could be a useful strategy to identify groups of patients with potentially unfavorable prognoses.

Keywords: PMN-MDSCs; Non-small cell lung cancer; Immunosuppression

P1.07: IMMUNOLOGY AND IMMUNOTHERAPY - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.07-041 CD47 EXPRESSION AND PROGNOSIS IN A COHORT OF PATIENTS WITH LUNG ADENOCARCINOMA (NSCLC)

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Background: CD47 is a cell-surface molecule that promotes immune evasion by engaging signal-regulatory protein alpha, inhibiting phagocytosis. Data on the clinical significance of CD47 expression in patients with different NSCLC subtypes remains limited. **Method:** 173 treatment-naïve patients with NSCLC diagnosis were evaluated. Tumor samples obtained by biopsy or surgical resection were collected for CD47 evaluation by immunohistochemistry. Tumor samples were scored according to the fraction of stained cells at each intensity. Staining intensity of cell membrane was visually scored on a scale from 0-3, (0 indicating absent staining and 3 representing maximal staining). In order to assess the prognostic and predictive value of CD47 as a biomarker, patients were stratified according to a cutoff point. This cutoff was optimized as a function of overall survival (OS) using the X-tile and Cutoff Finder software. CD47 mRNA was measured by RT-PCR. **Result:** CD47 ≥ 150 was associated with EGFR mutations in 73% of the positive cases (n=35, p=0.002). Longer overall survival was associated with ECOG 0-1 (p=0.006), adenocarcinoma histology (p=0.009) EGFR mutation status (p=0.001) and the H-score for CD47 (p=0.021). Multivariate analysis supports CD47 as an independent factor for survival (HR 1.8 IC95%: 1.1-2.8; p=0.007) Table 1. Patients with high levels of CD47 mRNA expression correlated with the score of CD47 ≥ 150 (p=0.066). **Conclusion:** The immune checkpoint molecule CD47 expressed on the surface of tumor cells allows them to escape immunosurveillance and therefore higher CD47 expression confers worse prognosis.

	Univariate			Multivariate		
Variable	Median	95% CI	*P*	HR	95% IC	*P*
Gender						
Female	21.4	18.7-24.1				
Male	23.9	17.3-30.4	0.642			
Age						
>60	20.9	18.1-23.7				
<60	28.9	18.4-39.4	0.123			
Wood-smoke exposure						
Absent	25.5	19.3-31.8				
Present	12.1	8.8-15.4	**<0.001**	2.3	1.3-3.9	**0.002**
Tobacco-smoking exposure						
Non-smoker	21.4	18.8-24.0				
Smoker	26.2	18.4-34.1	0.729			
Asbestos Exposure						
Absent	21.9	18.3-25.4	0.994			
Present	21.5	7.8-35.2				
Disease Stage						
IIIB	32.0	NR	0.327			
IV	21.4	18.5-24.4				
ECOG						
0-1	26.6	19.9-33.3				
2-3	15.4	8.5-22.2	**0.006**	2.1	1.3-3.4	**0.001**
Histological subtype						
Adenocarcinoma	22.7	18.0-27.3				
Carcinoma	7.2	0.0-23.2	**0.009**	2.2	1.1-4.4	**0.023**
Architectural histological grade						
Low	29.9	4.0-55.8				
Intermediate	21.9	11.3-32.5				
High	2.0	18.1-26.1	0.461			
Metastasis CNS						
Absent	21.9	17.1-26.6	0.629			
Present	20.7	13.7-27.7				
Metastasis Bone						
Absent	21.4	18.1-24.7	0.906			
Present	22.7	12.4-32.9				
Metastasis Lung and Pleura						
Absent	22.1	18.4-25.7				
Present	19.7	13.1-26.2	0.383			
Metastasis Liver						
Absent	21.9	16.2-27.6	0.621			
Present	21.4	16.8-26				
EGFR						
wild	19.5	16.5-22.5				
mut	51.6	19.6-83.6	**0.001**	0.27	0.14-0.51	**<0.001**
***ALK* rearrangement**						
Negative	21.9	17.2-26.6				
Positive	12.9	4.2-21.5	0.510			
***KRAS* mutation**						
Negative	21.9	18.4-25.3	0.274			
Positive	8.0	NR				
***CEA* at diagnosis**						
<5ng/ml	22.7	4.7-40.6	0.717			
>5ng/ml	26.6	19.8-33.4				
CD47						
<150	26.2	20.3-32.2	**0.021**	1.8	1.1-2.8	**0.007**
>150	19.5	16.3-22.7				

***EGFR*: Epidermal Growth Factor, *ALK*: Anaplastic Lymphoma Kinase, *KRAS*: Kirsten rat sarcoma 2 viral oncogene homolog, *CEA*: carcinoembryonic antigen.**

Keywords: CD47

P1.07-042 PD-L1 AND CD8 EXPRESSION IN EGFR-MUTANT OR ALK-REARRANGED PATIENTS WITH LUNG CANCER

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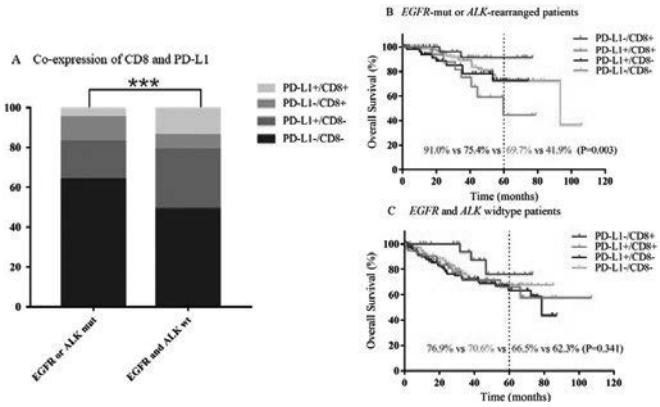
Background: Several studies indicate no response to check-point inhibitors on non-small-cell lung cancer with either *EGFR*-mutant or *ALK*-rearranged patients,of whom majority of international clinical trials involving PD-1/L1 inhibitors excluded. No solid evidences to interpret the underlying mechanism of poor clinical benefit to patients through PD-1/L1 inhibitors with driver genes mutation. **Method:** From 2010 to 2016, 482 patients and 263 patients with clinically operable lung cancer and advanced lung cancer respectively were collected at Guangdong Lung Cancer Institute (GLCI). All patients have detected for EGFR as well as *ALK* status. CD8 and PD-L1 expression was scored by immunohistochemistry with SP142 antibody. Five years survival rate was also analyzed. **Result:** Patients were assigned to *EGFR/ALK* positive group (344 cases) or negative group (401 cases). *EGFR/ALK* positive group contains 5.52% PD-L1+/CD8+; 11.92% PD-L1-/CD8+; 18.90% PD-L1+/CD8- and 63.66% PD-L1-/CD8-. *EGFR&ALK* negative group contains 13.97% PD-L1+/CD8+; 6.98% PD-L1-/CD8+; 30.42% PD-L1+/CD8- and 48.63% PD-L1-/CD8-. In *EGFR/ALK* positive group, PD-L1+/CD8+ is lower but PD-L1-/CD8- is higher than that of *EGFR* & *ALK* negative group (P<0.001). Significant statistical differences of 5 years survival rate were observed between four subgroups in *EGFR/ALK* positive group (PD-L1+/CD8+:41.9%, PD-L1-/CD8+: 91.0%, PD-L1+/CD8-: 75.4%, PD-L1-/CD8-: 69.7%; P=0.003). And there were no survival differences in *EGFR&ALK* negative group ((PD-L1+/CD8+: 66.5%, PD-L1-/CD8+: 76.9%, PD-L1+/CD8-: 62.3%, PD-L1-/CD8-: 70.6%; P=0.341). **Conclusion:** Immunotherapy with PD-1/L1 inhibitors may not be suitable for *EGFR*-mutant or *ALK*-rearranged lung cancer patients with little co-expression of PD-L1 and CD8. However, these patients with such diver genes mutation reveal the best survival in PD-L1-/CD8+ subgroup and the worst survival in PD-L1+/CD8+ subgroup.



Keywords: EGFR, ALK, PD-L1

P1.07-043 BARRIER MOLECULE OVEREXPRESSION IS ASSOCIATED WITH INCREASED CD8 T CELLS AND DECREASED B/TREG CELLS IN HUMAN LUNG CANCER

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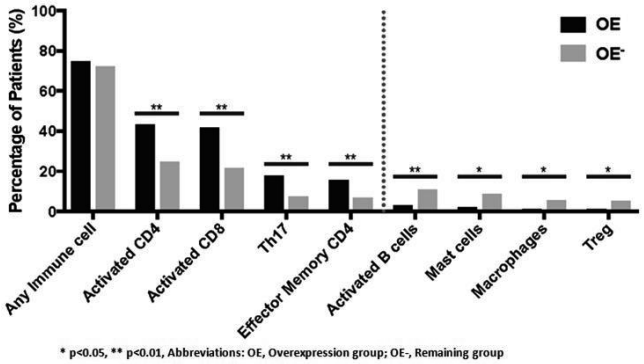
Background: Immunotherapy is an encouraging therapeutic option for lung cancer therapy. For immune cells to interact with tumors, they must first traverse the cell junctions between neighboring cells. While it is expected that higher expression of barrier molecules is linked to lesser immune cell infiltration in general, little progress has been made in our understanding of how these barrier molecules mechanistically interact with immune cells in lung cancer. **Method:** Barrier molecule genes were divided into 3 types: tight junction, adherens junction, and desmosome. mRNA-seq values of each type were analyzed in 504 patient samples with lung squamous cell carcinoma(SCC) and 522 patient samples with lung adenocarcinoma from the TCGA database. Immune cell infiltration of each set was evaluated using Gene Set Enrichment Analysis(GSEA), and p values were analyzed from Chi-squared and Fisher's exact tests. **Result:** In lung adenocarcinoma, overexpression(z-score>2.0) of desmosome genes significantly correlated with increased infiltration of activated CD4/CD8 T cells, and Th17 cells, but decreased infiltration of activated B cells, mast cells, macrophages, and regulatory T cells (Figure 1). There was no significant difference in the immune cell landscape of groups overexpressing desmosome genes in lung SCC. In addition, there was no significant difference in groups overexpressing tight or adherens junction genes in both types of cancer. Overall survival also showed no significant difference in all 3 barrier molecular gene overexpression groups in both types of lung cancer.

Figure 1. Immune cell infiltration landscape by barrier molecule status in human lung adenocarcinoma.



Conclusion: Our study demonstrates that elevated barrier molecule(desmosome) gene expression is associated with increased infiltration of cytotoxic CD8 T cells and decreased infiltration of activated B/Treg cells in human lung adenocarcinoma. The inverse association between cytotoxic CD8 T cells and activated B/Treg cells aligns with previous reports of tumor-infiltrating B cells inhibiting T cells. Further investigation is required to understand the roles of barrier molecules and its immune modulatory effect in various types of cancers.

Keywords: NSCLC, Desmosome, CD8 T cell

P1.07-044 THE IMPACT OF NEUTROPHIL/LYMPHOCYTE RATIO AS THE PREDICTIVE MARKER TO ANTI-PD-1 ANTIBODY TREATMENT IN NSCLC PATIENTS

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Background: Anti-Programmed death 1 (PD-1) antibody which enhances anti-tumor activity of cytotoxic T lymphocytes by blockade of PD-1/PD-L1 pathway has demonstrated improvement of survival in the patients with advanced non-small-cell lung cancer (NSCLC). PD-1 and its ligand PD-L1 is also known as key players in the formation of tumor microenvironment, closely related with inflammatory cytokines. Here, we retrospectively analyzed the potential of peripheral blood biomarkers for predicting outcome of anti-PD-1 antibody therapy. **Method:** Patients treated with anti-PD-1 antibody nivolumab from February 2016 to March 2017 in our hospital were selected. We investigated the tendency of differential leukocyte counts and c-reactive protein (CRP) in peripheral blood as inflammatory markers on the treatment progress with nivolumab. **Result:** 19 patients were enrolled. Median age was 67, ECOG-PS 0 or 1 were 16 (84.2%). Histological subtypes were non-squamous 10 (52.6%), and squamous 9 (47.4%). Median follow-up was 7.2 months (range: 2.2-16.1 months), median progression free survival was 2.5 months. Disease control rate was 42.1%, and overall response rate was 26.3%. Of some parameters in peripheral blood, lower absolute lymphocyte count (ALC), higher absolute neutrophil count (ANC), neutrophil to lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) at baseline were associated with shorter survival. Interestingly, patient with longer PFS decreased NLR at baseline and its parameter remained at low levels until disease progression. **Conclusion:** Lower pre-treatment ANC, NLR and PLR are associated with longer survival, and increased NLR during nivolumab therapy is reflect disease progression in NSCLC patients. We suggest that peripheral blood biomarkers may predict response and acquisition of resistance to anti-PD-1 therapy.

Keywords: Neutrophil/lymphocyte ratio, Immunotherapy, NSCLC

P1.08-001 SURGICAL VERSUS NON-SURGICAL TREATMENTS FOR RESECTABLE STAGE III NSCLC: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: To determine if the surgical approach is the preferred curative treatment option over non-surgical approach for resectable stage III NSCLC. **Method:** We searched MEDLINE for comparative studies comparing the effects of surgical and non-surgical approaches on progression-free survival (PFS), overall survival (OS) and treatment related mortality (TRM). We assessed the methodological quality of the included studies using the MERGE criteria. We estimated the pooled hazard ratios (HR), risk ratios (RR), confidence intervals (CI), P values (P) and I squared statistic (I^2) with random effects model using Revman 5.3. We assessed the quality of the

summarized randomized trials evidence using the GRADE approach. **Result:** We found five randomized trials and one retrospective population based comparative study including 12,229 Stage III NSCLC patients. These studies have low to moderate risk of bias in their methodology. The randomized trials (n = 981) showed that surgery did not improve PFS (HR 0.93, 95% CI 0.74 to 1.17, P = 0.56, I^2 = 0%, low quality), OS (HR 0.95, 95% CI 0.82 to 1.11, P = 0.53, I^2 = 0%, moderate quality) and cause more TRM (RR 3.75, 95% CI 1.65 to 8.54, P = 0.002, I^2 = 0%, moderate quality). Subgroup analyses showed that the effect on OS was no different between the trials that use concurrent chemoradiotherapy versus those that do not and trials that use PET/CT for staging versus those that do not. Although retrospective study favored surgical approach (OS: HR 0.64, 95% CI 0.53 to 0.77, P < 0.00001, I^2 = 82%), this discrepancy in OS is likely due to selection bias. **Conclusion:** Surgical approach did not delay disease progression or improve survival and may cause more treatment related deaths compared to non-surgical approach in the curative treatment of resectable stage III NSCLC. Future research should focus on optimizing the non-surgical approach using more effective systemic agents and advanced imaging and radiotherapy techniques.

Keywords: Radiotherapy, Surgery, Non-small cell lung cancer

P1.08: LOCALLY ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.08-002 BLOOD SUPPLY TO THE TUMOR DO NOT PREDICT THE EFFECT OF INDUCTION THERAPY IN PATIENTS WITH LOCALLY ADVANCED LUNG CANCER

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Background: Induction therapy is a promising optional treatment for locally advanced lung cancer including superior sulcus tumors. However, predictors of the effect and pathologic complete responses have not been well-known. We hypothesized that those tumors invading neighboring structures would be more sensitive to induction therapy owing to the richer blood supply to them from involved organs. The purpose of this study was, therefore, to evaluate predictors for pathologic complete responses of induction therapy and whether the volume of blood supply to the tumor could predict the efficacy of induction therapy. **Method:** Patients who underwent induction therapy followed by surgery for locally advanced lung cancer were retrospectively reviewed. The volume of blood supply to the tumor was defined as the CT value (HU; Hounsfield Unit) calculated by subtraction of the non-enhanced value from the contrast-enhanced value (divided early phase and late phase) at the maximal dimension of the tumor on dynamic CT before induction therapy. The measured areas of the tumor were encircled by freehand with disengaging of bony structures. The efficacy of induction therapy was categorized to the pathologic complete response (pCR) and residual tumor (pRT) group. **Result:** From 2005, 50 patients were enrolled in this study. There were 43 males and 7 females, with a median age of 63 years old. The tumors consisted of 38 T3 lesions and 12 T4 lesions (40 chest wall, 7 mediastinum, and 3 vertebrae). Induction therapy included chemoradiotherapy in 39 patients, chemotherapy in 6, and radiotherapy in 5, and the dose of radiation was 40Gy in 33 patients, 45Gy in 1, 50Gy in 6, and 60Gy in 4, respectively. All patients except one underwent a complete resection, and the pathologic complete response was obtained in 15 (30%). The mean CT values of early and late phases in pCR groups were 14.1±12 HU and 30.6±14 HU, and those in pRT were 15.3±13 HU and 35.3±19 HU, respectively. By a logistic regression analysis, smaller size of the tumor (less than 42 mm) was the only trend of the predictor for pCR (p = 0.064), whereas maximum standardized uptake value on FDG-PET and CT values of early and late phases on contrast-enhanced CT had no correlations toward pathologic complete responses. **Conclusion:** The volume of blood supply to locally advanced lung cancers did not predict the effect of induction therapy, whereas smaller sized tumor tended to have a better effective response in this study.

Keywords: Blood supply, locally advanced lung cancer, induction therapy

P1.08: LOCALLY ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.08-003 CONCOMITANT CHEMOTHERAPY AND RADIOTHERAPY WITH SBRT BOOST FOR UNRESECTABLE, STAGE III NON-SMALL CELL LUNG CANCER: A PHASE I STUDY

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Background: Stereotactic Body Radiation Therapy (SBRT) is now the standard of care in medically inoperable stage I non-small cell lung cancer, yielding high rates of local control. It is unknown if SBRT can be safely utilized in the locally advanced NSCLC setting. This multi-institution phase I study evaluated the safety of 44 Gy conventionally fractionated thoracic radiation with concurrent chemotherapy plus a dose escalated SBRT boost to both the primary tumor and involved mediastinal lymph nodes. The primary endpoint of this study was to establish the maximum tolerated dose (MTD) of the SBRT boost. **Method:** Inclusion criteria included unresectable stage IIIA or IIIB disease, primary tumor ≤8 cm, and N1 or N2 lymph nodes ≤5 cm. Tumors were staged with PET/CT while four dimensional CT simulation was employed for radiation planning. The treatment schema was 44 Gy thoracic radiation (2 Gy/day) with weekly carboplatin and paclitaxel chemotherapy. A second CT simulation was obtained after 40 Gy was delivered, and a SBRT boost was planned to the remaining gross disease at the primary site and involved lymph nodes. Four SBRT boost dose cohorts were tested: Cohort 1 (9 Gy x 2); cohort 2 (10 Gy x 2); cohort 3 (6 Gy x 5); and cohort 4 (7 Gy x 5). Patients were treated in cohorts of three patients and using Bayesian Escalation with Overdose Control (EWOC) method to determine Maximum tolerated dose of the SBRT boost. Dose limiting toxicities (DLT) were defined as any grade 3 or higher toxicities within 30 days of treatment attributed to treatment, not including hematologic toxicity, or any grade 5 toxicity attributed to treatment. **Result:** The study enrolled 19 patients from 11/2012-12/2016. There were 4 screen failures and 15 patients were treated on study. There were no DLTs in dose cohort 1 (n = 3) and 2 (n = 6). One patient in dose cohort 3 (n = 3) developed a DLT, and 2 patients in dose cohort 4 (n = 3) developed a DLT. The calculated MTD was 6 Gy x 5. The DLT observed at this dose level was a tracheoesophageal fistula; given this substantial toxicity, there was investigator reluctance to enroll further patients in this dose level. Thus the calculated MTD is 6 Gy x5, however 10 Gy x 2 is felt to be a reasonable dose as well given no grade 5 toxicities occurred with this dose. **Conclusion:** The MTD of a SBRT boost combined with 44 Gy thoracic chemoradiation is 6 Gy x 5. A SBRT boost dose of 10 Gy x 2 could be considered very safe with no grade 3 or higher toxicities observed at this dose level.

Keywords: SBRT, Stage III NSCLC

P1.08: LOCALLY ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.08-004 ADJUVANT CHEMORADIOTHERAPY VS. CHEMOTHERAPY FOR COMPLETELY RESECTED UNSUSPECTED N2-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: We investigated whether concurrent chemoradiotherapy (CCRT) would increase survival in patients with completely resected unsuspected N2-positive non-small cell lung cancer (NSCLC), compared with adjuvant chemotherapy alone. **Method:** Eligible patients were randomly assigned (1:1 ratio) to either the CCRT arm or the chemotherapy arm. In the CCRT arm, patients received concurrent thoracic radiotherapy (50 Gy in 25 fractions) with five cycles of weekly paclitaxel (50 mg/m^2) and cisplatin (25 mg/m^2), followed by two additional cycles of paclitaxel (175 mg/m^2) plus cisplatin (80 mg/m^2) at three-week intervals. In the chemotherapy arm, patients received four cycles of adjuvant paclitaxel (175 mg/m^2) and carboplatin (AUC 5.5) every three weeks. The primary endpoint was disease-free survival. **Result:** We enrolled and analyzed 101 patients. The median disease-free survival of the CCRT arm was 24.7 months, which was not significantly different from that of the chemotherapy arm (21.9 months; hazard ratio [HR] 0.94, 95% CI: 0.58–1.52, P = 0.40). There was no difference in overall survival (CCRT: 74.3 months, chemotherapy: 83.5 months, HR: 1.33, 95% CI: 0.71–2.49). Subgroup analysis showed chemotherapy alone increased overall survival in never-smokers and multi-station N2-positive patients. The pattern of disease recurrence was similar between the two arms. **Conclusion:** There was no survival benefit from adjuvant CCRT compared with platinum-based chemotherapy alone for completely resected unsuspected N2-positive NSCLC.

Keywords: adjuvant chemotherapy, non-small cell lung cancer, microscopic N2

P1.08: LOCALLY ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.08-005 PREOPERATIVE ANALYSIS OF 18FDG-PET FEATURES MAY PREDICT LOCO-REGIONAL INVASIVENESS IN NSCLC

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Background: Prognosis of surgically resectable NSCLC is strongly affected by local invasiveness as well as unexpected lymph node diffusion found at surgery (nodal upstaging). Recently, texture analysis of PET imaging has emerged as a powerful tool to better define the metabolic features and behavior of neoplasms. This study is meant to evaluate the relationship of texture analysis features of surgically resected NSCLC with local invasiveness, represented by lymphovascular invasion (LI), and regional subclinical diffusion, evaluated as nodal upstaging (NU) at the pathological staging. **Method:** The study is a retrospective evaluation of prospectively collected data. We performed a spatial texture analysis of the preoperative PET-CT scans of completely resected clinical stage Ia-IIb (T1-3, N0-1) NSCLC, focusing

on 11 parameters: SUVmax, Metabolic Tumor Volume (MTV), Entropy (baseline), Homogeneity, High Intensity Run Emphasis, Low Intensity Run Emphasis, Coarseness, Busyness, Normalized Entropy, Normalized Homogeneity, Normalized Inverse Difference Moment (NIDM), SUV standard deviation (SUV SD), SUV Entropy. We then evaluated their relationship with LI, NU and Disease-Free Survival (DFS). **Result:** In the period between February 2012 and September 2016 we operated on 75 patients (53 male and 22 female); pathological stage revealed a nodal upstaging in 12 cases (6 pN1 and 6 pN2), while in 11 patients it showed a LI. Patients with NU had a restricted mean DFS of 19.8 months (CI 95% 12.7-26.8) and showed higher levels of SUVmax; SUV Entropy; Normalized Entropy; SUV SD and lower level of Normalized Homogeneity and NIDM. Patients with LI had a restricted mean DFS of 21.4 months (CI 95% 8.8-34,1) and displayed higher levels of SUVmax, SUV Entropy, Normalized Entropy, SUV SD and lower level of NIDM. ROC analysis confirmed a stronger predictive value of heterogeneity indexes when compared to SUVmax; in particular SUV SD had the best ROC area for LI and SUV entropy showed the best ROC for NU. Concurrently, both LI and NU emerged as significant prognostic factors for DFS both in univariate (p=0.0076 and p=0.0167 respectively) and multivariate analysis (p=0.005 and p=0.021 respectively). **Conclusion:** In our analysis, preoperative PET-CT texture analysis has a significant correlation with prognostic indicators and tumor local invasiveness; this analysis may provide a more precise stratification of patients affected by highly aggressive tumors from the very beginning of patient's diagnostic path.

Keywords: NSCLC, PET-CT, Texture analysis

P1.08: LOCALLY ADVANCED NSCLC -
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P1.08-006 PHASE I/II STUDY OF CARBOPLATIN, NAB-PACLITAXEL, AND CONCURRENT RADIATION THERAPY FOR PATIENTS WITH LOCALLY ADVANCED NSCLC.

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Background: A regimen of weekly paclitaxel plus carboplatin (CBDCA) with concurrent thoracic radiotherapy is recognized as standard for patients with unresectable stage III lung cancer. Nanoparticle albumin-bound paclitaxel (nab-PTX) is a cremophor-free formulation of paclitaxel to increase solubility and intratumor drug delivery and is effective for patients with advanced NSCLC. The purpose of this study is to determine recommended dose and investigate the efficacy and safety profile of a regimen of nab-PTX plus CBDCA with concurrent thoracic radiotherapy for patients with unresectable non-small cell lung cancer (NSCLC). **Method:** Patients with unresectable stage IIIA or IIIB NSCLC, good performance status, age between 20 and 74 years, and adequate organ function, a relative volume of normal lung receiving a dose of ≥ 20 Gy (V20) ≤35% were eligible. In a phase I study (standard 3+3 design), weekly nab-PTX plus CBDCA was administered intraveneously for six weeks. Doses of each drug were planned as follows: level 1, 40/2; level 2, 50/2 (nab-PTX [mg/m^2] / CBDCA [area under the plasma concentration time curve (AUC) mg/ml/min]). Concurrent thoracic radiotherapy was administered in 2 Gy fractions to a total dose of 60 Gy. Dose-limiting toxicity (DLT) was observed during concurrent chemotherapy and thoracic radiation and up to 28 days following the end of radiotherapy. After the evaluation of DLT, patients received an additional two cycles of consolidation chemotherapy that consisted of 3-week cycles of nab-PTX (100 mg/m^2 on Days 1, 8 and 15) plus CBDCA (AUC 6 mg/ml/min on Day 1). In a phase II study, we planned to enroll 50 patients treated with recommended dose. **Result:** In a Phase I study, 11 patients were enrolled and received treatment per protocol, with 9 evaluable for efficacy and toxicity. At nab-PTX dose level 1 (40mg/m^2), none of 3 patients experienced DLT. At nab-PTX dose level 2 (50mg/m^2), 1 of 6 patients experienced DLT: grade 3 leukopenia requiring a second consecutive skip in the administration of weekly nab-PTX plus CBDCA. The recommended doses (RDs) for the phase II study were nab-paclitaxel 50 mg/m^2 and CBDCA (AUC=2). From October 2015 to November 2016, a total of 52 patients were entered in the phase II portion (median age, 66 years; age range, 48–74 years; male/female 44/8). **Conclusion:** Concurrent chemoradiotherapy with nab-PTX 50 mg/m^2 and CBDCA AUC 2 was the recommended dose. We will report the latest efficacy and safety profile of the present therapy. Trial registration: UMIN000012719.

Keywords: nab-paclitaxel, chemoradiation, locally advanced NSCLC

P1.08: LOCALLY ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.08-007 SURGERY VERSUS CONCURRENT CHEMORADIOTHERAPY FOR RESECTABLE CIIIA-N2 NSCLC: A PROPENSITY SCORE MATCHED ANALYSIS

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Background: Clinical IIIA-N2 (cIIIA-N2) non-small cell lung cancer (NSCLC) is a heterogeneous group of diseases. Both surgery based multimodality treatment (S) and concurrent chemoradiotherapy (CCRT) can be applied. However, the optimal treatment modality remains controversial. This retrospective study aimed to compare the efficacy of two aforementioned treatment modalities in resectable cIIIA-N2 NSCLC. **Method:** From 2001 to 2010, 278 patients diagnosed with stage cIIIA-N2 NSCLC in our institution were enrolled, including 225 patients with surgery and 53 patients received CCRT. A propensity score matching (PSM) method (1:2) was utilized to obtain two matched groups: the S group and the CCRT group using the following variables: age, gender, smoking index, KPS, histology and T stage. The Kaplan-Meier method was used to calculate the overall survival (OS), progression-free survival (PFS), locoregional recurrence free survival (LRFS) and distant-metastasis free survival (DMFS), and the log-rank test was used to analyze differences between the groups. **Result:** There were 102 patients in the S group, including 65 patients (63.7%) treated with surgery followed by adjuvant chemotherapy and 37 patients (36.3%) treated with surgery followed by adjuvant chemotherapy and radiotherapy. Fifty-one patients received CCRT, including 29 patients (56.9%) treated with CCRT alone and 22 patients (43.1%) with consolidation chemotherapy. The median survival was 76.6 months in the S group, compared with 23.0 months in the CCRT group. The 1-, 3- and 5-year OS rates were 86.9%, 59.5% and 55.5% in the S group, which were statistically significantly higher than the rates of 59.2%, 36.7% and 31.5% in the CCRT group (p= 0.001). The 1-, 3- and 5-year DFS rates were 60.4%, 41.5% and 37.7% in the S group and 51.0%, 25.5% and 13.7% in the CCRT group, respectively (p= 0.002). The 5-year LRFS rate in the S group was 58.5% compared with 34.0% in the CCRT (p= 0.023). The 5-year DMFS rate was 55.7% in the S group versus 48.5% in the CCRT group (p= 0.674). **Conclusion:** In this retrospective study, surgery demonstrated significantly improved OS, DFS and LRFS compared with CCRT. Surgery based multimodality treatment may be preferred for patients with resectable cIIIA-N2 NSCLC.

Keywords: cIIIA-N2 NSCLC, Chemoradiotherapy, Surgery

P1.08: LOCALLY ADVANCED NSCLC -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.08-008 CHEMORADIOTHERAPY IN THE REGIME OF ACCELERATED FRACTIONATION IN THE TREATMENT OF LUNG CANCER

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Background: Radiation therapy is one of the main methods of treatment of inoperable lung cancer. The standard of treatment is simultaneous chemoradiotherapy in the traditional fractionation regimen. However, the results of treatment cannot be called satisfactory - the five-year overall survival and median are about 20% and 24 months respectively. Based on radiobiological data and previous studies, it was found that accelerated fractionation regimes have advantages over the traditional regime. The purpose of this study is to improve both immediate and long-term indicators of combined treatment of patients with lung cancer by applying the accelerated fractionation regimen. **Method:** The material was based on data on the treatment of 70 patients with a verified diagnosis of inoperable lung cancer or patients with contraindications to surgical treatment. All patients underwent simultaneous or sequential radiation therapy in the regime of accelerated fractionation (daily dose of 2.4 Gy, 25 fractions, a total dose of 60 Gy) and 4-6 cycles of chemotherapy with platinum doublets (cisplatin+etoposide or carboplatin+paclitaxel) in standart doses. **Result:** Direct results of treatment were assessed using computed tomography (RECIST 1.1 criteria) at 1-3 months after the end of radiation therapy, which were: complete response in 5 (7.2%) patients, partial response in 31 (44.3%) patients, stabilization in 28 (40%), progression in 6 (8.5%). Complications: acute esophagitis stage 1 - 25.7%, stage 2 - 18.5%, stage 3 - 7.2%. Acute pneumonitis stage 1 - 10%, stage 2 - 4.5%. **Conclusion:** Thus, it can be concluded that the application of the accelerated fractionation regime is satisfactorily tolerated by patients and allows achieving high rates of immediate efficacy, as well as reducing the overall treatment time of patients.

Keywords: Chemoradiotherapy, accelerated fractionation, lung cancer

P1.08-009 NEUTROPHILIA AS PROGNOSTIC BIOMARKER IN LOCALLY ADVANCED STAGE III LUNG CANCER

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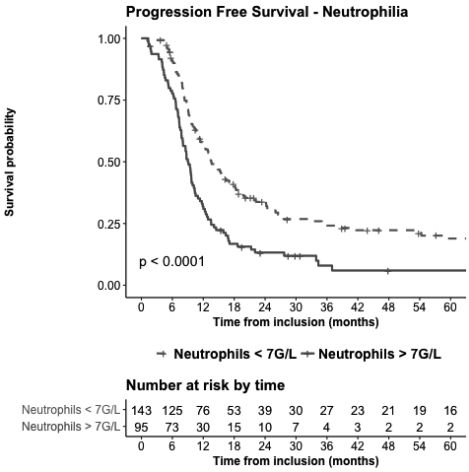
Background: To study the prognostic value of leucocyte disorders in two retrospective cohorts of stage III Non-Small Cell Lung Cancer (NSCLC) patients, and to compare their accuracy with established prognostic markers. **Method:** Clinical records of consecutive previously untreated NSCLC patients in our Institution between June 2001 and September 2016 for stage III NSCLC were collected. The prognostic value of pretreatment leucocyte disorders was examined, with focus on patterns of relapse and survival. Leukocytosis and neutrophilia were defined as a leukocyte count or a neutrophil count exceeding 10 and 7 G/L, respectively. **Result:** We identified 238 patients (145 patients prospectively registered through MSN study (NCT02105168) with 136 additional patients), displaying baseline leukocytosis or neutrophilia in 39% and 40% respectively. Most were diagnosed with adenocarcinoma (48%), and stage IIIB NSCLC (58%). 3-year actuarial overall survival (OS) and progression-free survival (PFS) were 35% and 27% respectively. Local relapses were reported in 100 patients (42%), and distant metastases in 132 patients (55%). In multivariate analysis, leukocytosis, neutrophilia, and induction chemotherapy regimen based on carboplatin/paclitaxel were associated with worse OS and PFS ($p<0.05$). Neutrophilia independently decreased Locoregional Control (LRC) (HR=2.5, $p<0.001$) and Distant Metastasis Control (DMC) (HR=2.1, $p<0.001$). Neutrophilia was significantly associated with worse brain metastasis control (p=0.004), mostly in adenocarcinoma patients ($p<0.001$).



Conclusion: In stage III NSCLC patients, treated with concurrent cisplatin-based chemoradiation, baseline leukocytosis and neutrophilia predict OS, PFS, LRC, and DMC. In addition with previously available markers, this independent cost-effective biomarker could help to stratify stage III NSCLC population with more accuracy.

Keywords: non-small cell lung cancer, Concurrent Chemoradiation, prognostic factor

P1.08-010 UNSUSPECTED N2 DISEASE IN PATIENTS UNDERGOING SURGERY FOR NON-SMALL CELL LUNG CANCER: ROLE OF EXTENT AND LOCATION OF THE LYMPH NODE METASTASIS

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Background: The role of surgery is controversial in the treatment of non-small cell lung cancer (NSCLC) spread to ipsilateral mediastinal or hilar lymph nodes. In this study we wanted to find out whether the location of lymph nodes positive for NSCLC in the mediastinum or hilum plays a role in the survival of these patients. **Method:** We reviewed retrospectively our 881 patients operated on for NSCLC between 2004 and 2014. Patients having unforeseen spread of cancer to mediastinal (N2) or hilar (station 10) lymph nodes in the final pathology report were further analyzed according to Naruke classification. The mediastinal N2 group was thereafter subdivided into upper (stations 1, 2, 3, 4, 5, 6) and lower mediastinal groups (stations 7, 8, 9). Clinical staging included computed tomography (100%), positron emission tomography (47.6%), and mediastinoscopy (9.8%). Median follow-up after surgery was 54 months. **Result:** Between January 2004 and December 2014 there were 108 pN2 patients and 35 patients with hilar pN1 (station 10 node) involvement. The 5-year overall survival (OS) of the whole group was 19.6%. Better OS was found in patients with nodes positive for upper mediastinal nodes compared to those with lower positive mediastinal nodes or multilevel N2 patients (p=0.027 and p=0.003, respectively). The OS of patients with positive hilar (station 10) nodes did not differ from that of the upper mediastinal positive N2 subgroup. OS of patients with multilevel N2 was significantly worse than the other groups lumped together (p=0.016). Progression free survival (PFS) patients with hilar and upper mediastinal positive nodes had a better outcome compared to multilevel N2 patients (p=0.014 and 0.003, respectively). No significant difference was noted between patients positive for lower positive mediastinal nodes and patients with multilevel N2. Also, PFS multilevel N2 patients had a significantly worse outcome compared to all other groups combined (p=0.004). **Conclusion:** Based on our results, lower positive mediastinal N2 node patients seem to have as unfavorable OS and PFS as multilevel N2 disease patients, and significantly worse prognosis than upper mediastinal node patients. Both OS and PFS of patients with positive hilar disease is similar to the upper mediastinal positive N2 group. We conclude that the location of lymph nodes positive for cancer is a significant factor in the prognosis of NSCLC.

Keywords: Prognosis, lymph nodes, Surgery

P1.09-001 MULTIPLEXED BIOMARKER STRATEGIES BASED ON TARGETED PROTEOMICS FOR DETECTION OF MALIGNANT PLEURAL MESOTHELIOMA IN BLOOD

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Background: Blood biomarkers are only infrequently used for the diagnosis of malignant pleural mesothelioma. Most of these biomarkers are single marker proteins relying on antibody assays and with limited accuracy for mesothelioma detection in the blood. In our study, we apply targeted proteomics technologies to investigate novel diagnostic strategies based on multiplexed protein biomarkers for mesothelioma detection in serum. **Method:** We studied more than 400 serum samples of early (I/II) and late stage (III/IV) mesothelioma and asbestos exposed donors collected in USA, Australia and Europe. For quantitative proteomics, 50 µl of serum were processed on 96-well plates over different days to enrich for N-linked glycoproteins based on hydrazide chemistry. After tryptic digestion, serum peptides were analyzed in replicates, separated by ultra-performance liquid chromatography followed by selected reaction monitoring on a triple quadrupole mass spectrometer (LC-SRM). Isotopically labeled peptides were spiked in each sample for quantification and to assess the performance of the LC-SRM platform. Two non-human N-linked glycoproteins were spiked in each serum sample before processing to monitor the performance of the targeted proteomics workflow across samples and plates. The software package MSstats was used for large scale quantitative data analysis. **Result:** We processed and quantified over 400 serum samples analyzed in LC-SRM replicates. We assessed the performance of the targeted proteomics platform for large scale quantification of a multiplexed six peptide signature (including peptides from the established mesothelin biomarker). The coefficient of variation (CV) for parallel peptide quantification on LC-SRM ranged from 2% to 11.4% with CVs below 8% for all peptides but for one. Based on quantification of the two non-human spiked-in glycoproteins, average standard deviation of the targeted proteomics workflow was 0.42 over all samples. We investigated the performance of the multiplexed six peptide signature in discriminating mesothelioma from asbestos exposed donors. For the signature we fit a multiple logistic regression model on a training set of 212 patients and a validation set of 193 mesothelioma and asbestos exposed donors. The multiplexed biomarker signature discriminated mesothelioma from asbestos exposed with AUC of 0.72 in the validation set. Here, compared with performance of the single marker mesothelin (assessed by LC-SRM), the multiplexed biomarker signature separated early stage mesothelioma from asbestos exposed with AUC of 0.74, with sensitivity of 37.8% at 90% specificity, whereas the single mesothelin peptide had AUC of 0.66 and sensitivity of 22.2%. **Conclusion:** Multiplexed biomarker strategies based on targeted proteomics technologies can improve mesothelioma diagnosis in blood samples.

Keywords: Mesothelioma, targeted proteomics, Biomarkers

P1.09-002 CELLULAR NOISE AND POSITIONAL EFFECTS DETERMINE THE CELL STEM STATE IN MALIGNANT MESOTHELIOMA

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Background: Rapid recurrence after first-line therapy is a major concern in malignant mesothelioma (MM) and cancer stem cells (CSC) are assumed to be responsible for this phenomenon. Cellular noise is defined as the random variability of quantities, of for example proteins, in individual genetically identical cells. Since a cell's differentiation status is also determined by levels of some transcription factors, as

the result of cellular noise, all differentiated cells might de-differentiate to a stem cell state, if enough time is given for this event to occur. **Method:** In order to provide direct evidence for this hypothesis, the "stemness" of individual cells was continuously monitored in human and murine malignant mesothelioma cells over the period of several months. Re-expression of the top hierarchical stemness markers Sox2 and Oct4 evidenced by the appearance of eGFP driven by a genetically-encoded stemness reporter construct was observed in the subpopulation of differentiated eGFP(-) cells in the above cell types. **Result:** A transition event from a differentiated to a de-differentiated cell was found to be extremely rare. Yet, when it was occurring, the probability of the neighboring cells, not only the direct descendants of a novel eGFP(+) stem cell, to also become an eGFP(+) stem cell, was increased by a positional effect. This led to a clustered "mosaic" re-appearance of CSC. eGFP(+) cells were found to re-appear even from cell cultures derived from one single bulk eGFP(-) cell. **Conclusion:** Based on these findings, a novel tumor growth model was developed; it is well suited to accurately predict the clustered localization of cancer stem cells within a tumor mass, in congruence with our experimental *in vitro* and *in vivo* findings. The robustness of the model is currently tested on a large collection of human pleural mesothelioma cell lines bearing different mutations and being of diverse histological subtypes.

Keywords: Positional effect, Mesothelioma, Cancer Stem Cells

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-003 MALIGNANT MESOTHELIOMA VERSUS SYNOVIAL SARCOMA: AN ANALYSIS OF 19 CASES WITH MOLECULAR DIAGNOSIS

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Background: Intrathoracic synovial sarcomas (SSas) are well documented in the literature and characterized by a distinctive t(X;18) translocation. The histologic appearances of a monophasic or biphasic SSa can lead to confusion with biphasic or sarcomatoid mesothelioma (MM). The distinction of pleural SSa from pleural MM is important, because SSas may be responsive to ifosfamide-based chemotherapy and have no proven causal relationship to prior asbestos exposure. Demonstration of the t(X;18) by cytogenetics, fluorescence in situ hybridization (FISH) or reverse-transcriptase polymerase chain reaction is the gold standard for diagnosis, but availability of molecular diagnosis can be limited and testing is time consuming. Recently, it has been suggested that immunohistochemistry (IHC) for transducin-like enhancer of split 1 (TLE) is reliable for diagnosis of SSa and may replace molecular diagnosis. **Method:** We reviewed 19 pleura-based malignancies that had either been referred for a potential diagnosis of SSa, or where SSa was a differential diagnosis considered by the authors, based on morphology. Only cases with molecular diagnostics and clinical follow-up and blocks or unstained slides for further IHC studies are included. **Result:** Fourteen (14/19) cases were diagnosed as MM with morphology indistinguishable from SSa, based on lack of the t(X;18) by FISH and/or PCR, whereas 5 cases were diagnosed as SSa based on molecular diagnostics in conjunction with morphology. The mean age at diagnosis was 40.6 and 70.35 years for SSa and MM respectively. In the MM group, 21% of the patients were female, compared to 80% in the SSa group. Median survival after diagnosis was 9 months for MM, whereas all of the SSa patients were alive after follow-ups ranging from 3 months to 21 years. On average, MMs were larger tumours (average size of 97 mm, ranging from 20 to 220 mm), compared to 37 mm (range 20-50 mm) in SSa. Pleural plaques were present in 9 of the MM patients, with no information on plaques for 4 patients, and with 1 patient not having plaques, whereas only one of the SSa patients was confirmed as having pleural plaques. Of note, 7 of the MMs showed positive labelling for TLE1, with 7 MM not showing labelling, whereas all 5 SSas showed positive labelling. **Conclusion:** This indicates that positive labeling for TLE1 in isolation is insufficient for discrimination between MM vs SSa in pleura-based lesions with SSa-like morphology, and that molecular studies remain the gold standard for diagnosis.

Keywords: Pathology Diagnosis, Mesothelioma, SYNOVIAL SARCOMA

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-004 YB-1 SUPPRESSES MIR-137 VIA A FEED FORWARD LOOP, INCREASING YB-1 LEVELS, MIGRATION AND INVASION IN MALIGNANT MESOTHELIOMA

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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. Besides numerous other functions, YB-1 has been described to stimulate migration and invasion via regulation of EMT-related factors such as Snail and Twist. The microRNA miR-137 is a small, non-coding RNA, which has been shown to have tumour-suppressor functions by targeting multiple oncogenes including YB-1. In this study we characterised the relationship between miR-137 and YB-1 expression in MPM and investigate their roles in regulating malignant behaviour such as migration and invasion. **Method:** Expression levels of miR-137 and YB-1 were determined by RT-qPCR and immunoblot. Synthetic mimics were used to overexpress miR-137. For YB-1 knockdown and overexpression, siRNAs or expression plasmids were used, respectively. Cell migration was measured by live cell videomicroscopy followed by manual single cell tracking. Invasion was assessed by an agarose spot invasion assay. **Result:** While miR-137 expression varied among our panel of MPM cell lines, YB-1 was consistently overexpressed in tumour cells compared to controls. We observed a trend towards an inverse correlation between YB-1 and miR-137 levels. Transfection with a miR-137 mimic resulted in significantly decreased levels of YB-1 and a direct interaction was confirmed by luciferase reporter assays. Interestingly, modulation of YB-1 expression led to inversely correlated changes in miR-137 levels, strongly suggesting that elevated YB-1 levels suppress miR-137. Thus, increases in YB-1 expression reduce expression of the YB-1 regulator miR-137, which in turn leads to further elevation in YB-1 via a feed-forward loop. In terms of functional effects, both miR-137 mimics and YB-1 knockdown significantly inhibited MPM cell migration and invasion. YB-1 overexpression, in contrast, stimulated cell motility and invasive growth. **Conclusion:** Our data highlight a crucial role of YB-1 in the regulation of migration and invasion, which are key characteristics of MPM. Additionally, we identified a regulatory circle between YB-1 and its targeting microRNA miR-137. Targeting this loop, by both miR-137 overexpression and YB-1 inhibition, could serve as a potential therapeutic strategy in MPM.

Keywords: Mesothelioma, invasion, YB-1

P1.09: MESOTHELIOMA -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-005 TARGETING YB-1 INDUCES EITHER DRUG SENSITISATION OR RESISTANCE VIA DISTINCT MECHANISMS IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy and current therapy is essentially palliative. YB-1 is a multifunctional oncoprotein associated with poor patient outcome in tumours including NSCLC and is related to increased chemoresistance. It is widely accepted that YB-1 plays a role in the cell growth of many tumours. YB-1 has been implicated in suppressing apoptotic pathways such as the mTOR/STAT3 pathway and disrupting the cell cycle via transcriptionally regulating cyclins A, B1 and D1 in multiple cancers. We recently found YB-1 to be overexpressed in MPM cells and that siRNA-mediated knockdown inhibited growth. Here we investigate the mechanisms behind YB-1's role in MPM cell growth and subsequent effects on drug resistance. **Method:** YB-1 expression and *YBX1* mRNA was determined by Western blot and RT-qPCR, respectively, in MPM cell lines and their drug resistant sublines. Growth assays and colony formation assays with or without siRNA transfection elucidated the role of YB-1 in MPM growth. These were also conducted in combination with cisplatin, gemcitabine and vinorelbine treatment. TALI apoptosis assays were conducted to investigate the effect of YB1 silencing in MPM cells. **Result:** YB-1 siRNA significantly inhibited the growth of MSTO, VMC23 and MM05 cells ($P<0.05$) and was overexpressed compared to the immortalised mesothelial cell line MeT-5A in MSTO and VMC23. TALI apoptosis assays revealed that growth inhibition was due to apoptosis and necrosis in MSTO cells but not in VMC23, suggesting cell cycle arrest to be the cause of growth inhibition in this cell line. Interestingly, YB-1 knockdown in MSTO cells resulted in a sensitisation to cisplatin, gemcitabine and vinorelbine, but increased resistance to these drugs in VMC23 and MM05, suggesting a link between the mode of growth regulation YB-1 plays and the effect of its silencing on innate drug resistance in MPM cells. Additionally, YB1 levels were upregulated in MSTO and MM05 cells with acquired drug resistance, compared to parental cells. **Conclusion:** YB-1 plays different roles in MPM cell growth which are cell type dependent. When acting upon apoptotic pathways, YB-1 knockdown sensitised MPM cells to chemotherapy. In other cases, YB-1-mediated cell cycle arrest resulted in heightened resistance. Finally, YB-1 is upregulated in cells with acquired drug resistance, indicating that it plays an important role in the acquired resistance to cisplatin, gemcitabine and vinorelbine in MPM.

Keywords: Cell cycle, drug resistance, Y-box binding protein 1

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-006 JMJ AND BRD DOMAIN FAMILY MEMBERS IN MALIGNANT PLEURAL MESOTHELIOMA: POTENTIAL THERAPEUTIC TARGETS OR NOT?

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Background: Malignant pleural mesothelioma (MPM) is an aggressive rare cancer affecting the pleura and is predominantly associated with prior exposure to asbestos. Treatment options are limited, and most patients die within 24 months of diagnosis. There is an urgent unmet need to identify new therapeutic options for the treatment of MPM. Asbestos fibres contain transition metals such as iron, and may cause an alteration of iron homeostasis in the tissue. In addition, asbestos fibres have also been shown to have high affinity for histones, and therefore may result in high accumulation of iron around chromatin. Lysine Demethylases (KDMs) containing a JmjC domain require both Fe2+ and 2-oxoglutarate as co-factors to regulate gene expression. Bromodomain containing proteins a family of chromatin reader proteins, have potential therapeutic efficacy against various malignancies. Long non-coding RNAs (lncRNAs) have also been shown to play a role as oncogenic molecules in different cancers. Several such lncRNAs have now been shown to locate to the same chromosomal region as various KDMs. We therefore examined the expression of various JmjC and Brd members (along with any associated lncRNAs) in MPM and assessed some for their clinical potential using existing small molecule inhibitors. **Method:** A panel of MPM cell lines and a cohort of snap-frozen patient samples isolated at surgery comprising benign, epithelial, biphasic, and sarcomatoid histologies were screened for expression of various BRD and JmjC members and associated lncRNAs by RT-PCR. IHC for KDM4A was performed on a cohort of FFPE specimens. The effects of treatments with small molecule inhibitors targeting these proteins on both cellular health and gene expression were assessed. **Result:** The expression of the various KDMs was detectable across our panel of cell lines. In primary tumours the expression of many of these genes were significantly elevated in malignant MPM compared to benign pleura ($p<0.05$), and significant differences were also observed when samples were analysed across different histological subtypes. Treatment of mesothelioma cell lines with various small molecule inhibitors caused significant effects on cellular health and on the expression of a panel of genes. **Conclusion:** The expression of various KDMs, BRD genes and associated lncRNAs are significantly altered in MPM. Small molecule inhibitors directed against these show potential therapeutic efficacy with significant anti-proliferative effects. We continue to assess the effects of these compounds on gene expression and cellular health to confirm their potential utility as novel therapies for the treatment of MPM.

Keywords: Bromodomain, lncRNA, Jumonji

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-007 TARGETING MET/TAM RECEPTORS IN MESOTHELIOMA: ARE MULTI-TKIS SUPERIOR TO SPECIFIC TKI?

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Background: Malignant pleural mesothelioma (MPM) is an aggressive inflammatory cancer associated with exposure to asbestos, and most patients die within 24 months of diagnosis. There is an urgent need to identify new therapies for treating MPM patients. Targeting "addicted" receptor tyrosine kinase (RTK) signalling networks has become a critical therapy option in cancer therapy. RTK hetero-dimerization may however, be a key element in the development of resistance to such therapy. As such Tyrosine kinase inhibitors (TKIs) with the ability to target multiple receptors may have superior efficacy to those targeting individual receptors. We and others have identified c-MET, MST1R (also known as RON), Axl and Tyro3 as RTKs frequently overexpressed and activated in MPM, making these attractive candidate targets. Several agents have been developed which target these. LCRF0004 specifically targets MST1R, whereas BMS-777607, RXDX-106 or Merestinib (LY2801653) are orally bioavailable small molecule inhibitors which inhibit c-MET, MST1R, Axl and Tyro3 at nM concentrations. These drugs may therefore have clinical utility in the treatment/management of MPM. **Method:** Expression of RON/MET/TAM and associated ligands were assessed in a cohort of patient samples and MPM cell lines comprising benign, epithelial, biphasic, and sarcomatoid histologies. *In vitro* and *in vivo* experiments were undertaken to determine the efficacy of single and multi RTK targeting agents (LCRF0004, RXDX-106, BMS-777607). The effects of LCRF0004 and BMS-777607 were subsequently examined in an *in vivo* SQ xenograft tumour model. **Result:** mRNA expression of the RON/MET/TAM family and associated ligands (MSP, GAS6) was detected in a large panel of normal pleural and MPM cell lines. In a cohort of patient samples, mRNA levels of c-MET, Axl, Tyro3 and various isoforms of MST1R (flRON, sfRON, t-ΔRON) and MSP but not Gas6 or MERTK were increased in tumours compared with benign pleural samples ($p<0.05$). No MET Exon 14 skipping mutations were detected. RTK targeting agents displayed *in vitro* efficacy in terms of reduced proliferation. *In vivo*, the multi-target TKI (BMS-777607) demonstrated superior anti-tumour activity compared with LCRF0004 (MST1R specific compound). IHC analysis of the xenograft tumours showed high cytoplasmic expression of Vimentin, Cytokeratin and Calretinin, with significant necrosis in many. **Conclusion:** Our data suggests that a multi-TKI, targeting the RON/MET/TAM signalling network, is superior to selective RTK inhibition as an interventional strategy in MPM.

Keywords: c-MET/MST1R, TAM Receptors, TKI

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-008 A 4-MICRORNA SIGNATURE IN SERUM CAN DISCRIMINATE BETWEEN NON-SMALL-CELL LUNG CANCER AND MALIGNANT PLEURAL MESOTHELIOMA

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Background: Differential diagnosis of malignant pleural mesothelioma (MPM) and non-small cell lung cancer (NSCLC) can be difficult. For both malignancies various studies have in recent years investigated circulating cell-free microRNAs (miRs) as potential diagnostic markers, with most of these focusing on NSCLC. One of the most recent studies has suggested a 4-miR signature consisting of miR-141, miR-200b, miR-193b and miR-301 in serum to be specific for NSCLC patients. Here, we investigated the value of this 4-miR signature in discriminating serum samples from NSCLC and MPM patients. **Method:** RNA was extracted from a series of serum samples from 98 NSCLC, 98 MPM and 96 healthy controls collected at the Netherlands Cancer Institute between 1995 and 2011. MicroRNA-specific TaqMan assays were used to quantify serum microRNA levels in the t groups which after initial quality control consisted of 65, 68 and 58 samples in the NSCLC, MPM and control groups, respectively. Expression levels of individual microRNAs between the different groups were analysed using one-way ANOVA with Tukey-Kramer Posthoc Test. Binary logistic regression modelling was used to generate the 4-miR-signature, for which accuracy in discriminating NSCLC from MPM or healthy was analysed by ROC curve analysis. **Result:** Analysis of the signature microRNAs showed for all 4 miRs trends towards higher abundance in serum from NSCLC patients. Statistical significance was however only reached for miR-141, which was found to be increased by 4.4-fold in NSCLC compared to healthy controls ($p=0.014$) and by 5.6-fold in NSCLC vs MPM ($p=0.004$). Although we did not observe significant differences in abundance for all microRNAs, ROC curve analysis of the 4-miR signature confirmed the discriminatory potential with an AUC 0.73 (95% CI: 0.62-0.85) for NSCLC vs healthy controls. When applying the best achievable Youden Index as cut-off point, the signature showed a sensitivity of 91.4% and a specificity of 44.4%. In addition to being able to discriminate NSCLC from healthy controls, the 4-miR-signature also proved to be valuable for discriminating NSCLC from MPM, where an AUC of 0.77 (95% CI: 0.66-0.89), a sensitivity of 74.3% and a specificity of 80.4% could be observed. **Conclusion:** Initial analyses have confirmed the diagnostic potential of the previously described NSCLC-specific serum-based microRNA signature for distinguishing NSCLC from healthy controls. In addition, we have shown that the same signature can also discriminate between NSCLC and MPM.

Keywords: MicroRNAs, NSCLC, Mesothelioma

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-009 EVALUATION OF A COMBINED MICRORNA-CLINICAL SCORE AS PROGNOSTIC FACTOR FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: In 2015, a 6-microRNA signature (miR-Score, Kirschner et al 2015) was demonstrated to show high prognostic accuracy in a series of surgical specimens (with and without induction chemotherapy) from patients with malignant pleural mesothelioma. In-depth analysis of matching pre- and post-chemotherapy tissue specimens has recently shown that a refined 2-miR-Score appears more suitable for use in diagnostic chemo-naïve specimens (Kirschner et al, WCLC 2016). Here, in addition to continued validation, we also aimed to further improve the prognostic accuracy by combining the 2-miR-Score with known clinical prognostic factors. **Method:** Binary logistic regression modelling was used to build a combined score consisting of the 2-miR-Score and the clinical prognostic factors age (<60 years vs >60 years at diagnosis), gender and histological subtype (epithelioid vs non-epithelioid). In addition, microRNA analysis (RT-qPCR) was performed in an additional 33 pairs of chemo-naïve (diagnostic biopsy) and chemo-treated (EPP) specimens. Accuracy of the investigated scores in predicting a good prognosis (>20 months survival post-surgery) was evaluated by ROC curve analysis. **Result:** Combining the refined 2-miR-Score with the clinical prognostic factors histological subtype and age

at diagnosis, increased the overall accuracy of the 2-miR-Score in both chemo-naïve diagnostic (AUC=0.80; 95% CI: 0.65-0.95) and post-chemotherapy (AUC=0.86; 95% CI: 0.73-0.98) specimens. Addition of gender as clinical prognostic factor, did not result in further increases, hence this factor was not included in the combined score. Investigation of an additional set of 33 matched pairs of chemo-naïve and post-chemotherapy tissue samples, confirmed the improved prognostic accuracy of the combined score, with AUCs of 0.76 (95% CI: 0.59-0.92) and 0.79 (95% CI: 0.64-0.95) for chemo-naïve and post-Chemotherapy specimens, respectively. Furthermore, addition of the clinical factors resulted in an increase in specificity of the prognostic score from previously 55-65% to now 65-75%, while keeping sensitivities at the previous levels of 75-85%. Importantly, the combined microRNA-clinical Score did not only outperform the 2-miR-Score, but also the clinical factors alone. **Conclusion:** This validation has confirmed the prognostic potential of the novel 2-miR-Score. Furthermore, addition of known clinical prognostic factors was shown to result in a combined Score with increased prognostic accuracy. In addition to continued validation, in currently ongoing analyses we are also investigating combining the 2-miR-Score with our previously proposed multimodality prognostic score (MMPS; Opitz et al 2015).

Keywords: Prognosis, Mesothelioma, MicroRNAs

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MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-010 PD-L1 REACTIVITY OF TUMOR CELLS CAN SUCCESSFULLY BE DETERMINED IN MALIGNANT MESOTHELIOMA EFFUSIONS

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Background: Malignant Mesothelioma (MM) is an aggressive, fatal tumor. Current therapeutic options only marginally improve survival. Programmed Cell Death Ligand 1 (PD-L1) is a dominant mediator of immunosuppression, binding to Programmed Cell Death 1 (PD-1). PD-L1 is up-regulated in cancer cells and the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion, thus providing a target for anti-tumor therapy. Further, a correlation between PD-L1 expression and prognosis has been reported. Studies performed on histological material have revealed expression of PD-L1 in MM but no study has so far been performed on MM effusions. **Method:** PD-L1 expression was determined by a commercially available antibody (clone 28-8) in 74 formalin-fixed, paraffin-embedded cell blocks from body effusions obtained at diagnosis from patients with MM. The presence of MM cells was confirmed with CK5/6, Calretinin and EMA and the admixture of macrophages was assessed with CD68. Only cases containing more than 100 tumor cells were assessed. Partial or total circumferential staining in tumor cells, regardless of intensity, was considered positive. Survival time was calculated from the appearance of the first malignant effusion until death. **Result:** Out of 63 samples with sufficient cell block material, only 2 had to be eliminated due to few tumor cells (<100). Reactivity was seen in 23/61 (38%) of cases and was classified as ≥ 1-5% (9 cases), > 5-10% (4 cases), > 10-50% (4 cases) and > 50% (6 cases) positive cells. Survival times did not differ significantly between patients with PD-L1 positive and PD-L1 negative tumors (median 16 resp. 10 months, log rank p=0.16) **PDL-1 reactivity in mesothelioma effusion** (> 50% PD-L1 positive malignant cells) Left**:** HTX staining; Right**:** PD-L1 **Conclusion:** MM effusions are suitable for immunocytochemical (ICC) assessment of PD-L1 expression in malignant cells and the results are similar to those reported for histological specimens

Keywords: effusions, PD-L1, malignant mesothelioma

P1.09: MESOTHELIOMA -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.09-011 LUME-MESO PHASE II/III STUDY: NINTEDANIB + PEMETREXED/CISPLATIN IN CHEMO-NAÏVE PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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Background: Pemetrexed/cisplatin is the standard first-line treatment for unresectable malignant pleural mesothelioma (MPM), with median overall survival (OS) of ~1 year. Nintedanib is a triple angiokinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, platelet-derived growth factor (PDGF) receptors α/β and fibroblast growth factor receptors 1–3. VEGF and PDGF overexpression are associated with poor prognosis in MPM, and nintedanib has demonstrated efficacy in preclinical MPM models. Nintedanib also targets the Src and Abl kinases, which are involved in MPM cell migration. A randomised Phase II trial of nintedanib or placebo + pemetrexed/cisplatin in MPM followed by maintenance nintedanib or placebo, with progression-free survival (PFS) as the primary endpoint, was performed. With regulatory authority guidance, the Phase II data were unblinded. At the primary analysis, PFS benefit was observed with nintedanib, and confirmed at the updated analysis (hazard ratio [HR]=0.54, 95% confidence interval [CI]: 0.33–0.87; p=0.010; median PFS: nintedanib 9.4 months vs placebo 5.7 months). A strong signal towards improved OS also favoured nintedanib (HR=0.77, 95% CI: 0.46–1.29; p=0.319; median OS: 18.3 vs 14.2 months). The study was expanded to include a confirmatory Phase III part based on the primary PFS results, and the Phase II data assisted in planning of the Phase III part, including sample size estimation. Nintedanib was granted US Food and Drug Administration orphan drug designation for the treatment of MPM in December 2016. **Method:** The Phase III part of the study (NCT01907100) is currently recruiting participants. Four hundred and fifty chemotherapy-naïve patients worldwide (~140 sites in 27 countries), aged ≥18 years with unresectable MPM of epithelioid histology and Eastern Cooperative Oncology Group performance score 0–1 will be randomised 1:1 to receive up to six 21-day cycles of pemetrexed (500 mg/m^2)/cisplatin (75 mg/m^2) on Day 1 + nintedanib or placebo (200 mg twice daily, Days 2–21), followed by nintedanib or placebo monotherapy until disease progression or undue toxicity. The primary endpoint is PFS with the key secondary endpoint being OS. An adaptive design will be used at the time of the primary PFS analysis to reassess the number of OS events for sufficient OS power. Other secondary endpoints are objective response and disease control (using modified Response Evaluation Criteria in Solid Tumors). The frequency and severity of adverse events, as well as health-related quality of life, will also be assessed. An exploratory analysis of predictive/prognostic biomarkers is planned. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: monotherapy, nintedanib, maintenance

P1.09: MESOTHELIOMA -
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P1.09-012 A PRE-CLINICAL INVESTIGATION OF INTRAPLEURAL CURCUMIN TREATMENTS AS AN ADJUNCT THERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy originating in pleural mesothelial cells with median survivals of approximately 12 months following diagnosis. Recently, anti-angiogenic therapies have been trialled with only a modest effect. This may be, in part, due to alternative mechanisms of tumour vascularisation such as vasculogenic mimicry (VM), the ability of tumour cells to form fluid carrying vascular channels. Curcumin, a polyphenol extracted from the spice turmeric, has numerous anti-cancer and anti-inflammatory properties. Our aims were to investigate the effect of curcumin on vasculogenic mimicry and to determine if curcumin acts by disrupting microRNA profiles of mesothelioma cells. In preparation for future clinical trials, we evaluated the safety of curcumin treatments *in vivo*, when applied to the pleural cavity. **Method:** Mesothelioma cell lines NCI-H226 and NCI-H28, as well as patient-derived primary mesothelioma cells isolated from pleural effusions, were used for *in vitro* experiments. Matrigel tube formation assays were performed to assess if curcumin could inhibit VM *in vitro*. Small RNAseq was performed to determine if 6 h curcumin (20 mM) treatments had an effect on microRNA expression. Curcumin (80 mg/kg) was injected into the pleural cavity of Fischer 344 rats (n=6) and blood was taken at 1.5 h, 24 h, 48 h, 7 days, 14 days and 21 days. Rats were euthanized at 48 h, 1 week and 3 weeks (n=2). Parietal pleura, lung, kidney, liver brain and heart tissues were obtained and examined for signs of gross tissue damage and histopathological changes such as inflammation, and necrosis. Curcumin plasma and concentrations were measured using UPLC-MS to determine systemic distribution of curcumin following intrapleural treatments. **Result:** Non-cytotoxic curcumin treatments (20-10 mM) significantly inhibited the ability of mesothelioma cells to perform vasculogenic mimicry *in vitro* in a dose dependent manner. The microRNA expression profiles differed greatly between each mesothelioma sub-type. Minimal curcumin-induced change was observed, however differential expression analysis revealed some potential microRNA targets. No adverse effects were observed following intrapleural curcumin administration. Encapsulated curcumin deposits were observed in the pleural cavity of rats at 1 and 3 weeks following curcumin administration. Histological analysis revealed focal reactive mesothelial hyperplasia and a histiocytic response towards curcumin. Lung, liver, heart, brain and kidney tissues all display normal histological appearances. Curcumin was detected in the plasma samples of rats receiving intrapleural curcumin with peak concentration observed at 1.5 h post curcumin treatment (387-100 μg/ml). **Conclusion:** Intrapleural curcumin treatments may be suitable as adjunct treatment for MPM.

Keywords: Vasculogenic Mimicry, Mesothelioma, curcumin

P1.09-013 PROFILING RESPONSE TO CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA AMONG HISPANICS (MESO-CLICAP)

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Background: Malignant pleural mesothelioma (MPM) is a rare malignant disease, and the understanding of molecular pathogenesis has lagged behind other malignancies. **Method:** A series of 53 formalin-fixed, paraffin-embedded tissue samples with clinical annotations were retrospectively tested for BAP1 and PI3K mutations and for mRNA expression of TS and EGFR. Immunohistochemistry staining for CD26 (dipeptidyl-peptidase IV, DPP-IV) and Fibulin3 (Fib3) proteins were also performed. Outcomes like progression free survival (PFS), overall survival (OS) and response rate (ORR) were recorded and evaluated according to biomarkers. Cox model was applied to determine variables associated with survival. **Result:** Median age was 58 years (range 36-76), 27 (51%) were men, 89% were current or former smokers, and six patients had previous contact with asbestos. 77% had a baseline ECOG 0-1 and almost all patients (n=52/98%) received cisplatin or carboplatin plus pemetrexed (Pem) as first line; 58% of them were treated with Pem as maintenance for a mean of 4.7 +/-2.8 cycles. 53.5% and 41.5% of patients were positive for CD26 and fibulin-3, while 49% and 43.4% had low levels of EGFR and TS mRNA, respectively. The majority of epithelioid and biphasic types expressed CD26 (p=0.008), Fibulin3 (0.013) and had lower levels of TS mRNA (p=0.008). Mutations in PI3K (c.1173A> G, c.32G> C and c.32G> T) were found in 5 patients and only one patient had a mutation in BAP1 (c.241T> G). First line PFS were significantly longer in CD26+ (p=0.0001), in those with low EGFR mRNA expression (p=0.001), in patients with positive Fib3 (p=0.006) and lower TS mRNA expression (p=0.0001). OS were significantly higher in patients with CD26+ (p=0.0001), EGFR- (p=0.001), Fib3 + (p=0.0002) and low TS mRNA expression level (p=0.0001). Multivariate analysis found that CD26+ (p=0.012), Fib3 (p=0.020) and TS mRNA levels (p=0.05) were independent prognostic factors. **Conclusion:** CD26, Fib3 and TS were prognostic factors significantly associated with improved survival in patients with advanced MPM.

Keywords: Mesothelioma, CD26, pemetrexed

P1.10-001 HOPE FOR PEOPLE LIVING WITH METASTATIC LUNG CANCER

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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.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: rural india, NGO, palliative care

P1.10-002 OUTCOME OF PILOT RCT IN LUNG CANCER SURGERY PATIENTS RECEIVING EITHER PREOP CARBOHYDRATE & POSTOP NUTRITIONAL DRINKS OR WATER

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Background: In recent thoracic surgical studies, malnutrition and/or weight loss are important risk factors for complications after surgery. However, it is uncertain whether modifying or optimising perioperative nutritional state with oral supplements results in a reduction in complications or malnutrition. Enhanced Recovery After Surgery (ERAS) programmes in non-lung surgery include pre-surgery optimisation with carbohydrate loading drinks and post-surgery nutritional supplements. These interventions have proven highly effective in reducing post-operative complications. No trials have been performed in thoracic surgery to assess the impact. **Method:** Single centre mixed method open label Randomised Controlled Trial (RCT) was conducted to assess the feasibility of carrying out a large multicentre RCT in patients undergoing lung resection. A nutritional intervention regime of preoperative carbohydrate-loading drinks 4x200mls evening before surgery and 2X200mls the morning of surgery, and early postoperative nutritional protein supplement drinks twice a week for 2 weeks was compared to the control group receiving an equivalent volume of water. Trial feasibility measures were collected as primary outcome. Postoperative pulmonary complications were measured using the Melbourne group scale along with additional surgical complications. Visual analogue scores of symptoms, Quality of Recovery score 40, quality of life (EQ-5D-5L) and satisfaction questionnaires were collected at baseline, in hospital, 3-4 weeks and 3 month post-surgery along with hand grip and peak flow. Qualitative semi structured interviews post-surgery were undertaken to assess patient experience of the trial and interventions. **Result:** Feasibility criteria's were met and the study completed recruitment 5 months ahead of target. All elective lung cancer surgery patients were screened of which 41% (n=64) were randomised over 6 month period. The 2 groups were well balanced and tools used to measure outcome robust. 97% of patients were compliant with nutritional drinks scheduled pre-surgery, 89% of 3 month questionnaires were returned completed. Importantly, qualitative interviews demonstrated that the trial and the intervention were acceptable to patients. Patients felt the questionnaires used captured their experience of recovery from surgery well. **Conclusion:** Current international guidelines for enhanced recovery following thoracic surgery cannot recommend pre or post-operative nutrition because of lack of evidence. We have shown an intervention and a trial design of pre-op carbohydrate-loading and post-surgery supplementation is highly acceptable to patients' with good compliance to both intervention and trial measures. A large multi-centre clinical trial is required to test clinical efficacy in improving outcomes after surgery.

Keywords: nutrition, lung surgery, Randomised Controlled trial

P1.10-003 SYNERGY IN MOTION: TRANSFERRING NURSING KNOWLEDGE FROM CLINICAL TRIALS TO STANDARD THERAPY TO ENHANCE CARE AND COMMUNICATION

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Background: Immunotherapy has changed the standard treatment for lung cancer. While Immuno-Oncology (IO) agents may be better tolerated compared to conventional chemotherapy, immune related adverse events differ from those seen with traditional chemotherapy and potentially involve every organ system. Dermatologic, gastrointestinal, hepatic and endocrine toxicities typically predominate the adverse events profile of these agents. Severe autoimmune side effects may be experienced by patients treated with these new drugs. Given the complex spectrum and varying onset of IO toxicities, (early or later in treatment), the Specialized Oncology Nurse needs to be prepared to help educate and assist patients, and identify symptoms early and navigate them promptly to the best therapeutic solution with the medical team. **Method:** A pilot questionnaire, to be administered by nurses, was developed to assess IO adverse events based on an existing toxicity algorithm in consultation with medical oncologists. Over a ten week period, from March 23rd-31 May, 2017, twenty-seven patients receiving standard of care IO (Nivolumab, Pembrolizumab) therapy were evaluated using this questionnaire by seven Ambulatory Care Nurses at the Princess Margaret Cancer Centre. The completed questionnaires were reviewed by the treating physician prior to the patients' physical assessment. **Result:** Feedback from nurses and physicians was evaluated through a multiple choice questionnaire (Likert scales). Nurses and physicians strongly agreed that the IO assessment tool was helpful in streamlining toxicity evaluation, improvement in the flow of busy clinics, alerting physicians to important toxicities. During this time period, there were fewer phone calls to the clinic regarding toxicities. With the increased awareness of patients and improved communication amongst the interprofessional team, the team was more proactive regarding the early detection and management of toxicities with the implication being safer care for patients receiving IO. **Conclusion:** Continuous monitoring of patients utilizing a validated toxicity tool is paramount with the vast array of IO agents used in the lung cancer patient journey. As Specialized Oncology Nurses in Clinical Trials, the synergistic impact of an IO toxicity questionnaire can enhance the collaboration among the interprofessional

team and ensure a proactive approach to care and symptom management. The IO questionnaire facilitated communication among the interdisciplinary team for patients on multiple IO agents, and deemed valuable by both nurses and physicians.

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P1.10-004 TESTING EFFICACY OF A PULMONARY REHABILITATION PROGRAM FOR POST LUNG CANCER RESECTION SURGERY

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Background: Lung cancer remains the number one cancer-related cause of death among Taiwanese. Surgery is to eradicate cancer cells and thus offer a cure. However, the surgery may decrease lung capacity due to the removal of the entire lobe of a lung and decrease the lung expansion due to the surgical damage . These may increase risks for postoperative pulmonary complications. Pulmonary rehabilitation enhancing lung expansion and ventilation may help to improve oxygenation and reduce postoperative lung complications in patients with lung resection for removing lung cancer. **Method:** An experimental design study. 90 lung cancer patients for a resection surgery were recruited and randomized to the control or intervention group. Patients in the control group received routine care. Patients in the intervention group practiced pulmonary rehabilitation exercise in home for 5 days before the surgery and post-operative pulmonary rehabilitation. Data on six-minute walk distance and level of fatigue werecollected at the baseline and before discharge. Information on diagnosis, stage of cancer, pre-operative lung capacity, surgery procedures, oxygen saturation, postoperative pulmonary compilations, and length of hospital stay were collected from the patients' charts. Descriptive analyses were used to describe patients' demographics, disease variables, and outcome variables. The Chi-square, T-test, and GEE were used to test the efficacy of the study interventions. **Result:** The result of GEE showed signification effects on S/F ratio, indicating the intervention group had better oxygenation compared with the control group(β = 34.13,Wald X2 = 8.32, p = .004). There was only one patient in theintervention group reported clinical significant postoperative lung complications which was statisticallysignificantly less (X2 = 8.389, p = .001) than what (n= 10) was reported in the control group. The average duration of chest drainage in the intervention group was 2.0 days (SD = 1.00) which was significantly shorter than (t =-2.324, p = .022) 2.56 days (SD = 1.25) reportedin the control group. The decrease in the six-minute walk distance from pre to post-test in the intervention group was significantly lower than it in the control group (t =3.594, p = .001). The increase in the level of fatigue from pre to post-test in the intervention group was significantly lower than it in the control group (t =5.906, p =.001). **Conclusion:** Results of the study support the efficacy of the pulmonary rehabilitation program for improvingoxygenation and aerobic capacity, as well as reducing pulmonary complications and level of fatigue in lung cancer patients after cancer resection surgeries.

Keywords: lobectomy of lungs, pulmonary rehabilitation, postoperative pulmonary complication

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P1.10-005 GENERATION OF SYMPTOM BURDEN PATIENT-REPORTED OUTCOMES FOR PATIENTS WITH LUNG CANCER

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Background: Systematic collection of patient experience of disease and treatment through validated patient-reported outcome measures (PROs) is recommended for research and practice. Symptom burden, the combined impact of disease- and therapy-related symptoms on daily functioning, is important to patients and appropriate for PRO measurement. PRO development should include literature reviews, patient input, and expert opinion for content domain specification and item generation. Our purpose is to describe initial development of symptom burden PROs for malignant pleural mesothelioma (MPM) and small-cell lung cancer (SCLC). **Method:** The MD Anderson Symptom Inventory (MDASI) Core is a 13-symptom-item (pain, fatigue, nausea, sleep disturbance, distress, shortness of breath, trouble remembering, appetite loss, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling) and 6-functional-item (general activity, mood, work, relations with others, walking, enjoyment of life) PRO measuring cancer symptom burden. Additional symptoms for specific diseases and treatments can be added. We performed systematic literature reviews for symptoms of MPM and SCLC. We conducted open-ended interviews with 20 patients with MPM and 25 patients with SCLC about their disease and treatment experiences. Descriptive exploratory analysis identified symptoms. Expert panels of physicians, other healthcare providers, patients, and family caregivers rated the relevance of symptoms from patient interviews. Symptoms consistently found in literature, mentioned in ≥ 20% of interviews, or with mean relevance ratings of "relevant/very relevant" were added to the MDASI Core to form the MDASI-MPM and MDASI-SCLC. **Result:** For MPM: Literature review found 5 major symptoms, patient interviews identified 24 symptoms, and experts rated 13 symptoms "relevant/very relevant." Five symptoms were added to the MDASI Core to make the MDASI-MPM. For SCLC: Literature review found 8 major symptoms, patient interviews identified 37 symptoms, and experts rated 20 symptoms "relevant" or "very relevant." Nine symptoms were added to the MDASI Core to make the MDASI-SCLC. Lung cancer-specific symptoms common to the two groups are: coughing, muscle weakness, malaise, and trouble with balance or falling. The additional MPM symptom was chest tightness. Additional SCLC symptoms were dizziness, constipation, difficulty concentrating, headache, and foot swelling. **Conclusion:** Patient report of the experience of MPM or SCLC frequently includes symptoms and how those symptoms interfere with daily activities. The MDASI-MPM and MDASI-SCLC are undergoing psychometric testing and may be modified based on the results. They will be the only validated measures of the symptom burden of MPM and SCLC.

Keywords: malignant pleural mesothelioma, small cell lung cancer, Patient-reported outcome

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P1.10-006 ADVERSE EVENTS AFTER FIRST-LINE TARGET THERAPY FOR NON-SMALL CELL LUNG CANCER PATIENTS IN A CASE MANAGEMENT MODEL

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Background: The application of integrated cancer treatment has improved the Nursing quality of patients with cancer. Therefore, recently the case management model has been actively implemented in Taiwan to achieve synergy between resource, communication, and coordination. By using the case management model as an analytic framework, Therefore, this study aimed to identify reasonssevere adverse events (AEs) of three epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in Non-Small Cell Lung Cancer(NSCLC) patients with EGFR mutant. **Method:** From January 2014 to December 2015, patients with lung cancer treated in a teaching hospital in southern Taiwan were recruited as the research participants, retrospectively analyzed the patients with advanced or metastatic EGFR mutation-positive NSCLC who received gefitinib, erlotinib, or afatinib as first-line treatment. **Result:** The analysis median age of the 88 patients (37 males, 51 females) was 63 years (range, 29-94 years). Sixty-two patients (70%) never smoked. 84 (95%) had adenocarcinoma(Table 1). Common adverse events in all three EGFR-TKIs included rash, diarrhea and liver dysfunction, mainly grade 3 or 4 toxicity, including rash (10.2%), diarrhea (11.4%) and hepatotoxicity (6.8%). the total frequency of AE that resulted in treatment withdrawal was 12.5%. Rash and diarrhea were the most common drug-related toxicities, of the 21.6% (19 out of 88) consult dermatology, among them females the most, fifteen patients (78.9%,15 out of 19) at dermatology for rash treatment.

Table 1. Patient characteristics

Characteristic		Number of patients	%
Gender	Male	37	42%
	Female	51	58%
Age (years)	Age (years), median(range)	63(29-94)	
ECOG-PS	0	12	14%
	1	55	63%
	2	12	14%
	3	7	8%
	4	2	2%
Histology	Adenocarcinoma	84	95%
	Squamous cell carcinoma	1	1%
	Other	3	3%
Smoking history	Current or former	26	30%
	Never	62	70%
Clinical stage	IIIA	1	1%
	IIIB	3	3%
	IV	84	95%
Type of treatment	Gefitinib	55	63%
	Erlotinib	10	11%
	Afatinib	23	26%
EGFR Mutation	18 G719X	2	2.3%
	19 Deletion	41	46.6%
	20 Insertion	1	1.1%
	20 S768I	2	2.3%
	21 L858R	30	34.1%
	21 L861Q	4	4.5%
	Double Exon	8	9.1%

Conclusion: First-line targeted therapy is the preferred standard of care for patients with advanced EGFR mutations in advanced NSCLC. a lack of adequate understanding of the disease and treatment by patients or family members. There support for case management and health education, patients can get more comprehensive treatment and Improvements to problems associated with cessation of treatment.

P1.10-007 PREPARING MESOTHELIOMA PATIENTS FOR TREATMENT: PROVIDING PSYCHOSOCIAL SUPPORT NETWORKS

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Background: As medical developments advance and individuals with mesothelioma are increasingly surviving outside of the mean, the mental health impacts of their diagnosis and of treatment on the patient remain critical to examine. Malignant Mesothelioma, with a latency period of approximately 20-40 years, has not shown a downward trend in deaths for the past 15 years (CDC). As treatment for mesothelioma continues to advance, the overall survival of MPM patients has increased. With the growing number of surviving patients, it is essential to begin a conversation about mental health impacts, such as depression, anxiety, or PTSD, as they can be detrimental to a patient's quality of life and survivorship. **Method:** We performed a literature review of the current DSM standards for temporary depression and anxiety in terminal illness, and drew recommendations about how to move forward in further discussing cancer-related PTSD and other psychosocial impacts of cancer diagnosis/treatment. **Result:** Individuals who experience the full diagnostic criteria for PTSD after a cancer diagnosis ranges from 3-4% for patient in early stages of cancer, to 35% for in patients who have completed active treatment. PTSDlike symptoms have been expressed in 20% of early stage patient experience and 80% of patients with recurrent cancer. **Conclusion:** Psychosocial advancements in mesothelioma patients need to be continually developed as medical treatments advance. Many feelings of anxiety and depression can be connected to treatment distress, and cancer-related PTSD needs to be viewed through the lens of diagnosis and treatment trauma. Anxiety, depression, and PTSD must be considered from a distinctive angle for cancer-related mental health issues; while symptoms for these mental health issues can be similar, the trauma of terminal illness is unlike other traumas. While we understand that mental health services are not a priority in underdeveloped countries, the advancement of psychosocial support networks should be a priority in treatment within developed countries to set a precedent. There must be a stronger emphasis on psychosocial research on patients in remission (NED), and to create programs to support patients that are not in active treatment. Support groups are one resource that can be thoroughly utilized, but psychosocial support networks should not be limited to support groups; programs need to be developed that are tailored to each individual's mental health issues, to sooth their anxieties, and providing coping mechanisms. Because of the distinctive void in psychosocial support networks as a whole, this is an excellent opportunity for international collaboration to improve survivorship standards in patients. Future steps should revolve around the priority of psychosocial support network discussions. Patient care needs to prioritize the mental health issues that result from the trauma of cancer diagnosis, and programs must be in place to further support the higher quality of life patients can experience.

Keywords: Mesothelioma, PTSD, Psychosocial support

P1.10-008 PALLIATIVE CARE AND HOSPICE RESOURCES ARE UNDERUTILIZED IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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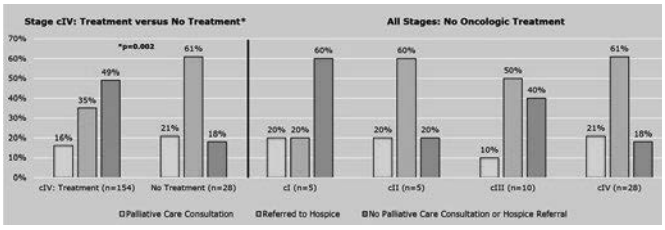
Background: The 2010 Temel et al. paper demonstrated a survival benefit from early implementation of palliative care (PC) in stage IV non-small cell lung cancer (NSCLC). Since this finding, medical systems have struggled with the adoption of clinical services for patients with advanced NSCLC, including PC and hospice resources for patients at the end of life. We aimed to document the utilization of PC and hospice resources in NSCLC patients within a large community healthcare system. **Method:** We reviewed a total of 406 stage cI-IV patients who were diagnosed and managed for primary NSCLC during 6/2013-6/2015, in a hospital network of 7 institutions with dedicated PC services. Patients were initially categorized according to the decision to undergo oncologic treatment (therapeutic or palliative) or to receive no oncologic treatment. Patients were further stratified into those who received PC consultation, those referred to hospice (without PC consultation), or those who received neither based on clinical stage. **Result:** We identified 182 stage cIV patients, of which 16% (30/182) received a PC consultation, 39% (71/182) were referred to hospice, and 45% (81/182) received neither. Of the stage cIV patients, those who received oncologic treatment were less likely to receive PC or hospice services (51%, 78/154) than patients without treatment (82%, 23/28); p=0.002 (figure). The figure also demonstrates services utilized by patients of all stages that were ineligible/refused oncologic treatment (48/406).



Conclusion: PC and hospice services were underutilized in patients with advanced disease, and in those likely to reap benefit from these resources. In addition, stage IV patients receiving oncologic treatment were less likely to receive PC or hospice services than patients undergoing no oncologic treatment. Quality improvement interventions and referral triggers targeting the implementation of PC and hospice services early in patient management are needed to meet patient's global oncologic needs.

Keywords: palliative care, Advanced Non-Small Cell Lung Cancer, Hospice

P1.11-001 ECONOMIC IMPACT OF IMMUNE CHECKPOINT INHIBITOR THERAPY IN BRAZIL AND STRATEGIES TO IMPROVE ACCESS

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Background: Immunotherapy was elected by ASCO as the most important advance in Oncology in the last 2 consecutive years. Harnessing the immune system to fight cancer cells has already changed clinical practice. Nevertheless, the cost of immune checkpoint inhibitors is a limitation to their incorporation in several countries, including Brazil. The objective of this study was to estimate the economic impact of immunotherapy and make suggestions in order to improve access for patients who benefit the most from treatment. **Method:** We assessed Brazilian cancer epidemiology data and the international literature to estimate the number of eligible patients each year. The authors estimated the economic impact according to the local medication acquisition costs converted to US dollars. The median duration of the treatment was based upon the randomized clinical trials. **Result:** We assessed 3 different agents (and one combo) for 4 indications in the treatment of lung cancer. The results are summarized in the tables below.

Drug	NSCLC1L	NSCLC2L	TOTAL	Number of Eligible Patients (% of all cancer patients)
Nivo	NA	173.0 mi All Comers	173.0 mi -10%: 154.1 -20%: 135.1	4,733 (1.0)
Pembro	354.0 mi PD-L1>50% (monoTx) 898.5 mi PD-L1<50% (+chemo)	100.0 mi PD-L1>1%	1,352 mi -10%: 1,211 -20%: 1,070	16,362 (3.5)
Atezo	NA	255.6 mi All Comers	255.6 mi -10%: 228.4 -20%: 201.2	4,733 (1.0)

Drug	Increase in Cancer Drug Total Expenditure Cost in the Public Health System	Add'l Cost Per Citizen	LYG	Cost per LYG
Nivo	+21.6% +19.3% +16.9%	$0.90 $0.77 $0.68	0.57	$99,467
Pembro	+169% +151% +134%	$6.76 $6.06 $5.35	Mono 0.73 +chemo 0.55 2L 0.69	$156,164 $200,684 $49,007
Atezo	+32.0% +28.6% +25.2%	$1.28 $1.14 $1.01	0.74	$103,095

Conclusion: The current cost of immune checkpoint inhibitors is prohibitive in the public health system in Brazil. While the country's GDP per capita is 78% lower than

that of the US, immune checkpoint inhibitors have similar prices in both. Biomarker selection, posology and lower cost drugs help decrease the total economic impact of therapy. Price discrimination and volume discounts would help improve access. Further studies and discussion with all stakeholders is needed to identify patients who would benefit the most and to implement strategies to increase access to these potentially life-saving therapies.

Keywords: pharmacoeconomics, Immunotherapy, health policy

P1.11: PATIENT ADVOCACY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.11-002 LUNG CANCER IN NONAGENARIAN PATIENTS

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Background: More than half lung cancer patients were aged more than 65-year-old. However the information in elderly patients is few, especially in nonagenarian (more than 90 year old). **Method:** We retrospectively collected clinical data of the lung cancer patient aged more than 90 year old between 2010 and 2014 in single medical center in Taiwan. The characteristics, treatment modality, and survival time were analyzed. **Result:** Eighty-three patients were enrolled: 76 patients (91.6%) were non-small cell carcinoma (NSCLC), and 7 patients (8.4%) were small cell carcinoma (SCLC), with the median overall survival (OS) of 30 and 13 weeks, p=0.005. Nine patients were stage I (10.8%), 4 patients were stage II (4.8%), 11 patients were stage III (13.3%), and 59 patients were stage IV (71.7%), with the median OS of 142, 79, 33, and 21 weeks for stage I, II, III, and IV, p<0.001. Better performance status (PS) had longer OS (median OS of 79, 66, 24, 12, and 3 weeks in PS of 0, 1, 2, 3, 4, p<0.001). Patients of simplified comorbidity score (SCS) >9 had shorter OS, but no statistical significance (median OS of 12 and 32 weeks in >9 and ≤ 9 group, p=0.065). For first-line treatment, 61.5% (8 in 13 stage I and II patients) received curative radiotherapy. For stage III patients, 63.6% (7 in 11 patients) received either radiotherapy or chemotherapy alone without concurrent chemo-radiotherapy; in stage IV, 59.3% (35 in 59 patients) received either chemotherapy or targeted therapy. Tumor *EGFR* mutation status in 30 of 46 stage IV non-squamous NSCLC patients: 55.6% was wild type and L858R was the most frequent. The response patterns in the E19D/L858R/G719X *EGFR* mutation under *EGFR*-TKI were 4 partial response, 5 stable disease, 1 progressive disease, and 3 patients were unevaluable (the response rate of 33.3% and the control rate of 75%). In 19 stage IV non-squamous NSCLC patients under *EGFR*-TKI, the *EGFR* mutated patients had longer OS than the wild type or unknown status (median OS of 36, 3, 22 weeks in *EGFR* mutated, wild type, and unknown status, p=0.018). **Conclusion:** Histology, staging, and ECOG PS had statistical significance affecting OS of nonagenarian patients. The lower SCS score patients had insignificant longer OS. The stage IV *EGFR* mutated non-squamous NSCLC patients under *EGFR*-TKI had longer OS than wild type or unknown status. Majority of nonagenarian patients could receive first line treatment, and it is important to find out the appropriate treatment for the "fit" patient.

Keywords: lung cancer, elderly, Nonagenarian

P1.11: PATIENT ADVOCACY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.11-003 A PERSONALIZED NAVIGATION PROGRAM TO INCREASE CLINICAL TRIAL PARTICIPATION OF LUNG CANCER PATIENTS

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Background: Only three to five percent of newly diagnosed cancer patients participate in clinical trials (Lara PN, 2001). We previously conducted a survey of U.S. lung cancer patients and found only 22% reported discussing clinical trial participation with their oncologist at the time of making treatment decisions (Fenton L, 2009). We hypothesized that a personalized navigation program could increase the amount of lung cancer patients initiating trial conversations with their oncologists and ultimately trial participation. Here we describe initial results from a pilot program, offering personalized, telephone-based clinical trial support to lung cancer patients. **Method:** Callers to Lung Cancer Alliance's 1-800 support line between 8/1/2016 and 6/7/2017 were asked if they had considered clinical trial participation and willing callers were referred to a clinical trial navigator for further discussion about clinical trial options. Navigators provided basic clinical trial education and a personalized list of clinical trial matches based on discussion. 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:** 36 callers were referred to a navigator during the pilot. Subsequently, 23 patients (64%) reported discussing clinical trials with their oncologist. Six of these approached a specific trial, with one enrolling, four being excluded due to not meeting eligibility criteria, and one not enrolling due to the trial being closed. Three others choose standard of care treatment over trials and one declined treatment. Two had doctors advise against trials in favor of other options. Three had disease progression preventing further trial consideration and one passed away. Seven of the 23 were still discussing trials at the end of follow up. Six of the initially referred callers chose not to discuss trials with their oncologist. The majority of these (five) reported not feeling a need to discuss trials due to having stable disease on a current treatment. The remaining caller reported feeling a lack of doctor support as reason for choosing not to discuss. Seven of the 36 initial callers were lost to follow-up. **Conclusion:** Given that 64% of the patients in the pilot program reported discussing trials with their oncologist, a personalized support program may represent an effective means of increasing clinical trial participation among lung cancer patients. This program will be expanded to include more participants and gather more information on barriers to clinical trial participation.

Keywords: clinical trials, lung cancer, patient navigation

P1.11: PATIENT ADVOCACY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.11-004 IMPACT OF LIQUID BIOPSY ON THE TREATMENT OF LOW-INCOME LUNG CANCER PATIENTS

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Background: A number of patients with lung cancer receive their oncologic care at safety net hospitals that primarily treat low-income patients. These hospitals lack resources for rapid tissue biopsy and do not routinely offer liquid biopsies. Up to 25% of patients with non-small cell lung cancer (NSCLC) have insufficient tissue recovered on biopsy for genotyping. Guardant360 is a non-invasive cell-free circulating tumor DNA (cfDNA) test providing comprehensive genomic profiling of genes recommended by the National Comprehensive Cancer Network (NCCN). **Method:** We enacted a program at Los Angeles County-USC Medical Center aimed at increasing patient access to Guardant360. For testing costs, qualified patients were enrolled in the testing company's financial assistance program, subject to meeting financial eligibility criteria. Additionally, patients had access to a mobile phlebotomy service. We identified patients with metastatic NSCLC who had undergone Guardant360 testing between August 2016 and February 2017. Medical records were reviewed for results of molecular testing (tissue and cfDNA) and the impact of Guardant360 on clinical decision-making. We also reviewed tissue-based testing for *EGFR* mutations and *ALK* rearrangements ordered at Los Angeles County-USC Medical Center on 664 patients with lung cancer from 2005 to 2015. **Result:** Guardant360 testing was sent on 10 patients with NSCLC, 9 with adenocarcinoma and one with squamous histology. Seven had somatic mutations on cfDNA analysis with 3 of these seven patients having a targetable mutation, as defined by NCCN. Tissue was sent for molecular testing on 5 of the 10 patients with four patients having cfDNA results concordant with tissue results. For the remaining five patients, there was either insufficient tissue for testing (N=3) or testing was not ordered (N=2). In this cohort of uninformative tissue results, cfDNA results found one patient with an *ALK* rearrangement, one patient with a *KRAS* mutation, and no targetable mutations in three patients. The patient with *ALK* rearrangement had therapy changed based on Guardant360 results. On review of tissue-based testing for 664 patients, ordered at Los Angeles County-USC Medical Center, there were no *ALK* and *EGFR* testing results available for 79% and 75.8% of patients, respectively. **Conclusion:** Liquid-based biopsies can be useful in identifying patients with targetable mutations. Implementation of programs that give patients access to liquid biopsy in resource-limited environments, in which over 75% had incomplete tissue results, has the potential to impact care. This data highlights the potential benefit of liquid biopsy and illustrates how this program lead to changes in therapy for some patients.

Keywords: liquid biopsy, low-income

P1.12: PULMONOLOGY/ENDOSCOPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.12-001 FLEXIBLE BRONCHOSCOPIC CRYOTHERAPY IN PATIENTS WITH MALIGNANT CENTRAL AIRWAY OBSTRUCTION

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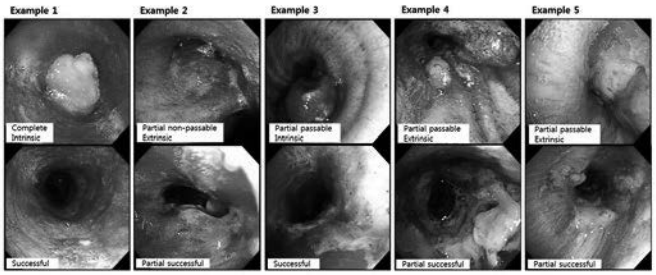
Background: Although malignant central airway obstruction has poor prognosis, cryotherapy can be used as a palliative treatment. The objective of this study is to evaluate the role of flexible bronchoscopic cryotherapy in patients with malignant central airway obstruction. **Method:** Clinical data of patients who performed flexible bronchoscopic cryotherapy for recanalization of malignant central airway obstruction from March 2014 to September 2016 were analyzed retrospectively. **Result:** 29 patients (21 males) were enrolled. Median age was of 65 years (range, 54-82) and median ECOG performance status was 3 (range, 1-3). Causes of malignant central airway obstruction were primary lung cancer of 21 cases (Squamous cell carcinoma, 12 cases; small cell carcinoma, 9 cases) and endobronchial metastasis of 8 cases (soft tissue sarcoma, 2 cases; renal cell cancer, 4 cases; glottis cancer, 1 case; endometrial cancer, 1 case). Obstruction sites were as follows: carina and both main bronchus, 4 cases; left main bronchus, 9 cases; right main bronchus, 8 cases; bronchus intermedius, 8 cases. Degree of obstruction was classified into three categories: complete, 6 cases; partial non-passable with scope, 5 cases; partial passable with scope, 18 cases. Type of obstruction was classified into two types: intrinsic obstruction, 8 cases (all endobronchial metastasis); extrinsic obstruction, 21 cases (all primary lung cancer). Complete recanalization was achieved in 8 cases (27.6%), and all of them were endobronchial metastasis. Partial recanalization was achieved 21 cases (72.4%). Dyspnea was improved in 23 patients (79.3%). There was no immediate complication, such as respiratory failure or massive bleeding.



Conclusion: Cryotherapy with flexible bronchoscopy is a feasible and effective treatment for malignant central airway obstruction, especially due to endobronchial metastasis. For more clarification, further prospective study of large scale will be required.

Keywords: cryotherapy, lung cancer, Airway obstruction

P1.12: PULMONOLOGY/ENDOSCOPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.12-002 NANOPARTICLE TARGETED FOLATE RECEPTOR 1 ENHANCED PHOTODYNAMIC THERAPY FOR LUNG CANCER

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Background: Despite modest improvements, the prognosis of lung cancer patients has still remained poor and new treatment is urgently needed. Photodynamic therapy (PDT), the use of light-activated compunds (photosensitizers) is a treatment option but its use has been restricted to central airway lesions. Here, we report the use of novel porphyrin-lipid nanoparticles (porphysomes) targeted to folate receptor 1 (FOLR1) to enance the efficacy and specificity of PDT that may translate into a minimally-invasive intervention for peripheral lung cancer and metastatic lymph nodes of advanced lung cancer. **Method:** The frequency of FOLR1 expression in primary lung cancer and metastatic lymph nodes was first analyzed by human tissue samples from surgery and endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA). Confocal fluorescence microscopy was then used to confirm the cellular uptake and fluorescence activation in lung cancer cells, and the photocytotoxicity was evaluated using a cell viability assay. In vivo fluorescence activation and quantification of uptake were investigated in mouse lung orthotopic tumor models, followed by the evaluation of in vivo PDT efficacy. **Result:** FOLR1 was highly expressed in metastatic lymph node samples from patients with advanced lung cancer and was mainly expressed in lung adenocarcinomas in primary lung cancer. Expression of FOLR1 in lung cancer cell lines corresponded with the intracellular uptake of folate-porphysomes in vitro. When irradiated with a 671 nm laser at a dose of 10 J/cm2, folate-porphysomes showed marked therapeutic efficacy compared with untargeted porphysomes (28% vs. 83% and 24% vs. 99% cell viability in A549 and SBC5 lung cancer cells, respectively. Systemically-administered folate-porphysomes accumulated in lung tumors with significantly enhanced disease-to-normal tissue contrast. Folate-porphysomes mediated PDT successfully inhibited tumor cell proliferation and activated tumor cell apoptosis. **Conclusion:** Folate-porphysome based PDT shows promise in selectively ablating lung cancer based on FOLR1 expression in these preclinical models.

Keywords: folate receptor 1 (FOLR1), lung cancer, photodynamic therapy (PDT)

P1.12: PULMONOLOGY/ENDOSCOPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.12-003 PHOTOTHERMAL ABLATION OF LUNG CANCER BY LOW POWER NEAR-INFRARED LASER AND TOPICAL INJECTION OF INDOCYANINE GREEN; A PRELIMINARY ANIMAL STUDY

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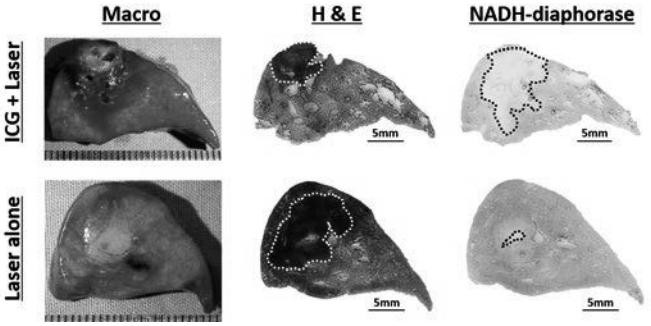
Background: Surgical resection by lobectomy with systematic lymph node dissection is the gold standard of treatment for early stage non-small cell lung cancer. However, minimally invasive tumor ablation can be an alternative treatment for patients not eligible for surgery due to comorbidities. The present study was designed to evaluate the efficacy of photothermal ablation therapy for lung cancer by low power near-infrared laser and topical injection of Indocyanine green (ICG). **Method:** 6 New Zealand white rabbits were employed for the study. Tumor suspension containing VX2 cancer cells with growth factor reduced Matrigel was inoculated into the lung using an ultrathin bronchoscope. 3 rabbits were treated by laser ablation therapy with topical injection of ICG. Another 3 rabbits were treated by laser ablation alone. All tumors were irradiated with a laser with 500 mW output at 808 nm for 15 min. The tumors were examined histopathologically to assess the ablated areas. **Result:**



The maximum surface temperature of the tumor in rabbits treated by ICG/laser and laser alone were more than 58°C and less than 40°C, respectively. The ablated areas in the rabbits using ICG/laser were statistically larger than those in the rabbits using laser alone (ICG/laser: 0.49±0.27 cm^2 vs laser alone: 0.02±0.002 cm^2) ($p < 0.05$). **Conclusion:** We clarified the efficacy of the photothermal treatment by low power near-infrared laser and topical injection of ICG using a rabbit VX2 orthotopic lung cancer model. This system may be able to be applied for transbronchial laser ablation of peripheral lung cancers.

Keywords: Indocyanine green, near-infrared laser, photothermal ablation

P1.12: PULMONOLOGY/ENDOSCOPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.12-004 THERAPEUTIC RIGID BRONCHOSCOPY FOR THE LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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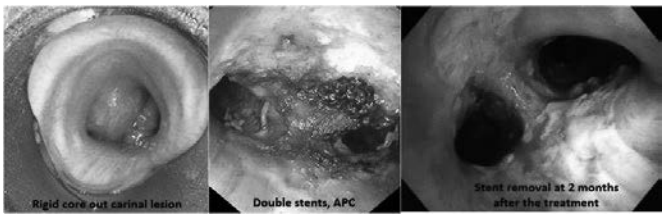
Background: Locally advanced airway obstructive NSCLC poses serious management challenges for oncologist due to coexisting obstructive pneumonia and hypoxemia. Although rigid bronchoscopic techniques have been largely replaced by flexible bronchoscopy in this century, therapeutic rigid bronchoscopy remains an important tool in the management of airway obstruction. **Method:** The present study is a retrospective cohort analysis in which all the available data were reviewed for patients referred to our service for a therapeutic airway intervention between October 2014 and May 2017. Patients who were diagnosed as having NSCLC and who underwent rigid bronchoscope airway intervention were analyzed in this study. **Result:** Thirty-one patients (13M, 18 F) were evaluated. Mean age was 65.5 years with stage IV (18), IIIB (7), IIIA (6). Twenty-two cases required endoluminal tumor debulking and/or core-out with or without Argon plasma coagulation. Self-expandable airway stents were used in 27 cases. Single stent (19), double stent (6), triple stent (2). All patients were extubated in the OR and none required a postoperative ICU stay. Four patients underwent stent removal procedure after the tumor shrunk. The average post-operative follow up period was 5.2 months (0-20 months). Median survival was 10 months. Fourteen of patients are alive and continue to receive oncologic treatment. One of the case pictures are shown in below. A 53 years old female transferred to our service SOB. Patient is doing well and continues oncologic treatment without SOB 10 months after the initial rigid bronchoscopy intervention.



Conclusion: Immediate re-establishment of a patent airway in the setting of a malignant airway obstruction can be achieved safely and with low morbidity, allowing continuation of therapy, improving respiratory status and quality of life. Our experience has shown that pre-and post procedural multidisciplinary team involvement is critical to this success.

Keywords: Locally advanced NSCLC, Rigid bronchoscope, Theraputic bronchoscope

P1.12-005 IMPROVEMENT OF PERFORMANCE STATUS AFTER THERAPEUTIC BRONCHOSCOPY IN PATIENTS WITH AIRWAY MALIGNANCY: SINGLE CENTER EXPERIENCE

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Background: Patients with airway involvement by malignancy usually have limited treatment options due to poor performance status. They are at increase risk of mortality when compared with patients without airway involvement. The treatment provided by therapeutic bronchoscopy relieves the airway tumor and leads to improve performance status[1,2]. We report our single center experience of the performance status improvement after therapeutic bronchoscopy in patients with airway malignancy. **Method:** This is a retrospective review of patients with airway involvement of malignancy either airway obstruction or fistula who underwent therapeutic bronchoscopy from 1 July 2016 to 31 December 2016 at King Chulalongkorn Memorial Hospital. Clinical data including age, sex, type of tumor, bronchoscopic treatment, were recorded. The ECOG performance status before procedure and at 7 days after therapeutic bronchoscopy were reviewed. Complications also reported. **Result:** 43 patients(35 males, 8 females) underwent therapeutic bronchoscopy due to airway involvement of malignancy. The total procedure was 55 procedures. The mean +/- SD age was 62+/- 12 years. Table 1 showed tumor characteristics and therapeutic procedures. Table1: Tumor characteristics and procedures

Characteristics	Number
Histology and Origin	43
Adenocarcinoma Lung	12
Squamous cell Carcinoma Esophagus	15
Squamous cell Carcinoma Lung	2
Small cell Carcinoma	3
Adenocystic Carcinoma	2
Anaplastic	1
Carcinoid	2
Lymphoma	1
Metastastic carcinoma (Breast, Sarcoma, Adenocarcinoma)	5
Airway esophageal fistula	5
Location	
Trachea	10
Left main bronchus	11
Right main bronchus	12
Carina or diffuse (2or more location)	10
Procedures	55
Rigid bronchoscopy with flexible bronchoscopy	16
Flexible bronchoscopy alone	39
Nd-Yag laser	33
Combined Laser with other modalities	22
Stent placement	15
Metallic stent	12
Y stent	3

The mean +/- SD of ECOG performance status prior to procedure was 3.65+/-1.23. At day 7 after procedure, the mean +/- SD of ECOG performance status was 1.78 +/- 2.24. The ECOG performance status in patients with stent placement prior and after procedure was 4.21 +/-2.01 and 2.85 +/- 1.77 respectively. The patients who received stent placement has poorer ECOG performance status but they received about the same amount of ECOG score improvement when compared with no stent placement. The major complications were bleeding that require intervention (n=3) and respiratory failure(n=1). There was no death in this study. **Conclusion:** Therapeutic bronchoscopy improved ECOG performance status. The results of treatment can be seen within 7 days after procedure with acceptable complications. References: 1. Chest. 2006 Dec;130(6):1803-7 2. Chest. 2015 May;147(5): 1282-1298

Keywords: therapeutic bronchoscopy, airway, lung cancer

P1.12-006 THE EFFICACY OF ELECTROCAUTERY USING WIRE SNARE AS THE PRIMARY ABLATION MODALITY FOR MALIGNANT AND BENIGN AIRWAY OBSTRUCTION

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Background: Endobronchial electrocautery has not been studied extensively, but a growing experience has demonstrated that, similar to laser, it can achieve high success rates for the relief of central airway obstruction with favorable safety profile. In our institution, we use electrocautery rather than laser as the first-line heat therapy for central airway obstruction. In this study we reviewed our experience with electrocautery using wire snare with focus on its efficacy and safety. **Method:** A retrospective review of all patients undergoing endobronchial electrocautery using wire snare alone at our institution between 2010 and 2015. Data on efficacy (luminal patency, symptomatic, radiographic, or physiologic improvement) and safety (time, bleeding, complication rate) were collected. **Result:** Five patients underwent electrocautery procedure with wire snare. Of these, 4 patients had malignances (4 metastatic tumors; 1 lung, 1 colon, 1 renal, 1 melanoma) and 1 had benign (1 schwannoma). The snare wire was used as a biopsy technique for all patients, and resulted in the establishment of a diagnosis. Endoscopic improvement was seen in 100% of patients. Eighty percent of patients reported symptomatic improvement. Radiographic examination revealed luminal improvement in 100%. There have been no major complications while utilizing the wire snare, whereas minor bleeding was occurred in 1 patient who was needed extra procedure by blunt cautery probe for hemostasis. Mean procedure time was 31min. **Conclusion:** Endobronchial electrocautery using snare probe is effective and safe when used as an ablative modality in malignant and benign airway obstruction for selected patients. Compare to laser, this procedure may be equally effective and safe with significantly lower equipment cost. Further study such as well-designed prospective trial comparing laser and electrocautery is necessary to establish the appropriate role of each modality in the treatment of central airway obstruction.

Keywords: Electrocautery, Wire-Snare, Airway obstruction

P1.12-007 OUTCOMES OF RADIOTHERAPY AND ENDOSCOPIC AIRWAY STENTING FOR CENTRAL AIRWAY OBSTRUCTION IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of death from malignancy within the United States, exceeding that from breast, colon, and prostate combined. A common complication and challenge of advanced stage lung cancer is central airway obstruction (CAO). CAO can present with minimal symptoms, but often associated with hemoptysis, progressive dyspnea, and even respiratory failure. Interventions such airway stenting and radiation therapy are offered to palliate symptoms, potentially prevent future complications, and prolong survival. However, to date, very little data exists on the comparison of external beam radiotherapy (EBRT) to endoscopic airway stenting in patients with CAO related to non-small cell lung cancer (NSCLC). **Method:** Patients with NSCLC treated for CAO within the Division of Thoracic Surgery and Interventional Pulmonology from 2010-2013 were identified from diagnosis and billing codes. Patient demographics and interventions were obtained from chart review. Using the Kaplan-Meier method and log rank test, overall survival was calculated from the time to intervention; time from initial intervention to treatment failure (requiring second intervention) and/or death; ECOG status at presentation to death. **Result:** A total of 34 patients were identified that underwent palliative interventions, including initial treatment with stenting (21/34, 62%) and EBRT (13/34, 38%). No difference was identified in overall survival calculated by the Kaplan-Meier method, p=0.583. However, median overall survival tended to be longer for EBRT at 135 days (interquartile range, IQR: 83-263) compared to stenting at 44 days (IQR: 23-301), p=0.228. In addition, comparative Kaplan-Meier times to failure (second intervention/death) were significantly different, p=0.049; with a similar trend in median time to failure for EBRT at 135 days (IQR: 23-263) versus 27 days (IQR: 6-82) for stenting, p=0.063. Median survival by ECOG status was ECOG 1 – 263 days (IQR:197-463), ECOG 2 – 69 days (IQR:26-147), ECOG 3 – 107 days (IQR:51-209), ECOG 4 – 6 days (IQR:4-23), p=0.003; with sustained separation in Kaplan-Meier survival, p<0.001. **Conclusion:** NSCLC patients developing CAO represent a challenging population. Overall median survival times are poor, but appeared improved in patients receiving EBRT compared to those receiving airway stenting. From a physiologic standpoint, airway stenting often provides immediate relief of airway obstruction and respiratory embarrassment; however, our current results may question the role of airway stenting in NSCLC patients with CAO. Alternatively, additional outcomes such as quality of life and utilization of healthcare resources may also need to be explored to evaluate the full impact that EBRT and/or airway stenting may have on CAO.

Keywords: airway stent, external beam radiotherapy, central airway obstruction

P1.12-008 PHOTODYNAMIC THERAPY FOR PERIPHERAL LUNG CANCERS USING COMPOSITE-TYPE OPTICAL FIBERSCOPE OF 1.0 MM IN DIAMETER

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Background: Photodynanic therapy (PDT), is a treatment modality for many cancers, and uses a tumor-specific photosensitizer and laser irradiation. PDT is recommended as a treatment option for centrally located early lung cancer. The detection of peripheral lung cancers is increasing, and stereotactic body radiotherapy (SBRT) and percutaneous thermal ablation are emerging as alternatives to surgical resection, but PDT has not been a modality. 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 1.0 mm in diameter composite-type optical fiberscope (COF), and we evaluated the feasibility of PDT using COF for peripheral lung cancer. **Method:** This phase I study enrolled patients with peripheral lung cancers (primary tumor< 20 mm, stage IA), which were definitively diagnosed by bronchoscopic modalities using radial-probe endobronchial ultrasound (EBUS) and guide sheaths. We conducted irradiation using a diode laser (664 nm) and optical fiberscope (COF), four hours after the administration of NPe6 40 mg/m2. Before performing PDT, we evaluated the tumor lesions using EBUS through the guide sheaths for peripheral small lesions. Then, we introduced the COF into the peripheral lung cancer, observed the lesions and irradiated of red light 664 nm (120 mW, 50 J/cm2). **Result:** Five patients met our criteria, and 4cases were adenocarcinoma and 1 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, there was no morbidity including pneumothorax, pneumonia, skin photosensitivity. **Conclusion:** The 1.0 mm COF was a very useful device of NPe6-PDT for peripheral lung cancers, and PDT using the COF was a feasible and non-invasive treatment. Now, we have started phase II study of PDT using the COF for peripheral lung cancers. In the future, for non-invasive adenocarcinoma such as AIS, NPe6-PDT using COF will play an important role.

Keywords: EBUS, photodynamic therapy (PDT), peripheral lung cancer

P1.12-009 EXPERIENCE WITH FULLY COVERED METALLIC STENTS IN PATIENTS WITH MALIGNANT AIRWAY OBSTRUCTION

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Background: Airway stenting provides a solution to restore patency of the airways in patients with malignant conditions that are unsuitable for surgical procedures. Their use has been associated with significant improvement in symptoms and quality of life. There is little experience with recent commercially available fully covered metallic stents. **Method:** All patients who underwent fully silicon covered nitinol mono-filament Aerstent® (Leufen, Bess, Germany) placement at the Hospital Universitari de Bellvitge from September 2013 and February 2017 were retrospectively reviewed for medical records, bronchoscopy and microbiological results, as well as stent related complications and patient survival. **Result:** 66 stents were implanted in 54 patients during this 36 months period, with mean age of 59 years (43-81 years). The main indication of stent placement was lung cancer in 41 (76%) patients (22 squamous, 9 adenocarcinoma, 5 undetermined NSCLC, 4 small-cell lung cancer and 1 atypical carcinoid). Stents were deployed with rigid bronchoscopy under fluoroscopic control in main bronchus (n=42), trachea (n=7), and main carina (Y shape n=17). Photocoagulation with YAP laser and/or mechanical debulking was necessary in 44 (66.6%) procedures prior to stenting. Seven stents (10.6%) required repositioning after deployment using rigid grasping forceps. Major bleeding occurred in 12 procedures (18.1%) and was successfully managed with endoscopic methods. No immediate complications occurred after the procedures. In 52 cases (96.3%) immediate and significative clinical improvement in dyspnoea was registered. Median survival after first stent deployment was 144 days (6-484). 7 patients died within 30 days after the procedure. 50 patients (92%) had stent related complications during follow up (table 1).

Table 1. Rate and time to complications

	Patients (n= 54)	Time (mean) in days to detection
Mucostasis	42 (77%)	28.2
Colonization	22 (40.1%)	47.1
Granulation tissue	20 (27%)	48.8
Migration	7 (13%)	18.7
Silicon detachment	12 (22.2%)	84.5

Conclusion: In our case series, Aerstent (Leufen, Bess) has provided immediate dyspnoea relief in 96.3% of patients, without significative complications during deployment or within the first 24 hours. Mucostasis is the most common complication (77%) and is detected during the first month (mean 28.2 days).

Keywords: bronchoscopy, central airway obstruction, airway stent

P1.13-001 T1 TUMOR(≪3CM) WITH VISCERAL PLEURAL INVASION SHOULD BE CLASSIFIED AS T2A IN THE 8TH TNM CLASSIFICATION FOR LUNG CANCER

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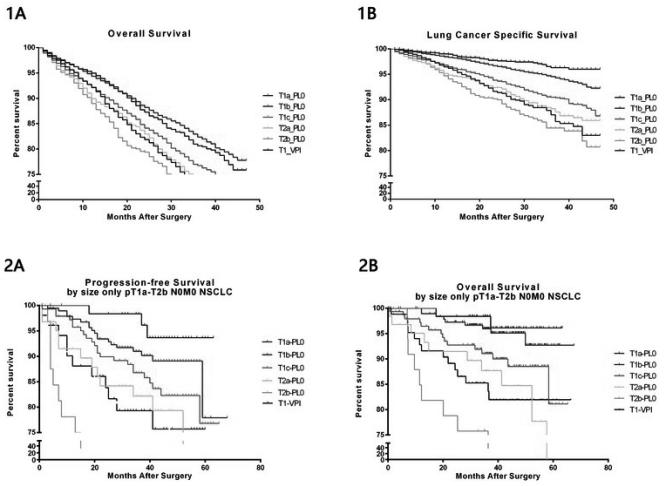
Background: The eighth edition TNM classification for lung cancer subclassified T2 into T2a (>3 to ≤4cm) and T2b (>4 to ≤5cm). T1 tumor(<3cm) with visceral pleural invasion(VPI) should be classified as T2a or T2b remain unclear. To elucidate this, we analyzed the survival of non–small-cell lung cancer(NSCLC) patients from Surveillance, Epidemiology and End Results (SEER) registry and our institute. **Method:** Within the SEER database, we selected 24245 resected pN0 NSCLC patients from 2010 to 2013 with a special interest in the prognostic impact of VPI. The VPI was defined as including PL1 and PL2 according to the TNM system. The classification of T1 tumor with VPI was investigated via discriminative power of survival curves. The further validation set was selected from Guangdong Lung Cancer Institute (GLCI). **Result:** The overall survival (OS) and lung cancer specific survival (LCSS) of T1-VPI and each stage (size only) were compared. The survival differences were statistically significant between T1-VPI and T1c, as well as T1-VPI and T2b. There were no significant survival differences between T1-VPI and T2a (OS: p=0.706; LCSS: p=0.792). And we retrospectively collected pN0 NSCLC patients between 2011-2013 from GLCI. The progression-free survival(PFS) and OS differences were also observed between T1-VPI and other groups except T2a (PFS: p=0.852; OS: p=0.970). **Conclusion:** In the 8th TNM classification for lung cancer, in which T1 tumors with VPI are upgraded to T2a, rather than T2b.



Keywords: TNM classification, NSCLC, visceral pleural invasion

P1.13-002 NEW CLINICAL T CLASSIFICATION IS ASSOCIATED WITH PATHOLOGICAL STAGE I INVASIVE ADENOCARCINOMA WITH SOLID HISTOLOGIC SUBTYPE

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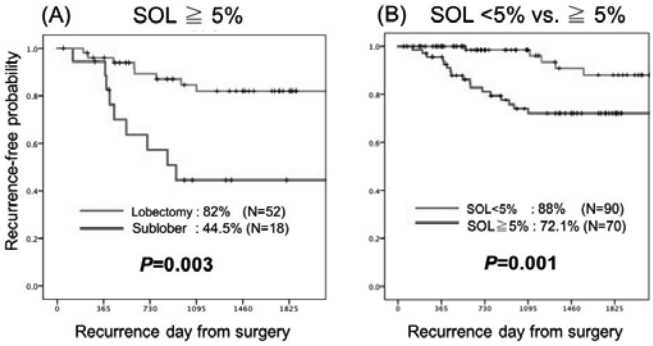
Background: Recent studies have reported that sublobar resection is not inferior to lobectomy for small-sized non-invasive adenocarcinoma; however, the adequacy for small-sized invasive adenocarcinoma (IAD) remains unclear. We have reported that, in patients with pathological stage I IAD, the presence of ≥5% solid (SOL) histologic subtype is a significant predictor of recurrence, especially for the patients undergoing sublobar resection (Figure A). The objective of this study was to identify the clinical factors associated with the presence of SOL in patients with IAD. **Method:** We retrospectively reviewed patients with therapy-naïve, pathological stage I (≤2-cm) lung adenocarcinoma, who had undergone complete resection from 1998-2015. Each tumor was evaluated by comprehensive histologic subtyping according to the 2015 WHO classification and re-evaluated preoperative thin-sliced computed tomography

to determine solid size and reclassified them according to the new TNM classification. We defined carcinoembryonic antigen (CEA) cut-off value as 2.2 ng/mL. Recurrence-free probability was estimated using the Kaplan-Meier method. **Result:** AD patients with available image was 160 cases (94 male and 66 female, 96 smokers, and median age: 69 years). Clinical T classification in the 7th edition was T1a:142, T1b:17, T2a:1, and in the 8th edition Tis:17, T1mi:3, T1a:37, T1b:100, T1c:3. The presence of ≥5% solid component (SOL) was identified in 70 patients (44%). In patients with IAD, the presence of ≥5% SOL was associated with increased risk of recurrence compared to those with SOL <5% (P=0.001, Figure B). The presence of ≥5% SOL was significantly associated with sex, smoking, clinical T classification in the 8th edition, and high CEA level (P= 0.001, P< 0.001, P< 0.001, P= 0.013, respectively). **Conclusion:** In patients with pathological stage I IAD, clinical T classification in the 8th edition, and high CEA level significantly correlated with the presence of ≥5% SOL, which was associated with recurrence after surgery.



Keywords: prognosis and predictive factors, lung adenocarcinoma histological subtype, solid adenocarcinoma

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-003 RECURRENCE DYNAMICS IN RESECTED PATHOLOGICAL STAGE I LUNG ADENOCARCINOMA DEPEND ON THE IASLC/ATS/ERS HISTOLOGICAL SUBTYPE

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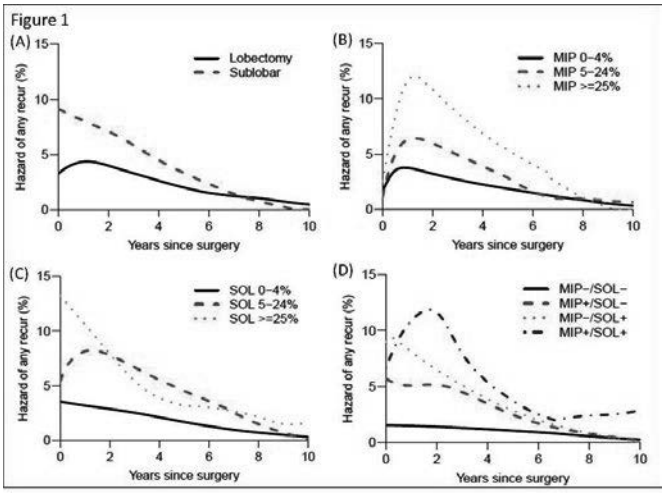
Background: Current practice guidelines recommend uniform follow-up protocol for all stage I lung adenocarcinoma (ADC) patients who underwent surgical resection. We hypothesized that the annual recurrence hazard of resected pathological stage I lung ADC patients vary according to the IASLC/ATS/ERS histological subtype. **Method:** Pathological stage I lung ADC patients who had undergone complete resection (R0) without induction therapy (N=1572, 1995-2012) were analyzed. **Result:** Among 1572 patients, 271 (18.5%) recurrences were identified (median follow-up 64.0 months) with highest peak of recurrence within first two years following resection. Patients who had undergone sublobar resection showed higher recurrence rate than those who had undergone lobectomy (Fig. 1A). The recurrence hazard increased as a function of the percentage of micropapillary (MIP) pattern (Fig. 1B), while the solid pattern contributed to the early recurrence (Fig. 1C). According to the presence of MIP and/or solid (SOL) pattern, the recurrence hazard is well stratified. Tumors without micropapillary and solid subtype show no peak with 2% of annual recurrence hazard within 10 years following resection, while tumors with both MIP and SOL patterns have the highest peak within 2 years compared to other MIP and SOL combinations. **Conclusion:** Patients with resected pathological stage I lung ADC show structured recurrence dynamics well stratified with the high risk histological subtypes, providing clinically useful prognostic information for patients and physicians.



Keywords: histologic subtype, micropapillary, solid, recurrence dynamics, follow-up

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-004 THE ROLE OF LYMPH NODE STAGING BY EBUS-TBNA IN STEREOTACTIC BODY RADIATION THERAPY FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER.

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Background: Stereotactic body radiation therapy (SBRT) is an option for treatment of patients with non-small cell lung cancer (NSCLC). Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive, diagnostic modality for mediastinal and hilar staging of NSCLC. We evaluated the diagnostic value of EBUS-TBNA in SBRT candidates and compared it to that of computed tomography (CT) and positron emission tomography (PET) scans. **Method:** Inclusion criteria for this single institutional retrospective study included 1) biopsy-proven or clinically suspicious NSCLC with diameter <6 cm; 2) no evidence of distant metastasis; 3) EBUS-TBNA staging between April 2008 and November 2014; 4) medically SBRT-eligible other than nodal staging. CT and PET positive nodes were defined as short axis ≧1cm and standardized uptake value ≧2.5, respectively. Node positive by clinical-pathologic confirmation (NPCP) was defined as confirmed malignancy by EBUS-TBNA or clinically diagnosed recurrence in hilar or mediastinal lymph nodes within one year after SBRT. The survival after SBRT was compared between CT or PET node-positive but EBUS-TBNA result-negative patients, and a matched cohort (tumor size; radiation dose; operability) who underwent SBRT in our institution within the same time period but without EBUS-TBNA staging. **Result:** There were 35 eligible patients (mean age 77±8.2, 24 male). Thirty-two (91.4%) patients had pathological confirmation of NSCLC (mean diameter 2.5±1.0 cm) (T1a N=12, T1b N=15, T2a N=7, T2b N=1). Thirty (85.7%) patients were medically inoperable. After EBUS-TBNA, 20 out of 24 patients who had positive nodes in CT (N=13) or PET (N=17) were ultimately pathologically N0. All eleven image-negative patients were N0 following EBUS-TBNA. Thirty-one patients (20 image positive plus 11 image negative) underwent SBRT. Sensitivity/specificity of CT, PET and EBUS-TBNA for NPCP were 42.9/64.3%, 100/64.3% and 57.1/100%, respectively. Positive predictive value of CT and PET for NPCP was 23.1% and 41.2%, respectively. Negative predictive value of CT, PET and EBUS for NPCP was 81.8%, 100% and 90.3%, respectively. A 1:4 (Case; N=20, Control; N=76) match was obtained. Regional failure-free survival (p=0.71, HR=0.88 CI 0.45-1.74) and disease-free survival (p=0.77, HR=1.10 CI 0.58-2.11) of the Case were not significantly different from the ones of Control. There were no major complications related to EBUS procedures. **Conclusion:** EBUS-TBNA can be considered for invasive staging in SBRT-eligible NSCLC patients with radiographically positive lymph nodes because of its safety and possibility of false positive imaging. If EBUS-TBNA result is negative, these patients may remain candidates for SBRT with comparable outcomes to those who are conventionally selected for SBRT.

Keywords: NSCLC, EBUS, SBRT

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-005 IS TUMOR SIZE FOR THE T4 DESCRIPTOR IN LUNG CANCER STAGING APPROPRIATE?

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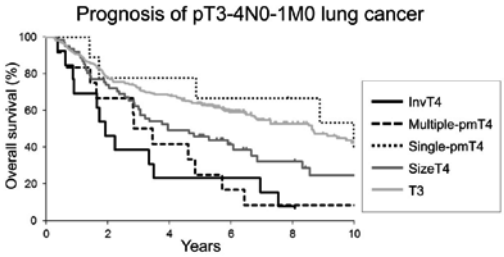
Background: According to the 8th Edition of the TNM Classification of Lung Cancer, a

tumor of >7 cm in diameter is upstaged to T4 from T3 based on the prognostic analysis of patients with pT1–4N0M0R0. However, there are two major problems with this classification. The first is selection bias; very few patients with non-size-based T4 undergo resection, whereas most patients with large tumors have surgery. The second is a diagnostic problem. Additional tumor nodules in a different ipsilateral lobe (pm2) are also T4 descriptors; however, multiple primary lung cancers may be misdiagnosed as T4 lung cancer with intrapulmonary metastasis. **Method:** A total of 378 patients with pT3–4N0–1M0 (according to the new classification) underwent complete or incomplete resection from 1992 to 2011. T4 was subdivided into invT4 (local invasion), multiple-pmT4 (pm2 with multiple nodules), single-pmT4 (single pm2), and sizeT4 (>7 cm). **Result:** The number of patients with invT4/multiple-pmT4/single-pmT4/sizeT4/T3 was 13/12/9/61/283; 5-year overall survival (OS) was 23%/25%/67%/46%/64%; and 5-year disease-free survival (DFS) was 15%/17%/67%/39%/55%, respectively. Patients with invT4 and multiple-pmT4 had poorer prognosis than those with sizeT4 in multivariate analysis (OS, hazard ratio = 2.6, $p < 0.05$; DFS, hazard ratio = 3.2, $p < 0.01$).



Conclusion: The extremely favorable outcome of single-pmT4 suggests the possibility of it being mixed up with multiple primary cancers. Non-size-based T4 patients had poorer prognosis than did sizeT4 patients even in surgical candidates, and the outcome of non-surgically treated patients seemed still worse. Tumors of >7 cm in diameter should not be treated the same as a non-size-based T4 and should be reclassified as T3b.

Keywords: T4, Tumor size, Staging

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-006 THE VALUE OF F-18 FDG PET/CT-GUIDED EBUS-TBNA IN NODAL STAGING OF NSCLC.

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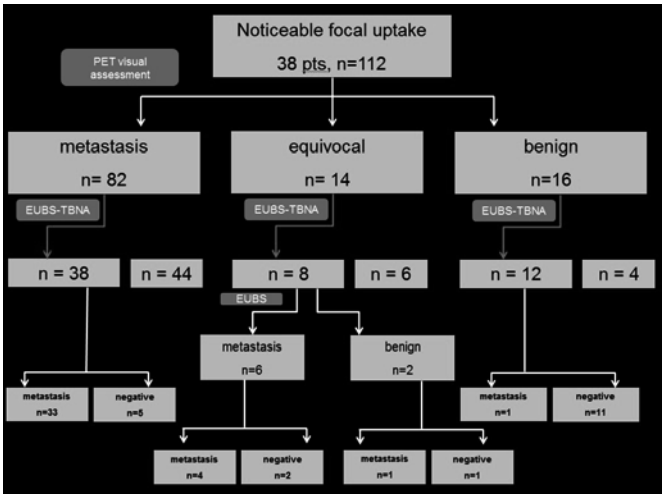
Background: Mediastinal lymph node staging in NSCLC is crucial to set treatment options. But correct nodal staging is also challenging, especially, in regions of endemic for granulomatous diseases. The purpose of the study is to evaluate the value of PET-guided EBUS-TBNA and the efficacy of PET/CT for prediction of cytopathological results of lymph node staging in NSCLC. **Method:** 38 patients who underwent F-18 FDG PET/CT for initial staging of NSCLC and subsequent mediastinal node staging by EBUS-TBNA for clarification of the hilar,mediastinal nodes between Sep.2013 and Jul.2014 were retrospectively reviewed. The clinical nodal staging with PET/CT were correlated with cytopathological results after TBNA. Overall sensitivity, specificity, PPV, NPV,and accuracy were evaluated. **Result:** From 38 PET scans, total 112 thoracic lymph node stations had noticeable focal hypermetabolisms.82 FDG avid stations were suspected to have metastasis,16 stations were considered as inflammatory nodes,and 14 stations were reported as equivocal findings. The majority of the primary lung pathology which showed equivocal nodal PET findings were adenocarcinoma (9/14). Total 58 thoracic lymph nodes (PET positive 38, PET negative 12, and equivocal PET finding in 8 nodes, respectively) were aspirated in 38 patients. Malignancy was detected in 39 (67.2%) out of 58 lymph nodes. (Figure 1. flow chart)



2 patients up-staged from N1 to N2,1 patient up-staged from N2 to N3,and 1 patient down-staged from N3 to N2 after PET-guided EBUS-TBNA. From 8 lymph nodes that showed equivocal PET finding,6 were enlarged and showed heterogenous hypoechogenicity on EBUS.4 node of those were proved to be cytologically metastatic lymph nodes. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of PET-guided EBUS-TBNA on a node-based analysis was 94.9%, 63.2%, 84.1%, 85.8%, and 84.5%, respectively when we combined EBUS findings with PET. **Conclusion:** PET-guide EBUS-TBNA offers an effective, accurate, and minimally invasive strategy for evaluating lymph node staging in NSCLC.

Keywords: F-18 FDG PET/CT, EBUS-TBNA, NSCLC

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-007 IS CENTRAL LUNG TUMOR LOCATION REALLY PREDICTIVE FOR OCCULT MEDIASTINAL NODAL DISEASE IN (SUSPECTED) NSCLC STAGED CN0 ON PET-CT?

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Background: Based on a 20-30% prevalence of occult mediastinal disease, current guidelines recommend preoperative invasive mediastinal staging in patients with central tumour location and negative mediastinum on PET-CT. A uniform definition of central tumour location is lacking. Our objective was to determine the best definition in predicting occult mediastinal disease. **Method:** A single institution prospective database was queried for patients with (suspected) NSCLC staged cN0 after PET-CT and referred to invasive staging and/or primary surgery. We evaluated 5 definitions of central tumour location (table 1). **Result:** Between 2005 and 2015, 822 patients were eligible. Radio-occult lesions were excluded from analysis (n=9). Preoperative histology was NSCLC in 49% and unknown in 51%. The lesion was subsolid in 7%. Tumour stage was cT1, cT2, cT3 and cT4 in 43%, 28% 17% and 11%, respectively. Invasive mediastinal staging (EBUS and/or mediastinoscopy) was performed in 31%. Surgical resection was performed in 97%, a median of 5 (IQR 3-6) nodal stations were examined. The final pathology was squamous NSCLC, non-squamous NSCLC, or other in 38%, 54% and 7%, respectively. Any nodal upstaging was found in 21% (13% pN1 and 8% pN2-3). Central tumour location demonstrated, compared to peripheral location, a 4 times higher risk for any nodal upstaging but not for N2-3 upstaging (table 1). **Conclusion:** When modern PET-CT fusion imaging points at clinical N0 NSCLC, the prevalence of occult mediastinal nodal disease was only 8% in our patient cohort. None of the five definitions of centrality we studied was predictive for occult pN2-N3. Overall nodal upstaging was 21%, however, and all definitions of centrality then had discriminatory value. These data question whether the indication of preoperative invasive mediastinal staging should be based on centrality alone. Table 1

Tumor Location Central / Peripheral	N	pN+ upstaging					pN2-3 upstaging				
		N	%	Odds ratio (95%CI)	P-value	AUC (95%CI)	N	%	Odds ratio (95%CI)	P-value	AUC (95%CI)
Inner 1/3* (=central)	257	99	39	4.21 (2.96;5.99)	<.0001	0.66 (0.62;0.71)	26	10	1.49 (0.89;2.51)	0.13	0.55 (0.48;0.61)
Outer 2/3	556	72	13				39	7			
Inner 2/3* (=central)	412	125	30	3.36 (2.32;4.88)	<.0001	0.64 (0.60;0.68)	39	9	1.51 (0.90;2.53)	0.12	0.55 (0.49;0.61)
Outer 1/3	401	46	11				26	6			
Contact** (=central)	291	105	36	3.90 (2.74;5.55)	<.0001	0.66 (0.62;0.70)	26	9	1.22 (0.72;2.04)	0.46	0.52 (0.46;0.59)
No Contact	522	66	13				39	7			
≤2cm around bronchus*** (=central)	281	103	37	3.95 (2.78;5.61)	<.0001	0.66 (0.62;0.70)	26	9	1.29 (0.77;2.17)	0.34	0.53 (0.47;0.59)
>2cm around bronchus	532	68	13				39	7			
Visualized by bronchoscopy**** (=central)	190	79	42	4.11 (2.86;5.91)	<.0001	0.65 (0.60;0.69)	18	9	1.28 (0.73;2.27)	0.39	0.52 (0.47;0.58)
Not visualized by bronchoscopy	623	92	15				47	8			
Total	813	171	21				65	8			

Table 1 Univariable logistic regression.
AUC: area under the curve; 95% CI: 95% confidence interval
* Location of tumor based on transverse CT imaging: centre of tumor in inner 1/3 (or inner 2/3 respectively) of the lung parenchyma, adjacent to the mediastinum
** Contact: Tumor contact with lobar or first segmental branches of bronchovascular structures
*** ≤2cm around bronchus: tumour within 2 cm of the proximal bronchial tree (distal 2cm of trachea, carina, named major lobar bronchi, up to their first bifurcation)
**** Visualized by bronchoscopy: standard bronchoscope of 5-6 mm diameter, i.e. not by endosonography or paediatric bronchoscope

Keywords: Staging, Central tumor, PET-CT cN0

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-008 EVALUATION OF CLINICAL ASSOCIATED FACTORS FOR LUNG ADENOCARCINOMA BY TNM 8TH EDITION WITH UNEXPECTED N2 DISEASE

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Background: Among patients with lung adenocarcinoma, some of them diagnosed as clinical N0 (cN0) are staged as pathological N2(pN2 ; unexpected N2 disease). The aim of this study is to analyze preoperative factors of unexpected N2 disease. **Method:** We retrospectively reviewed 361 cN0 lung adenocarcinoma patients who underwent curative resection between January 2005 to December 2016 in our institution. Patients were staged according to findings of computer tomography (CT), positron emission tomography (PET), and/or transbronchial needle aspiration (TBNA). We analyzed their clinical features, comparing pN0 group with pN2 group. Especially, we focused on the diameter of solid component by TNM classification 8th edition. **Result:** There were 37 patients (10.2%) with unexpected N2 disease. Of the 37 patients, 10 patients (27.0%) had metastasis in Single-station N2 without N1 involvement (skip N2 disease), 14 patients (37.8%) had in Single-station N2 and 13 patients (35.1%) had in Multiple-station N2. There was no difference in the tumor size between pN0 and pN2 (p=0.100). However, the diameter of solid component was larger in pN2 than in pN0 (p<0.001), C/T ratio (p<0.001), maximum standard uptake value (p<0.001), and CEA (p=0.005) were higher in pN2 than in pN0. Multivariate logistic regression analysis identified the diameter of solid component and CEA as significant associated factors for unexpected N2 disease (p=0.006,p=0.01). **Conclusion:** The possibility of unexpected N2 disease increases with the larger diameter of solid component or higher CEA. Particularly, in order to discover unexpected N2 disease in lung adenocarcinoma, it is reasonable to evaluate T-factor by TNM classification 8th edition.

Keywords: the diameter of solid component, lung adenocarcinoma, unexpected N2 disease

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-009 MACROSCOPIC AND MICROSCOPIC LYMPHATIC REMODELING CAUSED BY VEGF-C PLAY A KEY ROLE IN LYMPHATIC METASTASIS OF NON-SMALL CELL LUNG CANCER

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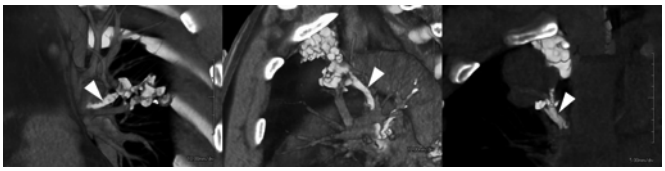
Background: Computed tomography (CT) lymphography by transbronchial injection of a water-soluble extracellular CT contrast agent was developed as a new method for identifying sentinel nodes (SNs) in patient with non-small cell lung cancer (NSCLC). SNs were identified in 87.8% of patients, and the accuracy rate of SN identification was 97.5%. CT lymphography images sometimes show enlargement of lymphatic vessel (Fig), and we noticed this finding is related to lymph node metastasis. Lymphatic vessel enlargement was seen in 80% of lymph node metastasis positive cases whereas only 24.2% of lymph node metastasis negative cases showed lymphatic vessel enlargement (p=0.027). The aim of this study was to investigate the relationship between the finding of lymphatic vessel enlargement seen in CT lymphography and tumor lymphangiogenesis including lymphatic vessel density or vascular endothelial growth factor (VEGF)-C.



Method: Lymphatic vessel enlargement was defined as a finding of an enhanced lymphatic vessel ≥ 3mm on CT lymphography. We examined formalin fixed paraffin embedded tumor samples of 36 patients who received CT lymphography preoperatively. Lymphatic vessel density was determined based on the number of peritumoral vessels immunoreactive to anti-D2-40 antibody. The percentage of tumor cells exhibiting cytoplasmic staining for VEGF-C was evaluated and ≥ 30% was defined as VEGF-C positive. **Result:** Twelve out of 36 (33.3%) cases showed finding of the lymphatic vessel enlargement on CT lymphography. Peritumoral lymphatic vessel density of VEGF-C positive patients was significantly higher than that of VEGF-C negative patients (28.4 ± 11.6 vs 17.0 ± 10.5, p=0.005). Lymphatic vessel enlargement was more frequently seen in VEGF-C positive patients than in VEGF-C negative patients (53.8% vs 21.8% ± 10.5, p=0.056). **Conclusion:** Our study suggests VEGF-C secreted by tumor cells play a key role in the lymphatic remodeling and lymphatic vessel enlargement seen in CT lymphography may be a risk factor for lymph node metastasis of NSCLC.

Keywords: CT lymphography, lymph node metastasis, non-small cell lung cancer

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-010 IS MRI BRAIN MANDATORY IN ALL PATIENTS WITH EARLY STAGE NSCLC?

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Background: Non - small cell lung cancer(NSCLC) is known to have a high propensity for metastasis to brain. Conventional wisdom and guidelines recommend MRI brain as routine staging investigation for patients planned for radical treatment. However there is little data about the detection rate of brain metastasis using MRI brain in asymptomatic patients with operable/early stage NSCLC. **Method:** We conducted a prospective observational study to assess the incidence of MRI detected brain metastasis in early operable lung cancer. Consecutive patients presenting to the outpatient department with biopsy proven NSCLC were screened. All patients planned for radical treatment underwent PET CECT and MRI brain as per institutional protocol. Patients with early stage disease(Stage I to IIIA) on PET CECT with no symptoms suggestive of brain metastasis were included in the study. Data regarding histopathology, T stage, N stage, SUV uptake of primary, clinicoradiological stage, neurological symptoms and MRI brain findings was collected. **Result:** 1944 consective biopsy proven patients of NSCLC presenting in the outpatient department from Jan 1st 2015 to Dec 31st 2015, were screened. 168 patients in stage I to IIIA as per PET CECT, without obvious evidence of brain metastastis were included in the study, 81(48.2%) were in stage I&II and 87(51.7%) were in stage IIIA. Among the remaining 1776 patients, 213 patients had brain metastasis at presentation. Two patients with early stage disease and symptomatic solitary brain metastasis were treated with radical intent and excluded from the study. The incidence of MRI detected

asymptomatic brain metastasis in the study population(Stage I to IIIA) was 6/168 (3.5%) and all were in stage IIIA. MRI brain did not pick up any brain metastasis in asymptomatic Stage I&II NSCLC patients. No co-relation could be found between grade of tumour, SUV of primary, T stage or N stage with the incidence of brain metastasis. Three patients in the study population developed brain metastasis while on treatment. **Conclusion:** Although this study is limited by the small sample size, the role of MRI brain in staging of early stage NSCLC (Stage I & II) needs to be re evaluated in light of the low yield seen in asymptomatic patients. Rigorous evaluation of the patient's history and clinical symptoms may obviate the need of MRI brain in this subset. This may become increasingly relevant with the implementation of lung cancer screening programs.

Keywords: early stage NSCLC, MRI Brain, Brain metastasis

P1.13: RADIOLOGY/STAGING/SCREENING -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.13-011 PROSPECTIVE COHORT STUDY OF PATTERNS OF STAGING AND TREATMENT SELECTION WITH OR WITHOUT MULTIDISCIPLINARY (MD) CARE

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Background: Lung cancer survival depends on accurate staging and treatment selection. Because staging and treatment are increasingly multi-modal, we examined staging and treatment selection practices with or without MD care in a single healthcare system. **Method:** Eligible patients had untreated lung cancer, ECOG performance status of 0-2, and gave informed consent. Comparisons were made between patients seen in a co-located MD clinic (MDC) and those receiving standard care (SC). Some SC patients were discussed at a multidisciplinary tumor conference (MDTC), thus allowing comparison of MD care to pure SC and MDTC. Diagnostic, staging, treatment procedures and patient outcomes were prospectively recorded. Staging thoroughness was defined as biopsy of stage-defining lesion; bimodality staging (PET+CT or CT+invasive staging biopsy); trimodality staging (PET+CT+invasive staging biopsy). Stage migration was determined comparing baseline stage (from first radiologic scan) to final clinical stage prior to treatment. Stage-appropriate treatment was defined by NCCN guidelines using final, pre-treatment stage. Chi-squared test and multivariable logistic regressions adjusted for age, sex, and histology were used to examine differences between patient cohorts. **Result:** Of 527 patients, 178 were MDC, 77 MDTC, 272 SC. Race and gender were similar but median age (67 v 66 v 69 (p=0.0032) and insurance distribution (p=0.0021) differed across groups. MDC tended to have more thorough staging than MDTC and SC. Significant differences were observed in staging migration and appropriate treatment, favoring MDC and MDTC patients (Table 1). After adjusting for age, sex, and histology, MCD and MDTC were 2-3 times more likely to have more thorough staging and overall stage appropriate treatment (Table 1).

Table 1. Summary staging information and odds ratios (aOR) adjusted for age, sex, and histology for stage migration, staging confirmation thoroughness, and stage appropriate treatment for MD Clinic (MDC) vs MD Conference (MDTC) vs Serial Care (SC).

	MDC (n=178)	MDTC (n=77)	SC (n=126)	P-value for across the groups	Adjusted Odds Ratio MDC v SC	Adjusted Odds Ratio MDTC v SC	P-value
	N (%)				aOR (95% Confidence Interval)		
Stage Migration							
Stage migrated	74 (41.6)	41 (53.3)	91 (33.5)	0.0051	1 (0.6, 1.5)	1.8 (1, 3.2)	0.0838
Stage decreased	32 (18)	17 (22.1)	39 (14.3)	0.0313	Not applicable		
Stage remained the same	104 (58.4)	36 (46.8)	181 (66.5)				
Stage increased	42 (23.6)	24 (31.2)	52 (19.1)				
Stage Confirmation							
Invasive stage-confirmation	108 (60.7)	46 (59.7)	122 (44.9)	0.0017	2.7 (1.7, 4.2)	2.6 (1.5, 4.6)	<0.001
Invasive mediastinal nodal staging	92 (51.7)	40 (52)	86 (31.6)	<0.0001	2.5 (1.6, 3.9)	2.6 (1.5, 4.5)	<0.001
Bimodality staging	159 (89.3)	61 (79.2)	204 (75)	0.0009	3.1 (1.7, 5.9)	1 (0.5, 2.1)	0.0013
Trimodality staging	98 (55.1)	38 (49.4)	92 (33.8)	<0.0001	3 (1.9, 4.6)	2.2 (1.3, 3.8)	<0.001
Stage Appropriate Treatment							
Overall	137 (79.2)	58 (78.4)	172 (64.7)	0.0016	2.2 (1.3, 3.5)	1.7 (0.9, 3.3)	0.0054
Stage I	45 (93.8)	25 (96.2)	44 (81.5)	0.0605	Not applicable		
Stage II	19 (70.4)	4 (50)	7 (30.4)	0.0148			
Stage III	36 (76.6)	13 (86.7)	46 (68.7)	0.3042			
Stage IV	37 (72.6)	16 (64)	75 (62)	0.4123			
Stage I-IIIA	90 (84.1)	40 (87)	83 (69.2)	0.0069			
Stage IIIB-IV	47 (71.2)	18 (64.3)	89 (61.4)	0.3841			

Conclusion: Care within a structured MDC environment (whether co-located MDC or MDTC) was associated with significantly more thorough staging processes and higher rates of stage-appropriate use of treatment modalities than usual care. Survival analysis will be reported when data are mature.

Keywords: treatment, multidisciplinary, Staging

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-001 THE FEASIBILITY OF PREDICTING RADIATION PNEUMONITIS USING LUNG EQUIVALENT UNIFORM DOSE (LEUD) IN VOLUMETRIC-MODULATED ARC

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Background: The prediction of RP has become an important topic in medical field. Currently, the clinical assessment of lung injury is analyzing the dose-volume threshold based on the 3D-CRTor IMRT by controlling the percent lung volume receiving a certain amount of dose. Many literatures failed to provide an exact correlation coefficient due to data missing and nonlinear deviation in the modeling of RP prediction. Compared with the conventional radiation techniques, the low dose volume of lung is greatly enlarged especially for patients treated with VMAT or tomotherapy (TOMO). EUD is equivalent dose of inhomogeneous radiation that has the same radiobiological effect.The tissue characteristic parameter α in EUD shows the tolerance of tissue for radiation dose and the higher α, the better tolerance. Different α value are used to classify the tumor tissue, normal tissue and the serial and parallel organ in normal tissue according to "Stevens law". The tumor tissue has a negative α value which means that in dose will lead to uncontrolled tumor. The serial organ in normal tissue has a high α value for its abnormal sensitivity to high dose. And the parallel organ has a small α for its low sensitivity. **Method:** 65 patients receiving radiation therapy for lung cancer using VMAT were divided into two groups according to whether radiation pneumonitis occurred after radiation therapy. The dose-volume histogram (DVH) and its associated parameters of the patients were abstracted and analyzed by self-complied analysis program. The LEUD values of the two groups were calculated with α ranging from -50 to 50. The optimal α value was obtained when the relative LEUD difference between the two groups reached maximum. **Result:** The maximum relative LEUD difference between the group of radiation pneumonitis (GRP) and non-radiation pneumonitis (G-NRP) is obtained at α=0.5 (LEUD (GRP) =627.94 cGy, LEUD (G-NRP) = 510.23 cGy, relative LEUD difference =23.07%). The relative LEUD difference (R) reaches the maximum at α=0.5. the R tends to decrease slowly till the end of the parameter range of this study (α=50). The traditional correlation analysis of physical dose-volume threshold shows that the LEUD (α=0.5) is related to physical dose metrics including , and mean lung dose (MLD) with average person =0.929. **Conclusion:** The LEUD (α=0.5) (limited below 510 cGy) is possible to distinguish GRP from G-NRP for the thoracic tumor patients. The combination of LEUD and conventional physical dose metrics shows clinical prospective value for RP caused by non-uniform radiation.

Keywords: Radiation pneumonitis (RP), Lung equivalent uniform dose (LEUD), Volumetric-modulated arc therapy (VMAT)

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-002 COMPARISON BETWEEN STEREOTACTIC AND CONVENTIONAL RADIOTHERAPY FOR SOLITARY LUNG TUMORS AFTER RESECTION OF LUNG CANCER

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Background: No standard fractionation of radiotherapy (RT) has been established for solitary lung tumors after complete resection of non-small cell lung cancer (NSCLC). We retrospectively compared stereotactic body radiotherapy (SBRT) with conventionally fractionated radiotherapy (CFRT) with regard to efficacy and toxicity. **Method:** Between 2006 and 2015, 26 patients were treated with RT alone for solitary lung tumors that were postoperative local recurrence, pulmonary metastasis, or multiple primary lung cancer after complete resection of NSCLC. At the time of RT, 22 patients (85%) were medically inoperable. The median age was 79 years (range, 61-88 years). Histological confirmation was obtained in 4 patients (15%). The median maximum diameter of the solitary lung tumors was 15 mm (range, 6-30 mm). None of the patients had regional or extra-pulmonary distant metastasis. SBRT using 48 Gy in 4 fractions at the isocenter was administered to 15 patients with peripheral solitary lung tumors (SBRT group). CFRT using 66-70 Gy in 33-35 fractions was administered to 11 patients with central solitary lung tumors to avoid a risk of severe hilar or mediastinal toxicity with SBRT (CFRT group). **Result:** The median follow-up time was 32 months (range, 9-79 months). Regarding characteristics of the patients, adjuvant chemotherapy after surgery was significantly more often performed in the SBRT group than the CFRT group ($p = 0.036$; Fisher›s exact test). However, adjuvant chemotherapy after surgery was not a significant factor for overall survival and local control rates after RT ($p = 0.232$ and 0.547, respectively; log-rank test). No other characteristics of the patients differed significantly between the SBRT and CFRT groups. The 3-year overall survival rates in the SBRT and CFRT groups were 81% and 40%, respectively ($p = 0.008$; log-rank test). The 3-year local control rates in the SBRT and CFRT groups were 83% and 35%, respectively ($p = 0.035$; log-rank test). Regarding toxicities (CTCAE v4), no significant differences in the occurrences of grade 2 radiation pneumonitis and grade 2-3 dyspnea were found between the SBRT and

CFRT groups (p = 1.000 and 1.000, respectively; Fisher›s exact test). No other grade 3-5 toxicities were observed. **Conclusion:** SBRT may be more effective compared with CFRT in patients with solitary lung tumors after complete resection of NSCLC.

Keywords: Stereotactic body radiation therapy, Solitary lung tumors, postoperative

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-003 ANESTHESIA ALLOWS SAFE ADMINISTRATION OF SBRT FOR EARLY STAGE LUNG CANCER PATIENTS WITH ADVANCED COGNITIVE IMPAIRMENTS

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Background: Lung stereotactic body radiotherapy (SBRT) for medically inoperable early stage lung cancer involves extremely precise delivery and requires robust systems for patient (pt) immobilization, breathing control, and daily image guidance. Severe cognitive impairments [CIs] in pts may interfere with their suitability for lung SBRT. Herein, we report on the pt/tumor/treatment characteristics of CI cases for which out-pt anesthesia [OPA] was employed to ensure safe and rigorous SBRT delivery. **Method:** A survey of an IRB-approved institutional prospective SBRT registry of 1330 pts for the interval April 2004 to December 2016 revealed 7 pts with medically inoperable early stage T1-T3N0M0 non-small cell lung cancer (NSCLC) requiring OPA. SBRT was delivered by a stereotactic-specific LINAC platform with vacuum-bag based immobilization, and CBCT +/- infrared-based X-ray positioning system for image-guidance. Tumor motion management involved an abdominal compression device in all cases and SBRT dose/fractionation was selected at the discretion of the treating physician. **Result:** Seven OPA cases were treated between March 2006 and July 2016. Pt characteristics included: female sex (71.4%); median age 66 years (range 44-66); median Karnofsky performance status 70 (range 40-80). Four pts completed spirometry: median FEV1 was 1.005 L and 41 % predicted; only 2 were able to do diffusion capacity testing. CI causes were: Alzheimer's related dementia (n=3); chronic schizophrenia requiring institutionalization (n=3); severe mental disability from birth with tracheostomy (n=1). Tumor characteristics included: median diameter 3.8 cm (range 1.7-10.5); median PET SUVmax 10.5 (range 6.4-25.5); T stage 1a – 2 pts; 1b – 1 pt; 2a – 2 pts, 2b – 1 pt, 4- 1 pt; "central" location (per RTOG 0813): 6 pts. Treatment doses included 50 Gy/5 fractions (fx) in 3 pts, 60 Gy/3 fx in 1 pt, 60 Gy/8 fx in 2 pts and 50 Gy/10 fx for 1 pt. OPA consisted of a propofol 10mg/ml-including IV sedation regimen in all cases and was done at the time of simulation and daily with treatments. All SBRT was completed as planned. There were no complications attributable to OPA and no post-OPA hospitalizations. Median follow up was 17.7 months (range 6.6-105.5). At analysis, 5 pts (71%) were alive. One pt died of a grade 5 tracheo-esophageal fistula in the absence of cancer at 8.2 months after SBRT, otherwise there were no grade 3 or higher toxicities. One pt died from biopsy-proven loco-regional failure 105.7 months after SBRT. Otherwise, there has been no other local, regional nodal or distant failure at the time of analysis. **Conclusion:** OPA facilitated lung SBRT delivery for pts with CIs. SBRT outcomes were in keeping with expected values. CIs should not be considered contraindications to safe lung SBRT delivery in pts otherwise appropriate for this modality.

Keywords: Lung SBRT, anesthesia, cognitive impairment

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-004 OUTCOMES OF STEREOTACTIC BODY RADIOTHERAPY AND SURGERY IN TREATING EARLY STAGE NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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Background: To provide a promising option for early stage non-small-cell lung cancer (NSCLC) treatment, a meta-analysis of stereotactic body radiotherapy (SBRT) and surgery in lung cancer was carried out. **Method:** Literatures were retrieved from the databases of PubMed, Embase and the Cochrane library and qualities were assessed by Nine Stars System Scale. All of the statistical analyses were conducted using Stata 11.0. Risk ratios (RRs) with its 95% confidence interval (CI) were set as effective indicators. Heterogeneity was estimated by Q statistics and I^2, and the publication bias was evaluated by Egger test. **Result:** A total of 12 high-quality studies were enrolled in this study (Table 1). No significant difference was identified in 1-year overall survival (OS) rate between SBRT and surgery. An obvious higher 3-year OS rate was detected in surgery compared with SBRT (RR = 0.78, 95% CI: 0.63 - 0.97). Moreover, superior 5-year OS rates were also identified in surgery (RR = 0.69, 95% CI: 0.52 - 0.91) and lobectomy (RR = 0.58, 95% CI: 0.47 - 0.72) compared with SBRT. The 3-year loco-regional recurrence control rate in SBRT was remarkably higher than that in surgery (RR = 1.11, 95% CI: 1.01 - 1.22), but the pooled 5-year distant recurrence control rate of SBRT was markedly lower than that in surgery (RR = 0.87, 95% CI: 0.76 - 0.99). **Table 1 Characteristics of the included studies.** *(See next page.)*

RCT, randomized controlled trial; RCS, Retrospective cohort study; SBRT, Stereotactic body radiotherapy; SR, survival rate; SLR, sublobar resection; DCR, distant control rate. **Conclusion:** SBRT might have a superior loco-regional recurrence control in early stage of NSCLC, but the OS rate was lower than that in surgery. However, well-designed investigation with a larger sample was still need to verify and update this conclusion.

Keywords: non-small cell lung cancer, stereotactic body radiotherapy, Surgery

Study	Year	Country	Duration	Design	Stage	Follow up time	Treatment	Sample size	Male/ Female	Age (years)	Outcomes
Chang	2015	Multi centers	2008- 2014	RCT	I	40.2 months	SBRT	31	14/17	67.3 (9.2)	1y SR; 3y SR; 3y DCR
						35.4 months	Surgery	27	11/16	67.3 (8.2)	
Crabtree	2010	USA	2000- 2007	RCS	I	5 years	SBRT	57	NA	71 (50-94)	3y SR
							Surgery	57	NA	73 (47-90)	
Crabtree	2014	USA	2004- 2010	RCS	I	5 years	SBRT	56	29/27	70.7 (10.6)	1y SR; 1y DCR; 3y SR; 3y DCR; 5y SR; 5y DCR
							Surgery	56	32/24	70.0 (8.1)	
Hamaji	2015	Japan	2003- 2009	RCS	I	40.7 months	SBRT	41	31/10	73 (58-85)	3y SR; 5y SR
						54 months	Lobectomy	41	32/9	74 (61-86)	
Matsuo	2014	Japan	2003- 2009	RCS	I	6.7 years	SBRT	53	42/11	76 (58-86)	5y SR; 5y DCR
						5.3 years	SLR	53	37/16	76 (50-88)	
Mokhles	2015	the Netherlands	2003- 2012	RCS	I	28 months	SBRT	73	42/31	67 (10)	1y SR; 1y LGR; 1y DCR; 5y SR; 5y LGR; 5y DCR
						49 months	Lobectomy	73	44/29	67 (9)	
Palma	2011	the Netherlands	2005- 2007	RCS	I	43 months	SBRT	60	40/20	79 (76–81)	1y SR; 3y SR
							Surgery	60	40/20	79 (76–80)	
Paul	2016	USA	2007- 2013	RCS	I	6.25 years	SBRT	201	76/125	76.9 (6.1)	3y SR
							SLR	201	78/123	76.8 (6.0)	
Puri	2015	USA	1998- 2010	RCS	I	36.5 months	SBRT	5355	2407/2948	74.3 (8.5)	3y SR
						36.5 months	Surgery	5355	2382/2973	74.2 (8.4)	
Varlotto	2013	USA	1999- 2008	RCS	I	25.8 months	SBRT	72	NA	73.3	3y SR; 3y LGR; 5y SR; 5y LGR
							Lobectomy	72	NA	68.6	
							SBRT	17	NA	73.3	3y SR; 3y LGR; 5y SR; 5y LGR
							SLR	17	NA	67.5	
Verstegen	2013	the Netherlands	2007	RCS	I–II	60 months	SBRT	64	37/27	70.5(9.9)	1y SR; 1y LGR; 1y DCR; 3y SR; 3y LGR; 3y DCR
						48 months	Lobectomy	64	36/28	67.9 (8.8)	
Wang	2016	China	2002- 2010	RCS	I	58.7 months	SBRT	35	33/2	77.1 (5.2)	1y SR; 1y LGR; 3y SR; 3y LGR; 5y SR; 5y LGR
							Surgery	35	33/2	74.8 (6.6)	

P1.14-005 DEVELOPMENT OF A NOVEL SPACER TO REDUCE MEDIASTINAL ORGAN TOXICITY FROM STEREOTACTIC BODY RADIOTHERAPY

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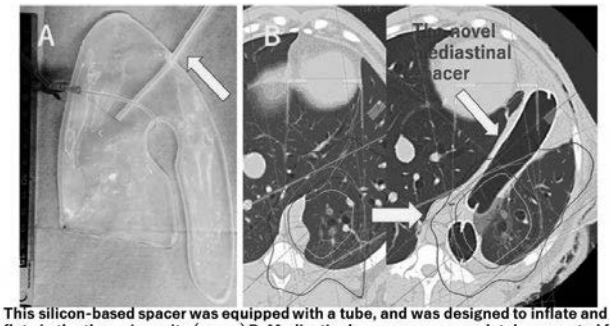
Background: Recently, stereotactic body radiotherapy (SBRT) has become available for patients who are at high risk for lung resection. Although SBRT for peripheral lung tumors produces excellent outcomes with low toxicity, it is associated with an increased risk of severe toxicity when used to treat central tumors. We hypothesized that using a spacer designed to provide a predetermined distance between the target lesion and mediastinal organs may reduce adjacent organ toxicity, thereby expanding the indication of SBRT for lung cancer. **Method:** We developed a novel silicon-based spacer that imitated the shape of a canine's left mediastinum. Animal experiments were performed on canine models to evaluate the feasibility, utility, and safety of the spacer. Two adult beagle dogs were used in this study. Video-assisted thoracoscopic surgery (VATS) was performed through two ports to insert the spacer between the lung and mediastinum of the left thoracic cavity. CT examination was performed with the spacer inflated at 1 week and 2 weeks after insertion. Four weeks after insertion, the spacer was removed. We created two virtual tumors that presented a high risk of severe mediastinal organ toxicity from SBRT. Radiation treatment planning of SBRT was conducted in both cases, and the radiation dose for mediastinal organs was compared between the cases with and without the spacer. **Result:** The spacer could be safely inserted between the lung and mediastinum via the VATS procedure. The novel spacer provided a distance of 5-10 mm between the virtual tumor and the mediastinal organs. The reduced radiation dose for risk organs were calculated as 7.0-27.5% in the aorta, 3.0-12.3% in the esophagus, and 7-25% in the spine. The spacer did not adhere to the mediastinal organs, and was removed smoothly.



A, This silicon-based spacer was equipped with a tube, and was designed to inflate and deflate in the thoracic cavity.(arrow) B, Mediastinal organs were completely separated from lung. The novel spacer could secure a certain distance (5-10mm) between virtual tumor and mediastinal organs. The area where planning target volume (PTV) overlapped risk organs disappeared after spacer insertion.

Conclusion: The novel mediastinal spacer may potentially reduce mediastinal organ toxicity from SBRT when treating centrally located lung tumors.

Keywords: lung cancer, stereotactic body radiotherapy, Lung cancer, Spacer, Spacer

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-006 CARBON-ION RADIOTHERAPY FOR ISOLATED LYMPH NODE METASTASIS FROM LUNG CANCER USING A REGIMEN OF 12 FRACTIONS DURING 3 WEEKS

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Background: Mediastinal and hilar lymph node metastases after definitive treatment for lung cancer is one of the main recurrence. Generally, isolated lymph node metastases without other recurrence are treated with local treatment, such as radiotherapy and surgery. Carbon-ion radiotherapy has a superior dose distribution and higher biological effectiveness compared with photon therapy. We retrospectively evaluated the efficacy and safety of hypofractionated carbon-ion radiotherapy for isolated lymph node metastasis in lung cancer patients. **Method:** Between April 2013 and August 2016, 15 patients were treated with carbon-ion radiotherapy. Median age was 72 years old (range: 51-83), and male patients were 11 (73%). Initial treatments were carbon-ion radiotherapy (n=8) and surgery (n=7). Pathological types were adenocarcinoma (n=9), squamous cell carcinoma (n=4), and others (n=2), respectively. All patients were treated using 12 fractions over 3 weeks. Fourteen patients received 52.8 Gy (relative biological effectiveness [RBE]) in and 1 patients received 48.0 Gy (RBE). Local control, progression free survival, and overall survival rates were statistically calculated by the Kaplan-Meier method. Acute and late adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. This retrospective study was reviewed and approved by our Institutional Review Board. **Result:** The median follow-up time was 14 months. One patient had local lymph node failure, and the 1-year local control rate was 90%. This patient had a primary tumor recurrence, accompanied with lymph node failure at the same time. Three patients died of lung cancer, and the 1-year OS rate was 93%. Distant metastases were observed in 6 patients, and the 1-year PFS were 64%. Acute grade 2 esophagitis and grade 2 cough were observed in 2 (13%) and 2 (13%) patients, respectively. These acute adverse events were immediately improved by conservative therapy. There were no patients with grade ≧2 pneumonitis. **Conclusion:** Although follow-up period was short, hypofractionated carbon-ion radiotherapy showed great local control and overall survival without severe toxicities in lung cancer patients with isolated lymph node metastasis. Carbon-ion radiotherapy is considered an option of salvage treatment for isolated lymph node metastasis. Further follow-up is required to evaluate local control, overall survival, and late adverse events.

Keywords: Isolated lymph node metastasis, Carbon-ion radiotherapy, Hypofractionated radiotherapy

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-007 MESENCHYMAL STEM CELLS LABELED WITH FLUORESCENT MAGNETIC NANOPARTICLES FOR TARGETED IMAGING AND HYPERTHERMIA THERAPY OF LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related mortality. It remains a challenge to simultaneously detect and treat early lung cancer *in vivo*. Herein, we report the use of fluorescent magnetic nanoparticles-labeled mouse mesenchymal stem cells to accomplish targeted imaging and hyperthermia therapy of lung cancer *in vivo*. **Method:** The silica-coated fluorescent supermagnetic nanoparticles (FMNPs) were prepared and characterized, and then were used to label mouse mesenchymal stem cells (MSCs). The FMNPs-labeled MSCs were injected via tail vein into nude mice bearing non-small cell lung cancer A549 cells, which were followed using small animal imaging system and magnetic resonance imaging system. Thesubcutaneous lung cancer tissues in the nude mice models were subsequently treated in external alternating magnetic field. **Result:** .Results showed that FMNPs -labeled MSCs could target and image *in vivo* lung cancer cells after being intravenously injected for 7 days, and FMNPs-labeled MSCs could inhibit the growth of *in vivo* lung cancer through hyperthermia effects. The potential mechanism is discussed. **Conclusion:** FMNPs-labeled MSCs may target *in vivo* lung cancer cells and have great potential in applications such as targeted imaging and hyperthermia therapy of early lung cancer in the near future.

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-008 ELEVATED PLATELET LEVELS AFFECT PROGNOSIS IN PATIENTS WITH NSCLC TREATED WITH CURATIVELY INTENDED CHEMORADIOTHERAPY

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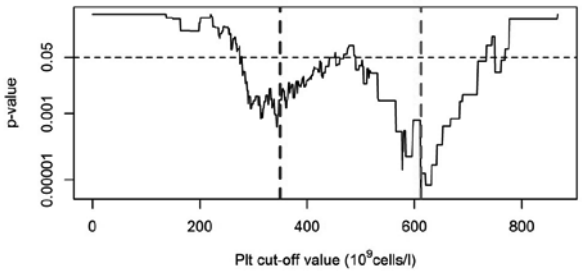
Background: For inoperable stage III NSCLC, chemoradiotherapy is the standard of care. However, this treatment is associated with significant side effects and only offers a small chance of cure. Having adequate prognostic information at the start of treatment is essential in order to select the most appropriate treatment strategy for each individual patient. This study investigates the prognostic value of pre-treatment platelet (Plt) levels in this treatment setting. **Method:** Data were collected retrospectively from two phase II trials conducted from 2002 to 2007 in Sweden with patients treated with chemoradiotherapy for stage IIIA-IIIB NSCLC. Clinical and laboratory data at enrollment were collected for all patients and studied in relation to overall survival using Kaplan-Meier product-limit estimates and a multivariate Cox regression model. An optimal prognostic cut-off point for Plt was estimated by using a stepwise log-rank testing of survival comparing patients with a Plt count below and above every Plt count in the dataset. The cut-off point was defined as the Plt count that gave the lowest p-value using the log-rank test. **Result:** Patients with thrombocytosis (defined as Plt > 350 x 10^9/L) had a shorter median overall survival than patients with normal Plt (≤ 350 x 10^9/L) at baseline (14.5 and 23.7 months, respectively), which was statistically significant (p=0.0025). This significant association was retained in a multivariate model where other laboratory and clinical factors, such as performance status, were included. The optimal prognostic cut-off point for platelet levels in this patient material was estimated at Plt = 610.



Conclusion: In stage III NSCLC treated with curatively intended chemoradiotherapy, elevated platelet levels showed to be an independent prognostic marker for shorter overall survival. Further research is needed to establish the role of platelet levels and appropriate cut-off limits when making treatment decisions in this clinical setting.

Keywords: survival, platelets, Prognostic

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-009 COMPARISON OF DOSIMETRIC PARAMETERS AND OUTCOME IN NON-SMALL CELL LUNG CANCER PATIENTS HAVING 3D CONFORMAL OR VMAT PLANS

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Background: Advances in lung cancer radiotherapy now permits increased accuracy of tumour targeting through image guided radiotherapy (IGRT) and advanced forms of intensity modulated radiotherapy (IMRT) such as volumetric modulated arc radiotherapy (VMAT), which helps minimise toxicity to normal tissues. We conducted a retrospective analysis to assess the impact of these new technologies on our patients. **Method:** We compared 2 radical (chemo)radiotherapy patient cohorts treated in our institution; Group A treated from February 2013 - February 2014 and Group B from September 2015 - September 2016. We analysed radiotherapy planning techniques, dose delivered, normal tissue doses and outcomes. **Result:** In Group B, we treated double the number of patients (26) with radical radiotherapy (64Gy/32# or 55Gy/20#) compared to Group A (13). Baseline characteristics were similar; median age 65yrs (A) and 70yrs (B). Most patients had stage III disease (69%-A, 81%-B). 77% of patients in both groups had concurrent cisplatin and vinorelbine chemotherapy. All patients in Group A had conventional CT planning scans and 3D-conformal planning. In Group B, all had 4D-CT planning scans and 85% (22/26) had VMAT plans. Patients treated with 55Gy/20# increased from 23% (3/13-A) to 46% (12/26-B). The median CTV increased from 64cm^3 (range 45cm^3 – 99cm^3 Group A) to 142cm^3 (range 15cm^3 – 656cm^3 Group B), (p-value 0.00005). Despite the increase in CTV, the median PTV remained similar (312cm^3- A vs 364cm^3- B). With VMAT plans, the lung doses remained low despite the increase in CTV; lung V20 (22%-A vs 20%-B), lung V5 (49% vs 49%) and mean lung dose (15Gy vs 12Gy). We selected the 5 largest CTVs from group B (CTV range 294 cm^3 – 656 cm^3) and compared 3D conformal plans with the respective VMAT plans. We found VMAT allowed optimal dose coverage without compromising the PTV. VMAT benefited large midline tumours most where constraints of cord, heart and brachial plexus were met without PTV compromise. All Group A and 25/26 Group B patients completed their planned treatment. Median overall survival in Group A was 20.1 months but not yet reached in Group B. **Conclusion:** Adoption of 4D-CT scanning and VMAT treatment delivery has enabled us to treat larger tumours which seems to be particularly advantageous for large midline tumours. We hypothesise that radiotherapeutic advancements can increase the number of patients treatable to a radical radiotherapy dose without PTV compromise and further work is underway to confirm this and the possible impact it might have on our workload and resources.

Keywords: Radiotherapy, non small cell lung cancer, VMAT or IMRT

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-010 SGA COULD BE A PREDICTIVE FACTOR FOR RADIATION PNEUMONITIS IN LUNG CANCER PATIENTS TREATED BY CONCURRENT CHEMORADIOTHERAPY

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Background: To investigate the relationship between malnutrition and the severity of radiation pneumonitis (RP) in lung cancer patients with normal baseline pulmonary function and lungs' V20<35% treated by intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy. **Method:** One hundred and fifty patients with lung caner who received definitive IMRT (≥60 Gy) and concurrent chemotherapy were enrolled. In the condition of normal baseline pulmonary function and strict constraints of the irradiation dose to normal lung tissues, we recorded Eastern Cooperative Oncology Group (ECOG) score, concurrent chemotherapy, clinical stage, the level of albumin (ALB), hemoglobin and C-reactive protein (CRP), Subjective Global Assessment (SGA) scores and radiation esophagitis (RE) grade. These factors were correlated with RP using univariate and multivariate regression analyses. **Result:** Of 150 patients, 12 patients (8.0%) developed Grade 3–5 RP, 37 (24.6%) patients developed Grade 3–5 esophageal toxicity. In univariate analysis, ALB level ($p = 0.002$), RE ($p < 0.001$) and SGA score ($p < 0.001$) were significantly associated with RP. Multivariate analysis revealed that SGA ($p < 0.001$) was the independent predictor of RP. **Conclusion:** SGA could be a predictor for RP in lung cancer patients treated with definitive IMRT and concurrent chemotherapy.

Keywords: Subjective Global Assessment, lung cancer, Radiation pneumonitis

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-011 AN ESOPHAGUS-SPARING TECHNIQUE TO LIMIT RADIATION ESOPHAGITIS IN LOCALLY ADVANCED NSCLC TREATED BY SIB-IMRT AND CONCURRENT CHEMOTHERAPY

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Background: To investigate the incidence of radiation esophagitis (RE) and tumor local control using esophagus sparing technique in locally advanced non-small cell lung cancer (LANSCLC) treated by simultaneous integrated boost intensity-modulated radiation therapy (SIB-IMRT) and concurrent chemotherapy. **Method:** Ninety-five patients with stage IIIA/B NSCLC who received definitive SIB-IMRT and concurrent chemotherapy had been divided into two groups: 1.with esophagus sparing technique; 2.without esophagus sparing technique. Chi-square test was performed to compare sex, clinical stage, histology, concurrent chemotherapy, RE and nutrition status between two groups. T-test was used to compare the dosimetric parameters. Overall survival (OS) and loco-regional failure free survival (LRFS) were calculated by the Kaplan–Meier method and compared by a log-rank test. **Result:** There were 50 patients in the esophagus sparing group and 45 in the non-sparing group. The incidence of severe RE (Grade 3-5) was significantly lower in patients with esophagus sparing technique ($p = 0.000$). Patients in esophagus sparing group had better nutrition status ($p = 0.029$). With a median follow-up of 23 months (range 0-37 months), the 3-year OS of all the patients was 33.4%. OS time was found to be longer in the esophagus-sparing group (32 vs. 27 months, $p= 0.010$). LRFS was comparable between two groups (29 vs. 24 months, $p=0.960$). **Conclusion:** Esophagus-sparing technique is an effective and essential method to limit RE in LANSCLC treated by SIB-IMRT and concurrent chemotherapy. Reducing severe RE when escalating radiation fraction size may help to achieve higher local control and better general performance status.

Keywords: esophagus-sparing technique, Esophagitis, non-small cell lung cancer

P1.14: RADIOTHERAPY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.14-012 HYPOFRACTIONATED SIMULTANEOUS INTEGRATED BOOST IMRT CONCURRENT WITH CHEMOTHERAPY IMPROVED LOCO-REGIONAL CONTROL IN LOCALLY ADVANCED NSCLC

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Background: This study investigated the loco-regional control (LRC) and toxicity of hypofractionated simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) for locally advanced non-small-cell lung cancer (LANSCLC) in the setting of concurrent chemotherapy. **Method:** One hundred and ten LANSCLC patients treated with SIB-IMRT and concurrent chemotherapy were retrospectively analyzed. Radical-intent radiotherapy was delivered at a fraction dose of 2.0~2.2, 2.4~2.6, and 2.9~3.1Gy respectively. Factors potentially predictive of LRC (age, sex, tumor stage, tumor volume, biological effective dose (BED), dose per fraction, overall radiation time (ORT) and concurrent chemotherapy) were assessed in the univariate analysis and Cox multivariate model. Toxicity data was collected and analyzed. **Result:** With a median follow-up of 24.4 months, the median duration of LRC was 21.4 months. LRC was 71.9% at 1 year, 45.9% at 2 years, and 41.8% at 3 years. In univariate analysis, BED (p=0.007), dose per fraction (p=0.002) and ORT (p=0.029) were associated significantly with LRC. In multivariate analysis, RT dose per fraction was independently prognostic of LRC (HR, 0.597; CI, 0.362~0.986). Grade ≥3 pneumonitis, pulmonary fibrosis and esophagitis were observed in 6 (5.5%), 2 (1.8%) and 19 (17.3%) of patients, respectively. There was no significant difference in toxicity among different doses per fraction. **Conclusion:** Our study showed that LRC was improved by the dose per fraction escalation in the setting of concurrent chemotherapy. Hypofractionated SIB-IMRT could be a feasible and effective approach for dose intensification, while maintaining tolerable toxicities.

Keywords: Locally advanced non small cell lung cancer, dose escalation, Loco-regional control

P1.14-013 HIGH DOSE RADIOTHERAPY (74GY) IMPROVED LOCAL PROGRESSION FREE SURVIVAL IN PATIENTS WITH INOPERABLE STAGE III NSCLC

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Background: Local failure is common after concurrent or sequential chemo-radiation therapy for non-small cell lung cancer (NSCLC). Hypothesizing that a higher dose of radiation to the gross tumor volume (GTV) might increase local control of advanced NSCLC. We investigated whether high-dose radiation improved local control in patients with stage III NSCLC. **Method:** Sixty-four patients with stage III NSCLC were treated with three-dimensional conformal radiation therapy. Clinical target volume (CTV) contains GTV, plus a margin which is determined to consider the anatomic structure. Elective nodal irradiation had not been allowed. Patients with NSCLC were received high dose radiotherapy, 74Gy at CTV. The volume of lung receiving at least 20Gy (V20) is restricted to 25% because of lung toxicity. Acute and late toxicities were scored per the Common Terminology Criteria for Adverse Events version 4.0. The primary endpoint was overall survival (OS) and local progression free survival (LPFS) the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse. All analyses were done by intention-to-treat. **Result:** Between Feb. 08, 2011 and Feb. 22, 2016, 64 patients received high dose radiotherapy and/or chemotherapy. 8 patients (12.5%) did not complete full dose radiotherapy. 3 patients stopped treatment voluntarily, 3 patients due to tumor progression during radiotherapy, and 2 patients dropped out of the treatment side effects – 1 neutropenia, 1 general weakness. Median follow-up was 14.6 months (1.2-51.6). Median OS was 20.0 months (1.2-65.6, and 3-year OS was 50.5%. Median LPFS was 15.7 months (1.2-57.0), and 3-year LPFS was 54.5%, retrospectively. Only one patient (1.6%) had grade 5 radiation induced pneumonitis. And other complication rates were tolerable which was compared with historical studies. **Conclusion:** High dose radiation is tolerable and contributes to improve outcomes, especially local progression free survival in patients with inoperable stage III non-small cell lung cancer, if radiation field is restricted to gross tumor only.

Keywords: non-small cell lung cancer, high dose radiotherapy

P1.14-014 COMPARATIVE EVALUATION OF VMAT & 3D-CRT IN LOCALLY ADVANCED NSCLC: IS THERE ANY RADIOBIOLOGICAL ADVANTAGE?

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Background: Our aim was comparative dosimetric evaluation of volumetric modulated arc therapy (VMAT) and 3-dimensional conformal radiotherapy (3D-CRT) in patients with locally advanced non-small cell lung cancer (LA-NSCLC) and to confirm whether this dosimetric benefit translates into a radiobiological advantage with respect to tumor control probability (TCP) and normal-tissue complication probability (NTCP) and finally to generate an algorithm and software to integrate the radiobiological component during plan evaluation and quality assurance. **Method:** A total of 25 3D-CRT naïve patients of LA-NSCLC, treated with radical radiotherapy were included in this study. We used copies of the Eclipse plan data, organized in separate study treatment courses. For each course, new VMAT plans were generated using the standard provincial dose-volume constraints. The DVH parameters for PTV (planning target volume), lung-GTV (gross tumor volume subtracted from lung), heart, esophagus and spine were reviewed and then the TCP and NTCP values for these regions of interest (ROI), cardio-pulmonary toxicity index i.e. C.P.T.I ($\sum_i NTCP_i$; i=1-2 representing heart, lung), morbidity index i.e. M.I ($\sum_i NTCP_i$; i=1-4 representing heart, esophagus, lung and spinal cord) and therapeutic gain (defined as the value of TCP when M.I=0; i.e. TG=TCP(1-M.I)) values were generated. The resulting data sets were compared using the Weltch two sample t-test and $p < 0.05$ was accepted as significant. Parameters were calculated using DVH data exported from the Eclipse and software written in the "R" programming language. The user interface has been developed with the "shiny" "R" web library. Dosimetric parameters included $V_{98\%}$ and $D_{99\%}$ of PTV, V_{50Gy} of esophagus and mean dose to esophagus, V_{45Gy} of spinal cord, V_{30Gy} and mean dose of heart and V_{20Gy}, V_{10Gy} and V_{5Gy} and mean dose of (lung-GTV). The radiobiological metrics included TCP, NTCP of heart, esophagus, lung and spinal cord,C.P.T.I, M.I and therapeutic gain. **Result:** Dosimetric evaluation did not show any significant difference in $V_{98\%}$ (*p=0.169*) and $D_{99\%}$ (*p=0.797*) of PTV between VMAT and 3D-CRT, however, there was significant improvement in V_{50Gy} of esophagus (*p=0.039*), V_{45Gy} of spinal cord (*p=0.003*) and V_{30Gy} of heart (p=0.038) with VMAT. V_{10Gy} of (lung-GTV) was higher with VMAT (*p=0.019*). Rest of the dosimetric paramters were not significantly different two modalities. TCP was better with 3D-CRT (*p<0.0001*) while NTCP of heart (*p=0.028*), esophagus (*p=0.053*) and spinal cord (*p=0.001*) was substantially improved with VMAT. There was no difference in NTCP of lung between two modalities. Overall C.P.T.I (p=0.039), M.I (p=0.019) was remarkably lower and therapeutic gain (*p=0.005*) was significantly better with VMAT. **Conclusion:** The study reveals that although TCP is higher with 3D-CRT, majority of the NTCP parameters including C.P.T.I and M.I are substantially improved with VMAT even in 3D-CRT naïve patients. The overall therapeutic gain is therefore notably higher with VMAT which emphasizes its potential to achieve superior oncologic outcome in patients with LA-NSCLC.

Keywords: tumor control probability and normal tissue complication probability, VMAT and 3D-CRT, locally advanced non-small cell lung cancer

P1.14-015 LOCAL RECURRENCE RATE AND TIMING AFTER STEREOTACTIC BODY RADIOTHERAPY FOR LUNG CANCER: NEED FOR LONG-TERM FOLLOW-UP

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Background: Local control rate by stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC) has been reported to be approximately 90%. But, most studies had relatively short follow-up time, and our group has previously published preliminary report that late local recurrence (LR) might not be negligible. Thus, the aim of this study was to assess LR rate and timing after SBRT, using long-term follow-up data of large cohorts from single institution. **Method:** Eligible patients were those who were treated with SBRT (isocenter prescription of 48Gy/4fr) between April 1998 and August 2014 for primary/recurrent NSCLC < 5cm and with > 6 months follow-up time. **Result:**

	No.	No. of LR	5y-Cumulative incidence of LR, % (95%CI)	P-value*
All tumors	229	45 (20%)	18 (13–23)	-
T stage (UICC 7th)				0.35
T1a	126	21 (17%)	15 (9–22)	
T1b	70	18 (26%)	24 (15–35)	
T2a	33	6 (18%)	16 (6–30)	
Histology				0.44
Adeno	83	15 (18%)	15 (8–24)	
SqCC	59	15 (25%)	24 (14–36)	
Unknown	72	13 (18%)	17 (9–27)	
Others	15	2 (7%)	13 (2–36)	
Location				0.55
Upper lobe	93	25 (27%)	22 (14–31)	
Middle/Lower lobe	136	20 (15%)	15 (10–20)	
Overall treatment time				0.62
< 9 days	172	35 (20%)	19 (13–25)	
≥ 9 days	57	10 (18%)	15 (7–26)	
Set up				0.77
without CBCT	180	38 (21%)	18 (13–24)	
with CBCT	49	7 (14%)	14 (6–26)	

* Gray's test

Abbreviations: LR, local recurrence; CI, confidence interval; UICC, Union for International Cancer Control; Adeno, adenocarcinoma; SqCC, squamous cell carcinoma; CBCT, cone beam CT

A total of 213 patients (229 tumors) were analyzed. Tumor and treatment characteristics are shown in Table. Median follow-up time was 7 years [95% confidence interval (CI) 6.2–7.8]. 5-year overall survival and progression-free survival rate was 47%[95% CI 40–54] and 32%[95% CI 26–39], respectively. The number of LR was 45, and 5- and 10-year cumulative incidence of LR was 18%[95% CI 13–23] and 26%[95% CI 18–33], respectively. Clinical T stage, histology, tumor location, overall treatment time and use of cone-beam CT for patient set-up did not impact LR rate, as shown in Table. Median time to LR was 1.7 years (range: 0.6–9.5, interquartile range: 1.0–3.2) and time to LR was significantly longer in adenocarcinoma (Adeno) than in squamous cell carcinoma (SqCC) (median: 2.7 vs. 1.1 years, p=0.04). The number of late LR > 5 years after SBRT was six. The histology of tumors with late LR was Adeno/SqCC/unknown=3/1/2 (one of two unknown cases was proven to be Adeno by salvage surgery). Five of six late LRs were isolated LR as the first progression site. **Conclusion:** Late LR was not uncommon. Long-term follow-up after SBRT is needed, especially for adenocarcinoma.

Keywords: stereotactic body radiotherapy, local recurrence, non-small cell lung cancer

P1.14-016 ASSESSING THE FEASIBILITY OF FLT-PET FOR EVALUATION OF NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT)

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Background: Distinguishing fibrosis from tumor recurrence following lung SBRT remains a clinical challenge since CT has poor sensitivity and specificity for detecting recurrence. 18F-Fluoro-L-thymidine-PET (FLT-PET) uptake correlates with cell proliferation. The purpose of this study is to investigate the feasibility of FLT-PET as an imaging biomarker for lung SBRT response assessment. **Method:** In this prospective study, three groups were included: 1) newly-diagnosed biopsy-proven NSCLC pre-SBRT, 2) established post-SBRT mass-like fibrosis on serial follow-up CT scans by co-investigators' consensus, and 3) biopsy-proven locally-recurrent NSCLC after SBRT. Non-gated, helical gated (3D-CT/4D-PET) and phase-matched (4D-CT/4D-PET) FLT-PET images were obtained. Group-1 underwent fluorodeoxyglucose (FDG)-PET scan according to clinical guidelines. FLT uptake was measured by SUV95 and SUV50 (95% and 50% of maximum pixel value plus average background value, respectively), SUV2Dpeak and SUV3Dpeak (1cm diameter circular or spherical around region of interest, respectively), SUVmean and SUVmax. Descriptive statistics were gathered. Kolmogorov–Smirnov test was used to determine normality. Statistical significance was reported using student's t-test. **Result:** 27 patients were included, with 19 primary tumors (group-1), 12 established fibrosis (group-2) and 1 recurrence (group-3). In group-1, 16 tumors were T1. Group-1, mean FDG-PET SUVmax, SUV95, SUV50, SUV2Dpeak, SUV3Dpeak and SUVmean were 7.40, 5.88, 2.39, 5.59, 6.02 and 2.78, respectively. Mean FLT-PET values for group-1 were 3.43, 2.84, 1.71, 2.9, 2.82 and 1.78, respectively. Group-2 SBRT dose was either 48Gy in 4 fractions (83%) or 60Gy in 8 fractions. Median time from radiation to FLT-PET scan in group-2 was 19.5 months (5.8-83.8mos). The patient in group-3 had SUV50, SUV95, SUV2Dpeak, SUV3Dpeak, SUVmean and SUVmax of 2.27, 3.85, 6.37, 6.05, 2.39 and 7.64, respectively. Mean FLT-PET SUVmax for groups 1 and 2 was significantly different (p=0.03) at 3.42(1.14-7.04) and 2.34(1.23-4.35) respectively. Similarly, mean (range) of SUV50, SUV95 and SUVmean for group-1 was 1.8(0.74-3.43), 2.97(1.03-5.83), 1.87(0.73-3.44), and for group-2 was 1.22(0.81-2.26), 1.85(1.13-3.8) and 1.25(0.83-2.39), respectively ($p<0.01$, <0.01 and <0.01). There was no statistically-significant difference between SUV2Dpeak and SUV3Dpeak between groups 1 and 2, with a mean of 2.97(0.99-6.30) and 2.91(0.90-6.11) for group-1 and 2.10(1.11-3.91) and 2.03(1.00-3.86) for group-2 (p=0.06 and 0.06), respectively. There was no statistically significant difference between the 3D and 4D image acquisition in group-1. There were no FLT-PET-related toxicities. **Conclusion:** FLT-PET is feasible in SBRT patients pre- and post-treatment, and may assist in distinguishing fibrosis from recurrent tumor. Further validation studies are needed.

Keywords: Early stage non-small cell lung cancer, radiotherapy, stereotactic

P1.14-017 IMPACT OF SYSTEMATIC EBUS-TBNA MEDIASTINAL STAGING ON RADICAL RADIOTHERAPY PLANNING IN NSCLC

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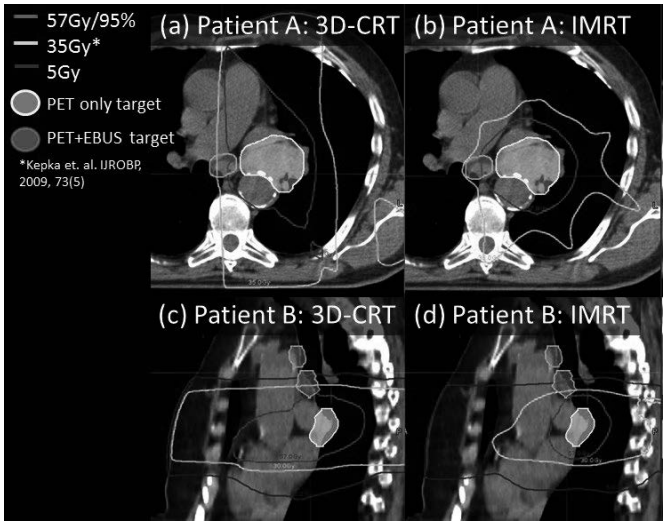
Background: Radical radiotherapy often relies solely on radiological imaging to determine treatment volumes. Systematic mediastinal staging with endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) may identify PET-occult sites of mediastinal disease, or demonstrate benign causes for PET-positive LN. This study evaluated 1) Involved nodal coverage 2) Doses to organs-at-risk when planned based on PET-CT and EBUS-TBNA and 3) Incident dose to mediastinal nodes between 3D-CRT and Intensity-Modulated-Radiotherapy (IMRT). **Method:** Radical radiotherapy plans (60Gy/30 fractions) were created for patients with stage change following EBUS-TBNA from a prospective clinical trial. We compared lung Normal-Tissue-Complication-Probability (NTCP, pneumonitis), oesophageal and heart dose for planning to targets based on PET-CT versus PET-CT+EBUS-TBNA. The incidental dose to PET-negative/EBUS-TBNA-positive nodes from 3DCRT and IMRT was evaluated using volume receiving 35Gy as a surrogate for control of sub-clinical disease (Kepka, IJROBP, 73(5) 2009). **Result:** Of 30 patients enrolled, four were upstaged by EBUS-TBNA; these patients had a significant geographic miss of nodal GTV when planned to PET-positive nodes only (Figure 1). When planned based on PET-CT alone, the incidental dose to PET-negative/EBUS-TBNA-positive nodes was higher with IMRT for two patients (v35Gy increased by 17% & 6%; Figure 1a&b) and lower with IMRT (v35Gy reduced by 16% and 6%; Figure 1c&d) for two, dependent on nodal position relative to the primary. Six patients had negative pathology for PET avid nodal stations; Inclusion of EBUS-negative, PET-positive nodes resulted in an average increased lung NTCP of 5% (range 1%-13%), mean oesophagus dose of 13Gy (range 4-23Gy) and mean heart dose of 4Gy (range -0.1-11Gy) over plans based on EBUS-positive nodes alone.



Conclusion: Systematic EBUS-TBNA has the potential to improve loco-regional control and limit the probability of lung and heart toxicity. The incidental dose to adjacent tissue is inherently related to involved node/tumour position and not solely dictated by the radiation delivery technique.

Keywords: EBUS-TBNA, NSCLC, TCP/NTCP

P1.14-018 CONSTRUCTION AND EVALUATION OF RAPIDPLANTM MODELS FOR RADICAL LUNG PLANNING

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Background: A Volume Modulated Arc Therapy (VMAT) service for our radical lung patients has been offered since 2011. Attention has now turned towards how this service can be improved further. The RapidPlan™ package has already been used to great effect in our Prostate service so was assessed for its potential in radical lung planning. **Method:** RapidPlanTM models were created using the Eclipse Treatment Planning System [Varian Medical Systems] v13.6: consisting of 50 randomly selected radcial right lung patients (M_R), left lung patients (M_L) and a combined model using all 100 of these same patients (M_COM). The models were assessed using the standard RapidPlanTM tools. A retrospective planning study was performed for 10 right lung and 10 left lung patients. Each of the 20 patient treatments were replanned using each model. All plans were normalised to ensure that the target mean was 100% and compared to the manually optimised plan (O_P) The PTV coverage was assessed using dose homogeneity indices. Differences in organ at risk (OAR) dose volume histogram parameters were calculated to assess plan quality. The plans were compared on a variety of criteria including but not limited to whole lung V5 (with tolerance considered 70%) and V20 (with tolerance considered 30%) and the maximum dose to spinal canal (tolerance considered to be 80 %). Significance was assessed by two-tailed t-test ($p<0.01$). **Result:** Although all models gave a clinically acceptable plan differences in the homogoeneity indices were observed with M_COM values showing an improvement on the other models. M_COM plans had a statistically significant increase in maximum spinal cord dose when compared to the other plans set, however doses were within tolerance. An increase in mean whole lung and whole lung minus PTV V20Gy was also observed. There was no significant difference in contra lateral lung V5Gy or whole lung minus PTV V5Gy. There was no statistical difference observed when comparing right sided tumour patient calculated with M_L and left sided tumour patients planned with M_R. **Conclusion:** M_COM outperformed the other models and O_P in relation to PTV coverage without impacting clinically acceptable OAR constraints. This model demonstrated improvement when compared to M_L and M_R suggesting that 50 plans are insufficient to perfect a lung model and that 100 plans is more effective. When compared with manually optimised plans the M_COM model demonstrates an improved relationship between balancing OAR objectives and PTV conformity.

Keywords: Radiotherapy, VMAT, Improvement

P1.15-001 IPILIMUMAB INCREASES TH1/TH2 AND INFLAMMATORY CYTOKINES COUNTERACTING CHEMOTHERAPY EFFECTS IN SMALL CELL LUNG CANCER

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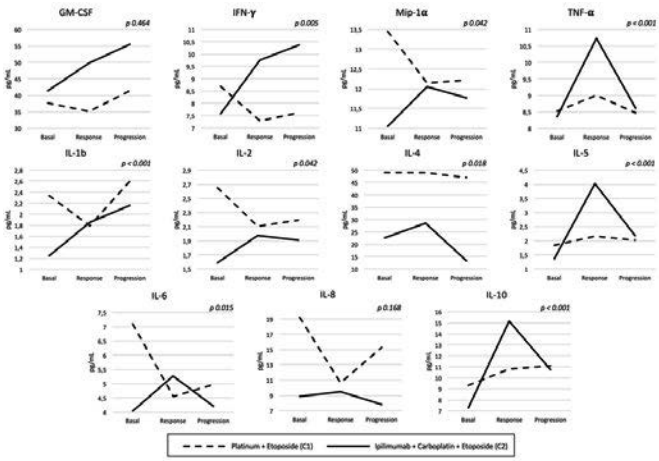
Background: Cytokines are soluble proteins with a relevant role in immune response that can be modulated by immunotherapy. In this study we aimed to evaluate the serum concentrations of Th1/Th2 and inflammatory cytokines and their changes in SCLC patients treated with ipilimumab and chemotherapy compared to chemotherapy alone. **Method:** We evaluated 2 cohorts (C) of patients with SCLC: in C1, 47 patients were treated with standard platinum/etoposide (PE); in C2, 37 patients with ipilimumab, carboplatin and etoposide (ICE trial). We analyzed serum samples at baseline and subsequent time points with the Cytokine Human Magnetic 10-Plex (GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10 and TNF-α) plus MIP-1a. Serum samples from 30 healthy volunteers were used as controls. Statistical analysis was carried out with SPSS 22.0 (SPSS Inc.) and Prism 6.0 (GraphPad). **Result:** Patients with SCLC showed significantly lower levels of IL-1b, Mip-1a, IL-5 and IL-10 and higher TNF-a compared to healthy volunteers. Patients treated with chemotherapy alone (C1), showed a decrease of Th1 and inflammatory cytokine median concentrations at tumor response and an increase at progression, while no such pattern was observed in Th2 cytokines and TNF-a. In contrast, patients treated with ipilimumab in addition to chemotherapy (C2), showed a global increase on the level of all cytokines after treatment initiation (Figure 1).



Conclusion: In patients with SCLC, Th1 and inflammatory cytokines (except TNF-a) reflect tumor burden. Chemotherapy reduces these levels targeting cytokine secreting tumor cells. Th2 cytokines may be mainly secreted by immunological cells as they remain unaltered upon chemotherapy treatment. Interestingly, ipilimumab increases globally Th1, Th2 and inflammatory cytokine secretion counteracting the effect of chemotherapy. The correlation of these changes to outcome and toxicity warrants further investigation.

Keywords: small cell lung cancer, cytokines, Ipilimumab

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-002 A RETROSPECTIVE STUDY OF AMRUBICIN MONOTHERAPY FOR THE TREATMENT OF RELAPSED SMALL CELL LUNG CANCER IN ELDERLY PATIENTS

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Background: Amrubicin is one of the most active chemotherapeutic agents for small-cell lung cancer (SCLC). Previous studies reported its effectiveness and severe hematological toxicity. However, the efficacy of amrubicin monotherapy in elderly patients with SCLC has not been described. The objective of this study was to investigate the feasibility of amrubicin monotherapy in elderly patients, and its efficacy for relapsed SCLC. **Method:** A retrospective cohort study design was used. We retrospectively evaluated the clinical effects and adverse events of amrubicin treatment in elderly (≥70 years) SCLC patients with relapsed SCLC at one of four Japanese institutions (Gunma Prefectural Cancer Center, Tochigi Prefectural Cancer Center, Ibaragi Central Hospital, and Fukushima Medical University). **Result:** Between November 2003 and September 2015, 86 patients (aged ≥70 years) received amrubicin monotherapy for relapsed SCLC at four institutions There were 42 cases of sensitive relapse (S) and 44 of refractory relapse (R). S cases with median age of 75 years (range, 70–85 years) and R cases with median age of 74 years (range, 70–84 years) were included in our analysis. The median number of treatment cycles was 3 (range 1–9), and the response rate was 33.7% (40.5% in the S and 27.2% in the R cases). Median progression-free survival time was 4.0 months in the S and 2.7 months in the R patients (p = 0.013). Median survival time from the start of amrubicin therapy was 7.6 months in the S and 5.5 months in the R cases (p = 0.26). The frequencies of grade ≥3 hematological toxicities were as follows: leukopenia, 60.4%; neutropenia, 74.4%; anemia, 11.6%; thrombocytopenia, 16.2%; and febrile neutropenia, 17.4%. Treatment-related death was observed in 1 patient. **Conclusion:** Although hematological toxicities, particularly neutropenia, were severe, amrubicin showed excellent anti-tumor activity, not only in the S, but also in the R cases, as shown in previous studies. Amrubicin could be a preferable standard treatment in elderly patients with relapsed SCLC. These results warrant further evaluation of amrubicin in elderly patients with relapsed SCLC by a prospective trial.

Keywords: small cell lung cancer, Amrubicin, Elderly patients

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-003 SURVIVAL BY RESPONSE TO FIRST-LINE PLATINUM-BASED THERAPY AMONG PATIENTS WITH EXTENSIVE DISEASE SMALL CELL LUNG CANCER

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Background: Patients with extensive disease small cell lung cancer (ED-SCLC) have limited treatment options after recurrence, and their overall survival (OS) remains poor. This study explored the OS benefit of second-line therapy in patients with platinum-refractory versus platinum-sensitive ED-SCLC. **Method:** Linked data from Surveillance, Epidemiology, and End Results program and Medicare claims were used. Eligible patients were ≥66 years of age, and had pathologically confirmed first primary ED-SCLC diagnosis between January 1, 2007 and December 31, 2011 and Medicare Parts A and B coverage. Patients were followed from diagnosis until death, end of follow-up, second primary cancer diagnosis, or switch to managed care coverage. Therapy was determined using Medicare claims for outpatient chemotherapy, and lines of therapy were inferred from changes and gaps in therapy. Platinum-refractory status was defined in 2 ways based on criteria used in clinical trial enrollment and from clinical guidelines: 1) a gap of ≤90 days between the last administration of first-line therapy and the start of second-line therapy and 2) a gap of ≤183 days from start of first-line therapy to the start of second-line therapy. Cox proportional hazards models were used to identify factors associated with OS from the start of second-line therapy. **Result:** In all, 1059 patients with ED-SCLC received first-line platinum-based therapy. At diagnosis, mean age was 73 years, 53% were male, 87% were white, 30% had ≥1 indicator of mobility limitations, and 21% lived in a high-poverty area. Median OS for all patients was 4.3 months. There were 572 patients (54%) classified as platinum-refractory according to ≥1 definition, of whom 402 (70%) were classified as refractory according to both definitions. Based on the 90-day gap and the 183-day gap, respectively, median OS was 3.7 and 3.8 months for platinum-refractory patients, and 5.3 and 5.1 months for platinum-sensitive patients. In adjusted models using both definitions, factors associated with significantly shorter OS included male sex, stage IV disease at diagnosis, and platinum-refractory status. **Conclusion:** Median survival was <6 months for both platinum-refractory and platinum-sensitive patients, with refractory patients faring slightly worse. These findings highlight the need for new treatments for patients with ED-SCLC irrespective of their platinum sensitivity.

Keywords: small cell lung cancer, overall survival, platinum-based therapy

P1.15: SCLC/NEUROENDOCRINE TUMORS -
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P1.15-004 AN OPEN-LABEL, MULTITUMOR PHASE II BASKET STUDY OF OLAPARIB AND DURVALUMAB (MEDIOLA): RESULTS IN PATIENTS WITH RELAPSED SCLC

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Background: The prognosis of small cell lung cancer (SCLC) remains poor and there is a high unmet need for effective therapies. Poly (ADP-ribose) polymerase (PARP) inhibitors and immunotherapies hold promise due to expression of PARP and high mutational burden in SCLC. PARP inhibition leads to upregulation of anti-programmed cell death ligand-1 (PD-L1) and enhanced cancer immunosuppression. This led us to investigate the combination of olaparib and the PD-L1 inhibitor, durvalumab in SCLC (NCT02734004). **Method:** Individuals with relapsed SCLC at least 12 weeks after platinum-based therapy were eligible. Patients received olaparib tablets 300 mg PO BID for a 4-week run-in, followed by a combination of olaparib 300 mg PO BID and durvalumab 1.5 g IV q 4 weeks. The combination was continued until progressive disease by RECIST 1.1. Tumor assessments were done at baseline, 4 weeks and every 8 weeks thereafter. The primary endpoints were disease control rate (DCR) at 12 weeks, as well as safety and tolerability. The secondary endpoints included DCR at 28 weeks, objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Biomarker endpoints included PD-L1 expression and evaluation of tumor infiltrating lymphocytes (TILs). A target DCR of 60% was used to calculate the sample size in a Bayesian predictive probability design. **Result:** Among the 38 patients, the median age was 63 years (range 44-76) and median line of prior chemotherapies 1 (range 1-3). At the time of analysis, each patient was followed up for at least 12 weeks. The most common grade 3 or higher AEs included anemia (34.2%), hyponatremia (10.5%), lymphopenia (10.5%), chronic

obstructive pulmonary disease (5.3%), increased GGT (5.3%) and increased lipase (5.3%). DCR at 12 weeks was 29%. Confirmed responses included one partial response and one complete response. Three additional patients had unconfirmed responses. The updated primary and secondary endpoints, as well as biomarker and PK data will be presented. **Conclusion:** Although AEs of all grades were seen commonly, the combination of olaparib and durvalumab was relatively well tolerated, as most of the AEs were attributed to underlying disease. While efficacy of the combination in this SCLC population did not reach the target DCR and is below the futility boundary (<40%), a minority of patients obtained significant benefit and will be followed up for further clinical and translational analyses.

Keywords: small-cell lung cancer, olaparib, durvalumab

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-005 RELATIONSHIP BETWEEN MYC FAMILY STATUS AND SENSITIVITY TO AURORA KINASE INHIBITORS IN NEUROENDOCRINE AND OTHER LUNG CANCER CELL LINES

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Background: Recently, it has been reported that MYC-driven SCLC cell lines exhibit synthetic lethality with Aurora kinase (AURK) inhibitors. The aims of this study are to evaluate sensitivities to neuroendocrine (NE) lung cancer cell lines with or without any MYC family overexpression and/or amplification using representative AURK inhibitors and to investigate the associations between drug sensitivities, MYC family status and NE differentiation. **Method:** We screened a panel of 62 cell lines including 33 SCLC, 18 other NE, and 11 NSCLC, with various MYC family status for growth inhibition upon AURK inhibitors. MYC family copy number, gene expression, and protein status were examined by quantitative real-time PCR, microarray and Western blotting. Relative cell growth was analyzed by MTS assay, and selective AURK A and B inhibitors, MLN8237 (Alisertib) and AZD1152 (Barasertib), respectively, were used in this study. Cell lines with IC50 values < 0.1 μM were defined as sensitive. Drug effects on cell cycle and morphology were determined by flow cytometry and examination of formalin-fixed paraffin embedded cell pellets. **Result:** Of 31 NE cell lines with MYC family overexpression/amplification, 21 (68%) and 18 (58%) were sensitive to Alisertib and Barasertib, respectively. All 20 NE (and most NSCLC) cell lines lacking MYC family overexpression/amplification were resistant to AURK inhibitors**.** There was an excellent concordance (86%) between response to the two AURK inhibitors. Both MYC family overexpression and amplification were predictive of sensitivity; however, some overexpressing lines had normal copy number. Cell cycle analysis showed a mitotic arrest in some sensitive cell lines with treatments of these drugs. Representative sensitive cell lines showed cell ballooning and bizarre multinucleated polyploid cells, which indicated cell cycle arrest in G2/M. **Conclusion:** MYC family overexpression/amplification in NE lung cancer cell lines confers sensitivity to AURK inhibitors in approximately 70% of cases**.** Lack of MYC family overexpression/amplification was always associated with drug resistance. MYC family overexpression may occur in the absence of gene amplification, and, thus, overexpression is a better predictor of sensitivity than amplification. We are currently investigating the mechanism of resistance in overexpressing NE cell lines and determining whether NE differentiation plays a role in drug sensitivity.

Keywords: MYC family overexpression/amplification, Aurora kinase inhibitors, Neuroendocrine Lung Cancer

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-006 ENRICHED ENVIRONMENT AND ANTI-DEPRESSANTS ENHANCE PLATINUM CHEMOSENSITIVITY OF SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is one of the most lethal malignancies with rapid chemoresistance. Based on our previous study, enriched environment (EE) has a clear effect on improving the mental state of mice and can reduce chemoresistance caused by platinum regimens. In this study we investigated the complex links between benign mental stress (EE) and chemosensitivity of SCLC, and use anti-depressants to improve the mental state of mice to observe its impact on chemosensitivity to platinum regimens, and the underlying mechanism was explored. **Method:** The mental state of mice was evaluation by behavior tests include: elevated plus maze (EPM), open field experiment (OF), forced swimming (FS). Then, the mice were transplanted subcutaneously and treated with cisplatin, carboplatin and oxaliplatin. The tumor was analyzed by gene expression profiling and the differential genes were screened. The expression level of differential genes were examed by real-time PCR, and verified by western bolt and immunohistochemistry, respectively. And then ABCG2 blocker was used for chemosensitivity verification in vivo and *in vitro*. **Result:** EE significantly increased the movement on openarms in the EPM (35.24 sec V.S. 16.78 sec, P<0.01), increased the center area time in OF test (54.25 sec V.S. 35.24 sec, P<0.05), significantly increased the struggling time in the FS test (46.02 sec V.S. 25.81 sec, P<0.01). Antidepressants can also significantly improve the state of depression of mice, but can not achieve the effect of EE. For platinum chemosensitivity test, the antidepressant drugs (Diazepam, Quetiapine and Clomipramine) have no direct inhibition to tumor cells. A can significantly increased the sensitivity of chemotherapy in mice, but can not achieve the inhibitory effect of EE. Next we found the serum BDNF levels significantly decreased in EE mice. Similarly, antidepressants also significantly reduced serum BDNF levels in mice. Gene expression profiles showed that a variety of genes were downregulated mainly in ABC transporters and drug metabolic pathways by EE and antidepressants. The expression level of ABCB1, ABCC2, ABCG2, ABCC9, PPARa, DPYD, GST-P1 and GSTM1 in SCLC sample were examed by real-time PCR, and verified by western bolt and immunohistochemistry, respectively. ABCG2 expression in tumor of EE and antidepressants mice were even 3 fold higher than control (P<0.001). Nicardipine blocks ABCG2 expression can restore chemosensitivity to platinum based drugs (P<0.001). **Conclusion:** Antidepressants can partially mimic the chemotherapeutic effect of EE and we confirm that the mechanism is partially achieved by increasing BDNF and reducing the expression of ABCG2.

Keywords: Enriched environment, Chemosensitivity, antidepressants

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-007 RANDOMIZED PHASE III TRIAL OF ENOXAPARIN IN ADDITION TO STANDARD TREATMENT IN SMALL CELL LUNG CANCER: THE RASTEN TRIAL

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Background: Hypercoagulation is a hallmark of cancer, and several coagulation factors contribute to tumor development and progression in addition to development of venous thromboembolism (VTE), which is a major cause of morbidity and mortality in lung cancer. Early studies suggested that coagulation inhibition with low molecular weight heparin (LMWH) may improve survival specifically in small cell lung cancer (SCLC) patients, whereas other studies showed contradictory results. The aim of RASTEN was to investigate the survival effect of LMWH enoxaparin in a trial powered to demonstrate a clinically significant difference in a homogenous group of SCLC patients. (ClinicalTrials.gov: NCT00717938) **Method:** We performed a randomized, multicenter, open-label trial to investigate the effect of LMWH enoxaparin administered at a supraprophylactic dose (1 mg/kg) and continuously during standard treatment in patients with newly diagnosed SCLC. The primary outcome was overall survival (OS), and secondary outcomes were progression free survival (PFS), incidence of VTE and hemorrhagic events. **Result:** In RASTEN, 390 patients were randomized over an 8-year period, of which 186 and 191 were included in the final analysis in the LMWH and control arm, respectively. We found no evidence of a difference in OS or PFS by the addition of enoxaparin (HR 1.11; 95% CI: 0.89-1.38, *P*=0.36, and HR 1.18; 95% CI: 0.95-1.46, *P*=0.14, respectively). Subgroup analysis of patients with limited and extensive disease did not show any reduction in mortality by enoxaparin. The incidence of VTE events was significantly reduced in the LMWH arm (HR 0.31; 95% CI: 0.11-0.84, *P*=0.02). Hemorrhagic events were more frequent in the LMWH-treated group but fatal bleedings occurred in both arms. **Conclusion:** Anticoagulants have previously been found to exert impressive tumor inhibiting properties in experimental models; however, results from clinical trials have been conflicting. This may partly be explained by the use of suboptimal, prophylactic LMWH dosages. In the present study, LMWH enoxaparin in addition to standard therapy did not improve OS in SCLC patients despite being administered at a supraprophylactic dose and despite resulting in a significant reduction in VTE incidence. Based on these results, the addition of LMWH cannot be generally recommended in the management of SCLC patients. Further, our data underline that predictive biomarkers of VTE and LMWH-associated bleeding are warranted for individualized anticoagulant therapy of cancer patients.

Keywords: low molecular weight heparin, small cell lung cancer, enoxaparin

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-008 CLINICAL FEATURES AND GENE MUTATION PROFILING OF PULMONARY CARCINOID TUMORS

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Background: Carcinoid tumors of the lung are an uncommon group of pulmonary neoplasms. Carcinoid tumors represent the most indolent form of a spectrum of bronchopulmonary neuroendocrine tumors, however little is known about its molecular features. We analyzed pulmonary carcinoid tumors to identify biologically relevant genomic alterations. **Method:** We reviewed all the patient data from 2006 to 2016 in our hospital and collected 20 cases of lung carcinoid tumors. We summarized their clinical features and imaging data. Among 20 cases of lung carcinoid tumors, quality control was passed for 6 patients. We performed targeted

capture sequencing of 56 cancer-related genes. Moreover, we made a literature review of pulmonary carcinoid tumors and summarized the clinical features and gene mutations. **Result:** Among the 20 pulmonary carcinoid tumors cases, which include 9 typical carcinoid and 11 atypical carcinoid tumors, there was a male predominance of this disease (Male vs Female: 15 *vs* 5). The range of age is 14 to 71 with the median age of 48. For gene mutation profiling on 6 pulmonary carcinoid tumors, we detected 27 mutations in 21 genes, including 22 missense mutations, 2 deletion mutations, 1 frameshift mutation and two others. Among the 21 genes, there are 11 proto-oncogenes and 6 tumor suppressor genes, which were reported to participate in the tumorigenesis, growth, invasion and metastasis of tumor. **Conclusion:** Through the next generation sequencing, we detected 27 mutations in 21 gene on the 6 pulmonary carcinoid tumors. Among these genes, the mutation of gene IGF1R, ERBB4, KIT and TSC2 showed the most frequent. We supposed that these genes might be involved in the tumorigenesis of pulmonary carcinoid tumors and the potential targets of therapy. Further functional studies of these genes are worthy of being explored.

Keywords: pulmonary carcinoids, mutation, NGS

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-009 SAFETY AND EFFICACY OF NAB-PACLITAXEL MONOTHERAPY AS 2ND OR LATER LINE SETTING IN PTS WITH EXTENSIVE SCLC, A PHASE II SINGLE ARM STUDY (NCT02262897)

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Background: There is still an unmet need for patients with extensive small cell lung cancer(SCLC) who failed from the previous treatment even though topotecan was approved by Food and Drug Administration as second line setting in this population. Nab-paclitaxel (nab-P) has showed promising efficacy in pancreas cancer, breast cancer and nonsmall cell lung cancer, this phase II trial try to evaluate the safety and efficacy of nab-paclitaxel (nab-P) monotherapy as the secondary or later line therapy in patients with extensive SCLC. **Method:** Main included criteria were performance status 0-2, extensive disease, failed or insensitive relapse from the previous treatment, sufficient myeloid function. Sensitive relapsed from the last line chemotherapy was excluded. Patients who met these criteria received weekly nab-paclitaxel 130mg/m2, d1,8,15, every 4 week or nab-paclitaxel of 230 mg/m2, d1 every 3 weeks. The Primary end point is objective response rate. The secondary end point included progression free survival(PFS), overall survival, and side effects. **Result:** From Sep, 2014 to Mar, 2017, 40 patients were included into this study, included 39 males, 6 never smokers, PS 1/2:27/13 with a median age of 66 years. The median line of nab-P monotherapy is 3(2-5). Among them, 30 patients received weekly nab-P and 10 received nab-P every 3 weeks. 9, 27, 4 patients were resistant, refractory and sensitive relapse to first line chemotherapy respectively. 7 patients got partial response,17 stable diseases and 16 progression disease. The objective response rate was 17.5% and disease control rate(DCR) was 60%. The median PFS was 3 months and the during of response was 5.8 months. Subgroup analysis showed that patients who were refractory or sensitive relapse to first line chemotherapy had a significant higher DCR (67.8% vs 28.5%, p=0.042) and longer PFS(3.3 vs 1.4 months, p=0.04), while similar results were found in different PS, smoking status and lines of therapy. Toxicity was mild and manageable including alopecia, neuritis, neutropenia and anemia, no grade 3/4 adverse event observed. **Conclusion:** Nab-P showed promising efficacy together with acceptable toxicity in patients with extensive SCLC who failed or insensitive relapse from the previous treatment, especially in the subgroup of refractory or sensitive relapse to first line chemotherapy, large cohort study is needed to validate these findings.

Keywords: small cell lung cancer, Chemotherapy refractory, nab-paclitaxel

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-010 SMALL CELL LUNG CANCER: EXPERIENCE OF A PORTUGUESE DISTRICT HOSPITAL

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Background: Small cell lung cancer (SCLC) originates from neuroendocrine-cell percursors and is characterized by rapid growth, high response rates and development of treatment resistance in patients with metastatic disease. In the past few years its heterogeneity in form of presentation, behaviour in response to therapy and time to progression has raised several questions. **Method:** Review of clinical files of patients with SCLC diagnosed between may 2012 and may 2017 in our hospital, according to demographic characteristics, risk factors, comorbidities, form of presentation and diagnostic approach, clinical stage, therapy performed and outcome. **Result:** In this period 46 patients were followed, of whom 80% were male, with an average age of 65.5 ± 9.2 years (min 45, max 88). About 96% had active or past smoking habits. Regarding to comorbidities, it was found that 61% had a history of chronic obstructive pulmonary disease, 57% of cardiovascular disease, 17% of type 2 diabetes mellitus and 9% had a history of a second tumor. One patient had a severe usual intersticial pneumonia. The most frequent forms of presentation were pneumonia (28%) followed by constitutional symptoms (15%). Histological diagnosis was achieved in most cases by bronchial biopsy (59%). At the time of diagnosis most of the patients had ECOG performance status 1 (67%) and presented stage IV disease (72%), followed by stage IIIB (13%). In 65% of patients therapy was conducted with palliative intent, 17% with curative intent and the remaining were eligible to Best Supportive Care. Only 1 patient performed surgery with curative intent. In the 30 patients submitted to first line palliative chemotherapy with platinum doublet and etoposide, 13 partial responses and 3 stable disease (according to RECIST 1.2 criteria) were observed. About outcome, there were 35 deaths (76%), 94% of whom were patients whose initial approach was palliative. Median survival was 246 days (CI 95%). **Conclusion:** SCLC comprehends a heterogeneous group of patients. In recent years diferent subtypes of SCLC have been identified and new therapeutic molecules have been tested in order to improve management of these tumors. More studies are necessary.

Keywords: Heterogeneity, neuroendocrine, pulmonary

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-011 LONGITUDINAL MUTATION MONITORING IN PLASMA WITHOUT MATCHING TUMOR TISSUE BY DEEP SEQUENCING IN SMALL CELL LUNG CANCER (SCLC)

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Background: SCLC is a devastating cancer with poor overall survival. Mutation profiles and treatment regimens differ significantly from non-small cell lung cancer (NSCLC). Here we demonstrate feasibility of monitoring patients with SCLC by deep sequencing from only 2 ml of plasma, without prior knowledge of the tumor tissue mutations relative to CT imaging. **Method:** Cell free DNA (cfDNA) was isolated from 64 longitudinal plasma samples (2ml) from 23 subjects with advanced SCLC using the **cobas**® cfDNA Sample Preparation Kit. The AVENIO ctDNA Surveillance kit (RUO, Roche, Pleasanton, CA, USA) with 197 genes detects SNVs, fusions, CNVs and InDels, and was used for sequencing the cfDNAs. Library preparation with 10-50ng cfDNA yielded a mean pre-capture library yield of 1,728ng. Mean % reads on-target was 65% with a mean deduped coverage of 3,397 fold. CT scans were reviewed to assess disease burden. **Result:** 47 longitudinal plasma samples from 8 subjects were successfully analyzed without access to matched tumor tissue. Sixteen subjects with only one baseline plasma sample were excluded from further analysis. Subjects had 3-10 longitudinal plasma samples. Somatic variants were detected with allele frequency (AF) of >0.5% to 30% and 60-90% if they were present in cfDNA from at least three different time points. Germline variants were identified and removed if AFs were 40-60%, and >90%. All variants with frequencies >1% in ExAC were removed. Somatic variants were identified in TP53 (5), APC (2), NPAP1 (2), MKRN3 (2), BRAF, NFE2L2, CDKN2A, TIAM1, LRRTM1, NYP2, FAM135B, FAM71B, PIK3CG, KEAP1, DCAF12L1, PCDH15, EGFLAM. Tracking somatic variants in the longitudinal plasma samples allowed monitoring of treatment response at the molecular level for 6 of 8 subjects. In one subject with 10 longitudinal plasma samples mutations in five different genes were tracked at 1-3% AF before rising to 5- 20% at month 8 and 12-55% at month 9. Molecular progression was detected 1 month earlier than clinical progression by CT. Another subject had a TP53 splice mutation over 10 time points and through 3 lines of treatment and AF correlated with clinical response as measured by imaging. **Conclusion:** Subjects with advanced SCLC and mixed SCLC/NSCLC can be monitored at the mutation level using molecular barcoded duplex sequencing in longitudinal plasma samples. 2ml of plasma yielded sufficient cfDNA for testing with the Surveillance kit. Somatic mutation monitoring is possible without matching tumor tissue samples where longitudinal mutation profiles correlate with clinical response by CT imaging.

Keywords: Monitoring of somatic mutations in plasma over three lines of treatment correlates with response, ctDNA sequencing with molecular barcodes & digital background error surpression using 197 gene panel, Longitudinal mutation monitoring in patients with small cell lung cancer (SCLC) from 2 ml of plasma

P1.15: SCLC/NEUROENDOCRINE TUMORS -
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P1.15-012 CLINICAL PROGNOSTIC FACTORS OF ELDERLY PATIENTS WITH EXTENSIVE STAGE SMALL CELL LUNG CANCER IN KOREA

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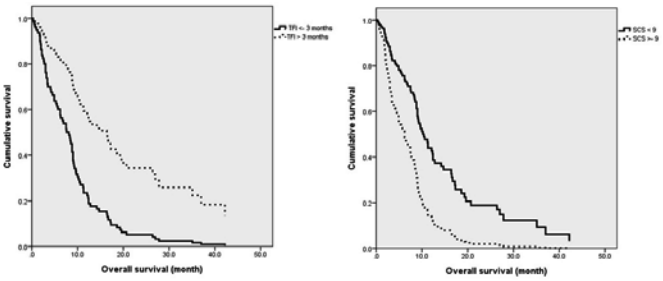
Background: SCLC represents 15% of all lung cancers and is one of the most aggressive types with rapid progression. Because of this, two thirds of patients are diagnosed with ED. The ED-SCLC is highly sensitive to chemotherapy. However, many patients are diagnosed in ages 65 and older. This retrospective study was designed to examine factors associated with chemotherapy administration among elderly patients

with SCLC and to quantify the survival benefit. **Method:** Between Jan 1995 and Dec 2015, we analyzed 88 cases of elderly patients with ED-SCLC who treated chemotherapy in Korea University Medical Center. **Result:** A total of 88 patients were diagnosed ED- SCLC at the age 65 and older. Median age is 71 years old (range 65-83). Most of cases were male (82%) and 16 patients were female (18%). The most common chemotherapy regimens included etoposide combined with platinum. Median overall survival was 8.65 months. In multivariate analysis, ECOG PS <2, SCS <9, administration > 4 cycles of 1st line chemotherapy and treatment-free interval (TFI) > 3 months were defined as a favorable prognostic factors.



	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
ECOG PS 0,1 ≥2	0.34 1	0.18-0.67	0.002	0.60 1	0.31-1.16	0.13
SCS <9 ≥9	0.42 1	0.26-0.66	< 0.001	**0.52** 1	**0.32-0.82**	**0.005**
1st line chemotheraly ≤4cycles >4cycles	1 0.44	0.28-0.70	0.004	1 **0.44**	**0.27-0.72**	**0.005**
Response to 1st line Tx. CR,PR SD,PD	0.49 1	0.31-0.79	0.003	**0.45** 1	**0.28-0.72**	**0.001**
TFI* (months) ≤3 >3	1 0.36	0.17-0.76	0.007	1 **0.37**	**0.17-0.78**	**0.01**

Conclusion: Even an elderly patient with ED- SCLC who has lower SCS< 9 and good ECOG PS <2 should consider first line chemotherapy more than 4cycles.

Keywords: small cell lung cancer, extensive disease, elderly

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-013 SMALL CELL LUNG CANCER. METHODOLOGY AND PRELIMINARY RESULTS FROM THE SMALL CELL STUDY

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Background: Small cell lung cancer (SCLC) is the most aggressive histologic type of lung cancer. It consists in approximately 10-15% of all lung cancer cases. There are very few studies on its risk factors besides tobacco, and even less have analyzed the effect of residential radon. We aim to know the risk factors of SCLC. **Method:** We designed a multicentre, hospital-based case-control study with the participation of 11 hospitals in 4 regions of Spain. An interview about personal, family and work history, as well as tobacco and alcohol consumption and diet habits, was made to each case. Also the cases were provide with a radon detector, and a genetic blood test was made. **Result:** Results of the first 113 included cases, 63 of them with residential radon measurements, were analyzed. Median age at diagnosis was 63 years old and 11% of cases were younger than 50. 22% of cases were women. 57% had extended disease and 95% were smokers or ex-smokers. Median residential radon concentration was 128 Bq/m3. 8% of cases had concentrations higher than 400 Bq/m3. The only remarkable difference by gender was the percentage of never smokers, which was higher in women compared to men (p<0,001). Radon concentration was higher for extended disease (non-significant difference) and was higher for patients diagnosed at 63 or older (p=0,032). **Conclusion:** A high percentage of SCLC cases are diagnosed at an earlier age. There is a predominance of extended disease at diagnosis (57%). Age and stage at diagnosis are similar between men and women, although it appears that men tend to be diagnosed with stage IV cancers more often. Regarding the concentration of radon, it is elevated in SCLC when compared, for example, with data from the general population of Spain. It can be seen that subjects with extended cancer have a slightly higher radon concentration and that older subjects at diagnosis have significantly higher radon concentrations than younger cases.

Keywords: epidemiology, small cell lung cancer, residential radon

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-014 CAN LIMITED RESECTION BE ACCEPTED AS AN ALTERNATIVE TREATMENT OPTION FOR PATIENTS WITH EARLY-STAGE SMALL CELL LUNG CANCER?

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Background: Surgical resection can be considered for the treatment option for early-stage small cell lung cancer (SCLC). However, few reports have evaluated the use of limited pulmonary resection for patients with SCLC. This study was undertaken to evaluate the clinical impact of limited resection for SCLC patients with c-stage I. **Method:** We retrospectively analyzed surgically resected 40 SCLC patients with c-stage I from 2006 to 2016. We compared patients who underwent limited resection and those who underwent curative resection. In addition, factors affecting survival and recurrence were evaluated by Kaplan-Meier survival and Cox regression analysis. **Result:** Sixteen patients who underwent limited resection, including 13 wedge resection and 3 segmentectomy, were compared with 24 patients who underwent curative resection, including lobectomy and pneumonectomy. All patients were considered to be treated with standard chemotherapy or chemoradiotherapy. Twenty eight patients with pure SCLC and 12 patients with combed SCLC were identified. Histological examination showed a component of adenocarcinoma in 3 cases, squamous cell carcinoma in 4 cases, large cell neuroendocrine carcinoma in 4 cases and adenosquamouns cell carcinoma in a case. The median age was 73 years old (range, 39 to 90), and six (15.0%) patients were female. Almost all patients (39 out of 40; 97.5%) had a smoking history, and median pack-years was 53.5 (range, 0-150). Mean follow-up for cancer survivors was 33.0 months. In patients who underwent limited resection, significantly worse 5-year overall survival (5-OS) and 5-years disease-free (5-DFS) survival were observed compared to patients who underwent curative resection (5-OS; 20.4 months vs. 27.3%, p-value = 0.03, 5-DFS; 14.8 months vs. 36.5 months, p-value=0.04). Among patients who underwent limited resection, 5 patients experienced intrathoracic recurrence. Limited resection for patients with SCLC is associated with an increased risk of intrathoracic recurrence compared with those who underwent curative resection (hazard ratio 0.136, p=0.075). **Conclusion:** Surgical resection followed by chemotherapy or chemoradiotherapy can be a treatment option for early-stage SCLC, however limited resection increased the risk of recurrence and was associated with poor survival significantly. For patients who can not tolerate curative resection, limited resection may not be an effective therapeutic alternative.

Keywords: SCLC, Surgery, recurrence

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-015 PROGNOSTIC IMPLICATION OF THE FEV1/FVC RATIO IN LIMITED-STAGE SMALL CELL LUNG CANCER

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Background: The aim of this study was to evaluate whether the pretreatment forced expiratory volume 1 (FEV1)/forced volume vital capacity (FVC) ratio could predict survival in patients with limited-stage small cell lung cancer (LS-SCLC). **Method:** We assessed 74 patients with LS-SCLC treated with chemoradiotherapy who were divided into two groups: those with FEV1/FVC <0.74 (n=24) and those with FEV1/FVC ≥0.74 (n=50). **Result:** The 3-year overall survival (OS) and 3-year progression-free survival (PFS) rates were significantly lower in patients with FEV1/FVC ratios <0.74 than in those with ratios ≥0.74 group (35.4% vs. 61.2%, *P*=0.0033; and 11.7% vs. 51.8%, *P*=0.0072, respectively). On multivariate analysis, a low FEV1/FVC ratio was independently associated with OS and PFS (hazard ratio [95% confidence interval]: 2.15 [0.99–4.63], *P*=0.052; and 2.13 [1.04–4.39], *P*=0.039, respectively). **Conclusion:** The pretreatment FEV1/FVC ratio appears to be a potential prognostic factor for LS-SCLC.

Keywords: Limited Stage Small Cell Lung Cancer, FEV1/FVC ratio, Prognosis

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-016 THE STUDY OF POPULATION PHARMACOKINETICS AND INDIVIDUALIZED DOSAGE OF LOBAPLATIN-BASED REGIMENS IN ELDERLY PATIENTS WITH SMALL CELL LUNG CANCER

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Background: Elderly patients with SCLC have limited treatment options and poor survival. Lobaplatin(LBP) is a representative of the third-generation platinum compound, which has showed significant efficacy and favorable toxicity for SCLC. Therefore, we adopt population pharmacokinetic methods to explore the pharmacokinetics and its correlation with adverse reactions, and to make individualized dosing regimens of lobaplatin for elderly SCLC patients.(ChiCTR-OPN-15006057) **Method:** SCLC patients aged≥65 years and creatinine clearance(Ccr) ≥60ml/min were divided into two arms, receiving four cycles of lobaplatin regimens according to Ccr. LBP was administrated at dose of 30mg/m^2 in Arm A(Ccr≥80ml/min) or 20mg/m^2 in Arm B(60ml/min≤Ccr<80ml/min). Four blood samples were randomized collected from each patient in the first cycle. For the subsequent cycles, only one blood sample were collected. The primary endpoint was plasma concentrations at different time points after administration of LBP. The secondary endpoints were PFS, OS, ORR, DCR and safety. **Result:** Between January 2014 and July 2016, 100 patients(30 with limited stage and 70 with extensive stage disease) were enrolled into the study at 7 institutions in China. There were 51 patients in Arm A and 49 patients in Arm B. The median PFS and OS for Arm A and B were 155 days vs.170 days, 306 days vs. 272 days, respectively. The ORR and DCR were 50% vs. 51.22%, 88.64% vs. 90.24% respectively. Grade III/IV AEs incidence of Arm A and B were 60.8% vs. 51.0%. In terms of population pharmacokinetic, we can get the following conclusions by computer simulation that if the total doses of LBP are fixed, the exposure levels of lobaplatin in the body have great differences when the body surface areas(BSA) are different. If administrated according to the BSA, the AUC differences of individual with different BSA are little, and there is only about 8% AUC differences between the two arms. As administrated in accordance with the protocol, the AUC of Arm B is about 39% lower than that of Arm A. If dose of LBP in Arm B was increased from 20 mg/m2 to 27 mg/m2, the AUC difference between the two groups was only 3%. **Conclusion:** When Ccr≥60 ml/min, it's necessary to administration on the basis of BSA. It's reliable and safe to use LBP-based regimens to treat elderly patients with SCLC. Lobaplatin may offer an alternative choice for Chinese elderly patients with advanced SCLC.

Keywords: Lobaplatin, SCLC, Population Pharmacokinetics

P1.15: SCLC/NEUROENDOCRINE TUMORS -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.15-017 ADOPTION OF PROPHYLACTIC CRANIAL IRRADIATION FOR EXTENSIVE STAGE SMALL CELL LUNG CANCER: A POPULATION BASED OUTCOMES STUDY

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Background: The survival benefit of prophylactic cranial irradiation (PCI) in extensive stage small cell lung cancer (ES-SCLC) is unclear. This study aimed to determine the use of PCI and the factors associated with its use as well as its impact on overall survival (OS) in the Singapore population. **Method:** We conducted a retrospective cohort study including patients diagnosed with ES-SCLC without brain metastases treated in the only two Singapore national cancer centres from 2003 to 2010. We identified the patients using the institutions' pathology registries and linked the electronic medical records to the National Death Registry. We used multivariable logistic regression to identify factors associated with the use of PCI and its impact on OS. All analyses were performed using STATA version 11.0. **Result:** We identified 224 eligible patients. 65 of 224 patients did not receive chemotherapy. 71 of 159 patients had at least stable disease (SD) after first line chemotherapy. 16 of these 71 patients received PCI. There was an increase in the use of PCI from the period 2007 to 2010 compared with 2003 to 2006 (13 patients versus 3 patients, chi-square P value = 0.01). The use of consolidation thoracic radiation therapy (TRT) was associated with use of PCI (odds ratio 18.3, 95% confidence interval (CI) 4.70 to 71.96, P value (P) < 0.001). PCI improved OS (adjusted hazard ratio 0.47, 95% CI 0.24 to 0.91, P = 0.02) compared to no PCI use among the 71 patients who had at least SD after first line chemotherapy. Consolidation TRT did not improve OS among this group of patients. **Conclusion:** The utilization rate of PCI remained low in the Singapore population between 2003 to 2010 despite an increase in its use since 2007. Patients who had at least SD after first line chemotherapy or had consolidation thoracic radiation therapy were more likely to receive PCI. Among patients who had at least stable disease after first line chemotherapy, the use of PCI was associated with an improved survival outcome.

Keywords: small cell lung cancer, prophylactic cranial irradiation, Radiotherapy

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-001 CHARACTERISTICS OF RESECTED LUNG CANCER IN PATIENTS AGED UNDER 60: A SINGLE–CENTER EXPERIENCE

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Background: The proportion of younger patients with lung cancer is smaller than the older. But, as with older patients, the number is on the rise and clinical features of younger patients might be different compared to older patients. So we investigated the characteristics of younger patients with resected lung cancer through reviewing medical records. **Method:** From January 2010 to December 2014, 424 patients underwent operation for lung cancer at Pusan national university hospital. Mean age was 63.4±9.8 years old. Of them, 135 were under 60 years old (younger group). Medical records including demographic factors, histological type, surgical factors and outcomes, disease free survival rate (DFS) and overall survival rate (OS) were reviewed retrospectively. **Result:** In younger group, mean age was 52.2±7.6 years old and proportion of female was significantly higher (p value=0.00). Co-morbidity and other combined malignancies were smaller (respectively, p value = 0.00 and 0.007) and proportion of adenocarcinoma were higher than older group (p value = 0.03). Mean operative time was shorter than older group (4.57 versus 4.90 hours, p value= 0.03). There was no significant difference in other factors (postoperative complications, surgical approach, FEV1, hospitalization, and etc.). Mean follow up duration was 34.0±17.7 months, and 3 year DFS and 3 year OS of younger group in stage IA was 97.9% (versus 94.0% in older patients, p value = 0.009) and 96.4% (versus 93.3% in older patients, p value = 0.07). In other stage, there was no significant difference of DFS and OS. **Conclusion:** This study shows that there were significantly different characteristics between younger and older patients group including DFS in pathologic stage IA, sex, and proportion of histological type, and suggests that development and application of more adequate modalities for early diagnosis and treatment in younger patients is needed.

Keywords: lung cancer, young patients, clinical characteristics

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-002 MANAGEMENT OF LOCAL RECURRENCE AFTER SEGMENTECTOMY FOR STAGE IA LUNG CANCER

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Background: Segmentectomy is thought to be able to spare lung parenchyma compared with lobectomy. On the other hand it might cause more local recurrences. The management of local recurrence after segmentectomy is thought to be an important issue. The aim of this study is to evaluate the management of local recurrence after segmentectomy. **Method:** From June 2005 to March 2009 we performed segmentectomy for clinical stage IA lung cancer, 88 male and 91 female with mean age of 66 year-old (32-83). The histological types of 179 lung tumors according to WHO histological classification are as follows: atypical adenomatous hyperplasia (2), adenocarcinoma in situ (34), minimally invasive adenocarcinoma (27), invasive adenocarcinoma (96), Squamous cell carcinoma (2), adenosquamous carcinoma (4), and carcinoid (2), respectively. Median follow-up time was 2920 days. During follow up there were 15 recurrences. Of 15 cases with recurrence 6 cases had local recurrences without distant metastasis. **Result:**

Age/sex	Size	His	MIP	Seg	time 1	manage	time 2	status
76M	18	lep	0	lt S3	1836	CL	1086	AWD
70F	16	pap	20	lt S3	2965	RT	555	NED
65M	35	lep	30	rt S3S2a	1904	CL	1397	DOD
81M	18	pap	20	lt S1+2	2112	RFA	955	NED
58F*	9	ac	20	rt S3	394	CL	994	DOD
70F	18	ac	10	rt S1+S2	356	CL	2821	NED

Size: pathological maximal diameter of cancer (mm): His: histology of lung cancer; MIP: percentage of micropapillary > 5%; Seg: operative method of segmentectomy; time 1: time to recurrence after segmentectomy; management: management for recurrence; time 2: time after the management; status: current status; lep: lepidic predominant adenocarcinoma; CL: completion lobectomy; AWD: alive with disease; pap: papillary predominant adenocarcinoma; RT: radiation; NED: no evidence of disease; DOD: death of disease; RFA: radio frequency ablation; * multiple lung cancer; ac: acinar predominant adenocarcinoma

Mean time to local recurrence after segmentectomy was 1595 ± 1027 days (356-2965). Of 6 cases with local recurrence 5 cases had micropapillary component more than 5 %. The initial treatments for local recurrence were as follows: completion lobectomy (4), radiation (1), radiofrequency ablation (1), respectively. Three of 6 cases have been alive without evidence of disease since initial treatment for local recurrence of lung cancer. **Conclusion:** Management of local recurrence after segmentectomy is important. Local treatment, such as, completion lobectomy, radiation, or radio frequency ablation may effective for selected cases.

Keywords: local recurremce, lung cancer, segmentectomy

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-003 LEARNING CURVE FOR ADOPTION OF ROBOTIC LOBECTOMY FOR EARLY STAGE NON-SMALL CELL LUNG CANCER BY A THORACIC SURGEON EXPERIENCED IN OPEN LOBECTOMY

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Background: Optimal minimally invasive approach in treatment of non-small cell lung cancer (NSCLC) is controversial. Our goals were: 1.To profile the learning curve of adoption of robotic lobectomy by an experienced open thoracic surgeon, novice with VATS-lobectomy techniques; 2. To compare the clinical outcomes of robotic lobectomy vs. historical open lobectomy by the same surgeon (AA). **Method:** We conducted a retrospective review of 157 consecutive patients undergoing lobectomy for clinical stage I and II NSCLC by one surgeon, previously novice in performing minimally invasive lobectomy, at a single facility between 2007 and 2014. Robotic platform was adopted in 2011. 57 patients underwent open thoracotomy (OT), 40 prior to 2011, and 100 patients underwent robotic lobectomy. **Result:** The preoperative characteristics and risk profile of the two groups were similar. Aside from longer operative time (a bimodal learning curve), the robotic group (including 13% of patients with open conversion) had significantly lower intraoperative blood loss and overall morbidity rate, significantly shorter chest tube duration and length of stay, and a statistical trend toward lower 90 day mortality and 30 day readmission rate (Table 1). Median number of lymph node stations dissected and percentage of pathologic nodal upstaging were equivalent between robotic and OT groups (5 vs. 4; 17% vs. 14%, respectively). The conversion rate for the latter half of the robotic group was significantly lower (6% vs. 20%, $p<0.05$).

TABLE 1. Perioperative Outcomes

	Robotic (n = 100)	OT (n = 57)	*P* value
Overall operative time, median minutes (range)	195 (94-350)	175 (134-305)	<0.01
EBL, median mL (range)	75 (10-800)	150 (50-1000)	<.001
Intra- and/or postoperative blood transfusion, no. (%)	8 (8)	5 (8.8)	0.87
Prolonged intubation, no. (%)	0 (0)	4 (7)	<.01
Pneumonia, no, (%)	12 (12)	8 (14)	0.71
Atrial fibrillation, no. (%)	20 (20)	12 (21)	0.87
Chest tube duration, median days (range)	3 (1-20)	6 (2-26)	<.001
LOS, median days (range)	6 (2-22)	10 (5-28)	<.001
Morbidity, no. (%)	35 (35)	28 (49)	<.05
Mortality 30-days, no. (%)	0 (0)	1 (1.8)	0.15
Mortality 90-days, no. (%)	1 (1)	3 (5.3)	0.08
Readmission within 30 days, no. (%)	4 (4)	6 (10.5)	0.07
Reoperation within 30 days, no. (%)	2 (2)	2 (3.5)	0.56
Pathological staging, no. (%)			
IA	50 (50)	21 (37)	0.20
IB	23 (23)	16 (28)	
IIA	8 (8)	11 (19)	
IIB	7 (7)	4 (7)	
IIIA	12 (12)	5 (9)	
LNs sampled, median no. (range)	5 (1-9)	4 (1-7)	0.13
Nodal upstaging, no. (%)	17 (17)	8 (14)	0.63

OT, open thoracotomy; EBL, estimated blood loss; LOS, length of stay. LNs, lymph nodes

Conclusion: Adoption of robotic platform for lobectomy for NSCLC is safe and feasible without significant preceding VATS experience. In our hands, the learning curve entails approximately 50 robotic lobectomies after which the operative times and conversion rates significantly diminish. In comparison to open thoracotomy, robotics, even during the learning phase, result in a significant reduction in perioperative morbidity and permit equivalent nodal sampling in performing lobectomy for clinical stage I and II patients.

Keywords: robotic, lobectomy, lung cancer

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-004 INTUBATED VERSUS NON-INTUBATED ANESTHESIA FOR LUNG CANCER VATS IN OCTOGENERIANS

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Background: In recent years, non-intubated video-assisted surgery (VATS) is gaining popularity worldwide, especially in elderly lung cancer patients (ELC). The main goal of this surgical practice is to achieve an overall improvement of patients management and outcome thanks to the avoidance of side-effects related to general anesthesia and single-lung ventilation. We compared non-intubated anesthetic technique with intubated general anesthetic technique for VATS. . **Method:** Forty octogenerians (patinets aged 80 years or more) scheduled for VATS lung cancer surgery, were allocated randomly into two groups with 20 patients each. First group received standard general anesthesia with double lumen tube. Second group went under non-intubated anesthetic technique. Heart rate, mean arterial pressure, end-tidal CO2 and the visual analog pain score (VAS) measurements were recorded during the surgery and 24 hours after the surgery. Both group received ultrasound guided paravertebral block before surgery with single injection of 20 ml 0.25% levobupivacaine. VATS lobectomy followed by sample mediastinal lymphadenectomy was performed in all patients.

Result: Time for anesthetic procedure was shorter in the nonintubated group. VATS lobecotomy was performed in usual manner in all patients without any intraoperative complications. VAS score in the first 24 hours was comparable. We found significantlly shorter recovery time, reduced oxygen requirement, shorter chest tube drainage and hospital stay in the non-intubated group. There where no significant differences in intraoperative blood loss, operation time or postoperative complications between the non-intubated group and the intubated group of patients. **Conclusion:** Tthis pilot study has shown that non-intubated VATS is a safe and feasible surgery for elderly lung cancer patients with certain advantages for the patients undergoing VATS. Our results indicated that we can achieve day surgery for selected patients. Further clinical studies should be carried out in order to improve surgical outcome in elderly lung cancer patients.

Keywords: VATS lung cancer surgery, octogenerians, nonintubetad general anesthesia

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-005 COMPARISON SUBLOBAR VS LOBAR RESECTION IN EARLY STAGE LUNG CANCER IN OCTAGENARIAN PATIENTS

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Background: Non-small-cell lung cancer (NSCLC) is a very common disease in the elderly population.Incidence in this particular population is expected to increase further, because of the ageing of the Global population. Numerous studies have shown a benefit of the surgery over medication in octogenrian people.However, limited data are available for the treatment between sublobar vs lobar resection in octagenerian groups. Our object is to compare the overall survival between sublobar vs lobar resection in early stage lung cancer in octogenarian group. Secondary outcome is to demonstrate a disease free survival between sublobar vs lobar resection and Co-morbidity after operation between sublobar vs lobar resection. **Method:** From 2003-2016, a total of 77 patients who age over 80 with stage I non small cell lung cancer and underwent sublobar or lobar resection in Bundang hospital, Seoul university. The clinical data were retrospectively analyzed as regards characteric such as underlying disease, histology, smoking status, pulmonary functiontest, complication and overall survival. Survival was analyzed by the Kaplan-Meier method and log-rank test. Univariate and multivariate logistic regression analyses were performed to identify patient characteristics associated death and recurrence of disease **Result:** Overall survival and overall free disease free survival were similar in both groups.Median follow up time was 24 months However, an incidence of complications after lobar

resection was more than sublobar resection with 26.4% and 12.5%, respectively. Patient who recieve sublobar resection had a shorter hospital stay than lobar resection. In multivariate analysis, COPD and family history were a risk factor that associated with recurrence of disease and tumour size, vascular invasion associated with overall mortality. **Conclusion:** Sublobar resection is an alternative treatment for early lung cancer in octogenarians which does not increase risk of recurrence or death after the operation and also could be benefit in shorter period of hospital stay and complication after surgery.

Keywords: stage I non small cell lung cancer, sublobar vs lobar resection, Octogenarian

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-006 LESS IS MORE: VIDEO ASSISTED THORACIC SURGERY (VATS) VS OPEN THORACOTOMY IN THE MANAGEMENT OF RESECTABLE LUNG CANCER

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Background: Video Assisted Thoracic Surgery (VATS) has become the recommended approach for treatment of early stage lung cancer. No large randomized clinical trial has been conducted to formally compare VATS to open thoracotomy (OT).Our study sought to assess differences in recurrence-free survival (RFS),overall survival (OS),positive margins and postoperative length of stay (LOS) between VATS and OT. **Method:** A single institution retrospective charts review was conducted for patients diagnosed with stage I-III lung cancer and treated with VATS or OT from May 2005 - May 2015.Patients and tumor characteristics included age at diagnosis, sex, tobacco use, tumor location, stage,size and receipt of chemotherapy or radiotherapy. Chis-square and Wilcoxon-Mann-Whitney tests were used to compare demographic, tumor characteristics and LOS. Multiple logistic and Cox regressions were used to compute relative risk (RR) for positive margins and mortality hazards ratio along with 95 percent confidence interval limits (95%CI),respectively. **Result:** A total of 235 patients underwent lung resection for cancer diagnosis; VATS n = 101 and OT n = 134. Age at diagnosis, sex, tobacco use, tumor location,and size were comparable for VATS and OT. No significant difference was observed in the risk of positive margins for VATS versus OT [RR= 0.56 (95%CI= 0.26, 1.05)]. However,VATS (4 days) had shorter median LOS compared to OT (6 days), *P*=0.002.Recurrence [HR= 1.21 (95%CI= 0.74, 2.00)] and mortality hazards [HR= 1.34 (95%CI= 0.88, 2.06)] were comparable for VATS versus OT,with consistent results observed for analysis limited to subjects having negative margins and across tumor stage at diagnosis.

Figure 1. Kaplan-Meier survival curves.

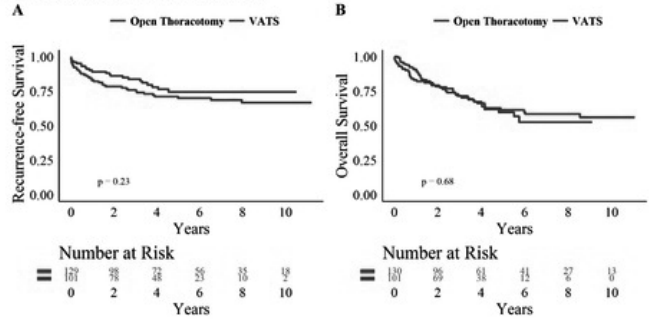
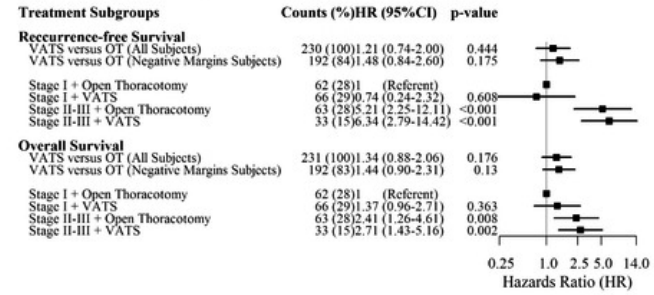


Figure 2. Forest plot for various treatment subgroups.



Conclusion: Our results show that compared to OT, VATS leads to shorter LOS while achieving comparable margins status, recurrence-free and overall survival regardless of tumor stage at diagnosis. By reducing LOS, VATS is cost effective while achieving similar outcomes and should be considered as the approach of choice for patients undergoing lung resection for cancer.

Keywords: Video Assisted Thoracic Surgery (VATS), Open Thoracotomy (OT), Recurrence-free survival, Overall survival

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-007 MOBILE COMPUTED TOMOGRAPHY IN VIDEO-ASSISTED THORACOSCOPIC SURGERY FOR GROUND-GLASS OPACITY LUNG NODULES

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Background: In the thoracic surgery for non-palpable and invisible ground-glass opacity (GGO) lung nodules , various methods have been reported, such as needle sticking or infusion of roentgen non-permeable substances around the tumor under computed tomography (CT) guidance. However, there are serious problems such as air embolism and/or tumor dissemination into the thoracic cavity. Mobile computed tomography, O-arm Surgical Imaging System (Medtronic), can provide an image intraoperatively. In this study, we evaluated the usefulness of mobile computed tomography in thoracic surgery for the GGO lung nodules. **Method:** From December 2016 to May 2017, 3 patients with ground-glass opacity lung nodules were evaluated under video assisted thoracoscopic surgery using O-arm system. Before surgery, the patient was placed in lateral decubitus position in the CT room, and the skin directly above the tumor was marked with a skin marker. In the operation room, a port was made on the marked position, and a Naruke's thoraco cotton dyed with indigo carmine was introduced into the port to mark the visceral pleura just above the lesion. Then, the tumor-side lung was deflated, and the marked visceral pleura was grasped with non-traumatic forceps. Intraoperative CT imaging was reconstructed with O-arm, and the GGO lesion was comfirmed and resected under the guidance of positional relationship between the forceps and the tumor. **Result:** In all 3 patients, the tumor could be seen intraoperatively with computed tomography using the O-arm system, and resected properly. No complications were experienced in this study on the use of the O-arm system. **Conclusion:** The O-arm system could be a new strategy for the surgical treatment of non-palpable lung lesions.

Keywords: ground-glass opacity, Thoracic Surgery, Mobile computed tomography

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-008 NEAR-INFRARED FLUORESCENCE-GUIDED PULMONARY SEGMENTECTOMY FOLLOWING ENDOBRONCHIAL INDOCYANINE GREEN INJECTION

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Background: Near infrared (NIR) fluorescence-guided pulmonary segmentectomy following endobronchial or intravenous indocyanine green (ICG) administration has been developed and reported. The aim of this study is to prospectively validate the feasibility and safety of NIR fluorescence-guided pulmonary segmentectomy following endobrochial ICG injection using navigational bronchoscopy. **Method:** Patients who underwent pulmonary segmentectomy were prospectively enrolled in this study. Using preoperative CT datasets a 3D image of target segments was reconstructed for lung volumetry and a bronchial road map was created to determine the bronchus for ICG injection. The ICG concentration was 0.125 mg/mL. Immediately after intubation the ICG was injected into the target bronchi using an ultrathin bronchoscope followed by air flushing to expedite ICG dispersion to the periphery. A NIR thoracoscope (PINPOINT, Novadaq) was used to detect ICG fluorescence and determine intersegmental plane for pulmonary segmentectomy. Usefulness and safety of this technique were evaluated by 1) whether ICG demarcation lines correspond to intersegmental lines expected from pulmonary veins, 2) whether large bronchi and vessels in adjacent segments emerge when dividing intersegmental planes using electrical cautery. The patients were followed up to 1 month after surgery to see if any complication existed. **Result:** Eight male and 7 female patients with a mean age of 66.5 ± 9.6 years were enrolled. Segmentectomy regions included right S1, S2, S6, S8 and S10 segments, and left S1+2+3, lingular, S6, S8, S9+10, and basilar segments. The average bronchoscopic procedure time was 14.3 ± 8.0 minutes. Vital signs were kept stable before and after the bronchoscopic procedure. The mean injected volume of ICG solution was 21.2 ± 8.8 mL as per a case. In 13 out of 15 cases (86.7%), NIR fluorescence guidance was recognized as effective for pulmonary segmentectomy. Intersegmental plane could not be determined in 2 cases likely due to insufficient air flushing, leading to the failure of ICG dispersion to the periphery. There was no complications developed intraoperatively. The average operation time was 193 ± 41 minutes, with a mean bleeding of 110 ± 101 mL. The average duration of drainage was 3.1 ± 1.0 days. Recurrent air leakage happened on postoperative day 6 in 1 case. Otherwise, no procedure related adverse event was noted. **Conclusion:** NIR fluorescence-guided pulmonary segmentectomy following endobrochial ICG injection using navigational bronchoscopy appeared to be safe and feasible. Sufficient air flushing may be the key for clear ICG demarcation of referred segments.

Keywords: Pulmonary segmentectomy, Near infrared fluorescence, Indocyanine green

P1.16-009 COMPARING LYMPH NODE DISSECTION IN VATS VERSUS OPEN LUNG CANCER SURGERY: HOW, HOW LONG, AND HOW DOES IT MATTER?

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Background: Adequacy of lymph node dissection is often used to compare video-assisted thoracoscopic surgery (VATS) with open surgery for lung cancer, but no consensus exists over how best to assess nodal yield (by weighing or counting) and to correlate this with survival. This study uses one of the longest follow-up periods to date to address these unanswered questions. **Method:** From February 2006 to July 2010, 230 consecutive adult patients with non-small cell lung cancer received lobectomy with curative intent. Surgical approach was determined by the surgeon's discretion: 118 (51%) ultimately received VATS and 112 (49%) received open or 'hybrid' surgery. **Result:** A summary of the data is shown in the Table. Mean numbers and weights of lymph nodes dissected in the two study arms were similar overall, but VATS yielded more in stations 3 and 7, and non-VATS in station 10. A change in staging was more frequent after non-VATS, but was due mostly to more downstaging. VATS more frequently fulfilled the European Society of Thoracic Surgeons (ESTS) guidelines for adequacy of nodal dissection. Previous tuberculosis reduced nodal yields with non-VATS (p=0.033) but not VATS. On regression analysis, the counted numbers of nodes dissected correlated well with the measured weights in both VATS and non-VATS groups (F ratios: 26.0, p<0.001 and 58.6, p<0.001 respectively). VATS gave a trend for better 5-year overall survival in stage I disease (p=0.108). No significant correlation was found between nodal dissection, surgical approach and survival after a median postoperative follow up of 111 months (range: 82-136), but 33 (26.4%) of the 125 total deaths occurred after 5 years.

	VATS (n=118)	Non-VATS (n=112)	P value
Demographic and Clinical Characteristics			
Male	58 (49.2%)	75 (67.0%)	0.006
Mean age (years)	62.9±10.7	65.6±9.0	0.036
History of smoking	40 (33.9%)	47 (42.0%)	0.207
History of Tuberculosis	14 (11.9%)	18 (16.1%)	0.357
Right side surgery	78 (66.1%)	60 (53.6%)	0.053
Upper lobectomy	65 (55.1%)	61 (54.5%)	0.925
Mean operation time (minutes)	184.0±67.7	209.6±77.5	0.009
Mean blood loss (ml)	147.4±163.6	349.3±602.8	0.070
Mediastinal (N2) Lymph Node Dissection			
Mean number of mediastinal (N2) nodal stations dissected	3.5±1.9	2.5±1.8	<0.001
Mean weight of mediastinal (N2) nodal tissue removed (g)	1.2±1.1	1.3±1.2	0.253
i. Mean number of lymph nodes dissected at specific stations			
Station 3	0.4±0.7	0.1±0.4	<0.001
Station 7	1.0±1.0	0.6±0.8	0.002
Station 10	0.5±0.8	1.3±1.3	<0.001
ii. Mean weight of lymph nodes dissected (g) at specific stations			
Station 3	0.1±0.3	0.0±0.1	0.007
Station 7	0.2±0.4	0.2±0.5	0.855
Station 10	0.1±0.2	0.3±0.5	<0.001
Impact of nodal dissection			
Change in staging after surgery	30 (25.4%)	43 (38.4%)	0.035
Upstaged after surgery	20 (16.9%)	24 (21.4%)	0.388
Downstaged after surgery	10 (8.5%)	19 (17.0%)	0.053
Nodal dissection fulfilled ESTS criteria	63 (53.4%)	25 (22.3%)	<0.001
Long-term follow-up			
Median survival after surgery (months)	107 (95% CI: 72 - 111)	67 (95% CI: 51 - 98)	0.087 *(Logrank test)*

VATS = Video Assisted Thoracoscopic Surgery; ESTS = European Society of Thoracic Surgeons

Non-VATS includes: open thoracotomy, 'hybrid' approach ('assist VATS'), conversion from VATS to open

Conclusion: Counting and weighing give similar results for comparing lymph node yields after VATS versus non-VATS. VATS gives non-inferior nodal yields, but follow-up for longer than the conventional 5 years may be potentially important in correlating yields with long-term survival.

Keywords: lymph nodes, survival, Surgery

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-010 DEVELOPMENT OF A NOVEL SURGICAL MARKING METHOD USING LOW POWER LASER LIGHT

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Background: Small lung nodules which appear to be ground glass opacity in peripheral lung are difficult to identify during surgery. In order to identify the site of such lesions, various types of preoperative or intraoperative marking methods have been reported. However all of them have advantages and disadvantages, so there is no definitive way. Therefore, we developed a new safe and reliable intraoperative marking method using a thin laser fiber. This is a method to confirm a low power laser light from lung surface irradiated from a small diameter laser fiber inserted into or close to the lesion transbronchoscopically using a navigation system. In this study, we conducted an animal experiment to confirm whether the laser light can actually be observed safely from lung surface. **Method:** Bronchoscopy was performed to a hybrid dog under general anesthesia. A plastic laser probe was inserted into a peripheral bronchus from the biopsy channel of the bronchoscope. The plastic laser probe was a very thin (0.8 mm diameter) and flexible cylindrical-type probe. Therefore, it can be inserted into the peripheral lung. It was developed jointly with Keio University. The probe was induced just below the pleura and 50 mW low power laser irradiation was performed. We examined whether laser light could be confirmed from lung surface under thoracotomy. We also examined the difference in appearance from direct-type laser irradiation. **Result:** When the probe was guided to just below the pleura, laser light could be clearly observed from the lung surface. After that, the probe was gradually withdrawn. The laser light could be observed until the depth of 2.0 cm from the pleura. Moreover, laser irradiation was able to be performed safely without any damage around the laser irradiated area. The laser light was observed consistent with laser irradiation site by the cylindrical probe. On the other hands, it was observed on the pleura ahead of laser irradiation by the direct-type probe. Therefore, it is suggested that cylindrical probe might indicate the target area more accuracy. **Conclusion:** It might be possible to confirm the localization of small nodules in peripheral lung using low power laser light during surgery.

Keywords: ground glass nodule, surgical marking, lung cancer

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-011 THE ROLE OF 3D-CT IN PATIENTS WITH PULMONARY MALIGNANCIES UNDERGOING SEGMENTECTOMY

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Background: Progress in diagnostics and surgery in thoracic oncology is associated with increasing number of patients-candidates for sublobar anatomic pulmonary resection. Vascular variability of pulmonary segments anatomy requires special tools for individual preoperative planning. **Method:** We retrospectively analyzed 114 patients who underwent segmentectomy due to low pulmonary function, severe comorbidity or previous history of lung resection. Indications for surgery were clinical T1aN0M0 peripheral non-small cell lung cancer (NSCLC) ≤2 cm (n=53), resectable pulmonary metastases not suitable for wedge resection due to deep parenchymal location (n=47) and benign lesions (n=14). Segmentectomies were divided into typical (where parenchymal division involves 2 planes) and atypical (more complex and technically demanding, when the segmental excision involves 3 planes). 38 patients underwent VATS segmentectomy. Three-dimensional computed tomography (3D-CT) with bronchovascular separation was used preoperatively in 58 patients from October 2014 to April 2017. Mortality, morbidity, proportion of typical versus atypical and VATS versus open segmentectomies in two groups: with or without 3D-CT bronchovascular reconstruction, were compared. **Result:** There was no mortality in whole group. Morbidity rate was 7,9% not exceeding grade 3a according thoracic mortality and morbidity (TMM) score. The difference in morbidity rate was not statistically significant between two groups (6,9% and 8,9%; p=0,23) The most common complication was prolonged air leak > 7 days (2,6%). 3D-CT powered by separation of arterial, venous and bronchial structures enabled surgeons to perform atypical segmentectomies and use VATS approach more often (31,3% vs 13,5%; p>0,05 and 50,0% vs 11,5%; p<0,05, respectively). 8 atypical segmentectomies were performed by VATS due to 3D-CT reconstruction with bronchovascular separation. 5-year survival was 86% and 21% in NSCLC and pulmonary metastases groups, respectively. **Conclusion:** 3D-CT reconstruction with bronchovascular separation provides precise preoperative planning of individual pulmonary segments anatomy and allows to increase the proportion of atypical and VATS sublobar anatomic pulmonary resections.

Keywords: 3-D CT, segmentectomy, sublobar resection

P1.16-012 APPLICATION OF FLUORESCENT AND IODIZED DUAL MARKER FOR PRE-OPERATIVE LOCALIZATION AND IMAGE-GUIDED SURGERY OF PULMONARY NODULE

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Background: This study evaluated the feasibility of pre-operative localization of pulmonary nodule using dual marker composed with indocyanine green (ICG) and lipiodol for minimal and accurate resection in video-assisted thoracoscopic surgery (VATS). **Method:** To minimize separation of two materials, we mixed with different frequency and ratio of ICG and lipiodol using a 3-way stopcock, and investigated their distribution with fluorescent microscope. Three rabbits were undergone thoracotomy after computed-tomography (CT) fluoroscopy-guidance injection of each 0.1 ml emulsions into different lobes of rabbit lung at 6, 12 or 24 hours. The localized lesions were evaluated by near-infrared optical imaging and radiograph. The 0.3 ml of emulsion was pre-operatively injected into 22 patients under CT fluoroscpy-guidance, and the localization was then evaluated during surgery by near-infrared imaging and mobile C-arm fluoroscopic x-ray. All freshly excised specimens were diagnosed by pathologic examination. **Result:** In *in vitro*, the separation time of ICG and lipiodol emulsion was delayed proportionally to mixing frequency and ratio. The emulsion mixed with 90 passages and 90% lipiodol was the least separated at 24 hours. On the rabbit lung, the optimal emulsion remained stably on injection site until 24 hours after injection. Pulmonary nodule localization using the optimal emulsion was performed successfully on the 22 patients without complications. **Conclusion:** This easy optimal method for pre-operative localization of pulmonary nodule was successfully established. The emulsion can be a useful marker to show the location of lesion to surgeons. However, ICG and lipiodol were not mixed perfectly and evenly. Therefore, there will be needed a future research to stabilize two materials completely.

Keywords: Localization of pulmonary nodules, Indocyanine green and lipiodol, Image-guided surgery

P1.16-013 VIDEO-ASSISTED THORACOSCOPIC SURGERY (VATS) VERSUS THORACOTOMY IN LOCALLY-ADVANCED LUNG CANCERS – A META-ANALYSIS

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Background: Video-assisted thoracoscopic surgery (VATS) has been established as the preferred approach for surgical resection of early-stage non-small cell lung cancers. It is shown to have improved oncological outcomes with lower perioperative complication rates when compared with conventional open lobectomy. However, there is a paucity of high-level evidence supporting its use in locally-advanced lung cancers. Moreover, published results have shown contrasting outcomes. We conducted a meta-analysis to compare oncological outcomes as well as perioperative complications for VATS versus conventional thoracotomy in this population. **Method:** Electronic databases (PubMed MEDLINE, EMBASE and Web of Science) were searched for studies evaluating VATS versus conventional thoracotomy for the resection of locally-advanced lung cancers. Individual outcome data was pooled to investigate the summary effect. **Result:** A total of 5 studies comparing the two approaches were identified. Of these, only 3 studies reported long-term survival data appropriately and were analysed separately. There was no difference in 3-year overall survival (HR 0.67, 95% CI 0.29-1.53) or 3-year disease-free survival (HR 1.09, 95% CI 0.77-1.55) when comparing VATS against open thoracotomy. However, VATS was associated with a shorter length of stay (2.02 days, 95% CI 0.65-3.39 days). There was no difference in blood loss between the two approaches. **Conclusion:** Oncological outcomes of VATS resection appear to be at least equivalent to conventional thoracotomy in locally-advanced lung cancers. Length of stay is shorter for VATS, which has been shown to correlate with better cost-effectiveness. Ideally, randomised controlled trials should be designed to confirm and further investigate these conclusions.

Keywords: Locally-advanced lung cancer, VATS, thoracotomy

P1.16-014 THE EFFICACY OF THORACOSCOPIC RIGHT UPPER LOBECTOMY USING FISSURELESS TECHNIQUE IN PATIENTS WITH DENSE FISSURES

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Background: We adopted the 'thoracoscopic fissureless technique' for patients with dense fissure undergoing right upper lobectomy to avoid postoperative air leakage. This technique is considered useful in thoracoscopic approach which has the limited direction in dissection. We investigated the efficacy of thoracoscopic right upper lobectomy using fissureless technique in this study. **Method:** Between April 2012 and March 2017, 77 patients underwent thoracoscopic right upper lobectomy with three or four ports, of whom 23 adopted fissureless lobectomy. We compared the characteristics and perioperative outcomes of the patients undergoing the fissureless technique (fissureless group, n=23) and the traditional fissure dissection technique for pulmonary artery exposure (traditional group, n=54). The details of the fissureless technique is as follows. While the upper lobe is retracted towards the back, the upper lobe vein and the anterior PA trunk to the upper lobe are exposed and divided. After the division of right upper lobe bronchus by a stapler, the ascending artery is divided. However, it is better to dissect and divide the ascending A2 prior to right upper bronchus when the ascending A2 branches from a comparatively proximal portion. The fissure is finally divided. **Result:** The patients' characteristics and perioperative results in the 2 groups are shown in the table. There was no significant inter-group difference about sex ratio, age, blood loss (p=0.95), intraoperative massive bleeding rate (p=0.66), conversion rate (p=0.55) or morbidity (p=0.13), fissureless group had shorter operation time (p=0.047) or postoperative hospital stay (p=0.0004). Additionally, fissureless group had tendency to reduce the duration of postoperative chest tube drainage (p=0.07).

Variable	Fissureless group, n=23 (%)	Traditional group, n=54 (%)	p-value
Operation tim (min.)	197±45	225±61	0.047
Blood loss (ml)	93±150	95±165	0.95
Intraoperative massive bleeding (n)	1 (4.3)	5 (9.3)	0.66
Conversion to thoracotomy (n)	0 (0)	3 (5.6)	0.55
Duration of chest tube drainage (days)	2.7±1.6	3.9±3.2	0.07
Length of postoperative hospital stay (days)	4.6±1.3	7.5±3.5	0.0004
Morbidity (n)	2 (8.7)	14 (25.9)	0.13

Conclusion: Thoracoscopic right upper lobectomy using fissureless technique is considered useful because it had a tendency to reduce the duration of postoperative drainage, and significantly reduced operation time and the length of postoperative hospital stay.

Keywords: fissureless technique, Thoracoscopy, Right upper lobectomy

P1.16-015 MIMRST THORACOTOMY CURES AGED, SICKLY WEAK AND/OR CARDIOPULMONARY DYSFUNCTION PATIENTS WITH LUNG CANCER

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Background: Lung cancer is increasing rapidly in China. More and more aged, sickly weak and/or cardiopulmonary dysfunction patients are found with lung cancer, but even for small lung cancer (≤2cm) patients, surgery was usually denied because they could not tolerate traditional large-incision standard posterolateral thoracotomy (SPLT); video-assisted thoracoscopic surgery (VATS) is expensive not always avalable in all hospitals, let alone most Chinese patients still could not afford VATS. miMRST, minimally invasive small incision, muscle- and rib-sparing thoracotomy, minimally invasive lung cancer radical surgery, was developed to help resolve these problems: resecting the tumor minimally invasively, not cost too much, with improved prognosis, widely accepted by Chinese patients. **Method:** Case 1: man, aged 67 in Aug 2012, left lower lobe 2.0cm tumor, hypertension for years, feard of SPLT large-incision. Case 2: man, aged 64 in Jan 2013, left lower lobe 1.0cm tumor, smoking 44 years, with serious chronic bronchitis 15 years, asthma episodes per year, coronary heart disease 13 years, coronary stenting 10 years, serious gastric ulcers, colorectal polyps 2 years, could not tolerate SPLT. Case 3: woman, aged 70 in Feb 2013, left lower lobe 2.0cm tumor, sickly weak and cardiopulmonary dysfunction for years , feard of and could not tolerate SPLT. miMRST was scheduled. **Result:** About 10cm lateral chest incision, with the latissimus dorsi and serratus anterior muscles protected, no rib cut needed, was enough for most lung cancer resection and mediastinal lymph node dissection, no need for the surgeon's hands entering into the thoracic cavity, not as large-incision standard posterolateral thoracotomy (SPLT) and modified muscle and rib sparing thoracotomy (MRST) usually do. Left lower lobe lobectomy and mediastinal lymph node desection was performed for all three cases, for Case 1: No.5,6,7,9,10,11,12 group, Case 2: No.3A,4,5,6,7,8,9,10,11,12,1 2u,13,14 group, Case 3: No.3A,5,6,7,8,9,10,10R,11,12,12u,13,14 group lymph nodes and surrounding adipose tissue were dissected. Post-operative pathological diagnosis

was adenocarcinoma, squamous carcinoma and adenocarcinaoma, respectively; all pT1N0M0 Stage IA. All recoverd quickly and no adjuvant tratment was used. Follow-up: all healthy in their 5th year postoperatively, 58, 53, 52 months, respectively. No sign of recurrence and metastasis. **Conclusion:** miMRST, minimally invasive small incision, muscle- and rib-sparing thoracotomy, shows advantage of less damage, quick and better recovery than SPLT, cost less than VATS. miMRST is very suitable for lung cancer surgery in developing countries like China, where most patients could not afford for the expensive VATS. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05)

Keywords: miMRST thoracotomy, small lung cancer, muscle- and rib-sparing thoracotomy

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-016 COMPARING SAFETY AND EFFECTIVENESS OF IMAGE-GUIDED VATS VERSUS CONVENTIONAL VATS FOR SMALL OR DEEP PULMONARY NODULES

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Background: Video-assisted thoracic surgery (VATS) is currently performed to diagnose and treat solitary pulmonary nodules (SPN). However, the intra-operative identification of small and/or deep nodules can be challenging with VATS as the lung is difficult to palpate. Single-stage image-guided VATS(iVATS) performed in a hybrid operation room has been introduced in recent years for the simultaneous localization and removal of small SPN. However, its efficacy and safety compared with traditional workflow has not been studied. **Method:** Patients with undiagnosed SPN who required tumor localization prior to surgical resection between 2017/3 to 2017/6 were retrospectively reviewed. Based on the type of tumor localization method , patients were divided into two groups(Group1 : iVATS ; Group 2: preoperative computed tomography guide tumor localization followed by VATS). The efficacy in localizing the tumor, complications, necessity to convert VATS to thoracotomy and radiation dose were compared. **Result:** The cohort comprised 24 patients(12 in each group). The median SPN diameter was 7 mm (range: 3 – 11 mm) and the median distance of the lesion from the pleural surface was 13 mm (range: 0 – 47 mm) with no intergroup difference(P>0.05). Tumor localization procedure was successful in all patients with similar procedure time(group1: 28 mins[range: 16~41 mins] ; group2: 20 mins[range:14-35 mins] , p>0.05). However, the time interval from completion of localization to surgery was significantly longer in group2(median: 159 mins[range:78~313mins]) than in group1(median:10mins[range:3~20 mins], p<0.001). In group 2, migration of the hook wire occurred in 1 patients during the waiting period although it did not affect the success of VATS resection (nodule location guided by the lung puncture site). The mean effective radiation dose for group1 was 11.53 mSv and that for group2 was 13.50 mSv, respectively(P>0.05) . **Conclusion:** Compared with the traditional workflow(based on preoperative CT-guided lesion localization followed by its surgical removal), single-stage iVATS for simultaneous localization and removal of small SPN is equally safe and accurate but more efficient .

Keywords: localization, lung nodule, image-guided video-assisted thoracoscopic surgery

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-017 MIDDLE TERM SURVIVAL OUTCOME OF SINGLE PORT VIDEO ASSISTED THORACOSCOPIC ANATOMIC LUNG RESECTION: TWO CENTER EXPERIENCE

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Background: Lung cancer is the leading cause of cancer-related death all over the world. Surgery is the treatment choice for patients with non -small cell lung cancer stage I through IIIA. Dr McKenna first described video-assisted thoracoscopic lobectomy (VATS) in 1994. Thereafter, VATS is like mushrooming rapidly spreading all over the world. During recent two decades, minimal invasive thoracoscopic anatomic lung resection with lymph node dissection is now widely accepted as a safe and oncological sound treatment option. The move forward minimal invasive VATS has driven the development of sophisticated instruments and different concepts to cope with the demanding need of working through smaller and fewer incision wounds. Until recently, single port VATS (SPVATS) is now being used for a growing number of applications, even including major lung resection for lung cancer. However, majority of single port VATS related studies are only related to its perioperative outcomes and feasibility. There are still few studies reporting its oncological results. The objective of this study is not only to evaluate the perioperative outcome but also to discuss the middle term oncological outcome in two medical centers' experience **Method:** We retrospectively reviewed patients who underwent SPVATS anatomic resections between January 2014 and February 2017 in Coruña University Hospital and Minimally Invasive Thoracic Surgery Unit (Spain) and Chang Gung Memorial Hospital (Taiwan). Survival outcomes were assessed by pathological stage of American Joint Committee on Cancer (AJCC) 7th and 8th classifications **Result:** 307 patients were finally enrolled in this study. The 2-year disease free survival and 2-year overall survival of the cohort were 80.6 %and 93.4% for 1A , 68.1 %and 84.3% for 1B , 67.5 % and 72.3% for 2A, 18.4% and %49.6 % for 2B , 52.2 % and 61.6 % for 3A, respectively forAJCC 7th classifications. For AJCC 8th classifications, there were 92.3% and 100% for 1A1, 73.7% and 91.4% for 1A2 , 75.2 % and 93.4% for 1A3, 60.9 %and 85.5% for 1B, 55.6% and 72.7 %for 2A, 60.5%and 84.3 % for 2B, 45.4 % and 62.4% for3A **Conclusion:** Our preliminary results revealed that SPVATS anatomic resection achieves non-compromised middle term survival outcomes for early stage lung cancer. For advanced stage NSCLC patients, further evaluation was warranted

Keywords: lung cancer, Single port VATS, Middle term survival outcome

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-018 INTRAOPERATIVE DETECTION OF TUMOR RESECTION MARGIN VIA INHALATION OF FLUORESCENT IMAGING AGENTS

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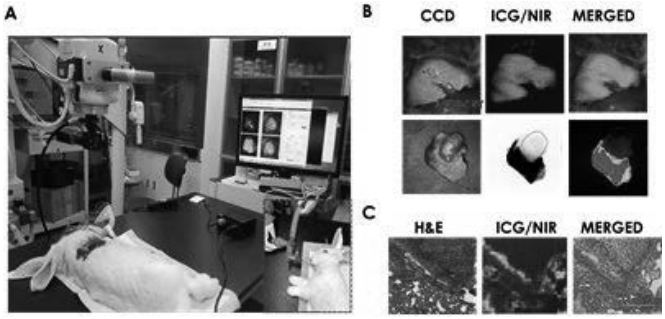
Background: Near Infrared (NIR) fluorescent (Indocyanine green, ICG)-based EPR (enhanced permeability and retention) effects on identifying surgical margins are being used in lung cancer surgery. However, as ICG is equally likely to accumulate in tumors and inflamed tissue, this can cause false-positive results. In this study, we developed the novel method of Inhaled fluorescent based detection of intraoperative tumor resection margin by distinguishing cancerous tissue from normal tissue in mouse and rabbit lung cancer models. **Method:** ICG (1 mg/kg) was administered to healthy mice and mice with lung cancer via inhalation for 1h, and the lung distribution of ICG was investigated using a fluorescence imaging system. And, we established a computed tomography-guided VX2 lung cancer model in 6 rabbits. ICG was administered to these rabbits and resected tumor from lung cancer patients via nebulizer, and the lung cancer was resected under fluorescence imaging system after 1h. The resected tumor margins were investigated using confocal microscopy. **Result:** In normal mice, the inhaled ICG signal was significantly higher in lung compared to other organs (liver, brain, spleen, and kidneys), and this signal decreased over time. In metastatic lung cancer mouse models, the inhaled ICG was distributed only in normal tissues, except cancer. In the rabbit and resected cancer of human, the margin between cancer and normal tissue were distinguished clearly, and the tumor was successfully resected under ICFIS guidance in all 6 rabbits (Fig 3). Additionally, fluorescence and histological microscopy demonstrated that ICG was localized in normal lung tissue. The difference of fluorescent intensity between normal versus cancer tissue showed significantly higher in inhaled ICG



Conclusion: Fluorescent signal was dominantly observed in normal lung tissue comparing to cancer area after inhalation of ICG. The aerosolized ICG could provide better image information for intraoperative identification of resection margin during lung cancer surgery than the intravenous ICG injection.

Keywords: Inhalation, Lung cancer, Fluorescent Imaging agents,

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-019 THREE DIMENSIONAL CT ANGIO-BRONCHOGRAPHY DOESN'T CONTRIBUTE TO THE SHORTENING OF THE OPERATION TIME IN SEGMENTECTOMY

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Background: In the field of surgical treatment for lung malignancy, segmentectomy has been accepted as a choice of surgical resection for some of early lung cancer cases, for patients with poor ventilatory function, and for some of metastatic lung tumor cases. Meanwhile, thoracic surgeons are familiar with the variety of branching pattern of pulmonary vessels as well as bronchial tree. Before each surgery, surgeons usually reconstruct the branching image from CT. Recently three dimensional angio-bronchography (3D-CTAB) is easily retrieved from the

DICOM data of Dynamic CT. Reconstructed 3D-CTangiography has been shown its contribution to the enhancement of the safety of various field of surgery. We conducted a retrospective research whether 3D-CTAB can shorten operation time in segmentectomy cases with lung tumor. **Method:** During May 2012 through May 2017, we conducted lung resection for 272 cases. Among them 39 procedures are segmentectomy that consist of 35 lung neoplasm cases and 4 inflammatory cases. We analyze 35 lung neoplasm cases. Demography of patients are as follows, Male/Female 20/15, Age range 44-87y/o (mean 68.5), operation time was distributed 131-281 minutes (mean 182); blood loss was 1-252ml (mean 37ml). 17 cases underwent surgery without 3DCTAB and remaining 18 cases underwent surgery after 3DCTAB image reconstruction. **Result:** Operation time was 196+/-40min in non 3DCTAB group 173+/-35min in 3DCTAB group. Blood loss was 43.2+/-59.3ml in non-3DCTAB group and 31.2+/-19.8ml in 3DCTAB group. Statistically there are no significant differences between non3DCTAB group and 3DCTAB group in regards to operation time and blood loss. We conducted subgroup analysis. When S6 segmentectomy and lingulectomy were defined as basic procedures (n=17) and remaining segmentectomy procedures as complex procedures (n=18) and analyze the effect of 3DCTAB. There are still no significant differences between non3DCTAB group and 3DCTAB group in regards to operation time and blood loss. **Conclusion:** It seemed that 3DCTAB didn't contribute to the shortening of the operation time and decrease of blood loss during surgery. However, surgeons perceive that 3DCTAB enhances the safety of surgery and leads to precision medicine.

Keywords: three dimensional CT angio-bronchography, operation time, segmentectomy

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-020 OUTCOMES OF PULMONARY METASTASECTOMY IN HEPATOCELLULAR CARCINOMA ACCORDING TO APPROACH METHOD-THORACOSCOPIC VERSUS OPEN APPROACH

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Background: Proper management for pulmonary metastasis (PM) after control of primary hepatocellular carcinoma (HCC) has not been established and chemoradiation therapy has been largely ineffective. We investigated clinical outcomes of pulmonary metastasectomy and risk factors for survival rates, and disease-free survival rates in HCC with PM. With propensity score matching analysis, we compared the results according to surgical approach: video-assisted thoracic surgery (VATS) versus open (thoracotomy or sternotomy) method. **Method:** 136 patients (112 men) underwent pulmonary metastasectomy for isolated PM of HCC from October 1998 to December 2010 at Seoul Asan Medical Center. 86 patients were operated by VATS (VATS group) and the other 50 patients were operated by thoracotomy or sternotomy (Open group). Propensity score analysis between VATS group and Open group was utilized and matched the groups by age, sex, level of preoperative AFP, treatment method for primary HCC, and PM characteristics (number, size, location, time to interval and range of resection). **Result:** There was no operative mortality and minor complication in 10 patients (7.3%) including prolonged air-leak. During 36 month-follow-up period, 112 patients (82.4%) experienced recurrence and 102 patients (75%) died of disease progression. Matching based on propensity scores produced 50 patients in each group for analysis of survival and disease-free survival. There were no survival and disease-free survival differences between matching VATS group and Open group. Multivariate analysis revealed hepatic recurrence, preoperative level of alpha-fetoprotein, liver cirrhosis to be an independent prognostic factor for survival and disease-free survival. **Conclusion:** Pulmonary metastasectomy may prolong survival in selected patients with HCC. VATS metastasectomy provided comparable outcomes to open metastasectomy in regard to survival rate and disease-free survival rate. Liver recurrence, preoperative level of alpha-fetoprotein, liver cirrhosis were independent prognostic factors for survival and disease-free survival.

Keywords: metastasectomy, hepatocellular carcinoma

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-021 MIDTERM ONCOLOGIC OUTCOMES OF SINGLE PORT THORACOSCOPIC LOBECTOMY FOR LUNG CANCER BY PROPENSITY MATCHED ANALYSIS

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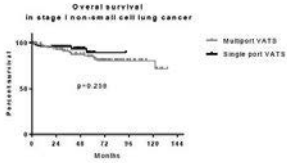
Background: Current evidence is still weak to establish the oncologic equivalence of single port thoracoscopic approach compared to conventional multiport thoracoscopic surgery as one of minimally invasive approach for lung cancer surgery. The purpose of this study is to evaluate the midterm surgical outcomes of single port approach compared to conventional multiport approach in thoracoscopic lobectomy for lung cancer. **Method:** A total of 228 patients in propensity matched group (both 114 patients with pathologic stage I who underwent lobectomy by conventional multiport or single port VATS) were compared the operative outcomes and we analyzed midterm survival and recurrence to evaluate the feasibility of single port VATS lobectomy for lung cancer. **Result:** Both propensity matched groups showed comparable preoperative variables (age, gender, FEV_1, and tumor size) (Table 1). The mean operation time, the number of resected lymph node, and conversion to open thoracotomy or multiport VATS in both group did not show differences (respectively, P=0.076, P=0.291, P=0.253). There was no difference in postoperative major morbidity (P=0.807) and 30-day mortality (p=0.247). The duration of chest drain was shorter in single port VATS group (p<0.001) (Table 2). The survival (P=0.258) and freedom from intrathoracic recurrence (p=0.797) for mean 32 (6-62) months follow up in patients with pathological stage I were not statistically different between groups (Fig).

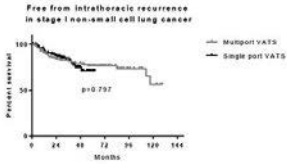
Table 1. Propensity matched group.

	Conventional VATS (N=114)	Single port VATS (N=114)	*P* value
Age	64 ± 9	62 ± 10	0.17
<70	80 (70.2)	83 (72.8)	0.769
>70	34 (29.8)	31 (27.2)	
Sex			
Male	67 (58.8)	68 (59.6)	0.893
Female	47 (41.2)	46 (40.4)	
FEV1%			
≥80	71 (62.3)	67 (58.8)	0.683
<80	43 (37.7)	47 (41.2)	
Tumor size	2.3 ± 0.4	2.7 ± 0.6	0.826
clinical stage			
IA	73 (64)	65 (57.9)	0.415
IB	41 (36)	49 (42.1)	

Table 2. Perioperative outcomes

	Conventional VATS (N=114)	Single port VATS (N=114)	*P* value
Operation time (min)	193 ± 62 (65-418)	178 ± 59 (72-395)	0.076
No. of lymph node dissection	20 ± 12 (2-59)	18 ± 9 (4-56)	0.291
Conversion to open	4 (3.5)	9 (7.9)	0.253
Morbidity	8 (7)	10 (8.8)	0.807
Postoperative mortality (<30days)	2 (0.8)	3 (2.6%)	0.247
Chest drain removal (days)	5 ± 1 (3-8)	4 ± 1 (2-7)	<0.001
Follow-up duration (months)	62 ± 34 (12-129)	32 ± 14 (6-62)	<0.001





Conclusion: Single port thoracoscopic lobectomy in lung cancer showed acceptable oncologic outcomes for midterm follow ups with oncologic equivalence compared to conventional multiport thoracoscopic lobectomy.

Keywords: lobectomy, Minimally invasive thoracoscopic surgery, lung cancer

P1.16: SURGERY -
MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.16-022 INCORPORATING ROBOTICS TO THE SURGICAL TREATMENT OF THORACIC NEOPLASMS: 5-YEAR EXPERIENCE AT AN ACADEMIC CENTER

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Background: Video-assisted thoracoscopic surgery (VATS) is a well-recognized oncologically sound and safe surgical modality to treat appropriately selected thoracic neoplasms. It is, however, limited by 2D imaging and rigid instrumentations. Such restrictions are addressed by robotic platform offering high-definition 3D optics and angulated instrumentations with multiple degrees of movements. We incorporated this novel technology to our thoracic surgical armamentarium in June 2012 to augment our minimally invasive thoracic surgery (MITS) capability. Between 6/1/2012 and 5/30/2017, we have performed 566 robotic video-assisted thoracic surgical (R-VATS) procedures **Method:** The objective of this retrospective analysis of our prospectively maintained database is to appraise our short-term outcomes and to perform comparative analysis of our data with published results. **Result:** We performed 231 anatomic lung resections (lobectomy/segmentectomy; 98% for lung cancers) and 256 wedge lung resections (196 therapeutic/137 for lung cancers), 60 mediastinal procedures (50% for neoplasm) and 9 esophageal procedures (all benign). Regarding R-VATS anatomic lung resection, there were 8 conversions to open thoracotomy (3.4%); the 30-day morbidity and mortality for the remaining 231 cases are 25% (3% potentially life-threatening) and 0.4% (1/231). The postoperative hospital length of stay (LOS) is 3.46±2.48 (median 3.00) days. 25% patients undergoing R-VATS lobectomy/segmentectomy were ≥75 years old (79.78±3.64 (median 79.00), n=53). Comparing to those ≤75 years old (67.19±10.21 (median 68.00), n=170), older patients had a slight increase in LOS (4.46 ±3.75 (median 3.00) versus 3.15±1.83 (median 3.00), p<0.001) but similar morbidity (34% versus 24%, p=0.16). Our single institution short-term surgical outcomes including LOS, number of intrathoracic lymph node harvested, incidence of nodal upstaging (cN0 to pN1/2), 30-day perioperative mortality and morbidity compare very favorable to data reported by individual academic centers or by databases. The learning curve for robotic anatomic lung resection as judged by the duration of time spent at the console performing the complete procedure is long as it would take about 100 cases to achieve a steady-state average of 150 minutes per case. **Conclusion:** We successfully incorporate this novel technology to our current thoracic surgery practice without adversely affecting surgical outcomes of lung resections for malignancies as exempified by our short-term outcomes of R-VATS anatomic lung resections. Our own results are very comparable to those reported by other single instituitons or better than those reported by large multi-institutional database analysis. Long-term oncologic outcomes and financial impacts of adopting R-VATS are being evaluated.

Keywords: lung cancer, lobectomy, robotic thoracoscopic surgery

P1.16-023 A USEFUL AND SAFE METHOD OF INTRAOPERATIVE LOCALIZATION OF SMALL-SIZED PERIPHERAL PULMONARY LESIONS

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Background: Percutaneous computed tomography(CT)-guided marking is a useful method of intraoperative localization of small-sized peripheral pulmonary lesions. However, severe complications may be caused by visceral pleura puncture. Therefore, we report the safe method without visceral pleura puncture. **Method:** The subjects were from November 2016 to May 2017, 6 males and 5 females, average age 70.7 years (59-86 years), total 11 cases of 12 lesions; 6 cases on the right (1 case: 2 lesions in the same lobe) · 5 cases on the left. Before the operation, with the CT-guided , marking on the body surface near the lesion was performed. In cases where ports can be inserted at the marking section, we inserted the ports with both lung ventilation and marked directly on the lung surface. On the other hand, in case of difficult to insert, first we punctured a venous indwelling needle from the marking point and indwelled the outer tube. Second, with both lung ventilation, we inserted a infant nutrition catheter with crystal violet on the tip, and marked the lung surface. Third, we localized the lesion by palpation using marking as an index with partial lung ventilation. And finally, lung partial resection was performed. **Result:** We were able to localize the lesions in all cases, the average operation time was 80 minutes (37 to 147 minutes), and there were no complications during the perioperative period. The resected lesion had an average diameter of 8.8 mm (3 to 16 mm). **Conclusion:** Our method is considered to be quite useful and safe in intraoperative localization of small-sized peripheral pulmonary lesions.

Keywords: peripheral pulmonary lesion, CT-guided marking, intraoperative localization

P1.16-024 A CASE OF BRONCHIAL ATRESIA TREATED WITH COMPLETE THORACOSCOPY-ASSISTED RIGHT S6 SEGMENTECTOMY USING FLUORESCENCE NAVIGATION

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Background: Bronchial Atresia is a congenital anomaly of the tracheobronchial tree and often pointed out as an incidental finding on routine examinations. Bronchial atresia often complicates tumor at abnormal lung segment. However it is very difficult to obtain a diagnosis of such a tumor. Because there are no bronchi into the tumor and lung tissue occurs emphysematous changes around the tumor, we can not perform bronchoscopy and computed tomography (CT) guided lung biopsy. Thus, it is important to resect abnormal lung segment clearly. Although there are several reports about imaging findings and treatment for bronchial atresia, they often do not mention about detail surgical procedure. Here we report the case of a 24 year old man with bronchial atresia successfully treated with anatomical pulmonary resection using fluorescence navigation with indocyanine green (ICG) by video-assisted thoracic surgery (VATS). **Method: Case**: A 24 year man pointed out abnormal shadow by chest X-ray in health check. A CT scan of the chest was performed and revealed limited emphysematous changes and tumor at right lower lobe superior segment (S6). According to the previous reports, our preoperative diagnosis was bronchial atresia and proposed operation was right S6 segmentectomy. **Methods:** The initial part of the procedure, we confirmed pulmonary artery, vein and bronchus of S6 and cut off. ICG was then injected into the peripheral vein catheter by anesthesiologist and the thoracoscope visual system changed to fluorescence mode. Tissue with blood flow appeared green within 30 to 40 seconds after ICG injection. Although perfused lung parenchyma appeared green, the isolated segment remained uncolored. **Result:** We could remove this segment with endoscopic staplers. Pathological diagnosis of removal tumor was granuloma and not cause of obstruction. After 6 months from the operation, CT scan shows no emphysematous changes lesion in right lung. **Conclusion:** Segmentectomy using fluorescence navigation with ICG is useful procedure to resect congenital bronchial atresia.

Keywords: bronchial atresia, complete VATS, ICG

P1.16-025 SAFETY OF SIMULTANEOUS TEVAR AND COMBINED AORTIC WALL RESECTION AT THE TIME OF LUNG RESECTION FOR T4 LUNG CANCER INFILTRATING THE AORTA

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Background: Combined resection of lung cancer and aortic wall for T4 lung cancer is highly invasive and is a challenging procedure for thoracic surgeon. With the advent of minimally invasive endovascular therapy with thoracic endovascular stent (TEVAR) in recent years, there is a possibility that resection of the aorta may be undergone with minimally invasive approach. The aim of this study is to report the safety of simultaneous TEVAR and combined resection of aortic wall on the same day at the time of lung resection. **Method:** We started this minimal invasive procedure form 2013 with the approval of the ethics committee, treatment using TEVAR in cooperation with cardiovascular surgery upon resection of the aorta. Four cases of primary lung cancer with aortic invasion, one case of recurrent lung cancer with aortic invasion after SBRT for second primary lung cancer after left upper lobectomy. Thoracic surgeon and cardiovascular surgeon discussed on predicted tumor invasion range and resection site, stent placement position and stent length, size, surgical procedure considering safe margin. TEVAR was performed on the same day as open chest surgery in all cases. At first aortic invasion was confirmed by thoracotomy in right lateral decubitus position and, then TEVAR was performed in supine position. After TEVAR, the patient was positioned in the right lateral decubitus position again and lung resection combined aortic resection was completed. **Result:** The site of endovascular stent insertion was the aortic arch and descending aorta in two (the subclavian artery occlusion in one, the fenestration for SCA in one), the distal arch just beneath the subclavian artery in two, and descending aorta in one case. The time required to place the stent was 49 to 149 minutes, and in all cases the stent could be placed at the target position. Procedure of lung resection was upper lobectomy in two, pneumonectomy in two, completion pneumonectomy in one. The depth of aortic wall resection was adventitia in three and adventitia + media in two. TEVAR-related complication was observed in one case; external iliac artery intimal damage requiring vessel repair. There were no complications associated with aortic resection. Two postoperative complications of atrial fibrillation and chylothorax were observed but there was no surgery related death. **Conclusion:** Simultaneous TEVAR and combined resection of aortic wall on the same day at the time of lung resection is feasible. Prior to surgery, thoracic surgeon should share information with cardiovascular surgeon to make this procedure safe.

Keywords: Aortic invasion, TEVAR (thoracic endovascular stent), T4 lung cancer

P1.16-026 MULTIMODAL IMAGE-GUIDED VATS RESECTION OF SUB-CENTIMETER PULMONARY NODULES BY CONE BEAM CT AND BRONCHOSCOPIC NIR FLUORESCENCE MARKING

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Background: Small-sized pulmonary nodules such as ground grass nodule and metastatic nodules are difficult to identify the localization during video-assisted thoracic surgery (VATS). The authors have developed the bronchoscopic indocyanine green fluorescence (ICG-FL) marking of small-sized pulmonary nodules to localize them durging VATS. The ICG-FL marking have some advantages. Near infra-red (NIR) light has excellent tissue penetrating property so that the ICG-FL marked in the lung parenchyma can be detected from the surface of lung with ICG-FL detecting thoracoscope. Also, NIR fluorescence spectrum can be isolated from the visible color spectrum so that ICG-FL can be detected with high sensitivity regardless of the color tone of the background lung. In the current study, taking advantage of the hybrid operating room (Hybrid OR), all procedures such as navigation bronchoscopic injection of ICG, real-time image-guidance by cone beam CT, intraoperative detection of ICG-FL and VATS wedge resection were performed all at one time under general anesthesia. The purpose of the current study was the validation of the presenting procedure in terms of the accuracy of localization, the surgical invasiveness, and operation time. **Method:** The patients with sub-centimeter pulmonary nodules which were diagnosed as the indication of video-assisted wedge pulmonary resection were enrolled in the study (n=5). At Hybrid OR under general anesthesia, thin bronchoscope was inserted into the peripheral bronchus which lead to the pulmonary nodule. Virtual bronchoscopy navigation was utilized to increase the accuracy of bronchoscopy. Transbronchial aspiration cytology (TBAC) needle was inserted to peripheral bronchus adjucent to the pulmonary nodule. After confirming the location of TBAC needle by Cone beam CT, the 0.05mL of 0.025mg/mL of ICG mixed with iopamidol was injected into lung parenchyma. During VATS resection, the infra-red fluorescence spot of ICG adjucent to the pulmonary nodules were visualized by ICG-FL thoracoscopy (Pin-point, Novadaq. Canada). The successful pulmonary resection was confirmed with macro- and microscopic examination during surgery. **Result:** ICG-FL marking was successful in all 5 cases 8 lesions without any complication. All tumors were successfully excised with the sufficient surgical safety margin. No adverse events were experienced throughout the entire study. **Conclusion:** Cone-beam CT in Hybrid OR can increase the accuracy of bronchoscopic ICG-FL marking. Multimodal cone-beam CT-guided bronchoscopic ICG-FL marking is a precise method to excise the multiple, small-sized pulmonary noddules by minimally invasive thoracic surgery.

Keywords: infra-red fluorescence, localization of small-sized pulmonary nodules, minimally invasive thoracic surgery

P1.16-027 ROBOTIC SURGERY, VATS, AND OPEN SURGERY FOR EARLY STAGE LUNG CANCER: COMPARISON OF COSTS AND OUTCOMES AT A SINGLE INSTITUTE

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Background: Robotic surgery is increasingly used to resect lung cancer. However costs are high. We compared costs and outcomes for robotic surgery, video-assisted thoracic surgery (VATS), and open surgery, to treat non-small-cell lung cancer (NSCLC). **Method:** We retrospectively assessed 103 consecutive patients given lobectomy or segmentectomy for clinical stage I or II NSCLC. Three surgeons could choose VATS or open, the fourth could choose between all three techniques. Between-group differences were assessed by Fisher's exact, two-way analysis of variance, and Wilcoxon-Mann-Whitney test. P values <0.05 were considered significant. **Result:** Twenty-three patients were treated by robot, 41 by VATS, and 39 by open surgery. Age, physical status, pulmonary function, comorbidities, stage, and perioperative complications did not differ between the groups. Pathological tumor size was greater in the open than VATS and robotic groups (P=0.025). Duration of surgery was 150, 191 and 116 minutes, by robotic, VATS and open approaches, respectively (p<0001). Significantly more lymph node stations were removed (p<0.001), and median length of stay was shorter (4, 5 and 6 days, respectively; p<0.001) in the robotic than VATS and open groups. Estimated costs were 82%, 69% and 68%, respectively, of the regional health service reimbursement for robotic, VATS and open approaches. **Conclusion:** Robotic surgery for early lung cancer was associated with shorter stay and more extensive lymph node dissection than VATS and open surgery. Duration of surgery was shorter for robotic than VATS. Although the cost of robotic thoracic surgery is high, the hospital makes a profit.

P1.16-028 IS VIDEO-ASSISTED THORACIC SURGERY A SAFER PROCEDURE FOR LUNG CANCER PATIENTS?

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Background: Video-assisted anatomical lung resections(VATS) have been increasingly performed worldwide for lung cancer with excellent results. Nonetheless, no comparative analysis has been done in Latin America where we find a different mix of cases when compared to the US or Europe. The purpose of this study was to compare the outcomes of VATS versus open thoracotomy (OT) for anatomical lung resection in patients from the Brazilian Society of Thoracic Surgery (BSTS) database. **Method:** This study was a propensity score analysis of 728 lung cancer patients who underwent anatomic lung resections (358 thoracotomies and 370 VATS) registered in the BSTS database from its inception in August 2015 until May 2017. Pneumonectomies were excluded for analisis purposis A propensity-score model was built using the following baseline characteristics: age at surgery, gender, BMI, comorbidities, type of resection, staging. The main outcomes were mortality, complications and major cardiopulmonary complications. **Result:** Overall in hospital mortality was significant higher in OT(3.6%) in comparison to VATS(0.8%) (OD=4.75, 95%CI=1.28-17.62). Major cardiopulmonary complications were more frequent in patients who underwent OT (17.3%) in comparison to VATS (13%) (OR=1.32; 95%CI:0.85-2.05), but not significant. When analyzing all complications, both technics were similar (OD=1.08, 95%CI0.77-1.51).

Characteristics	VATS	Thoracotomy
Male gender	161(43.5%)	189(52.8%)
Age mean (SD)	66 (10.80)	64.5 (12.9)
BMI kg/m$^{2\,(SD)}$	26 (4.66)	25.7 (4.43)
ASA		
I	52(14%)	35(9.8%)
II	208(56.2%)	210(58.6%)
III	100(27%)	106(29.6%)
≥IV	10(2.7%)	7(2%)
Coronary artery disease	15(4%)	26(7.3%)
Cerebral vascular disease	8(2.2%)	10(2.7%)
Chronic kidney disease	4(1.1%)	10(2.8%)
DM insulino-dependent	52(14%)	52(14%)
Lung Excision		
Lobectomy	326(88.1%)	309(86.3%)
Segmentectomy	37(10%)	16(4.5%)
Bilobectomy	7(1.9%)	33(9.2%)
Staging (7th Ed)		
0	6(1.6%)	4(1.1%)
1	215(58.1%)	160(44.7%)
2	44(11.9%)	92(25.7%)
3	53(14.8%)	30(8.1%)
4	5(1.4%)	8(2.2%)
Missing	70(18.9%)	41(11.5%)

Conclusion: In Brazil, minimally invasive surgery (VATS) for anatomic lung resections is associated with a significantly lower rate of mortality when compared to conventional thoracotomy.

Keywords: VATS, lung cancer, thoracotomy

P1.17-001 THE OPTIMAL FIRST-LINE TREATMENT FOR ADVANCED THYMIC CARCINOMAS

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Background: Thymic carcinomas (TC) are remarkably rare aggressive tumors. Due to this, the optimal first-line regimen in patients with advanced TC has not been clarified since the previous studies included a relatively small number of TC patients. The purpose of this study was to evaluate the optimal first-line regimen in patients with advanced TC. **Method:** We conducted a retrospective study in patients with advanced TC from 2006 to 2015. The primary end point of this study was to evaluate the objective response rate (ORR) and progression free survival (PFS) of different chemotherapy regimens. Age, gender, stage (IVa or IVb), radiation therapy after chemotherapy, resection of primary lesion, different chemotherapy regimens and cycles of chemotherapy were analyzed for significance on PFS. Multivariate Cox model was used to identify significant factors. **Result:** Sixty-seven patients with stage IV (Masaoka stage) TC were enrolled. Thirty-six patients were treated with paclitaxel-platinum regimen every 3 weeks for a maximum of six cycles. Thirty-one patients were treated with gemcitabine-platinum regimen every 3 weeks for a maximum of six cycles. Resections of primary lesion were performed in fourteen patients before chemotherapy. Thirty-three out of 67 patients were given radiation therapy after chemotherapy. Multivariate analysis demonstrated that different stages (HR = 2.47, *P* = 0.003), surgical resection (HR = 0.32, *P* = 0.0049) and radiation therapy after chemotherapy (HR = 0.32, *P* = 0.0001) were significantly associated with PFS. The ORR were 31% (11/36) and 29% (9/31) in paclitaxel-platinum regimen group and gemcitabine-platinum regimen group (*P*=0.89), respectively. The median PFS, 1-/2-year PFS rates in paclitaxel-platinum regimen group were 7.0 (95% CI 4.0–8.0) months, 26%/6% respectively compared to 12 months (95% CI 11.2–24.0), 48%/24% in gemcitabine-platinum regimen group (*P*=0.03). The median PFS, 1-/2-year PFS rates were 18.0 (95% CI 12.0–36.0) months/7.3(95% CI 5.0–11.3) months, 57%/31% and 33%/7% for patients with and without resection of primary lesion (*P* = 0.0302). The median PFS, 1-/2-year PFS rates were 13.0 (95% CI 11.3–17.0) months/4.3(95% CI 3.0–7.3)months, 52%/22% and 20%/7% for patients with and without radiation after chemotherapy (*P* = 0.0013). Major adverse event was grade 3–4 neutropenia in both paclitaxel-platinum regimen (27.7%) and gemcitabine-platinum regimen group (12.9%). Grade 1-2 sensory neuropathy and/or muscle pain were seen in 25.0% of patients treated with paclitaxel-platinum regimen. **Conclusion:** Both gemcitabine-platinum and paclitaxel-platinum regimen showed promising efficacy in advanced TC. Resections of primary lesion and radiation after chemotherapy might be an option for selected patients.

Keywords: thymic carcinomas, first-line treatment

P1.17-002 CLINICOPATHOLOGICAL SIGNIFICANCE OF EPITHELIAL MESENCHYMAL TRANSITION IN THYMIC CANCER

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Background: The epithelial to mesenchymal transition (EMT) is a fundamental biological process during which epithelial cells change to a mesenchymal phenotype which has a profound impact on cancer progression. It has been proposed that increased expressions of EMT markers, loss of epithelial markers such as E-cadherin, and altered expressions of mesenchymal markers such as N-cadherin are called as cadherin switching and associated with poor prognosis in cancer case. We analyzed the expression of E-cadherin and N-cadherin in thymic cancer to determine the relationship to clinicopthological factors and prognosis. **Method:** We collected the data of 31 patients with thymic cancer from our institution between 2000 and 2014. Immunohistochemistry was used to examine the expression of EMT markers, E-cadherin and N-cadherin in tumor specimens. We evaluated the correlation between EMT and prognosis in patients with thymic cancer. We also compared expressions of the cadherins in tumor specimens obtained both before and after preoperative chemoradiotherapy or chemotherapy from 14 patients with thymic cancer who underwent preoperative biopsy in our hospital. **Result:** Eighteen patients underwent preoperative treatment. The resection was extended to the surrounding organs in addition to thymectomy including thymic tumor and anterior mediastinal lymphadenectomy. Twenty-six patients had a R0 resection. Pathological findings revealed that one patient had Masaoka stage I disease, one had II, 20 had III, one had IVa, and 8 had IVb. The histological diagnosis was squamous cell carcinoma in 24, undifferentiated carcinoma in 4, and others in 3 patients. Immunohistochemically, decreased expression of E-cadherin or upregulation of N-cadherin was detected in surgically resected specimens in 15 patients whose tumor was classified as EMT marker-positive. According to a clinicopathological comparison of these groups, EMT status was not related to preoperative therapy, Masaoka staging, or histology. The 5-year survival rate for all patients was 86 %, 63 % for EMT marker-positive, and 100 % for EMT marker-negative. The survival rate of patients with EMT marker-positive tumors was significantly lower than that of those with EMT marker-negative tumors. Decreased expression of E-cadherin or upregulation of N-cadheirn was detected in surgically resected specimens after preopetative treatment compared with biopsy specimens obtained before treatment in 10 of 14 patients. **Conclusion:** EMT marker expression such as cadherin switching was detected in thymic cancer tumor and was more often detected after preoperative treatment, indicating that EMT may affect the degree of malignant potential in thymic cancer and make them insensitive to treatment.

Keywords: thymic cancer, Prognosis, epithelial mesenchymal transition

P1.17-003 IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES BETWEEN THYMOMA AND PARANEOPLASTIC THYMIC TISSUE

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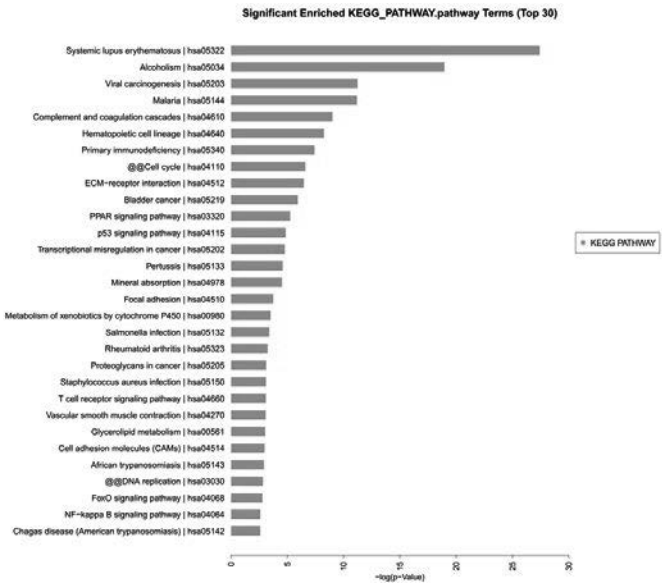
Background: Our study tries to demonstrate the underlying genetic mechanisms of tumorigenesis of thymoma and understand the related features: association with myasthenia gravis, and histologic variability. **Method:** This study uses CapitalBio mRNA microarray analysis of 31 cases of thymoma (including 5 cases of type AB, 6 B1-type cases, 12 B2-type cases, 5 B2B3-type cases, 3 type- B3 cases of; only 6 cases of thymoma were not associated with myasthenia gravis, 25 cases with myasthenia gravis). **Result:** Some differentially expressed genes after comparisons between thymoma and the thymus tissue around tumor were identified preliminarily. Among them, 292 genes increased more than 2-fold, 2 genes more than 5-fold; on the other hand, 596 genes were decreased more than 2-fold, 115 genes more than 5-fold, 21 genes more than 10-fold, 6 genes more than 20-fold. Among these genes upregulated or downregulated, 6 driver genes, such as FANCI,NCAPD3,NCAPG,OXCT1,EPHA1 and MCM2, were identified. We selected 2-fold upregulated and 2-fold downregulated genes to generate a supervised clustering heat map. 6 distinct clusters were identified. In cluster 1, two were type B2 tumors; in cluster 6, three were type B2/B3 tumors. KEGG database analysis, utilized for research and education, found that the pathogenesis of thymoma might be associated with several signaling pathways, which provides important information for revealing genetic mechanisms of thymoma; By comparing with genetic differences of thymoma with myasthenia gravis and without, 4 genes (PNISR,NBPF14,PIK3IP1和RTCA)were upregulated more than 2-fold, more than 30 genes were downregulated more than 2-fold, and 2 signaling pathways with more than 2-fold upregulated genes (TGF- beta signaling pathway and HTLV-I signaling pathway)were found.



Conclusion: The study would be shed light on the molecular bases for selecting appropriate oncological management, predict prognosis and provide important information on the genetic background of thymoma. But Confirmation of the data will be performed using immunohistochemical and multiplex quantitative RT-PCR methods.

Keywords: Thymoma, Signaling pathway, differentially expressed genes

P1.17-004 EXTRAPLEURAL PNEUMONECTOMY FOR PATIENTS WITH STAGE IVA THYMOMA: PATHOLOGICAL EVALUATION OF DISSEMINATED PLEURAL NODULES

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Background: The optimal treatment method for thymoma with pleural dissemination remains controversial. We have performed a multimodality treatment including extrapleural pneumonectomy (EPP) for patients with stage IVa thymoma and pleural dissemination. There are few literatures investigating malignant behavior of disseminated nodules at the parietal and visceral pleura. Therefore, whether complete resection can be accomplished by EPP is not known. **Method:** Our treatment strategy for those patients was induction chemotherapy with cisplatin, doxorubicin, and methylprednisolone (CAMP therapy), followed by thymectomy combined with EPP. We pathologically investigated parietal and visceral pleural nodules obtained by EPP in 8 patients with thymoma and pleural dissemination. **Result:** The median age was 49 (31 to 60) years old. Seven patients had stage IVa disease and 1 had recurrent disease. Preoperative CAMP therapy was performed in 5 patients. Macroscopic complete resection was archived in all patients. Parietal pleural invasions by disseminated nodules were found in 6 patients, invasions to the diaphragm in 6 and visceral pleural invasions in 7. Invasions into the muscle layer of the diaphragm were discovered in 4 patients. Pathological complete resection (R0) was archived in all patients, and the 5-year recurrence free survival rate was 80.0%. **Conclusion:** EPP could be a successful complete resection and might be beneficial for patients with stage IVa thymoma and pleural dissemination. In those some patients, resection of the muscle layer of the diaphragm is needed to obtain R0.

Keywords: Thymoma, pleural dissemination, Extrapleural pneumonectomy (EPP)

P1.17-005 PURE RED CELL APLASIA ASSOCIATED WITH THYMOMA: A REPORT OF A SINGLE-CENTER EXPERIENCE

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Background: Acquired pure red cell aplasia (PRCA) associated with thymoma is relatively rare and relevant reports are limited. The optimal treatment and expected clinical outcomes are not yet standardized. **Method:** We have experienced 8 patients with PRCA in 146 patients who underwent surgical resection of thymoma at Nagoya City University Hospital between 2004 and 2015. These patients were retrospectively reviewed. **Result:** There were 5 males and 3 females, with a mean age at PRCA

diagnosis of 61 years old (range 49-80 years). One patient had a complication of myasthenia gravis. Extended thymectomy (n=4) and thymectomy (n=4) was undergone in 8 patients with thymoma. In WHO classification of thymoma, subtypes were diagnosed as A (n=1), B2 (n=5), and B3 (n=2). According to the Masaoka's classification, stages were classified into II (n=1), III (n=2), IVa (n=3), and IVb (n=2). Complete resection was achieved macroscopically in only 4 patients. Five patients received preoperative chemotherapy using cytotoxic agents (n=1) and high-dosed steroid (n=4). Postoperative radiotherapy was given in 6 patients. Recurrence of thymoma occurred in 3 patients who underwent complete resection. Six patients were diagnosed with PRCA after surgical resection of thymoma (range 1-88 months, median 56.5 months), 2 patients before 60 months and 1month of surgical resection. Ciclosporin was used for PRCA in 6 patients with or without corticosteroid and immunosuppressive agents were not used in the other 2 patients only with occasional transfusion. As treatment-related complications of ciclosporin, pneumonia was seen in 5 patients and renal insufficiency in 1 patient of 6 patients who received it. Follow-up period ranged 9-137 months (median 49.5 months) after PRCA diagnosis. Two patients obtained complete remission of anemia by ciclosporin with and without corticosteroid. Two patients remained transfusion-dependent. Four patients have died. In one patient, ciclosporin could be stopped because of complete remission of anemia. However, re-administration of ciclosporin was needed following 6 years interruption. Main causes of the death were diagnosed as pneumonia (n=2), thymoma (n=1), and cardiac failure (n=1). **Conclusion:** PRCA associated with thymoma was diagnosed postoperatively in three quarter patients. We should pay attention to the occurrence of PRCA even after the resection of thymoma especially in patients with incomplete resection or advanced disease. Ciclosporin was effective for PRCA, but treatment-related complications occurred, particularly as pneumonia. As treatment for PRCA associated with thymoma and its complications were combined complexly, it is not easy to treat PRCA associated with thymoma.

Keywords: Thymoma, pure red cell aplasia

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-006 RADIOGRAPHIC ASSESSMENT FOR TUMOR RESPONSES OF THYMIC CARCINOMA USING THE ITMIG MODIFIED CRITERIA

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Background: Pleural metastases of thymic carcinoma are relatively common, and their unique growth pattern makes accurate and consistent tumor measurement difficult. To minimize intra-observer variability, The ITMIG proposed modified criteria for measurement of tumor response to nonsurgical therapies for thymic carcinoma. **Method:** We conducted a retrospective review of the medical record of advanced or recurrent thymic carcinoma patients treated with chemotherapy between 1980 and 2016 in our institution. The best objective responses were assessed and concorded using the Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST 1.1) and the ITMIG modified criteria. **Result:** 27 patients ----. All of 6 patients showing PR assessed by the RECIST criteria remained PR using the ITMIG criteria. Of 19 patients showing SD assessed by RECIST, 18 remained SD and 1 reclassified as PR using the ITMIG criteria. Both of 2 patients showing PD assessed by the RECIST criteria remained PD using the ITMIG criteria. The overall response rate assessed by the two methods did not differ significantly, with kappa value of 0.996. **Conclusion:** ITMIG modified criteria showed a high concordance rate with RECIST 1.1 criteria in response assessment of thymic carcinoma.

Keywords: ITMIG, Thymic carcinoma, RECIST

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-007 PLATINUM BASED CHEMOTHERAPY IN LOCALLY ADVANCED NON-METASTATIC THYMIC CARCINOMA

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Background: Thymic carcinoma is a rare malignant tumor. At present, cisplatin based doublet or triplet antitumor drugs are used in neo-adjuvant setting for advanced thymic carcinomas. However, no optimal chemotherapeutic regimen is well established and recent small case studies with carboplatin and paclitaxel doublet demonstrates the similar efficacy with less toxicity. We retrospectively evaluated effectiveness and toxicity of platinum based doublet chemotherapy for patients with advanced thymic carcinoma. **Method:** Between 2013 and 2016, we retrospectively identified 21 patients from hospital information system with pathologically confirmed advanced thymic carcinoma, who were treated with platinum based doublet chemotherapy followed by surgical resection. The most commonly used regimen being carboplatin plus docetaxel in 75% of the patients. Other regimens included cisplatin plus gemcitabine, carboplatin plus gemcitabine and cisplatin plus doxorubicin plus cyclophosphamide. **Result:** The clinical response rate was achieved in 61.5 % of the patients. The disease control rate was achieved in 92% of the patients. The median progression-free survival was 7.9 months (95% CI 1.3–10.0) and median overall survival was 33.8 months (95% CI 8.3–45.9). The toxicity profiles of platinum doublets demonstrated grade 3-4 hematological and non-hematological toxicities in 18% and 24% of the patients respectively. No febrile neutropenia and toxic death was recorded. **Conclusion:** We concluded that platinum doublet chemotherapy is active and tolerable for advanced thymic carcinoma in the front-line setting with regard to efficacy, toxicity, and usage in clinical setting.

Keywords: Thymic carcinoma

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-008 CLINICAL AND ONCOLOGICAL OUTCOMES ON RESECTED THYMOMAS OVER A DECADE AT THE NATIONAL CANCER INSTITUTE AT MEXICO CITY

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Background: Despite the fact that Thymic tumors are considered as an orphan disease, they represent the most common adult tumor in the anterior mediastinum. Most of evidence in this neoplasm comes from small, single institution reports. Moreover, the low incidence and a wide spectrum of clinical and morphological characteristics are well-known factors that difficult treatment decisions. **Method:** Single Institution, retrospective chart review of patients with resected thymoma, from January 2005 to December 2016. **Result:** We found 25 patients, with complete clinical data available for review, who underwent thymectomy for epithelial thymic neoplasm. There were 14 females (56%) and 11 males (44%), mean age 56.6 years (27 to 82 years). A total of 22 patients underwent up-front surgery and only 3 patients required neo-adjuvant treatment due to advanced disease. Trans-esternal thymectomy was the most common approach with 18 cases (72%), lateral thoracotomy in 4 cases (16%) and VATS in 3 cases (12%). A complete resection was achieved in 92% of patients. Most of cases, 15 (60%) required an extended thymectomy due to their extension, in 7 (28%) a standard thymectomy was performed,1 case (4%) required a maximal thymectomy and in 2 cases (8%) only a biopsy was performed. R0 resection was achieved in 88% (22 cases) and one patient (4%) was reported as R1 and 2 cases were R2 resections (8%). Distribution according to WHO classification was: A 12%, AB 36%, B1 8%, B2 28%, B3 8% and C 8%. Staging according to Masaoka-Koga Classification was: I 28%, IIA 16%, IIB 24%, III 8%, IVA 12% and IVB 8% Median size of thymomas was 82mm (47-140mm). Mean operative time was 194 minutes (88 – 480), mean blood loss was 362 ml (15 – 2000). Chest tube mean duration was 5.4 days, with a mean hospital stay of 6.2 days (3-18) Morbidity was 24%, but none of patients required re-intervention. Only 2 patients die in the 90 days after surgery for an 8% mortality. In 12 patients (48%) adjuvant treatment was required. Median follow-up was 11.03 months (1.8-108.5) and Median OS was 12.4 months. To date, 21 patients (84%) still alive and only 2 relapses were documented. **Conclusion:** Surgical resection stills the mainstay of treatment for thymomas. Our series comprises mostly large size thymomas requiring extended thymectomy for complete resection. Despite this fact, our perioperative and oncological results and are encouraging

Keywords: thymectomy, Thymoma, Thymic tumors

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-009 CLINICAL SIGNIFICANCE OF PREOPERATIVE NEUTROPHIL-LYMPHOCYTE RATIO IN PATIENTS WITH THYMIC EPITHELIAL TUMOR UNDERGOING SURGERY

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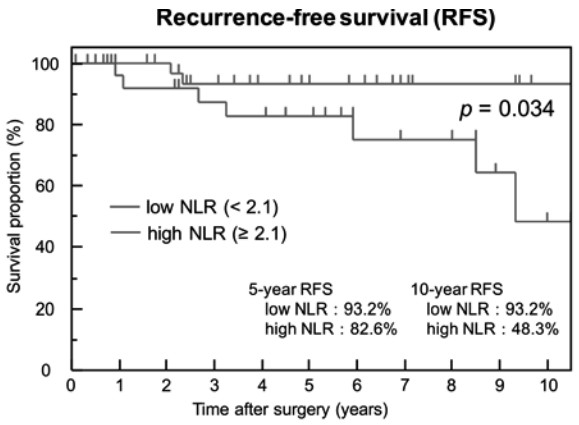
Background: Preoperative neutrophil-lymphocyte ratio (NLR), which is an inflammatory marker, has been reportedly associated with a poor prognosis in patients with various cancers. This study aimed to investigate the clinical significance of preoperative NLR in patients with surgically resected thymic epithelial tumor. **Method:** A retrospective review was conducted of 64 patients who underwent surgical resection for thymic epithelial tumor between January 2000 and April 2017. Preoperative NLR was calculated as peripheral blood neutrophil (cells/m^3) divided by lymphocyte (cells/m^3). Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal value for NLR predicting recurrence. Univariate analysis was performed to assess the association between preoperative NLR and relevant clinicopathological variables. Recurrence-free survival (RFS) after first surgery was calculated using the Kaplan-Meier method. **Result:** The median follow-up period was 66 months. The patients were 32 men and 32 women with a median age of 60 years. The WHO classification was type A (n=10), AB (n=20), B1 (n=9), B2 (n=12), B3 (n=8), and thymic carcinoma (n=5). The patients were classified into two groups according to preoperative NLR: high NLR (≥2.1, n=29) and low NLR (<2.1, n=35) group. Univariate analysis showed that aggressive histology (B2/B3 and thymic carcinoma) and a lower incidence of myasthenia gravis were significantly correlated with high NLR. The RFS rate of the high NLR group was significantly poorer than that of the low NLR group (5- and 10-year RFS rates: 82.6% vs 93.2% and 48.3% vs 93.2%, p=0.034).



Conclusion: Preoperative high NLR value was significantly associated with aggressive histology (type B2/B3 thymoma and thymic carcinoma) and a lower incidence of myasthenia gravis. Preoperative high NLR could be a predictorof poor outcome in patients undergoing surgical resection of thymic epithelial tumor.

Keywords: thymic epithelial tumor, neutrophil-lymphocyte ratio, survival

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-010 THE DIAGNOSTIC VALUE OF SERUM CYTOKERATIN FRAGMENT 19 (CYFRA21-1) FOR THYMIC SQUAMOUS CELL CARCINOMA

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Background: Preoperative diagnosis of anterior mediastinal tumor has been depending on the radiographic findings and clinical findings. We investigated the diagnostic value of serum tumor markers in patients with anterior mediastinal tumor. **Method:** Consecutive anterior mediastinal tumor patients referred to our hospital who had examined either of the serum tumor markers (CEA, SCC, CYFRA 21-1) preoperatively and underwent radical surgery or surgical biopsy between January 1999 and February 2016 were retrospectively reviewed. **Result:** One hundred eighteen patients were eligible, including 16 thymic carcinomas, 48 thymomas, 11 lymphomas, 13 mature teratomas, 7 other malignant tumors, 23 other benign legions. Preoperative serum CYFRA 21-1 was significantly higher in thymic carcinoma group (median = 2.4 ng/ml) than other anterior mediastinal tumor group (median = 1.1 ng/ml, p = 0.0005), whereas CEA (median 2.0 vs 2.1) and SCC (median 0.7 vs 0.8) showed no significant difference. The ROC curves identified an optimal serum CYFRA 21-1 cut off value of 1.65 ng/ml for predicting the diagnosis of thymic carcinoma (AUC = 0.80; sensitivity = 76.9%, specificity = 79.3%; P = 0.046). Pre- and post operative serum CYFRA 21-1 were measured in 6 patients who underwent radical resection. All those patients showed decrease of serum CYFRA 21-1 after resection. **Conclusion:** To measure serum CYFRA 21-1 may help the diagnosis of thymic carcinoma. The level of CYFRA 21-1 reflected the condition of the tumor in each patients. The optimal serum CYFRA 21-1 cut off value for predicting the diagnosis of thymic carcinoma was 1.65 ng/ml.

Keywords: Thymic carcinoma, Mediastinal Tumor, CYFRA 21-1

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-011 EFFICACY AND TOXICITIES OF GEMCITABINE AND CISPLATIN COMBINATION CHEMOTHERAPY IN ADVANCED THYMOMA AND THYMIC CARCINOMA

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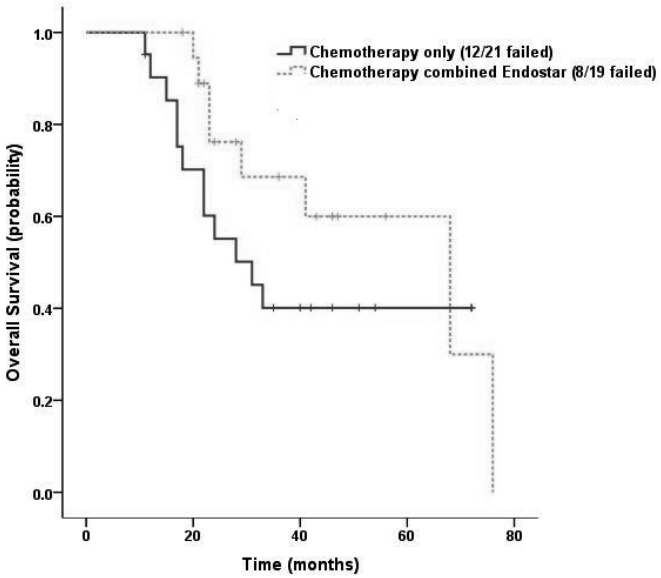
Background: Thymoma and thymic carcinoma are rare thymic epithelial tumours. This study investigated the efficacy of first-line gemcitabine and cisplatin combination chemotherapy in advanced thymoma and thymic carcinoma. **Method:** Retrospective review of patients with histologically-confirmed invasive, metastatic thymoma or thymic carcinoma treated with gemcitabine plus cisplatin as a first-line therapy between August 2008 and July 2016 at the Department of Respiratory Medicine II Peking University Cancer Hospital and Institute. The objective response rate was the primary end point. **Result:** Forty patients, 14 with thymoma and 26 with thymic carcinoma, were identified. 19 received gemcitabine and cisplatin combined with Endostar (injectable recombinant human Endostatin); 21 received gemcitabine and cisplatin only. Of the 14 patients with thymoma, five (35.7%) achieved a partial response (PR) and nine (64.3%) had stable disease (SD); no patients had a complete response (CR) or progressive disease (PD). Among the 26 patients with thymic carcinoma, 14 (53.8%) achieved a PR, 12 (46.2%) had SD; no patients had a CR or PD. In thymic carcinoma, median progression free survival (PFS) was 16 months and median survival (OS) was 41 months; in thymoma, median PFS was 29 months and median OS was 68 months. In chemotherapy combined Endostar group, median PFS was 25 months and median OS was 68 months. In chemotherapy only group, median PFS was 18 months and median OS was 31 months. But PFS and OS were not significantly different between chemotherapy combined Endostar and chemotherapy only ($P = 0.931$, $P = 0.184$; respectively).



Conclusion: This retrospective analysis indicates gemcitabine plus cisplatin has moderate efficacy and could represent a suitable first-line therapy for thymic carcinoma and thymoma, especially for patents who cannot tolerate anthracyclines. Chemotherapy combined with anti-vascular drug Endostar may improve the OS of patients with thymic carcinoma or thymoma, but more patients need to be included in the study.

Keywords: Anti-vascular, Thymic carcinoma, chemotherapy

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-012 THYMIC NEOPLASMS: THE EXPERIENCE OF A CANCER INSTITUTE

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Background: Thymic epithelial neoplasms (TN), thymoma and thymic carcinoma are a rare heterogeneous category of lesions with a broad spectrum of pathologic characteristics and clinical presentations. The histologic classification and staging are complex and controversial; however they remain the most important prognostic factors to consider. Complete radical surgical resection remains the gold standard of therapy. Radiation and chemotherapy are important elements of the multimodality approach. The objective of this study is to describe demographic variables, staging, performed treatment and overall survival (OS) of patients diagnosed with TN followed in our institution, in the last 13 years. **Method:** Retrospective analysis of medical records of patients diagnosed with TN, followed in our cancer Institute from January 2004 to February 2017. **Result:** We followed 43 patients (22 female, and 21 male) with TN diagnose, 3 thymic carcinoma (1 squamous cell carcinoma) and 40 thymoma. The average age at diagnose was 52 years (min 22, max 84). 79% were symptomatic at diagnosis (45% with respiratory symptoms, no differences found for early and advanced stage). In 18,6%, the TN was associated with paraneoplastic autoimmune syndrome (7 pts Miastenia Gravis, 1 pt pure red cell aplasia). The most frequent *performance status* (ECOG scale) at diagnosis was 0 (41,8%) and 1 (48,8%). The majority of pts (60.4%) were at Masaoka stage I and II (13 pts each group). 6.9% stage III, 11.6% (5 pts) stage IVA and 20.9% (9 pts) stage IVB. Regarding to the OMS Classification, 27.9% were type AB, 16.3% type B1 and 11.6% type B2/B3. 81.4% of the patients were treated with surgery. 23.3% (10 pts) received chemotherapy (3 pts preoperative). 39.5% (17 pts) received adjuvant radiotherapy, and 7% pts received palliative radiotherapy. Overall survival (OS) at 5 years is 81%; at 10 years is 66%. The median survival time was 16,36 years (IC95%: 8,716 - 24,007). Disease progression was documented in 8 pts, with a median time to progression of 5,8 months. Median survival wasn't reached for stage I, and for stage II, III, IVa, IVb was, respectively: 9,9 years, 5,76 years, 0,9 years and 6,4 years. **Conclusion:** In this retrospective study, we found an important percentage of pts symptomatic at diagnose, almost 20% with paraneoplastic syndromes, but with a good performance status. As expected most (86%) were treated with surgery, but many with a multimodal approach (46,5%). Prognosis is good even in stage IV disease.

Keywords: Thymic neoplasms, Thymoma

P1.17-013 PROGNOSTIC IMPACT OF PROGRAMMED CELL DEATH-1 (PD-1) AND PD-LIGAND 1 (PD-L1) EXPRESSION IN THYMIC CANCER

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Background: Thymic cancer is one of the aggressive thoracic malignancies. Chemotherapy, radiation therapy, and surgery are the main therapeutic options. However, no standard therapy has not been established because of the rarity, and the mortality rate remains high. Therefore, additional therapeutic options are needed. Recently, cancer immunotherapy has been developed and shown promising results against some malignancies in clinical trials. One of the immuno-check point proteins; the programmed cell death 1/ Programmed cell death 1-Ligand 1 (PD-1/PD-L1) pathways play one of the main role in cancer immunology. The expression of PD-L1 in cancer cells and PD-1 positive tumor infiltrating lymphocytes (TIL) are reportedly one of the useful prognostic and predictive factor for the therapeutic effect of anti-PD-1 or anti-PD-L1 immunotherapies in several malignancies. However, clinical significance of PD-1 and PD-L1 in thymic cancer remains unclear. In this present study, we retrospectively investigated the relationships between the expression of PD/1PD-L1 and clinical backgrounds in thymic cancer. **Method:** A total of 30 patients of thymic cancer surgically resected from 1998 to 2016 in our institutes were retrospectively analyzed. Median follow up periods was 4.2 years. The expression of PD-L1 and PD-1positve TIL was evaluated by immunohistochemical staining using formalin-fixed paraffin embedded surgically resected tissues and analyzed the relationships between those expressions and clinical backgrounds. A Pearson's chi-square test was used to compare the variances. Disease-free survival (DFS) were analyzed by using the Kaplan–Meier method, and the Log-rank test was used to compare the survival distributions of subgroup. **Result:** 14 cases were positive in immunohistochemistry staining of PD-L1 (47%). While, 16 cases were positive in PD-1 TIL staining (55%). There were no significant relationships between PD-1/PD-L1 positive staining and Masaoka-Koga stage. In tumor size, age and gender, there were also no significant difference among IHC results of PD-1/PD-L1. While, in disease free survival rate (DFS), the PD-1 and PD-L1-positive cases were significantly worse as compared to negative cases (PD-1; P=0.001, PD-L1; P=0.03). Uni- and multivariant analysis showed the PD-1 and PD-L1 expression were independent prognostic factors ($P < 0.05$). **Conclusion:** Our results suggested that the high PD-L1 expression and the PD-1 positive TIL are indicators of poor prognosis, and anti PD-1/PD-L1 immunotherapy may be reliable option to treatment in thymic cancer.

Keywords: thymic cancer, PD-1/PD-L1, Immunotherapy

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-014 PLATINUM RECHALLENGE IN ADVANCED THYMIC EPITHELIAL TUMORS: STILL AN OPTION IN THE AGE OF TARGET THERAPY? A MONOCENTRIC EXPERIENCE

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Background: Advanced unresectable thymic epithelial tumors (TETs) are usually treated with platinum-based chemotherapy, although no randomized trials have been conducted and no clear recommendation on the regimens choice are available. Actually, the modern scenario of TETs treatment has become more complex after the introduction of biological agents, but no clear evidences on the more effective sequence treatment between chemotherapy and target therapy have been stated. Here we investigate the effectiveness of platinum rechallenge in advanced TETs. **Method:** All the clinical data of patients with advanced/unresectable or metastatic TETs, treated with first line platinum-based chemotherapy at our institution during a 10-year period were retrospectively reviewed, and those who received platinum rechallenge from the third line and beyond, were included in this study. Patients characteristics, disease control rate (DCR), overall survival (OS), progression free survival (PFS) and post-rechallenge (P-Re) OS and PFS were analysed. **Result:** Platinum rechallenge was administered in 22 patients, of whom 17 had thymoma and 5 thymic carcinoma. A DCR of 95.4% (stable disease (SD) 63.6%, partial response (PR) 31.8%) was achieved after the first line platinum-based chemotherapy according to RECIST criteria, while a DCR of 81.8% (SD 63.6%, PR 18.1%) was registered after platinum rechallenge. All the responders to first line, were confirmed as responders also to rechallenge, only 3 patients with stable disease to first line, had a progressive disease after rechallenge. The median OS of 122 months was statistically correlated with histotype (p=0.015) and with the median treatment free interval (TFI) of 18 months (p=0.019). No statistical correlation has been found between the median P-Re OS of 27 months, the histotype and the TFI. To point out that a statistical correlation between the P-Re PFS of 7 months and the administration of target therapy before rechallenge, has been observed (p=0.04). **Conclusion:** Our retrospective analysis showed that platinum rechallenge may be considered a suitable treatment for advanced, heavily pretreated TETs, especially in case of previous response and longer TFI. Moreover, in the light of our results, we assume, as already stated for other solid tumors, that the chemo-resistant clones can be re-sensitized to platinum by target agents. Prospective trials are needed.

Keywords: platinum chemotherapy, Rechallenge, Target therapy

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-015 LONG ACTING OCTREOTIDE PLUS PREDNISONE IN ADVANCED THYMIC EPITHELIAL TUMORS: A REAL LIFE CLINICAL EXPERIENCE

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Background: The effectiveness of long acting octreotide and prednisone has been already observed in some cases of advanced, heavily pretreated thymic epithelial tumors (TETs) and confirmed in small phase II study with an overall response rate of about 30-38%. Based on these reports, here we investigate the outcome of patients treated with LAR octreotide and prednisone in a real life clinical experience. **Method:** All the patients with advanced and heavily pretreated TETs, who received LAR octreotide and prednisone from January 2007 to January 2017, were included in this monocentric, retrospective analysis. As for local practice, all the patients performed OctreoScan and the treatment schedule consisted of administration of LAR octreotide (30 mg/every 28 days intramuscularly) plus prednisone 0.2 mg/kg/day until documented progressive disease. Patients characteristics, survival outcome, overall response rate and toxicity were evaluated. **Result:** 26 patients (12 males and 14 females) were included in the study. The median overall survival was 88 months, which statistically correlates with histotype (thymoma vs thymic carcinoma) (p=0.0006), but no with stage disease (Masaoka-Koga IVA vs IVB) (p=0.21). The median progression free survival of 21 months, statistically correlates with stage disease (p=0.008); age at diagnosis (p=0.04) and previous surgery (p=0.04). No correlation has been found with histotype (p=0.12) and line of therapy (third vs beyond) (p=0.50). In the whole population, an overall response rate of 42% was achieved and only 2 patients, both with thymic carcinoma, showed a progressive disease. Treatment was safe and no severe side effects were registered. **Conclusion:** Our clinical real life data confirm that somatostatin analogs plus prednisone is an effective and safe treatment in advanced, heavily pretreated TETs and, despite the new available therapy options, it may be still considered in the therapeutic algorithm for obtaining a prolonged control disease.

Keywords: LAR octreotide, prednisone, PROGRESSION FREE SURVIVAL

P1.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - MONDAY, OCTOBER 16, 2017 - 09:30-16:00

P1.17-016 IMMUNOHISTOCHEMICAL MARKERS AS PROGNOSTIC FACTORS IN MALIGNANT THYMIC EPITHELIAL TUMORS

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Background: Thymic epithelial tumors (TET) are rare neoplasms with inconsistent treatment strategies. When researching for molecular pathways to find new therapies, the correlation between specific molecular markers and outcome has been rarely investigated. The aim of this study was to investigate the correlation between survival, metastatic potential and invasiveness of aggressive subtypes of TET and immunohistochemical markers. **Method:** We performed retrospective analysis on patients with WHO type B2/B3 mixed type thymoma (MT), thymoma type B3 (B3) and thymic carcinoma (TC) who underwent surgery from 1998 to 2013. Overall survival (OS), disease-free survival (DFS), progression-free survival (PFS) and metastasis-free survival (MFS) were examined. Tumor specimens were stained using a tissue microarray (TMA) (CD117, CD5, p63, p40, p21, p27, p53, Bcl-2, Ki67, podoplanin, synaptophysin, PTEN and Pax8). Invasive behavior of primary tumors and the presence of extrathoracic metastases were assessed. **Result:** In 23 patients included into this study (four MT, ten B3, nine TC), we found (I) p21 expression in the cytoplasm significantly correlated with a decrease of OS (P=0.016), PFS (P=0.034) and MFS (P=0.005); (II) MFS was significantly shorter when the combination of p21-low p27-low p53-high was present (P=0.029); and (III) nuclear p27 (P=0.042), Ki-67 (P=0.024) and podoplanin (P=0.05) expression correlated with the presence of extrathoracic metastases. **Conclusion:** The main finding of this study is that cytoplasmic p21 expression negatively influences the outcome of malignant TETs and correlates with metastatic activity. Additionally, selected immunohistochemical markers correlate with the distant metastatic potential of TETs. These results may contribute to the stratification of diagnosis and improvement of treatment strategies for thymic malignancies.

Keywords: Thymic carcinoma, Immunohistochemistry, Thymoma

P1.17-017 USEFULNESS OF FDG-PET FOR DIFFERENTIATING THYMIC EPITHELIAL TUMORS FROM MALIGNANT LYMPHOMAS

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Background: It is difficult to diagnose the tumor in the anterior mediastinum by computed tomography. Distinguishing between thymic epithelial tumors and malignant lymphoma is important, because therapeutic strategy is difficult in each disease. The objective of this study was to clarify the usefulness of positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) for distinguishing thymic epithelial tumors and malignant lymphoma. **Method:** We retrospectively reviewed FDG PET-CT scans of 62 patients pathologically diagnosed by surgery or biopsy as thymic epithelial tumors or malignant lymphoma. FDG uptake was measured as the maximum standard uptake value (SUVmax). Student *t* tests were used to assess association between SUVmax and pathological diagnosis. **Result:** Among the 62 patients, 36 patients had a pathological diagnosis of thymoma: WHO classification type A in 3 patients (11%), type AB in 9 patients (19%), type B1 in 6 patients (19%), type B2 in 15 patients (42%), and type B3 in 3 patients (7%). Eleven patients had the thymic carcinoma. Fifteen patients had the malignant lymphoma. The SUVmax in malignant lymphoma (14.9 ± 6.4) was significantly higher than that in the thymic epithelial tumors (5.1 ± 2.5) (p<0.001). The SUVmax in thymic carcinoma (7.8 ± 3.2) was higher than that in the thymoma (4.0 ± 1.5) (p=0.002). The ROC curve of SUVmax for predicting malignant lymphoma indicated that the optimal cutoff value was 7.3. This value had a sensitivity of 0.89 and a specificity of 0.87 **Conclusion:** FDG PET-CT is helpful for distinguishing malignant lymphoma from thymic epithelial tumors with cut off value of 7.3.

Keywords: Thymic epithelial tumors, malignant lymphomas, FDG-PET

P1.17-018 DISTRIBUTION OF ECTOPIC THYMUS IN CHINESE PATIENTS: A PRELIMINARY STUDY

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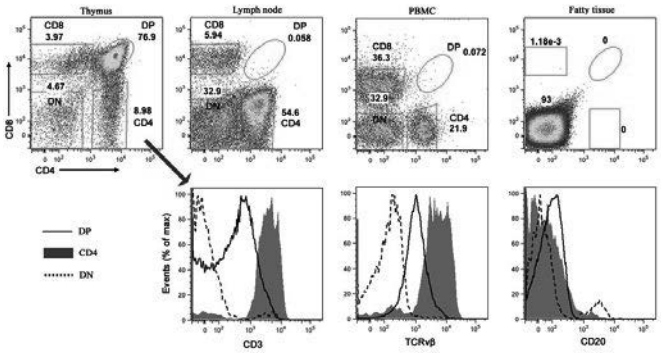
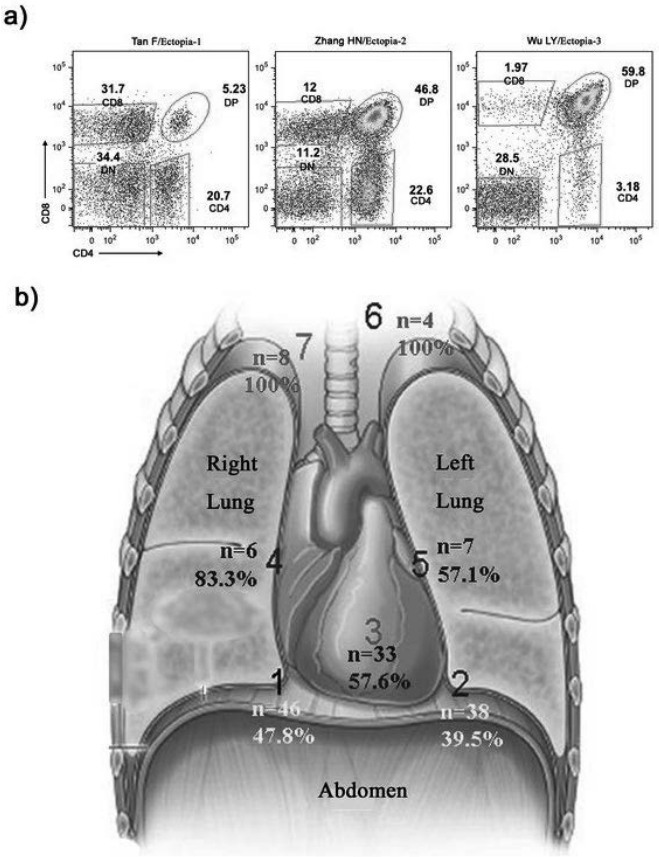
Background: Thymectomy has been a mainstay in the treatment of myasthenia gravis. However, the situation of ectopic thymic tissues remains unknown .The aim of this study was to investigate the distribution of ectopic thymic tissue in Chinese patients using flow cytometry (FCM). **Method:** The resected tissues from 54 patients with MG was divided and classified into: right pericardiacophrenic angle (Number 1), left pericardiacophrenic angle (2), peritracheal (3), right phrenic nerve (4), left phrenic nerve (5), superficial cervical (6) and deep cervical (7). Cells were then stained with anti-CD4, anti-CD8, anti-CD3, anti-TCRvβ, anti-CD56, anti-CD20, anti-CD14,anti-CD11b and labelled with live/dead for analyzing by BD LSRFortessa. **Result:** Ectopic thymic tissue incidence in individual locations was as follows: 47.8% (22 in 46)right pericardiacophrenic angle, 39.5% (15 in 38) left pericardiacophrenic angle, 57.6% (19 out of 33) peritracheal, 83.3% (5 in 6) right phrenic nerve, 57.1% (4 out of 7) left phrenic nerve, 100% (4 specimens) superficial adipose and 100% (8 specimens) deep neck adipose (Fig 2).





Conclusion: Our study indicated that the incidence of ectopic thymic tissues was more frequently than former acknowledge by HE staining test.

Keywords: Myasthenia gravis, Surgery, ectopic thymus

P1.17-019 B7-H3 PROTEIN EXPRESSION IN THYMIC EPITHELIAL TUMOUR SUBTYPES AND ITS ASSOCIATION WITH PD-L1 AND CLINICAL CHARACTERISTICS

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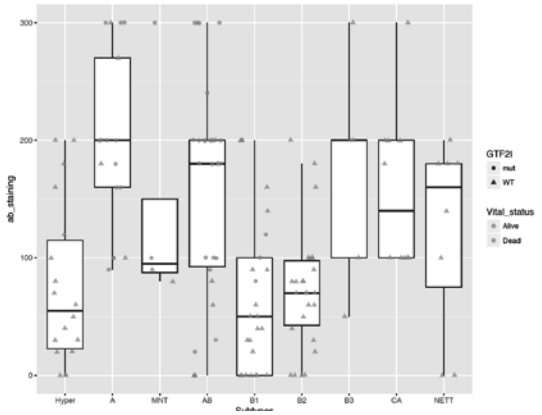
Background: B7-H3 (CD276) belongs to the B7 immunoregulatory family that includes PD-L1. Its expression is associated with poor overall survival (OS) in a range of solid tumours but its expression in TETs is unknown. Phase II clinical trials with anti-PD-1 inhibitors are on-going and exhibit good efficacy although they are often complicated by severe autoimmune toxicities. We measured the levels of B7-H3 in TETs and associated them with PD-L1 levels, OS and GTF2I status. **Method:** TMA sections from each of 125 TET FFPEs and 18 thymic hyperplasias were stained separately with antibodies to PD-L1 (clone 28-8, Abcam) and B7-H3/ CD276 (clone 6A1, Abcam). CD45 and cytokeratin (MF116) stains were used to differentiate epithelia and lymphocytes. All sections were scored with an H-score, giving a final score range of 0-300. For each antibody scores for each TET subtype were compared to each other with the Mann-Whitney test. Positive staining was defined as any staining above 0. Associations between the antibody scores and clinicopathological variables were determined. **Result:** The histological breakdown of analyzed samples was 17 A, 4 MNT LS, 30 AB, 25 B1, 26 B2, 5 B3, 10 CA, 8 NETT and 18 hyperplasias. B7-H3 protein was detected in the epithelia of 110 of 125 TETs (88%) and in 15 of 17 hyperplasias (88%) (Subtype breakdown in Diagram 1). No link between OS and *GTF2I* mutations status (previously described) was found. B7-H3 and PD-L1 were co-expressed in 94 of 125 TETs (75%). Only 2 B1 TETs were negative for both.



Conclusion: B7-H3 protein is expressed in the large majority of TETs, being highest in A and AB thymomas followed by squamous and neuroendocrine carcinomas. Trials with anti-B7-H3 monoclonal antibodies are already underway and given these findings, patients with TETs are likely to be good subjects for these trials.

Keywords: thymic epithelial tumours, PD-L1, B7-H3

POSTER SESSION 2 | TUESDAY, OCTOBER 17, 2017

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-001 SERUM ALBUMIN LEVEL PREDICTS THE SURVIVAL BENEFIT OF CHEMOTHERAPY IN ELDERLY ADVANCED NSCLC PATIENTS WITH POOR PERFORMANCE STATUS

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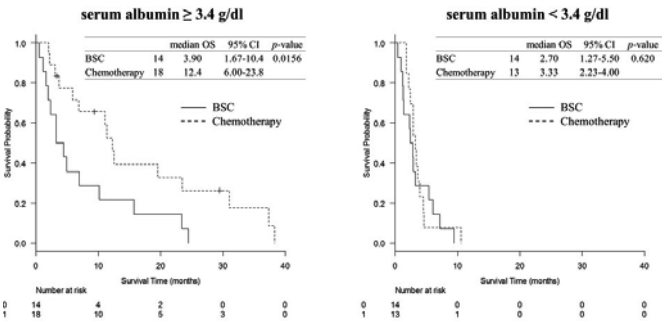
Background: There have been few data on the chemotherapy in elderly advanced non-small cell lung cancer (NSCLC) patients with poor performance status (PS), and usefulness of chemotherapy for such patients remains unclear. **Method:** All consecutive patients with advanced NSCLC, elerly (≥75 years old), ECOG PS ≥2, EGFR mutation negative/unknown, and newly diagnosed from January 2009 to December 2012 at Kurashiki Central Hospital, were retrospectively reviewed to clarify the factors which predicts the survival benefit of chemotherapy. **Result:** 59 patients were enrolled. 31 patients received at least one chemotherapy regimen (chemotherapy group), whereas 28 patients received best supportive care (BSC) alone (BSC group). The proportion of PS 2 and serum albumin level were significantly higher in the chemotherapy group than in the BSC group. The overall survival (OS) was longer in the chemotherapy group than in the BSC group (median OS of 4.7 months and 3.1 months, p = 0.0119). In the chemotherapy group, log-rank testing did not show statistically significant differences in OS between single-agent therapy group and carboplatin-based doublet therapy group, whereas the OS of the patients who received chemotherapy for only 1 cycle was significantly better than those of the patients who received chemotherapy for ≥ 2 cycles. Hypoalbuminemia was not only the risk factor for the early termination of chemotherapy, but also the independent prognostic factor in the chemotherapy group. A receiver operating characteristic curve analysis showed that the best cut-off value was 3.40 g/dl. In the patients with serum albumin ≥ 3.40 g/dl, OS was significantly longer in chemotherapy group than that in BSC group (p=0.0156), whereas, the patients with serum albumin < 3.40 g/dl exhibited poor prognosis regardless of presence/absence of chemotherapy.



Conclusion: In the elderly advanced NSCLC patients with poor PS, serum albumin level may help identify the patients who are more likely to benefit from chemotherapy.

Keywords: non-small cell lung cancer, elderly, performance status

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-002 SURVIVAL OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER AT SINGLE INSTITUTE IN EASTERN THAILAND, 2013-2016

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Chonburi Cancer Hospital, Chonburi/TH

Background: In 2012, lung cancer was the leading cause of death from malignancy in Thailand. The management of advanced non-smll cell lung carcinoma (NSCLC) was rapidly developed in the last decade. The patients were tailored treated according to their histology and molecular profiles, which contributed to significant improvement of survival, especially in the molecular-selected patient. **Method:** This retrospective study was conducted by reviewing medical records of stage IIIB-IV NSCLC patients treated at Chonburi Cancer Hospital, from July 2013 to June 2016. To study the survival of the patient, also focus on an epidermal growth factor receptor (EGFR) mutation testing including an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy in clinical practice and to find a prognostic factor for the survival. **Result:** This study enrolled 148 patients with median follow up time 7.90 months. Median age was 60.5 (range 25-91). There were male 64%, non-smokers 37%, stage IIIB/IV 17/83% and adenocarcinoma/squamous cell carcinoma 74/13 %. The Eastern cooperative oncology group (ECOG) 0-1, 2-4 and no record were found 35%, 36% and 29 %, respectively. The median survival time of all patients was 8.04 months. Median survival times of patients receiving and not receiving systemic therapy were 10.60 months and 3.00 months, respectively (p <0.001). However, a median survival of the EGFR mutation patient was not reach. One hundred twenty one patients (121/148, 81.7%; chemotherapy118, EGFR-TKI 3) received first-line systemic therapy.Fifty patients (50/148, 33.8%) and fifteen patients (15/148, 10.1%) received second- and third-line systemic therapies, respectively. The most common first-and second-line systemic therapies were platinum doublet (116/121) and docetaxel (32/50), respectively. Eighteen percent (27/148) of the patients were tested for EGFR mutations. Fifty five percent (15/27) of the patients tested for EGFR status were sensitive mutations. Unfortunately, only some of sensitive EGFR mutation patients could really access to an EGFR-TKI therapy and mostly received it as a late-line of treatment. Multivariate analysis showed that ECOG performance status 2-4 (p<0.001), no record for ECOG (p=0.001), no lung metastasis (p=0.012) and unknown EGFR (p=0.001) indicated significantly unfavorable prognostic factors for the survival. **Conclusion:** The survival time of advanced NSCLC in our institute was comparable to pivotal studies. Obviously, in real-life clinical practice in Thailand, EGFR mutation testing was quite low because of financial limitation to get access to a targeted therapy. The poor ECOG performance status, no record for ECOG performance status, no lung metastasis and unknown EGFR mutation were poor prognostic factors for the overall survival.

Keywords: survial of advanced non-small cell lung cancer,EGFR , prognostic factor

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-003 DOES ASTRAGALUS MEMBRANACEUS ROOT EXTRACT HAVE ANY SURVIVAL BENEFIT FOR METASTATIC NON-SMALL CELL LUNG CANCER?

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Background: We aimed to determine whether *Astragalus membranaceus* root extract (AmE), which has immunomodulatory activities mainly on macrophages and Th1 type immune response, improve the overall survival (OS) of patients with metastatic non-small cell lung cancer (NSCLC). **Method:** The medical charts of 117 patients with metastatic NSCLC were retrospectively assessed. Thirty-four patients (A group) using AmE during systemic anti-cancer treatment were compared with 83 controls (C group) who did not use AmE following the diagnosis of NSCLC. The histological subtype, performance status, age, gender, smoking status, comorbidities, chemotherapeutics (CT), and erlotinib that were received in any line of treatment were recorded. We compared the OS of the patients in the A and C groups. **Result:** The median (±SD) age of the patients was 61(±7) years and all patients were administered systemic treatment (CT or erlotinib). The histological subtype, performance status, age, gender, smoking status, comorbidities, usage of different type of CT agents and erlotinib were similar in the A and C groups. The median follow-up period was longer for the A group than the C group (18 *vs* 11 months, p <0.001). At the time of the analysis, 83.8% of the patients had died. In the univariate analysis, the median OS (±SE) was significantly longer in the A group compared with the C group (21±4.2 *vs* 11 ±0.9 months, p= 0.004) (Fig 1). In addition to AmE usage, female gender, smoking status, presence of hypertension and erlotinib usage had also significant impact on OS (p <0.05 for all). In the multivariate analysis, only AmE (HR: 0.46, 95% CI: 0.27-0.76, p= 0.003) and erlotinib (HR: 0.45, 95% CI: 0.22-0.89, p= 0.02) usage had significant benefit on OS

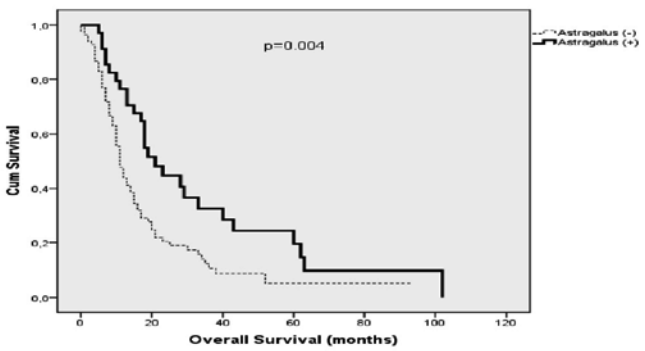

Fig 1. The Kaplan-Meier curves of OS according to AmE usage. **Conclusion:** The use of AmE during systemic anti-cancer treatment may significantly prolong OS of patients with metastatic NSCLC.

Keywords: non-small cell lung cancer, overall survival, Astragalus membranaceus

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-004 SAFETY AND EFFICACY OF NAB-PACLITAXEL PLUS CARBOPLATIN IN ELDERLY PATIENTS WITH NSCLC (ABOUND.70+)

C. Langer[1], E. Anderson[2], R. Jotte[3], J.W. Goldman[4], D. Haggstrom[5], D. Smith[6], C. Dakhil[7], K. Konduri[8], E. Kim[5], T.J. Ong[9], A. Sanford[9], K. Amiri[9], J. Weiss[10]

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Background: A subanalysis of a phase III registrational trial demonstrated a 9.5-month survival benefit with *nab*-paclitaxel/carboplatin vs paclitaxel/carboplatin for patients ≥70 years with advanced NSCLC. ABOUND.70+ evaluated 2 schedules of *nab*-paclitaxel/carboplatin to determine whether a 1-week break could improve tolerability. **Method:** Patients ≥70 years with locally advanced/metastatic NSCLC were randomized to receive first-line *nab*-paclitaxel 100mg/m^2 on days 1, 8, 15 and carboplatin AUC 6 on day 1 of a 21-d cycle (Arm A) or the same regimen with a 1-week break between cycles (Arm B). Primary endpoint: the percentage of patients with grade ≥2 peripheral neuropathy or grade ≥3 myelosuppression; key secondary endpoints: progression-free survival (PFS), overall survival (OS), and overall response rate (ORR), for which statistical analyses did not control for type I error (*P* values unadjusted). **Result:** At interim evaluation, the primary endpoint was similar across treatment arms leading to early closure of enrollment. Baseline characteristics were well balanced between arms (Arm A, n = 71; Arm B, n = 72). Primary endpoint results are presented in the table. Overall, confirmed ORR was 23.9% vs 40.3% (*P* = 0.038), median PFS was 3.6 vs 7.0 months (HR 0.48 [95% CI, 0.30-0.76]; *P* = 0.002), and median OS was 15.2 vs 16.2 months (HR 0.72 [95% CI, 0.44-1.19]; *P* = 0.197). Among patients who received second-line therapy across treatment arms (n = 61), median OS from start of first-line treatment was 22.7 months (95% CI, 11.79-not estimable [NE]) and 16.4 months (95% CI, 12.12-NE) in patients receiving chemotherapy and immunotherapy, respectively. **Conclusion:** *nab*-Paclitaxel/carboplatin was well tolerated and efficacious in elderly patients with advanced NSCLC. Incidence of grade ≥2 peripheral neuropathy or grade ≥3 myelosuppression (primary endpoint) was similar in both treatment arms. A signal of improvement was observed in PFS and ORR in Arm B. NCT02151149

Primary Endpoint		
Event, n (%)	**Arm A** n = 68	**Arm B** n = 70
Patients with either grade ≥ 2 peripheral neuropathy or grade ≥ 3 myelosuppression	52 (76.5)	54 (77.1)
Grade ≥ 2 peripheral neuropathy	25 (36.8)	25 (35.7)
Grade ≥ 3 myelosuppression	48 (70.6)	45 (64.3)
Neutropenia	39 (57.4)	39 (55.7)
Anemia	14 (20.6)	17 (24.3)
Thrombocytopenia	17 (25.0)	12 (17.1)

Keywords: elderly, NSCLC, nab-paclitaxel

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-005 A RANDOMIZED PHASE II TRIAL OF ERLOTINIB VS S-1 IN PATIENTS WITH NSCLC AS THIRD- OR FOURTH-LINE THERAPY (HOT1002)

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Background: Because of the improved efficacy of first and second-line therapy in patients (pts) with non-small cell lung cancer (NSCLC) with wild type EGFR, a high proportion of patients receive third-line therapy and beyond. When this study was planned, erlotinib, an EGFR tyrosine kinase inhibitor, was recommended as standard second-line therapy, irrespective of EGFR status, based on the results of BR 21 study. We conducted the Hokkaido Lung Cancer Clinical Study Group (HOT) 1002 trial, to compare erlotinib (E) with S-1 (S) for NSCLC as third or fourth-line therapy. **Method:** This study was a multicenter, randomized phase II study in Japan. All eligible pts had a recurrent or advanced NSCLC with wild type or unknown EGFR and had progressed after two or three previous chemotherapies. Pts were randomly assigned and treated with E or S until either disease progression or unacceptable toxicity. The primary endpoint was the disease control rate (DCR). The secondary endpoints included the overall survival (OS), progression-free survival (PFS), response rate (RR), toxicity and quality of life (QOL). **Result:** From May 2011 to March 2016, 37 pts were randomly assigned to receive erlotinib (n=19) or S-1 (n=18). This study was terminated immaturely because of the poor pts accrual. The median number of treatment cycles was 3 (range 1-10) in E and 4 (range 1-11) in S. DCR/RR was 42.1%/15.8% in E and 66.7%/16.7% in S. Median PFS/OS (months) was 1.6 (95% CI; 0.8-3.7)/ 8.0 (95% CI; 4.2-13.3) in E and 3.3 (95% CI; 1.5-5.8)/12.2 (95% CI; 5.5-16.3) in S (p=0.094/0.42). Although the patient number was too small for statistical comparison, S group showed better PFS than E group both as third-line (1.5 vs 2.7 months) and fourth-line (3.3 vs.5.9 months). In both treatment groups, the most commonly reported Gr 3-4 non-hematological toxicities were fatigue, anorexia and nausea. There was one Gr 5 event pneumonitis in S. No significant difference was seen in QOL. **Conclusion:** Although this trial had no statistical power to draw any conclusions, treatment with S-1 as a third-/fourth-line showed numerically better clinical outcomes compared with erlotinib.

Keywords: EGFR wild type, third-line therapy, non-small cell lung cancer

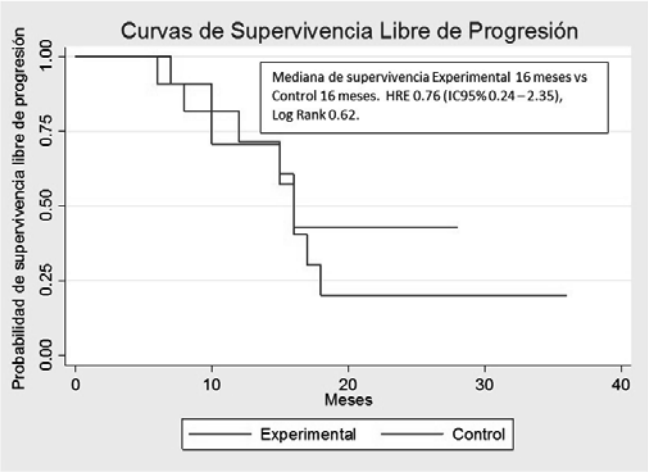
P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-006 EFFECT OF MAINTENANCE USING PEMETREXED WITH AND WITHOUT BEVACIZUMAD IN PATIENTS ADVANCED LUNG CANCER IN NON-SMALL CELLS

M. Galeana Hernandez, M. Magallanes Maciel

Hospital Central Militar, Ciudad de Mexico/MX

Background: Lung cancer is the first cause of death by cancer in Mexico, the chemotherapy based on platin is the regular treatment for the advanced stages of this disease; adding bevacizumab to the chemotherapy gave better results in the average response and the progression-free survival. A common strategy is the maintenance therapy, which is used to maintain the response to the initial therapy after the chemotherapy. The objective is to evaluate and to contrast the effect on the progression-free survival of the combined scheme of "Bevacizumab and Pemetrexed" versus the use of only "Pemetrexed" as a maintenance therapy in patients with advanced lung cancer in non-small cells.better results in progression-free survival. **Method:** Observational, analytic, transversal, retrospective studies. Patients with advanced lung adenocarcinoma negative EGFR and ALK who received maintenance therapy with pemetrexed/bevacizumab after have shown response at the first line of chemotherapy based on platin/pemetrexed. **Result:** Twenty-two patients were analyzed. Eleven of them received pemetrexed/carboplatin and bevacizumab at the first line followed by pemetrexed/bevacizumab. And, the other eleven received pemetrexed/carboplatin followed by a maintenance therapy with pemetrexed. All of them were in the clinic stage IV. 45% of the patients in both groups showed distance metastasis (meaning more frequent). The progression-free survival was the same in both groups of treatment with an average of sixteen months (HRE 0.76 (IC 95% 0.24-2.35), Log Rank P=0.62)



Conclusion: Patients having lung adenocarcinoma without activating mutations using bevacizumab as maintenance therapy do not have better results in progression-free survival.

Keywords: pemetrexed, Maintenance Non-Small Cell Lung Cáncer (NSCLC), bevacizumab

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-007 MOLECULAR CHARACTERIZATION OF NON-SMALL CELL LUNG CANCERS (NSCLC) IN YOUNG PATIENTS FROM AN ARGENTINE POPULATION

V. Denninghoff[1], G. Recondo[2], M. Cuello[3], M.M. García Falcone[4], V. Romano[3], M. Greco[2], V. Wainsztein[2], F. Galanternik[2], M. De La Vega[2], E. Rojas Bilbao[5], M.A. Avagnina[4], G. Recondo[2]

[1]Molecular Pathology Section, Department of Pathology, Centro de Educación Médica E Investigaciones Clínicas (Cemic-Conicet), Ciudad Autónoma de Buenos Aires/AR, [2]Medical Oncology Department, Cemic, Ciudad Autónoma de Buenos Aires/AR, [3]Molecular Pathology Section, Cemic, Ciudad Autónoma de Buenos Aires/AR, [4]Pathology Department, Cemic, Ciudad Autónoma de Buenos Aires/AR, [5]Pathology Department, Instituto de Oncología Angel H. Roffo, Ciudad Autónoma de Buenos Aires/AR

Background: NSCLC is the leading cause of cancer-related deaths in Argentina. NSCLC is rarely observed in young adults (aged 18-40 years) and presents distinctive molecular characteristics. This study analyzed the prevalence of oncogenic molecular alterations in tumor samples from young adults treated at our institution. Different molecular biology techniques were used and treatment outcomes were reported. **Method:** Retrospective observational study of FFPE tumor samples from individuals aged 18-40 years, presenting stage IV lung adenocarcinoma. ALK fusions were studied by IHC (clone-D5F3) and confirmed with FISH-Vysis. The areas selected for molecular studies were micro-dissected, and DNA/RNA were purified. EGFR mutations were studied by Sanger. If available, targeted NGS was done with Colon and Lung. Cancer Research Panel v2 (CLRP) for DNA analysis; and/or Oncomine™ Panel Focus Assay (OFA) for DNA/RNA analysis. Both panels were performed in an Ion 520 chip sequenced in the Ion S5 Next Generation Sequencing Systems. The sequences obtained were analyzed in the Ion Reporter™ Software 5.2.1. The OFA was informed by Ion Torrent™ Oncomine™ Knowledgebase Reporter. **Result:** Six patients were included, 5/6 tumors were lung adenocarcinoma and 1/6, poorly differentiated carcinoma. The male:female ratio was 2:1. Median age was 35y (range 32-37) and all subjects had stage IV disease. EGFR and ALK were tested in all patient's samples, and 4/6 had NGS analysis. Five samples (83%) harbored known targetable oncogenic drivers: EGFR sensitizing mutations occurred in 3/5, ALK translocation with KRAS co-mutation in 1/5, and HER2 exon 20 insertions in 1/5. Only one sample without NGS was negative for the studied oncogenes. Targeted therapies were administered to 4/5 patients.

				Sequencing			ALK				
Case	Gender	Molecular Driver	Name	Sanger	Colon & Lung 520 (v2.1) DNA Hotspot	Oncomine Focus 520 (v2.1) DNA and Fusions	IHC (Ventana)	FISH (Vysis)	Driver Targeted therapy	Response (RECIST)	PFS TKI / OS (months)
1	F	EGFR	p.delE746_A750insAP	Detected	Detected (FO:58%)	ND	Negative	ND	Afatinib	NP	23.6/ ongoing
2	M	EGFR (double heterozygous)	p.delE746_A750	Detected	ND	Detected (FO:86%)	Negative	ND	Afatinib	NP	4.6 / ongoing
			p.delL747_T751insQ	Detected	ND	Detected (FO:83%)					
3	M	EGFR	p.delE746_A750	Detected	ND	ND	Negative	ND	Afatinib	PR	4.1 / ongoing
4	F	ALK	ALK Fusion	ND	ND	RNA seq Failed	Positive	Positive	Crizotinib Ceritinib	PD Primary resistance KRAS	–/9.9
		KRAS	p.G12S (c.34G>A)	Detected	Detected (FO:56%)	Detected (FO:59%)					
5	M	ERBB2	p.E770_A771insAPVMI	ND	ND	Detected (FO:16%)	Negative	ND	None	–	–/4.9
6	M	Unknown	WT	WT	ND	ND	Negative	ND	None	–	–/20.8

Conclusion: Our series shows a high prevalence of known actionable oncogenic drivers in young patients with NSCLC tumor. In this population an extensive molecular profiling of tumors is required to improve the treatment strategy.

Keywords: Molecular, young, NSCLC

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-008 COMBINATION OF BAVACIZUMAB WITH CONVENTIONAL CHEMOTHERAPY SHOWS BETTER PROGNOSIS IN PATIENTS WITH LUNG CANCER WITH LIVER METASTASIS

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Background: Lung cancer is one of the worst prognostic cancers. The survival rate of patients with stage 4 lung cancer is low, especially when invading major organs such as the liver and adrenal glands. Bevacizumab, anti-angiogenesis monoclonal antibody, showed better prognosis combination with conventional chemotherapy of lung adenocarcinoma. We compared progression of liver metastasis and overall survival, the patients who had lung cancer with liver metastasis, conventional chemotherapy or target agents and adding bevacizumab to conventional chemotherapy. **Method:** From 2010 to 2016, we analyzed the differences in treatment outcome between classic chemotherapy or target agents and adding bevacuzimab with conventional chemotherapy among patients with hepatic metastasis in lung cancer patient. Compare the overall survival, response to liver metastasis, and progression of liver metastasis. **Result:** There are 10 patients with conventional chemotherapy or target agents and 5 patients with adding bevacizumab to conventional chemotherapy. Both of them are male predominance, more elderly at adding bevacizumab group. The time taken to worsen the hepatic metastasis was 77.7 days in conventional chemotherapy or target agents group and 174 days in the group with bevacizumab. Overall survival was 134 days in the chemotherapy or target agents group and 332 days in the bevacizumab combination group. **Conclusion:** In lung cancer patients with hepatic metastasis, the efficacy of inhibition of hepatic metastasis was better in patients with combined angiogenesis inhibitor therapy than cytotoxic chemotherapy. We suggest that individual metastatic organ, as like liver, which has poor prognosis, has to reevaluate response to therapy, because of tumor microenvironment.

Keywords: Liver Metastasis, lung cancer, bevacizumab

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-009 THE EFFICACY OF BEVACIZUMAB ADDING IN STANDARD FIRST LINE CHEMOTHERAPY AND MAINTENANCE TREATMENT IN ADVANCED NSCLC: A NETWORK META-ANALYSIS

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Background: Bevacizumab (bev) is used as a standard first-line treatment in combination with doublet platinum-based chemotherapy and as the maintenance therapy with either bev alone or bev with single agent chemotherapy for advanced non-small cell lung cancer (NSCLC). However, it was not well established which is the best chemotherapy of bev combination regimen and which is the optimal dose of bev in this setting. **Method:** Phase II-III RCTs of bev containing regimens of a first line and maintenance treatment of advanced NSCLC were identified from PubMed and Scopus databases until 20 February 2017. Data was independently reviewed and extracted by two oncologists. Network meta-analysis was performed to assess the efficacy of bev in both the induction and maintenance phase. We estimate the probability of being the best combination regimen with bev using surface under the cumulative ranking curve (SUCRA) analysis. This analysis was registered with PROSPERO (CRD42016027171). **Result:** All 4,108 studies were identified from PubMed and Scopus databases. After removal of duplications and exclude ineligible studies, 27 RCTs were included. Studies were analyzed by the period of treatment as at induction period and at maintenance period. Induction treatment with platinum+pemetrexed (pem) showed a strongest benefit to control disease [RR 1.33 (95% 1.05-1.70)]. Bev is best to combine with platinum+taxane [RR 1.26 (95%CI 1.06- 1.50)]. Low dose bev (7.5 mg/kg) and standard dose bev+doublet of platinum and taxane are comparable for controlling disease [(RR 1.00 (95%CI 0.73-1.36)]. Maintenance treatment with pem+bev could be the most effective regimen to prevent disease progression and to improve response rate, however the regimen was the first rank of increasing death from adverse event [RR 3.2 (95%CI 1.11-9.21)]. Maintenance with low dose bev could control disease and also decrease both cancer-specific death and all causes of death. Risk-of-bias assessment was done and the majority of the included RCTs are low risk of bias. **Conclusion:** Bev is best to combine with doublet of platinum and taxane for induction treatment. Adding bev to doublet platinum with pem may not enhance more efficacy of induction treatment. Maintenance with low dose bev is applicable given that it had lower toxicity profiles than a conventional dose (15 mg/kg) without significant differences of benefit. Maintenance with pem+bev could decrease death from cancer and all cause of death, however there was a very high toxicity profile. Therefore, pem+bev might be the option for only selected patients with good performance status in maintenance treatment.

Keywords: bevacizumab, advanced, NSCLC

P2.01-010 RISK SCORE FOR PREDICTING ACUTE EXACERBATION AFTER CHEMOTHERAPY IN LUNG CANCER ASSOCIATED WITH INTERSTITIAL PNEUMONIA

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Background: Fatal acute exacerbation (AE) of interstitial pneumonia (IP) may occur after chemotherapy for lung cancer. We developed and evaluated a scoring system for assessing the risk of AE after chemotherapy in patients with lung cancer associated with IP. **Method:** A review of medical records identified 107 patients with primary lung cancer associated with IP who had received chemotherapy during the period from June 2007 through September 2017. We developed a model to scoring AE risk after chemotherapy in lung cancer patients with IP, and logistic regression was used to evaluate this model. **Result:** The general score for anti-cancer agents was determined by using rates of AE reported in past studies. The risk score was calculated by using the following formula: (1 × anti-cancer agent general score) + (3 × smoking history [>70 pack-years]) + (4 × history of steroid medication) + (3 × %diffusing capacity of the lung carbon monoxide [<50%]). Patients were then classified into three groups. The AE rate was 12% for a risk score of 0–5, 47% for a score of 6–10, and 66.7% for a score ≥11. This sensitivity of the scoring system was 78.6%, and specificity was 67.8%. **Conclusion:** The present scoring system could identify IP patients at high risk for AE after chemotherapy for lung cancer.

Keywords: lung cancer associated with interstitial pneumonia, risk score, acute exacerbation

P2.01-011 THE EFFICIENCY AND SAFETY OF APATINIB PLUS S-1 AS SECOND-LINE OR LATERLINE CHEMOTHERAPY FOR ADVANCED SQUAMOUS CELL LUNG CARCINOMA

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Background: There is no standard treatment strategy for patients with advanced squamous cell lung carcinoma who experienced progression with one or more lines of chemotherapy. Apatinib, a new tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2), has been shown confirming antitumor activity and manageable toxicities in gastric cancers and other solid tumor. Moreover, clinical trials of S-1 on squamous cell lung carcinoma shows curative effect and lighter adverse reactions. This prospective study tried to investigate the efficacy and safety of apatinib plus S-1 as second- or third-line treatment in patients with advanced squamous cell lung carcinoma. **Method:** In this open-label single-arm study(ChiCTR-OPC-16009048), patients were treated oral apatinib, at a dose of 250-500 mg daily, and S-1, at a dose of 60mg/m^2 daily D1-14, repeat every 3 weeks, in the second- or third-line setting. The primary endpoint was progression-free-survival (PFS) and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Treatment was continued until disease progression or unacceptable toxicity occurs. **Result:** From August 19, 2016 to May 31, 2017, 16 patients were enrolled. In 16 patients, there were 7 patients available for efficiency evaluation and 12 patients available for safety evaluation. Computed tomography (CT) scan evaluation revealed that partial response (PR) occurred in 1 of 7 patients and other 6 showed stable disease (SD). However with 2 patients of 6 patients showed stable disease (SD), the tumor demonstrates central cavitation. Hypertension is one of the most frequent adverse reactions, which appeared in 3 of 12 patients who were getting to be normal under oral antihypertensive agent. Others like hand-foot syndrome, proteinuria, diarrhea and fatigue appeared in 1 of 12 patients respectively and could be better controlled. No treatment-related hemorrhage occurred. **Conclusion:** Apatinib plus S-1 exhibits superior activity and acceptable toxicity for evaluable patients with advanced squamous cell lung carcinoma. The research team will continue the study.

P2.01-012 IMPACT OF BRAIN METASTASES ON THE HUMANISTIC BURDEN INCURRED BY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (A-NSCLC)

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Background: It is well documented that brain metastases negatively impact the prognosis for patients with A-NSCLC. However, it is less well known how secondary brain tumours impact health status, quality of life (QoL) and productivity in these patients. As such, an analysis of data from A-NSCLC patients was conducted to evaluate whether the metastatic site (brain vs non-brain) impacts the burden of disease. **Method:** Data were collected between May 2015 and June 2016 from adult patients with Stage IIIB or IV NSCLC via medical chart reviews and patient self-completion forms as part of a multicentre, cross-sectional study conducted in France, Germany and Italy. Health status was measured using the EQ-5D-3L (including the visual analogue scale, EQ-VAS), QoL using the EORTC QLQ-C30 and work/activity impairment using the WPAI:GH questionnaire. Outcomes were stratified by metastatic site (brain vs non-brain); no adjustments were made for possible confounding factors. Statistical significance was assessed using Mann–Whitney U tests. **Result:** 1030 patients were recruited: mean patient age, 64.5 years; male, 65.9%; current/former smokers, 77.9%. Most patients had Stage IV NSCLC (88.4%), non-squamous histology (70.3%) and/or were receiving first-line therapy (70.5%). Patients were largely receiving chemotherapy, regardless of line of therapy. Of 910 evaluable Stage IV patients, 111 had brain metastases and 799 had non-brain metastases. Significant differences were observed between patients with brain metastases versus non-brain metastases for health status, QoL and activity-related impairments (TABLE). The percentage of work-related impairment was also numerically higher in patients with brain metastases.

Table: Humanistic burden of A-NSCLC stratified by site of metastases

	Measure (means)	Non-brain metastases	Brain metastases	*P*-value
Health status and QoL*	EQ-5D-3L utility index	0.67	0.57	0.0273
	EQ-VAS	57.6	53.1	0.0224
	EORTC QLQ-C30 global health status	47.9	42.8	0.0130
Work and productivity	WPAI:GH % overall work impairment†	36.2%	46.2%	0.1863
	WPAI:GH % activity impairment	52.6%	62.2%	0.0008

EQ-5D-3L, EuroQoL-5D 3-level questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer QLQ-C30 QoL questionnaire; WPAI:GH, Work Productivity and Activity Impairment: General Health questionnaire. *Lower scores represent worse health status or QoL; †Analysis performed using data only from patients in employment (non-brain metastases, n = 125; brain metastases, n = 17).

Conclusion: Patients with A-NSCLC and secondary brain tumours had significantly worse health status and QoL, and experienced greater work- and activity-related impairments, compared with A-NSCLC patients with non-brain metastases. These findings may indicate a need for specific management/support programmes for patients with A-NSCLC and brain metastases.

Keywords: Advanced Non-Small Cell Lung Cancer, quality of life, brain metastases

P2.01-013 NAB-PACLITAXEL/CARBOPLATIN IN ELDERLY PATIENTS WITH NSCLC (ABOUND.70+): ANALYSIS OF SAFETY AND QUALITY OF LIFE (QOL) BY CYCLE

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Background: ABOUND.70+ evaluated 2 schedules of first-line *nab*-paclitaxel/carboplatin in patients ≥70 years with advanced NSCLC to determine whether a 1-week break can improve tolerability. Safety and QoL by cycle are reported. **Method:** Patients ≥70 years with locally advanced/metastatic NSCLC were randomized to first-line *nab*-paclitaxel 100mg/m^2 on d1, 8, 15 and carboplatin AUC 6 on d1 of a 21-d cycle (Arm A) or the same regimen with a 1-week break between cycles (Arm B). Primary endpoint: percentage of patients with grade ≥2 peripheral neuropathy (PN) or grade ≥3 myelosuppression (laboratory values). QoL (exploratory endpoint) was assessed using Lung Cancer Symptom Scale (LCSS) on d1 of each cycle. Safety analyses included patients receiving ≥1 dose of study medication. AEs/QoL were analyzed at each of the first 6 cycles. **Result:** At interim evaluation, primary endpoint was similar across arms, resulting in early closure of enrollment. Of 143 randomized patients, 68 and 70 in Arms A and B received ≥1 dose of study drug. Table lists primary endpoint and key safety results by cycle. Grade ≥2 PN occurred earlier in Arm A. Incidence of grade ≥3 myelosuppression was highest in the first 2 cycles, progressively declining after cycle 3 (both arms). Dose reductions occurred in earlier cycles for Arm A; at the start of cycle 4, 36% vs 47% of patients received the maximum dose (100mg/m^2) of *nab*-paclitaxel in Arms A and B. Generally, QoL was maintained throughout treatment. LCSS item of cough improved with each cycle; mean change from baseline at the end of cycle 6 was 25.4 and 13.8mm (visual analog scale). **Conclusion:** Although the overall rate of grade ≥2 PN and grade ≥3 myelosuppression was similar between arms, analysis by cycle showed that grade ≥2 PN and dose reductions occurred earlier in Arm A. QoL was maintained in both arms. NCT02151149

	Arm A n = 68		Arm B n = 70	
Safety				
Primary endpoint, %	76		77	
P value	0.9258			
Peripheral neuropathy, %	Grade ≥ 2[a]	Grade ≥ 3[a]	Grade ≥ 2[a]	Grade ≥ 3[a]
All cycles	37	13	36	17
Cycle 1	6	0	0	0
Cycle 2	6	4	1	0
Cycle 3	7	4	9	1
Cycle 4	4	0	7	1
Cycle 5	6	3	4	1
Cycle 6	4	1	4	9
Myelosuppression, %	Grade ≥ 3		Grade ≥ 3	
All cycles	71		64	
Cycle 1	35		37	
Cycle 2	22		10	
Cycle 3	3		10	
Cycle 4	6		1	
Cycle 5	1		3	
Cycle 6	3		3	
[a]Calculated by first occurrence of adverse event of respective grade.				

Keywords: elderly, NSCLC, nab-paclitaxel

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-014 ABOUND.PS2: SAFETY AND EFFICACY OF NAB-PACLITAXEL–BASED THERAPY IN PATIENTS WITH NSCLC AND ECOG PS 2

A. Gajra[1], N. Abdel Karim[2], D. Mulford[3], M. Matrana[4], H. Ali[5], E. Santos[6], T.J. Ong[7], A. Sanford[7], K. Amiri[7], D. Spigel[8]

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Background: Patients with advanced NSCLC with poor ECOG PS can benefit from platinum-based doublet chemotherapy, although limited data exist from recent, randomized prospective trials. ABOUND.PS2 evaluated the safety and efficacy of *nab*-paclitaxel/carboplatin induction followed by *nab*-paclitaxel monotherapy in patients with advanced NSCLC and ECOG PS 2. **Method:** Chemotherapy-naive patients with histologically/cytologically confirmed stage IIIB/IV NSCLC and ECOG PS 2 received 4 cycles of *nab*-paclitaxel 100 mg/m^2 on days 1 and 8 plus carboplatin AUC 5 on day 1 q3w. Patients not progressing could receive monotherapy with *nab*-paclitaxel 100 mg/m^2 on days 1 and 8 q3w until progression or unacceptable toxicity. Primary endpoint: percentage of patients discontinuing within the first 4 cycles due to treatment-emergent adverse events (TEAEs). Other endpoints: progression-free survival (PFS), disease control rate (DCR), overall survival (OS), overall response rate (ORR), and quality of life (QoL) by Lung Cancer Symptom Score (LCSS). **Result:** Forty patients were treated. Median age was 67.5 years, 60.0% were male, 92.5% were white, and 62.5% had nonsquamous histology. During induction, 11 of 40 patients (28%) discontinued due to TEAEs (primary endpoint). In total, 16 of 40 patients (40.0%) received *nab*-paclitaxel as monotherapy. In all treated patients, the median percentage of per-protocol dose of *nab*-paclitaxel was 78.3% and the median *nab*-paclitaxel dose intensity was 52.2 mg/m^2/week (planned, 66.7 mg/m^2/week). See table for additional safety, efficacy, and QoL results. **Conclusion:** These results support the role of this *nab*-paclitaxel–based regimen in patients with NSCLC and ECOG PS 2. The regimen was well tolerated and appears to have resulted in a clinically meaningful improvement in QoL. Compared with historical data, this regimen is active in patients with stage IIIB/IV NSCLC and ECOG PS 2. NCT02289456

	All Treated Patients N = 40
Safety	
Grade ≥ 3 TEAEs of special interest, n (%) Neutropenia Anemia Thrombocytopenia Peripheral neuropathy	9 (22.5) 7 (17.5) 2 (5.0) 1 (2.5)
Efficacy	
PFS, median (95% CI), months	4.4 (2.99-7.00)
OS, median (95% CI), months	7.66 (4.93-13.17)
ORR (RECIST v1.1), n (%)	12 (30.0)
DCR, % Complete response Partial response Stable disease Progressive disease, % Patients with no postbaseline tumor assessment	30 (75.0) 0 12 (30.0) 18 (45.0) 2 (5.0) 8 (20.0)
QoL	
Mean maximum improvement from baseline	
LCSS Global QoL item, mm[a]	16.91

[a]A ≥ 10-mm improvement was considered clinically meaningful.

Keywords: performance status, nab-paclitaxel, NSCLC

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-015 LONGITUDINAL ASSESSMENT OF PERFORMANCE STATUS (PS) IN PATIENTS WITH NSCLC AND ECOG PS 2 ON NAB-PACLITAXEL–BASED THERAPY

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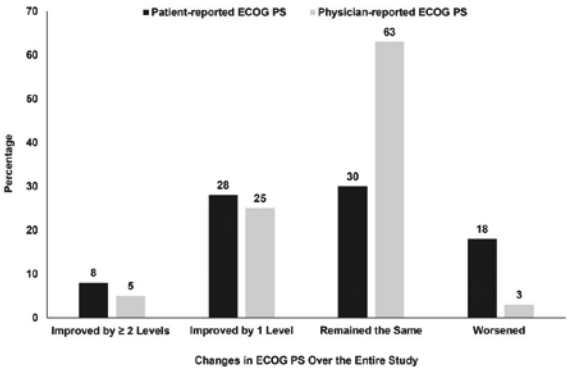
Background: ABOUND.PS2 evaluated *nab*-paclitaxel/carboplatin induction followed by *nab*-paclitaxel monotherapy in patients with advanced NSCLC and ECOG PS 2. Concordance between patient- and physician-reported PS as well as change in PS with chemotherapy were assessed longitudinally. **Method:** Chemotherapy-naive patients with histologically/cytologically confirmed stage IIIB/IV NSCLC and ECOG PS 2 received 4 cycles of *nab*-paclitaxel 100 mg/m^2 on days 1 and 8 plus carboplatin AUC 5 on day 1 q3w. Patients not progressing could receive monotherapy with *nab*-paclitaxel 100 mg/m^2 on days 1 and 8 q3w until progression or unacceptable toxicity. Primary endpoint was the percentage of patients discontinuing within the first 4 cycles due to treatment-emergent adverse events. ECOG PS was assessed by patients on day 1 of each cycle and at treatment discontinuation, and ECOG PS and spirometry were assessed by physicians at screening, on day 1 of each cycle, and at treatment discontinuation. **Result:** Forty patients were treated. Baseline ECOG PS was reported as 2 by 48% and 95% of patients and physicians, respectively. Only 53% of patients rated their ECOG PS the same as the physician at cycle 1 day 1. For patients with both pre- and post-treatment ECOG assessments, 14 of 33 patients (42%) and 12 of 38 physicians (32%) reported an improvement from baseline at least once during treatment (Figure). At baseline, physicians believed that ECOG PS would be reversible with treatment in the majority of patients (80%). Mean FEV1 was 1.29 L and mean PEF was 2.66 L/s at baseline; exploratory investigations of spirometry data indicate that lung function (FEV1 and PEF) remained stable over the course of treatment. **Conclusion:** These results from the ABOUND.PS2 study suggest that patient-reported PS assessments may differ from physician assessments. Improvements in ECOG PS were reported by both patients and physicians during treatment. NCT02289456



Keywords: NSCLC, nab-paclitaxel, performance status

P2.01-016 PROGNOSTIC IMPACT OF A NEW SCORE USING NEUTROPHIL-TO-LYMPHOCYTE RATIOS IN THE SERUM AND MALIGNANT PLEURAL EFFUSION IN LUNG CANCER PATIENTS

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Background: Various studies have reported that the neutrophil-to-lymphocyte ratio in the serum (sNLR) may serve as a cost-effective and useful prognostic factor in patients with various cancer types. However, no study has reported the prognostic impact of the NLR in malignant pleural effusion (MPE). To address this gap, we investigated the clinical impact of NLR as a prognostic factor in MPE (mNLR) and a new scoring system that uses NLRs in the serum and MPE (smNLR score) in lung cancer patients **Method:** We retrospectively reviewed all of the patients who were diagnosed with lung cancer and who presented with pleural effusion. To maintain the quality of the study, only patients with malignant cells in the pleural fluid or tissue were included. The patients were classified into three smNLR score groups, and clinical variables were investigated for their correlation with survival. **Result:** In all, 158 patients were classified into three smNLR score groups as follows: 84 (53.2%) had a score of 0, 58 (36.7%) had a score of 1, and 16 (10.1%) had a score of 2. In a univariate analysis, high sNLR, mNLR, and increments of the smNLR score were associated with shorter overall survival ($p < 0.001$, $p = 0.004$, and $p < 0.001$, respectively); moreover, age, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, M stage, hemoglobin level, albumin level, and calcium level were significant prognostic factors. A multivariable analysis confirmed that ECOG PS ($p < 0.001$), histology ($p = 0.001$), and smNLR score ($p < 0.012$) were independent predictors of overall survival. **Conclusion:** The new smNLR score is a useful and cost-effective prognostic factor in lung cancer patients with MPE. Although further studies are required to generalize our results, this information will benefit clinicians and patients in determining the most appropriate therapy for patients with MPE.

Keywords: malignant pleural effusion, Neutrophil-to-lymphocyte ratio, prognostic factor

P2.01-017 STUDY ON THE EFFECT OF APATINIB SALVAGE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER

Z. Xu[1], C. Xu[2], W. Wang[3], Q. Xu[4], W. Zhuang[5], Z. Song[3], Y. Zhu[6], M. Shi[7], G. Chen[2], M. Fang[3], T. Lv[8], Y. Song[8]

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Background: No definitive chemotherapeutic regimen has been established in patients with non-small-cell lung cancer (NSCLC) who failed second-or third-line treatment. The study of this aim is to investigate the effect of apatinib in advanced non-small cell lung cancer. **Method:** 72 patients with advanced non-small cell lung cancer treated in our hospital from March 2014 to March 2016 were selected and given oral apatinib (750mg, qd) to tumor progression, death or toxicity intolerance so far. The objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), and toxic side effects were observed and observed. Single factor analysis was used to compare the relationship between the clinical features and PFS. **Result:** The median PFS of the patients was 4.8 months (95%CI:4.7-5.0). The results of single factor analysis showed that there were no significant differences between different gender, age, PS score, histological type, drive gene mutation and metastasis foci, the number of metastasis, metastasis, treatment history, line number and duration of treatment in patients with PFS (P>0.05). The ORR of this group was 13.89%, DCR was 83.33%. According to the clinical data of 72 patients in the treatment of patients with the clinical efficacy of the waterfall plot, we can see that there are 54 cases of patients with lesions to reduce the diameter of tumor lesions as the effective treatment of the standard, there were 10 patients with of PR. There are various types of adverse events occurred in 60 patients, the incidence rate was 83.33%, including 22 cases (30.55%) for the aged III. **Conclusion:** Apatinib is a effective and safe treatment in advanced non-small cell lung cancer, and can be carried out more in-depth research and application in clinic.

Keywords: efficacy, Apatinib, adverse event

P2.01-018 RISK FACTORS IN PATIENTS WITH PATHOLOGICAL N1 OR N2 NON-SMALL CELL LUNG CANCER

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Background: Pathological (p) N1 or N2 non-small cell lung cancer (NSCLC) patients may experience poor prognosis despite complete resection; therefore, adjuvant chemotherapy is recommended for them. In this study, we investigated the risk factors for pN1 or N2 NSCLC. **Method:** From March 2005 to December 2015, we retrospectively reviewed 93 patients with completely resected pN1 or N2 NSCLC. Patients with synchronous or metachronous multiple lung cancer, malignancies from other organs, or who received neoadjuvant chemoradiotherapy were excluded. Clinicopathological factors analyzed included: age, sex, serum carcinoembryonic antigen levels, surgical procedures, histology, size of invasive tumor, pathological N status, pleural invasion, lymphatic invasion, vascular invasion, and histological grade. Univariate and multivariate analyses of disease-free survival and overall survival were conducted. **Result:** The study group comprised 93 patients (64 men, 29 women; age range: 38–86 years; mean: 68±9.9 years). The median follow-up period was 35.1 months. The preoperative serum carcinoembryonic antigen level was elevated in 36 patients. Complete resection was performed in all patients, comprising pneumonectomy in two patients (including sleeve pneumonectomy), bilobectomy in three, and lobectomy in 87 (including lobectomy with bronchoplasty or resection adjacent organs). Adenocarcinoma, squamous cell carcinoma, and other histology were observed in 59, 22, and 12 patients, respectively. The maximum diameter of invasive diameter was >30 mm in 39 patients and ≤30 mm in 54. There were 52 patients with pN1 and 41 with pN2. Forty-four were with pleural invasion, 52 with lymphatic invasion, and 48 with vascular invasion. Multivariate analysis showed histology to be an independent factor for recurrence, whereas older age (>70 years), pleural invasion, and adjuvant chemotherapy were independent factors for poor survival. There were 24 patients with no adjuvant chemotherapy, 10 could not receive it because of poor postoperative performance status, and 3 were ineligible because of older age. The 5-year overall survival in patients with adjuvant chemotherapy was 61.8%, compared with 23.8% for those without (p=0.002). **Conclusion:** Older age, pleural invasion, and adjuvant chemotherapy were found to be independent factors for poor survival in pN1 or N2 NSCLC. Adjuvant chemotherapy is a potential consideration for pN1 or N2 patients. Surgery to maintain performance status may be useful in relation to undergoing adjuvant chemotherapy.

Keywords: pathological N1 or N2, risk factor, non-small cell lung cancer

P2.01-019 THE NECESSITY OF CONTRAST-ENHANCED CT BEFORE CT-GUIDED PERCUTANEOUS TRANSTHORACIC NEEDLE BIOPSY FOR LUNG LESIONS

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Background: To evaluate the effect of pre-biopsy contrast-enhanced CT scanning on hemorrhage complicating percutaneous transthoracic needle biopsy **Method:** This retrospective study was approved by the institutional review board. We reviewed 1282 biopsy procedures, Chi-square test and multivariate analysis. We conduct propensity score matching by using MatchIt package in R with nearest-neighbor 1-to-1, 2-to-1 and 3-to-1 matching ,respectively **Result:** The incidence of pulmonary hemorrhage was 20.2% (259/1282), including 247(19.2%) mild hemorrhage, 7 (0.5%) moderate hemorrhage, and 5 (0.4%) severe hemorrhage. Pre-biopsy CECT scan was significantly associated with pulmonary hemorrhage, and had a positive effect (p=0.008, OR=0.671, 95% CI: 0.499-0.902). When matching hemorrhage and non-hemorrhage cases in proportion of 1 to 1, 1 to 2, and 1 to 3, the correlation of CECT and hemorrhage showed significancy and CECT was indeed a protective factor (p=0.039, 0.028 and 0.013, respectively). Additionally, biopsy position (p=0.016,OR=2.734, 95% CI: 1.207-6.194 for supine, lateral as reference), lesion sizes (p=0.005, OR=0.990, 95% CI: 0.983-0.997), puncture depth (P=0.000, OR=1.017, 95% CI: 1.009-1.025), number of pleural passes (P<0.05, for twice, third, fourth, OR= 1.546, 1.673, 8.746, 95% CI: 1.065-2.244, 1.082-2.588, 2.891-26.456, respectively) were also related with hemorrhage. **Conclusion:** Pre-biopsy contrast-enhanced CT scan is a protective factor for hemorrhage. To reduce the incidence of hemorrhage to the greatest extent. We strongly suggest the patients scheduled to perform percutaneous transthoracic needle biopsy do pre-biopsy contrast-enhanced CT scan routinely.

Keywords: Contrast-enhanced CT, CT-Guided Percutaneous Transthoracic Needle Biopsy , Lung Lesions, The Necessity, Single-Institution Experience

P2.01-020 CONTINUOUS INTRAVENOUS INFUSION ENDOSTAR COMBINED WITH PEMETREXED PLUS CISPLATIN IN CHINESE TREATMENT-NAÏVE METASTATIC NON-SQUAMOUS NSCLC

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Background: The treatment options of metastatic non-squamous non-small cell lung cancer patient who not harboring abnormal genes are very limited due to the inapplicability of targeting agents. Luckily, recombinant human endostatin (rh-endostatin) as an angiogenetic drug named endostar was approved in treating

non-small cell lung cancer (NSCLC) combined with doublet chemotherapy in China. Administration of rh-endostatin is optimized from 3-4 hours intravenous infusion to continuous intravenous infusion in order to improve the compliance. In this study, we observed the efficacy and safety of continuous intravenous infusion rh-endostatin combined with pemetrexed and cisplatin in first-line treatment of non-squamous NSCLC without any gene alternatives. **Method:** The main criteria for patient enrollment includes KPS≥80, stage IV non-squamous histology, EGFR negative, ALK-EML4 negative, ROS1 and MET negative. Forty-six patients were enrolled and received endostar 30mg day1 to day7 continuous intravenous infusion, pemetrexed 500mg/m2 day1, cisplatin 25mg/m2 day1 to day3, 21 days each cycle. All patient received this regimen at least 2 but no more than 6 cycles. The assessment (RECIST 1.1) was applied every 2 cycles during treatment process and then every 3 months afterwards. The primary endpoint is progression free survival (PFS). Secondary endpoints are overall response rate (ORR), disease control rate (DCR) and safety. **Result:** The efficacy of this regimen showed that 2 (4.34%) patients achieving complete response (CR). Nineteen (41.30%) patients have their tumors reach partial response (PR), while 11 (23.91%) patients have a stable disease (SD). The overall response rate was 45.65%. Disease control rate was 69.56%. The median time of progression free survival is 301 (95% CI, 250 – 352) days. Severe adverse events caused by hematological toxicity were rare for this regimen, only 2 cases of myelosuppression were found. The non-hematological side effects, particularly nausea and vomiting were observed in 6 patients during their treatment. There is no severe cardiotoxicity showed related to the regimen used in this trial. **Conclusion:** Continuous intravenous infusion endostar combined with pemetrexed plus cisplatin could be an efficient regimen as a first-line treatment for Chinese patients with metastatic non-squamous NSCLC but without any gene mutants. Patients received this regimen could have a relatively long progression free survival time and well-tolerance.

Keywords: Recombinant human endostatin, non-squamous NSCLC, Endostar

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-021 EFFICACY OF SINGLE-AGENT CHEMOTHERAPY AFTER EXPOSURE TO NIVOLUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Recently, some retrospective studies suggested improvement of clinical outcome of patients with non-small cell lung cancer (NSCLC) receiving chemotherapy after immune checkpoint inhibitor. **Method:** We performed a single-center, retrospective study to compare overall response rate (ORR) and progression-free survival (PFS) in NSCLC patients who received single-agent cytotoxic chemotherapy after nivolumab (Group A) with those in NSCLC patients who received single-agent cytotoxic chemotherapy as 3rd-line or 4th-ine treatment without preceding nivolumab treatment (Group B). Patients with EGFR mutation or ALK rearrangement were excluded from this study. **Result:** Fourteen and 61 patients were were included in Group A and Group B, respectively. There were no significant difference of clinical characteristics between the two groups in terms of age, sex, smoking history, performance status and histology. Nab-paclitaxel was most frequently used in group A, while docetaxel was most commonly used in group B. Docetaxel or gemcitabine was significantly highly used in group B (7.1% vs. 54.1%, $p < 0.01$). The median administered line of nivolumab in Group A was 4. ORR was higher in Group A, but not significantly (14.3% vs. 8.1%, $p = 0.610$). Median PFS was compatible between the two groups (median, 56 days vs. 63 days, $p = 0.425$). **Conclusion:** Nivolumab might improve the efficacy of subsequent chemotherapy.

Keywords: Nivolumab, chemotherapy, non-small cell lung cancer

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-022 NINTEDANIB/DOCETAXEL EFFICACY IN ADVANCED LUNG ADENOCARCINOMA TREATED WITH 1L CHEMOTHERAPY/2L IMMUNOTHERAPY IN NINTEDANIB NPU

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Background: Both antiangiogenic agents (nintedanib and ramucirumab) in combination with docetaxel and monotherapy with anti-PD-1/ PD-L1 immunotherapy have demonstrated efficacy as second-line (2L) treatment of patients with stage IV lung adenocarcinoma. However, selection of optimal candidates and the most appropriate therapeutic sequence is under discussion. Herein, we report on the efficacy of the nintedanib/docetaxel combination following first-line (1L) platinum-based chemotherapy and subsequent immunotherapy in a real-world setting. **Method:** From May 2014 to December 2015, 390 patients in 108 Spanish centers enrolled in the nintedanib Named Patient Use (NPU) program. NPU inclusion criteria were advanced lung adenocarcinoma with progressive disease following at least one line of platinum-based doublet chemotherapy. We retrospectively assessed patients that received immunotherapy (available through clinical trials or the nivolumab NPU program) prior to nintedanib/docetaxel. The aim of this analysis was to evaluate the efficacy of the nintedanib/docetaxel combination in this new clinical setting. **Result:** Eleven patients met the inclusion criteria for this analysis: 64% were men; median age of 67 years (range, 44–74); ECOG performance status 0-1 in 100% of patients; median number of treatment lines before inclusion in the nintedanib NPU program was 2 (range, 2-3); PD-L1 expression was positive (unknown cut-off) in 6 patients and was not determined in 5 patients. Median progression-free survival (PFS) of first-line platinum-based chemotherapy was 3.3 months (range 1.4-9.4): 9 patients (82%) had progressed <6 months since start of first-line treatment and 4 patients (36%) had progressed <3 months. Second-line immunotherapy was pembrolizumab (36.5%), atezolizumab (36.5%) and nivolumab (27%). Median PFS of second-line immunotherapy was 2.3 months (range, 0.7-11). The overall response rate (ORR) to second-line immunotherapy was 18% with a disease-control rate (DCR) of 45%. The median number of treatment cycles of nintedanib/docetaxel was 4.5 (range, 2-22). Median PFS of nintedanib/docetaxel post first-line chemotherapy and second-line immunotherapy was 3.2 months (range, 1.4-14.6). Best response was partial response in 4 patients (36%), stable disease in 5 patients (46%), and progressive disease in 2 patients (18%), for an ORR of 36% and a DCR of 82%. **Conclusion:** Our experience in the Spanish nintedanib NPU program in patients with adenocarcinoma NSCLC pretreated with platinum-based doublet chemotherapy and immunotherapy suggests an encouraging ORR and DCR of nintedanib/docetaxel as compared with clinical trial results. These results reinforce the importance of an optimal therapeutic sequence for managing advanced lung adenocarcinoma: 1) Nintedanib/docetaxel should be the recommended second-line treatment in early progressors and 2) Possible chemosensitization effect by immunotherapy.

Keywords: nintedanib, Immunotherapy, adenocarcinoma NSCLC

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-023 REASONS FOR WITHHOLDING SYSTEMIC THERAPY IN STAGE IV NSCLC: COMPARISON OF YEARS 2004 TO 2007 AND 2010 TO 2013

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Background: Inspite of being the commonest cause of death among all cancer deaths, approximately 25% of Stage IV Lung cancer receive systemic therapy; although more than 60% of NSCLC present with Stage IV disease. Prospective randomised studies and meta-analysis have demonstrated survival and quality of life improvement in patients receiving systemic therapy. With significant advancement of molecular pathophysiology have opened up access to new systemic therapy like anti-EGFR, anti-ALK, and Immunotherapy. We conducted the study in Kolkata - to define the rates of patient referral to Medical Oncologists after diagnosis of Stage IV NSCLC. the rates of systemic therapy administration both standard chemotherapy and targeted therapy. the reason why a Stage IV NSCLC may not be referred to a Medical Oncologist or receive standard systemic therapy. **Method:** We performed chart review on Stage IV patients in Single Institute (Community Hospital) between 2004 to 2007 and 2010 to 2013. Staging was based on the 7th Edition of American Joint Committee for Cancer Staging. The 2 stages are based on availability and non-availability of TKIs freely. We collected baseline patient characters and compared median overall survival, referrals and treatment in these 2 cohorts. **Result:** 900 patients from the period 2004 to 2007 and 800 patients for the period 2010 to 2013 were included (n=1700) in the 2 cohorts, In the 2 cohorts 60% vs 82% were referred for cancer care and 28% vs 74% received traditional therapy. There was a correlation between referral for cancer care and Medical Oncology with use of systemic therapy and survival, mOS = 11.2 months vs 1 month in those receiving systemic therapy. In those not receiving systemic chemotherapy the OS was 2 months vs 4 months. The major reasons for no referrals to Medical Oncology included poor functional status, rapid decline and doctors' preference and patients' preference. These were the similar reasons for patients not given systemic therapy. 9% vs 60% received EGFR inhibitors, those who received EGFR inhibitors had a mOS of 16.8 months. Multivariate analysis showed male sex (HR 1.16 p=0.008) and pulmonary embolism (HR 1.2 p=0.002) correlated with worse survival, while receiving chemotherapy (HR 1.2 p=<0.001) and having been enrolled in clinical trials (HR 0.76 p=0.049) correlated with better survival. **Conclusion:** We confirm that systemic therapy improves survival but as yet not been optimally used. Some modifiable factors would be improving referral guidelines, advocacy and patient teaching. There is a need for safe and effective therapy.

Keywords: Referral pattern, reason for no treatment, Stage IV NSCLC

P2.01-024 PROGNOSTIC VALUE OF BODY FAT MASS RATIO IN LUNG CANCER PATIENTS

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Background: Lung cancer is one of the most leading cause of death. One of the prognostic factors that affect survival in lung cancer is weight loss. İn this study, we aimed to investigate the effect of body fat mass ratio on prognosis and survival in advanced stage small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) patients. **Method:** Between September 2014 and July 2015, 200 patients who were diagnosed with advanced lung cancer and whose body fat mass percentage and Body Mass Index (BMI) were determined by using Tanita Body Composition Analyzer during the admission in our institution were included in the study. All patients were analyzed for survival in terms of body fat mass ratio and BMI and other parameters. **Result:** One hundred and sixty four of the patients (82%) were male. The median age was 56.5 (28-93) years. Forty seven (23.5%) of the patients were diagnosed with SCLC and 153 (76.5%) were diagnosed with NSCLC. In univariate analysis; There was no statistically significant on survival effect of, gender, age (<65,> 65), histological diagnosis (SCLC, NSCLC), smoking history, performance status, weight loss during the last 6 months and BMI (>30, <30) (p> 0.05). In the univariate analysis the survival was effected by comorbid disease presence [median 11.4 months in patients with comorbid disease and 19.2 months in patients without comorbid disease (p = 0.012)], and body fat mass ratio [median 16.4 months in <30% and 29.2 months in >30% (p = 0.038)], and they were found statistically significant. In multivariate analysis; There was no statistically significant on survival effect of gender, age (<65 ,> 65), histological diagnosis (SCLC and NSCLC), BMI (<25 and> 25), performance status, however comorbid disease (p = 0.01) and body fat mass ratio (p = 0.033) were found to have a significant effect on survival. **Conclusion:** In patients with advanced lung cancer, body fat mass ratio were found to be independent prognostic factor for over all survival.

Keywords: body fat mass ratio, prognosis, lung cancer

P2.01-025 EVALUATION OF CALCULATING CARBOPLATIN DOSAGE IN CARBOPLATIN–PEMETREXED THERAPY IN CHINESE PATIENTS WITH ADVANCED NSCLC

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Background: We conducted a study to explore the application of carboplatin in carboplatin–pemetrexed therapy and determine the recommended dose of carboplatin in Chinese patients with chemo-naive advanced nonsquamous nonsmall-cell lung cancer (NSCLC). **Method:** From January 2014 to April 2016, 151 patients with chemo-naive NSCLC, who were treated with carboplatin plus pemetrexed (500 mg/m2), was conducted. The area under the curve (AUC) of carboplatin was back-calculated from actual dosages using the Calvert formula. Patients were divided into two groups according to an AUC ≥4 or an AUC <4, respectively. The primary efficacy endpoint were overall response rate (ORR) and disease control rate (DCR). Adverse events (AEs) were evaluated with NCI-CTCAE 3.0. **Result:** The median AUC of carboplatin was 4.0 (1.8-5.5). A total of 79 patients had an AUC ≥4 and 72 patients had an AUC <4. The ORR and DCR of all patients were 33.8% and 90.1%, respectively. The ORR and DCR were 35.4% and 86.1%, respectively, in the AUC ≥4 group, 31.9% and 94.4%, respectively, in the AUC <4 group. No difference was observed in ORR (p=0.650) and DCR (p=0.086) in the AUC ≥4 or AUC <4 group. Furthermore, no significant difference was observed in all grade or grade ≥3 AEs in the two groups. **Conclusion:** Our study suggested that compared to Western populations, the calculating dosages of carboplatin using the Calvert formula was common insufficient for Chinese populations, fortunately, therapeutic efficacy remained equally. In addition, it was not increased by maintaining the AUC of carboplatin at ≥4.

Keywords: carboplatin–pemetrexed, area under the curve (AUC), nonsquamous nonsmall-cell lung cancer (NSCLC)

P2.01-026 DISTRIBUTION OF METASTATIC DISEASE IN SURVIVAL OUTLIERS WITH STAGE IV NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer deaths among men and women in Canada. Many non-small cell lung cancer (NSCLC) patients have metastatic disease at the time of diagnosis, which is associated with poor survival outcomes. However, there appears to be a small subset of patients with advanced disease that live substantially longer than anticipated. Studies have examined the association of various clinical parameters, such as metastatic disease, with survival in cancer patients. Our study aims to determine the impact of metastatic disease burden and distribution on survival in survival outliers with stage IV NSCLC. **Method:** Data on stage IV NSCLC patients diagnosed between 1999-2011 was obtained from the Glans Look Lung Cancer database. Survival outliers were defined as patients who lived > 5 years, or greater than 2 standard deviations from mean survival (adenocarcinoma, 47.5 months; squamous cell carcinoma, 57.4 months); patients not meeting survival outlier criteria were defined as average survivors. Clinical characteristics such as age, gender, smoking history, and treatments were compared between survival outliers and patients with average survival. Metastatic disease was evaluated by comparing differences in organ sites, number of metastatic sites, and local versus distant metastases. Fisher's exact test was used to analyze categorical factors, and Wilcoxon rank-sum test was performed to study continuous factors. Statistical analyses were implemented by R v3.3.0. **Result:** 1803 stage IV NSCLC patients (1291 adenocarcinoma and 512 squamous cell carcinoma) were identified. In the adenocarcinoma group, there were 29 patients who lived >5 years, and 49 who lived >47.5 months. There were 13 squamous cell carcinoma patients who lived greater than 5 years and >57.4 months. Survival outliers tended to be younger, and had a smaller smoking history. Metastatic disease distribution differed significantly between adenocarcinoma and SCC survival outliers. Among adenocarcinoma patients, longer survival was associated with local metastatic disease (stage M1a), ≤1 site of metastasis at diagnosis, the presence of solitary bone metastasis, and the absence of liver metastasis (all p-values <0.05). In comparison, M1a disease, and the presence of solitary bone metastasis and solitary brain metastasis was associated with longer survival in SCC patients (all p-values <0.05). **Conclusion:** Survival outliers with local metastatic disease lived longer than patients with distant metastases. There were marked differences in the sites of distant metastases between adenocarcinoma and squamous cell carcinoma patients, and this was associated with differences in survival outcomes. The present study helps us better understand the role of metastatic disease distribution on survival, in hopes of determining important prognostic factors for lung cancer patients in the future.

Keywords: Survival Outliers, Stage IV NSCLC, Metastatic Disease

P2.01-027 CLINICAL SIGNIFICANCE OF TOPOISOMERASE-II EXPRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER TREATED WITH AMRUBICIN

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Background: Amrubicin (AMR) is one of treatment options in patients with previously treated advanced non-small cell lung cancer (NSCLC). Although topoisomerase-I (Topo-I) and topoisomerase-II (Topo-II) are identified as a targeting molecular of AMR, it remains unclear about the relationship between the efficacy of AMR and the expression level of these markers. **Method:** Between April 2004 and May 2014, 56 patients with advanced NSCLC who had received AMR were retrospectively analyzed. Clinical data including histological type, response to treatment, and survival were collected from medical records. The expression level of Topo II within tumor cell were evaluated by immunohistochemical staining. **Result:** The majority of enrolled patients were men (66.1%) and median age was 69 years (range, 43-78 years). The tumor samples consist of adenocarcinoma (69.6%), squamous cell carcinoma (21.4%), poorly differentiated carcinoma (3.6%), pleomorphic carcinoma (1.8%) and unclassified NSCLC (3.6%) Twenty percent of tumors had EGFR mutations. Percentages of tumors overexpressing Topo-I and Topo-II were 57% and 30%, respectively. Median progression-free survival (PFS) and overall survival (OS) for all patients was 2.4 and 10.9 months, respectively. Patients with low Topo-II expression had significantly longer OS than those with high Topo-II expression (12.9 months vs. 7.0 months, p<0.05) whereas there was no significant association between Topo-II expression status and PFS. The number of AMR treatment cycles, poor performance status, advanced stage and elevated Topo-II expression were significantly associated with unfavorable OS (P<0.05). Meanwhile, Topo-I expression status was not significantly associated with PFS or OS in the patients with NSCLC. **Conclusion:** The present study suggests that the expression levels of Topo-II (but not Topo-I) are associated with in patients with NSCLC receiving AMR.

Keywords: topoisomerase-II, Amrubicin, non-small cell lung cancer

P2.01-028 CLINICAL CORRELATION BETWEEN CTCS ENUMERATION BASED ON NEW DETECTION METHOD AND CHEMOTHERAPY EFFICACY IN HUMAN ADVANCED LUNG CANCER

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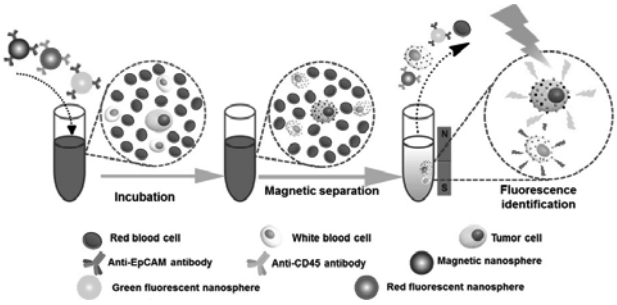
Background: Increasing emerging studies on circulating tumor cells (CTCs) suggest

that CTCs become more and more important in tumor area. However, the difficulty in isolating and enriching CTCs from the billions of blood cells in peripheral blood restricts its development. Recently, we found a new method with high sensitivity and efficiency for CTCs detection. This study aimed to utilize a new method to evaluate the correlation with the CTCs enumeration and chemotherapy efficacy in the human lung cancer patients with stage III or stage IV. **Method:** Blood samples collected from 38 patients with advanced lung cancer before and after treatment were conducted to detect CTCs by new magnetic nanospheres with prominent magnetic/fluorescence properties (Fig.1), which was different from CellSearch. The information of CTCs enumeration was recorded and analyzed with respect to after and before chemotherapy, and clinicopathological features.



Result: High level of CTCs number was found in 15 of 38(39.5%) samples with advanced lung cancer, and it related with stage (p=0.030) and metastasis (p=0.030). Our results suggested that CTCs enumeration could be a marker in reflecting the efficacy of chemotherapy in cases of partial responses (P=0.046) and progressive disease (P <0.001). There was no significant difference in stable disease group (p=0.549). **Conclusion:** This nanosphere-based one-step strategy enables viable CTC detection. These findings showed the change of CTCs enumeration could reflect efficacy of chemotherapy, providing an easier method to evaluate and adjust promptly therapy regimen.

Keywords: Circulating tumor cell, immunomagnetic nanospheres, chemotherapy efficacy

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-029 REAL WORLD REPORT OF CLINICAL OUTCOMES OF BEVACIZUMAB IN FIRST-LINE OR LATER-LINE TREATMENT FOR PATIENTS WITH ADVANCED NSCLC

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Background: Bevacizumab combined therapy has been demonstrated superior efficacy and well tolerability in first-line and later-line treatment by various scales of prospective control trials. But it is still lack of direct evidence endorsing bevacizumab as first-line (1L) over later-line (LL) use. **Method:** We retrospectively evaluated the effectiveness of bevacizumab contained therapy as 1L or LL treatment in patients with advanced NSCLC. Primary outcome was progression-free survival (PFS), and the secondary objectives were objective response rate (ORR), disease control rate (DCR) and safety. Subsequently, an exploratory analysis was conducted in subgroups regarding to patients drive genes status including EGFR and ALK. **Result:** From Jul. 2009 to Dec. 2016, a total of 159 patients with NSCLC were enrolled. Baseline characteristics were well balanced between 1L and LL groups. The median follow-up time was 10.7 months. Comparing to LL, the median PFS in 1L was significant longer (9.7 months vs 4.1 months, HR=0.28, 95% CI 0.15-0.52, P<0.0001). Short term effects of ORR and DCR both had improved trends in 1L than LL. Interestingly in subgroups, WT group (median PFS 11.3 vs 3.4 months, HR 0.2, 95% CI 0.08-0.48, P<0.0001) and WT+UN group (median PFS 11.3 vs 3.4 months, HR 0.25, 95% CI 0.12- 0.51, P<0.0001) had better effectiveness as 1L than LL over the whole population. The ORR and DCR had consistently similar response in subgroups comparison (Table 1). There was no unexpected safety issue documented.

Table 1. Comparison of clinical effectiveness of Bevacizumab contained therapy between 1L and LL use.

	All (159)		WT (71)		WT+UN# (110)	
	1L (62)	LL (97)	1L (30)	LL (41)	1L (43)	LL (67)
PFS (months)	9.7	4.1	11.3	3.4	11.3	3.4
HR, 95%CI,	0.28, 0.15- 0.52		0.2 , 0.08-0.48		0.25, 0.12- 0.51	
*P**	<0.0001		<0.0001		<0.0001	
ORR %	63.33	51.16	55.17	38.46	56.10	45.16
	(38/60)	(44/86)	(16/29)	(15/39)	(23/41)	(28/62)
*P***	0.1448		0.1712		0.2772	
DCR %	93.33	87.21	96.55	82.05	92.68	85.48
	(56/60)	(75/86)	(28/29)	(32/39)	(38/41)	(53/62)
*P***	0.2305		0.1251 ***		0.3543	

Notes: *, Log-Rank test; **, Chi-sq unless specified;***, Fisher test.

Conclusion: Although it was limited in retrospective design, this precious real world evidence indeed exhibited superior clinical effectiveness in first-line use of bevacizumab indicating a better choice rather than later line use, particularly to EGFR&ALK wild type or unknown patients.

Keywords: advanced NSCLC, bevacizumab, first-line or later-line treatment

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-030 REAL WORLD STUDY OF BEVACIZUMAB-CONTAINED REGIMEN AS FIRST LINE THERAPY IN CHINESE PATIENTS WITH ADVANCED NSCLC

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Background: Bevacizumab has been demonstrated significant survival benefits in addition to chemotherapy in patients with advanced NSCLC from several large scale randomized control trials. We aimed to explore the clinical impact of first-line bevacizumab-contained regimen (B+) versus non-bevacizumab regimen (non-B) for patients with advanced non-squamous non-small cell lung cancer (NS-NSCLC) in the real world setting. **Method:** From July 2009 to December 2016, patients with advanced NS-NSCLC who received first-line therapy with or without bevacizumab were retrospectively collected from Cancer Hospital Chinese Academy of Medical Sciences. Primary outcome was progression-free survival (PFS), and the secondary objectives were objective response rate (ORR), disease control rate (DCR) and safety. Meanwhile exploratory analysis was conducted in each sub-groups regarding to EGFR and ALK status. **Result:** 149 patients met selection criteria, 62 in B+ group and 87 in non-B group. Chemotherapy was the based treatment in each group, 57/62 and 71/87 respectively. Median follow-up time was 10.7 months. The baseline characteristics were well balanced. In overall population, median PFS were significantly longer in B+ than in the non-B group: 9.7 vs 7.0 months, HR 0.52, 95% CI 0.30-0.91, P=0.0184. Both ORR and DCR had improved trends in B+ group. In wild type patients, median PFS of B+ group was 11.3 months compared with 5.5 months in the non-B group (HR, 0.43; 95% CI, 0.20-0.91; P=0.0234). In wild-type and unknown population, median PFS was 11.3 months (B+ group) comparing to 6.0 months (non-B group) (HR, 0.53; 95% CI, 0.28-1.02; P=0.0520). The ORR and DCR had consistently similar response in subgroups comparison (Table 1). Safety profile was acceptable in both groups and no new unexpected findings were found.

Table 1. Comparison of clinical effectiveness between Bev-contained and non-Bev group.

	Overall (149)		WT (66)		WT+Unknown(102)	
	B+	non-B	B+	non-B	B+	non-B
	(62)	(87)	(30)	(36)	(43)	(59)
PFS (months)	9.7	7.0	11.3	5.5	11.3	6.0
HR, 95%CI,	0.52, 0.30-0.91,		0.43, 0.20-0.91,		0.53, 0.28-1.02,	
*P**	0.0184		0.0234		0.0520	
ORR (%)	63.33	51.9	55.17	38.24	56.10	46.30
	(38/60)	(40/77)	(16/29)	(13/34)	(23/41)	(25/54)
*P***	0.1818		0.1788		0.3440	
DCR (%)	93.33	85.71	96.55	79.14	92.68	83.33
	(56/60)	(66/77)	(28/29)	(27/34)	(38/41)	(45/54)
*P***	0.1565		0.0598***		0.1743	

Notes: *,Log-Rank test;**, Chi-sq unless specified;***, Fisher test.

Conclusion: Our real world analysis further confirmed that bevacizumab-contained therapy as first line treatment was indeed superior in clinical benefits than non-bevacizumab regimen in Chinese patients with advanced NS-NSCLC in a real world.

Keywords: bevacizumab, advanced lung cancer, first-line therapy

P2.01-031 USE OF GERIATRIC ASSESSMENT (GA) IN CLINICAL PRACTICE FOR STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC). THE GIDO EXPERIENCE

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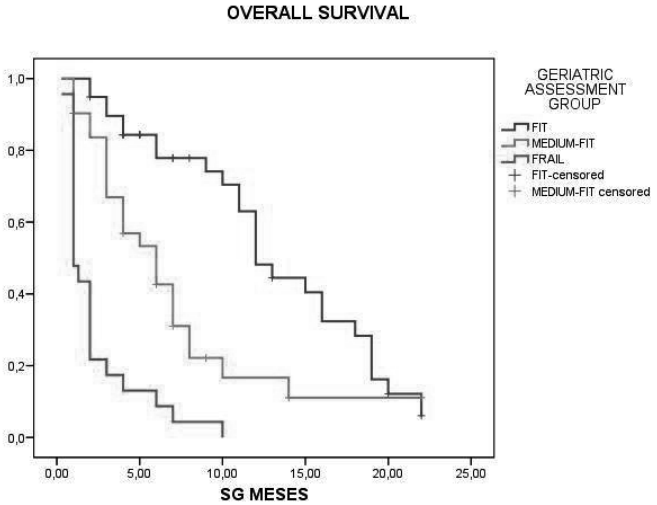
Background: Geriatric assessment is strongly recommended to assess the health status of older cancer patients. It can detect multiple health issues, even in patients with good performance status. However, its integration into clinical practice is very slow. In order to engage Medical oncologist on Oncogeriatrics, we developed a prospective protocol to assess GA in clinical practice. **Method:** Elderly patients (≥70), stage IV NSCLC wild type, underwent GA. Classified according to GA into fit and medium fi (candidates for antitumoral treatment), and unfit (best supportive care). Data from four teaching hospitals in Comunitat Valenciana (Spain) were entered into a prospective database. The institution's ethical review board approved the study. Spanish Medicine Agency classified it as a post-authorization study: GIDO-ONC-2015-01. All patients provided written informed consent. **Result:** From 01/2014 to 01/2017, 93 patients with stage IV NSCLC wild type were identified. Median age: 76 (70-92); 30% older than 80 years old. Gender (M/F): 88%/12%. Histology (SCC/AD/NOS): 52%/38%/10%. PS 0-1: 83%. PS was unrelated to GA (p:0.006). 19 PS 0, 10 (52%) were fit, 7 medium-fit (37%) and 2 were frail (11%). PS 1 (57), 47% (27) were fit, 33% (19) medium-fit and 19% (11) frail. Main reasons for medium-fit were comorbidities and dependence in IADL. Frailty patients were those unable for ADL and geriatric syndromes (depression and dementia). GA group was related to overall survival (13 m vs 7,2 m vs 2,2 m,p:0.000) (figure), treatment decision (p:0.0001) and toxicity (p:0.0001). 100% of fit patients were treated with chemotherapy (90%% platinum-combinations), 48% of medium-fit (42% platinum-combinations) and only 8% of frail patients received chemotherapy, none platinum-combinations (p:0.000). Multivariate analysis is pending



Conclusion: Our results suggest that GA identified patients with a poor natural prognosis. Despite generally good performance status, the prevalence of geriatric impairments was high. More research on GA-stratified treatment decisions is needed.

Keywords: Geriatric assessment, Elderly patients, stage IV non-small cell lung cancer

P2.01-032 A RANDOMIZED PHASE II TRIAL OF SELUMETINIB + PLATINUM-PEMETREXED (PEM-C) IN KRAS WILDTYPE (WT)/ UNKNOWN NSCLC: CCTG IND219

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Background: Selumetinib (SEL), an oral inhibitor of MEK 1 and 2, could be particularly effective in tumours with an activated Ras/Raf/MEK/ERK pathway, but has not been fully studied in KRAS WT nor in the first-line setting. The scheduling of SEL with chemotherapy might impact efficacy and/or toxicity. **Method:** IND219 is an open-label three-arm study of PEM-C±SEL. Arm A: PEM-C+SEL days 2-19; Arm B: PEM-C+SEL days 1-21; Arm C: PEM-C alone. Primary objective was response rate (ORR); secondary objectives were tolerability and progression-free survival (PFS). Pts were stratified by *KRAS* WT versus unknown and cisplatin versus carboplatin. Before the planned interim analysis (60 pts), pts were allocated 1:1:1 to arm A, B or C, with a plan to continue either Arm A or B plus Arm C a 3:1 ratio to ensure that the final analysis includes Arm A or B and Arm C in a 2:1 ratio. The trial would stop if neither Arm A or B had ≥4 responses; if both did, the arm would be selected based on response and toxicity data. Correlative studies included genomic testing. **Result:** Arm A/B/C enrolled 20/21/21 pts. PEM-C exposure was lower with SEL (median cycles 5 versus 6 for Arm C). Seven pts on Arm A (35%; 95% CI 15-59% median duration 3.8m), 13 on Arm B (62%; 95% CI 38-82%; median duration 6.3m), and 5 on Arm C (24%; 95% CI 8-47%; median duration 11.6m) had PR, meeting the criteria to continue. PFS was 7.5m (95% CI 4.0 to 9.0 m) for Arm A, 6.7m (95% CI 4.1 to 8.2 m) on Arm B, and 4.0m on Arm C (95% CI 1.4 to 6.8 m). HR for PFS of Arm A over Arm C was 0.76 (95% CI 0.38 to 1.51, 2-sided p=0.42); HR for PFS of Arm B over Arm C was 0.75 (95% CI 0.37 to 1.54, p=0.43). After adjusting for age, performance status, gender and KRAS, PFS comparisons remained NS. Toxicity was most commonly grade 1-2, but more frequent with SEL especially mucositis, diarrhea, anorexia, dehydration, edema and rash. A high rate of venous thromboembolism (VTE) was seen in all arms, highest in Arm A (Arm A 45 % versus 14 % [p=0.11]) **Conclusion:** SEL+PEM-C is associated with higher, but less durable ORR. In this small study, PFS is numerically prolonged adding SEL to PEM-C with expected additive toxicity. Further exploration of these intriguing results is ongoing.

Keywords: MEK, selumetinib, NSCLC

P2.01-033 LEPTOMENINGEAL METASTASIS FROM NON-SMALL CELL LUNG CANCER: A SINGLE CENTER EXPERIENCE IN CHINESE PATIENTS

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Background: Leptomeningeal carcinomatosis (LM) is a rare type of metastatic tumors of the central nervous system. In recent years, with the improvement of neoplasms therapies and longer survival of patients by better systemic control, incidence of LM has increased every year.The incidence of LM in patients with non-small cell lung cancer (NSCLC) ranges from 1%-5%.However, no standard therapy has been established yet.This study is to investigate the clinical characteristics and prognostic factors of LM from NSCLC and to develop better treatment strategies. **Method:** We collected and reviewed retrospectively the clinical characteristics, treatment methods as well as the outcomes of 45 consecutive patients with LM from NSCLC diagnosed and treated in our hospital from 2002 to 2017.Survival rates were analyzed using the Kaplan-Meier method.The multi-variate Cox proportional hazards model was used to determine the independent prognostic factors associated with improved survival.

Result:

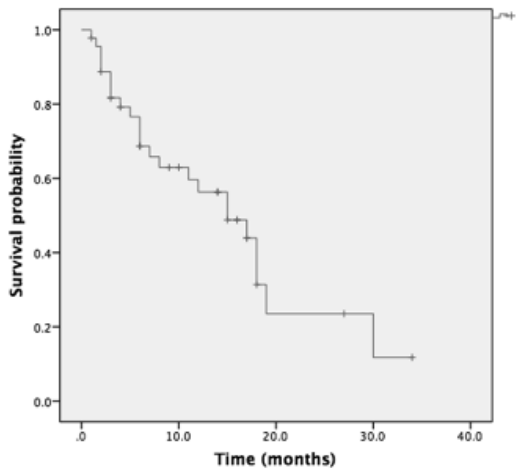

Fig.1 Kaplan–Meier analysis of survival of the 45 LM patients from NSCLC

Among 45 patients who were enrolled, 7(15.6%) had EGFR 19 deletion, 2(4.4%) had EGFR 20 mutation, 22(48.9%) had EGFR 21 mutation, 1(2.2%) had EGFR 18 and also EGFR 20 mutation(T790M negative), 2(4.4%) were ALK-positive, 5(11.1%) were EGFR wild-type, 6(13.3%) patients didn't perform EGFR test. The median overall survival from the diagnosis of LM for all the patients was 15 (range, 1–34)months. Gender, gene mutation and Tyrosine kinase Inhibitors (TKIs) treatment were correlated with survival time for the patients(P<0.05 for all). Other prognostic variables such as age,

initial ECOG, time to leptomeningeal dissemination, CSF cytology, CSF pressure, CSF biochemical, brain radiotherapy, chemotherapy and intrathecal chemotherapy were not statistically correlated to overall survival. In the multivariate analysis, Cox proportional hazard regression showed that TKIs treatment was the independent prognostic factor($P<0.05$). **Conclusion:** TKIs treatment was the independent prognostic factor for leptomeningeal metastases from non-smalll cell lung cancer. We suggest that in LM patients from NSCLC giving TKIs treatment may prolong survival.

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

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-034 PHASE I/II TRIAL OF WEEKLY NAB-PACLITAXEL AS 2ND OR 3RD LINE TREATMENT IN NSCLC WITHOUT DRIVER MUTATIONS. (OLCSG1303)

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Background: Although nab-paclitaxel (PTX) plus carboplatin is one of the standard treatment for chemo-naive advanced non-small cell lung cancer (NSCLC), the efficacy, safety and optimal schedule of nab-PTX monotherapy as 2nd or 3rd line for NSCLC patients without any driver mutations remains unknown. **Method:** This was a single arm phase I/II study. Eligible patients are advanced NSCLC without *EGFR* mutation and *ALK* rearrangement that progressed after platinum-doublet chemotherapy. The patients were received 100mg/m^2 of nab-PTX on day 1, 8, 15 and 22 (level 0) or on day 1, 8, and 15 (level -1) every 4-week in the phase I portion. Dose limiting toxicities (DLT) was assessed and the recommended schedule was determined. The primary endpoint was objective response rate (ORR), assuming that estimated ORR was 15% and threshold ORR was 5% with α error of 0.05 and β error of 0.2 in the phase II part. Total of 55 patients were planned to be enrolled. **Result:** The recommended schedule of nab-PTX was determined as the level -1, because the DLTs were found in 4 of 5 patients. The characteristics of the 55 patients enrolled in the phase II were as followings; median age, 66 years (range, 41–90 years), male/female=40/15, PS 0/1/2=12/39/4, 2nd/3rd line=34/21, adeno/squamous/large/others=34/17/2/2. The median number of treatment cycles was three (range, 1–10). The ORR was 7.3% (95% confidence interval [CI], 2.0–17.6%; 4 PR, 26 SD, 24 PD, 1 NE). At the median follow-up time of 5.3 months (range, 1.9–26.0 months) for all patients, the median PFS was 3.4 months (95% CI, 1.9–4.0 months). Treatment related grade 3 or 4 toxicities were neutropenia (36%), febrile neutropenia (5.5%) and pulmonary infection (3.6%). Three patients (5.5%) had grade 2 pneumonitis and one patient was died due to ARDS. **Conclusion:** This study failed to meet predefined primary endpoint although PFS was comparable and toxicity was acceptable for patients with advanced NSCLC without EGFR or ALK mutation as 2nd or 3rd line treatment. (UMIN registration number: 000012404).

Keywords: nab-paclitaxel NSCLC

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-035 PHASE II STUDY: WEEKLY DOCETAXEL AS FIRST LINE CHEMOTHERAPY FOR ELDERLY PATIENTS WITH SQUAMOUS-CELL NON-SMALL-CELL LUNG CANCER

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Background: Docetaxel monotherapy is one of the standard treatments for non-small-cell lung cancer in elderly patients. Docetaxel is usually administered as a 3-week schedule, yet there is significant toxicity with this therapy. There is increasing interest in Docetaxel weekly schedule to reduce its toxicity. In this phase II clinical study, we investigate the efficacy and safety of a weekly schedule of docetaxel monotherapy in a first-line chemotherapy for advanced squamous-cell non-small-cell lung cancer in elderly patients. **Method:** Patients with stage IIIb, or stage IV squamous-cell non-small-cell lung cancer aged 65 years or older who had not previously received cytotoxic chemotherapy were enrolled. Patients received docetaxel 25 mg/m2 days 1, 8, and 15, every 4 weeks. The primary endpoint of this study was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity profile. **Result:** The patient characteristics are showed in table below. Among 12 eligible patients, the ORR was 0%, (5 patients were confirmed with stable disease, 7 patients were progressive disease. Median OS and PFS were each days and days. There were 3 adverse event of grade 3/4 (2 were dizziness and 1 was diarrhea). Neutropenia was reported on only 1 patients and was grade 1.

Patient Characteristics	
Age (years)	78.16 ± 4.72
Sex (male / female)	18 / 1
Stage	
IIIB (%)	6 (31.58)
IV (%)	13 (68.42)
Performance Status	
0-1 (%)	15 (78.95)
2 (%)	4 (21.05)
Smoking	
Never (%)	1 (5.26)
Former (%)	13 (68.42)
Current (%)	5 (26.32)
Amounts (pack years)	49.05 ± 28.22
FEV1 (mL)	1.53 ± 0.53

Conclusion: Our data failed to demonstrate the efficacy of docetaxel weekly regimen. Because our patients were mostly elderly and of poor general conditions, our result might show poor overall response rate. However, the incidence of side effects include neutropenia was lower than docetaxel 3-week regimen as previous reported. Further larger studies are need to confirm the efficacy and safety of docetaxel weekly regimen.

Keywords: Squamous-cell NSCLC, docetaxel, elderly

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-036 SYMPTOM TRAJECTORIES DURING CHEMOTHERAPY PREDICT OVERALL SURVIVAL IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Patient–reported symptoms have shown prognostic value for patients with advanced non-small-cell lung cancer (NSCLC). The value of persistently high levels of critical symptoms during chemotherapy for predicting survival is seldom addressed. We examined symptom trajectories during first 15 weeks of chemotherapy and their relations to 3-year overall survival (OS) in patients with advanced NSCLC. **Method:** Stage IIIB-IV NSCLC patients scheduled to receive either intravenous chemotherapy or the oral tyrosine kinase inhibitor erlotinib were enrolled in a multicenter longitudinal study. Patients rated 15 symptoms on the MD Anderson Symptom Inventory-Lung (MDASI-LC) before chemotherapy and weekly thereafter for 15 weeks, on 0-10 severity scales. Group-based trajectory analysis was used to categorize patients into groups according to the level and trajectory of symptom severity (either high or low) that patients experienced over time. The 3-year OS was compared between high/low groups via Kaplan-Meier analysis. Hazard ratios (HRs) and 95% confidence intervals (95%CIs) were estimated by Cox regression modeling, with adjustment for demographic and clinical factors. **Result:** We analyzed data from 140 patients (90 died by end of study). High-severity trajectories of three symptoms (fatigue, shortness of breath (SOB), lack of appetite (LOA)) significantly predicted 3-year OS. Patients in the high-fatigue group (n=60) began with moderate fatigue (4.1±3.4) that increased significantly during weeks 1-4 of therapy (5.7±4.5 at week 4; estimated weekly change=0.33, p=0.0004) and remained at this level to week 15. Compared with patients in the low-fatigue group (mean=2.0±1.8, no significant change over time), high-fatigue patients had shorter OS (median=290 vs. 623 days, HR=2.3, 95%CI=1.4-3.8, p=0.001). The high-SOB group (n=62) maintained a moderate level of SOB (4.6±3.5) over 15 weeks and had lower 3-year OS rate than did patients in the low-SOB group (median=256 vs. 566 days; HR=2.7, 95%CI=1.6-4.4, p<0.0001). Compared with patients in the low-LOA group (n=66, mean=0.8±1.8, no change over time), high-LOA patients (n=74, mean=3.2±3.1, no change over time) had shorter OS (median=261 vs. 566 days, p=0.019). The prognostic value of LOA was insignificant after adjusting for other factors. **Conclusion:** Our results suggest that, through longitudinal patient-reported symptom profiling during chemotherapy, persistently high symptom burden can independently predict overall survival in patients with advanced NSCLC. Patients with persistently high symptoms should be targeted for alerts to providers about the need for symptom control during chemotherapy in routine care for advanced NSCLC. Such information could also be used as reference parameters for clinical trial/research design.

Keywords: longitudinal symptom monitoring, Patient-reported outcomes, overall survival

P2.01-037 CLINICAL IMPACT OF INTERSTITIAL LUNG DISEASE ON ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The advanced non-small cell lung cancer (NSCLC) is well known of poor survival. The advanced NSCLC patients with interstitial lung disease (ILD) to be expected poorer survival. The clinical features of patients with advanced NSCLC and interstitial lung disease (ILD) is not fully elucidated, and the role of chemotherapy in advanced NSCLC with ILD remain controversial. The aim of this study was to investigate the prevalence and clinical features of advanced NSCLC patients with ILD, particularly with idiopathic pulmonary fibrosis (IPF). **Method:** We retrospectively analyzed the patients diagnosed with advanced (i.e. stage IIIB and IV) NSCLC at Tosei general hospital, from January 2008 to December 2014. The diagnosis of ILD and IPF were made according to the 2013 and 2011 research statement respectively. **Result:** A total of 899 patients of lung cancer were reviewed, 282 patients were advanced NSCLC. Of these 282 patients, 34 (12%) received the diagnosis of ILD. 22 NSCLC patients (8%) had IPF in 34 ILD. 199/248 of non-ILD NSCLC patients (80%) and 26/34 of ILD NSCLC patients (76%), which includes 17 IPF patients, received chemotherapy. 49/248 (20%) of non-ILD NSCLC and 8 (24%) of ILD NSCLC were treated with best supportive care. There was no significant difference in disease control rate and objective response rate between non-ILD NSCLC and ILD NSCLC patients (72% vs 77%, p=0.696; 33% vs 23%, p=0.271). Overall survival in patients with ILD NSCLC was significantly worse than that in non-ILD NSCLC patients (median survival, 7 months vs 10.1 months; log-rank P=0.013). In patients who received chemotherapy, ILD NSCLC patients had significantly worse survival than non-ILD NSCLC patients (median survival, 7 months vs 10.1 months; log-rank P=0.013). However, there were no significant difference in overall survivals in ILD NSCLC patients between IPF and non-IPF (median survival, IPF-NSCLC vs non-IPF NSCLC: 6.1 months vs 8.2 months; log-rank P=0.375). Among ILD NSCLC patients who received chemotherapy, we found no significant difference in overall survival between IPF NSCLC and non-IPF (median survival, 9.6 months vs 9.7 months; log-rank P=0.275). **Conclusion:** Among advanced NSCLC patients in this cohort, 12% of them had a diagnosis of ILD including 8% with IPF. Survival in advanced NSCLC patients with ILD was worse than that without ILD. We found no significant difference between ILD NSCLC patients with IPF or without IPF in survival.

Keywords: Advanced Non-Small Cell Lung Cancer, interstitial lung disease

P2.01-038 DETERMINANTS OF FRAILTY AND TREATMENT TOXICITY IN NON-SMALL CELL LUNG CANCER PATIENT

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Background: Platinum-based chemotherapy remains a first line treatment for advanced non-small-cell lung cancers (NSCLC). Despite better individualization of treatment, some patients will seek frequent medical attention because of cancer-related complications or treatment toxicity. This can negatively impact patient's quality of life and health care resources. This study aimed to identify biological and clinical factors predictive of frailty and treatment toxicity among NSCLC patients eligible for first-line platinum-based chemotherapy. **Method:** Using our institutional medical charts, we retrospectively extracted data on stage III and IV NSCLC patients diagnosed between December 2011 and November 2015 who had received a first-line platinum based chemotherapy. The primary outcome is defined as any unplanned emergency visit and/or unplanned hospitalization for cancer or treatment related complications. Using multivariate logistic regression model with step by step method, we defined baseline biological and clinical determinants associated with the primary outcome. **Result:**

Table 1. First Multivariate Analysis

Variable	OR	95% CI
Age ≥ 62 Years-old	1.61	0.70 - 3.68
Adenocarcinoma - Squamous Cell Carcinoma - NSCLC other	1 2.43 0.50	0.61- 9.61 1.45 – 1.74
Performance scale ≥ 1	1.35	0.57 – 3.18
Number of metastasis ≥ 2	1.36	0.58 – 3.18
Pleural metastasis	2.04	0.53 – 7.86
Weight loss ≥10% or ≥3 kg	1.00	0.41 – 2.43

Table 1. First Multivariate Analysis

Variable	OR	95% CI
≥ 3 prescription drugs per day	0.98	0.42 – 2.28
Current smoker - Former Smoker - Never smoker	1 0.56 1.10	0.24 – 1.30 0.24 – 5.11
Neutrophils count ≥ 7500/ mm^3	1.57	0.70 – 3.54
Lymphocytes count ≤ 1000/ mm^3	1.04	0.34 – 3.22
Albumin ≤ 35 g/L	2.70	0.93 – 7.69
LDH ≥ 247 U/L	0.93	0.37 – 2.30

We included 227 patients. Mean age was 60 years old, 65% were male, 46% current smokers, 10% PS 2-3 and 74% had adenocarcinoma histology. 20,7% patients had locally advanced disease (Stage III) treated by chemoradiation and 78,4% had metastatic disease treated by exclusive chemotherapy. Median overall survival (OS) was 15 months and PFS 6 months. Overall, 55 % (122/227) met the primary outcome. There were 14 variables (**Table 1**) included in the first multivariate analysis before computer based step by step approach. In the final model (not shown), albumin level <35 g/L (OR 2.24 95% IC 1.14- 4.38, p= 0.02) was an independent predictor of the primary outcome. There was also a trend for squamous cell carcinoma subtype (OR 2.27 95% IC 0.872- 5.914, p= 0.09). **Conclusion:** Low albumin level is a determinant of frailty in patients eligible for platinum-based chemotherapy. Early intervention in these subgroups could benefit patient's quality of life and health care expenses. (*Medicoeconomic analysis will be presented).*

Keywords: frailty, NSCLC

P2.01-039 ERYTHROPOIESIS-STIMULATING AGENTS FOR CHEMOTHERAPY-INDUCED ANAEMIA IN LUNG CANCER: EFFICACY, TOXICITY AND EFFECT ON SURVIVAL

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Background: Erythropoiesis-stimulating agents (ESAs) are widely used for treatment of chemotherapy-induced anaemia (CIA) in patients with various solid tumors, mainly including lung cancer and gynaecological malignancies, but concerns regarding their potential effect on tumor growth and disease progression have been raised. We herein aimed to further investigate the efficacy, toxicity and correlation with overall survival (OS) of treatment with ESAs in a real-world cohort of lung cancer patients. **Method:** The medical records of all patients > 18 years old, with newly-diagnosed advanced-stage lung cancer (non-small cell lung cancer /NSCLC or small cell lung cancer/SCLC) and CIA, treated at the Oncology Unit of Sotiria Athens General Hospital from January 2007 to December 2016 were retrospectively reviewed. The ESAs administered in our cohort were epoetin alfa, epoetin zeta and darbepoetin alfa. Patients were stratified into two subgroups, according to use of ESAs (ESAs-treated vs. those not treated with ESAs). Demographic, laboratory and clinicopathological features, hematological response and toxicity, response to chemotherapy and overall survival (OS) of patients were compared between groups, using univariate and multivariate regression analysis. **Result:** A total of 138 patients (110 males/28 females; mean age ±SD : 66.4± 8.7 years) with baseline (pretreatment) hemoglobin (Hb) values <11 mg/dl and ECOG performance status (PS) 0-2 were included in final analysis. ESAs were administered in 70/138 patients (50.7 %). Age, sex, histological type of tumor (NSCLC vs. SCLC), baseline values of Hb and PS were evenly distributed between groups (p=0.672, p=0.155, p=0.078, p=0.01 and p=0.647, respectively). Hematological response rates and incidence of thromboembolic events were both increased in ESA-treated patients, albeit without reaching statistical significance (p=0.229 and p=0.288, respectively). Neither response to chemotherapy nor OS were found to be significantly correlated with use of ESAs (p=0.498 and p=0.119, respectively). **Conclusion:** According to our study results, administration of ESAs was not significantly correlated with hematological response, response to chemotherapy or OS. Furthermore, treatment of CIA with ESAs was, generally, well-tolerated, with no significantly increased risk of thromboembolic events. A trend for improved partial/complete hematological response and improved OS among ESA-treated patients in our cohort needs to be interpreted with caution. Further randomized trials and larger prospective studies are warranted to investigate the efficacy, toxicity and potential prognostic implications of CID treatment with ESAs in patients with lung cancer.

Keywords: erythropoiesis-stimulating agents, chemotherapy-induced anaemia, lung cancer

P2.01-040 PEMETREXED PLUS PLATINUM CHEMOTHERAPY WITH OR WITHOUT IMMUNOTHERAPY IN NON-SQUAMOUS NSCLC: DESCRIPTIVE SAFETY ANALYSIS

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Background: Pemetrexed/platinum doublet chemotherapy is under investigation in combination with various immunotherapeutic agents (atezolizumab, nivolumab, pembrolizumab) for treatment of advanced non-squamous (NS) NSCLC, with reported durable efficacy and tolerability in early-phase clinical trials. Recently, the combination of pembrolizumab plus pemetrexed/carboplatin received US FDA accelerated approval as front-line treatment for patients with this disease based on the data from a randomized phase II trial, KEYNOTE-021 Cohort G. We present our descriptive analysis of the safety outcomes of pemetrexed (combination) from 3 randomized trials (PRONOUNCE, PARAMOUNT, and KEYNOTE-021 Cohort G). **Method:** Criteria for selection of studies included randomized trials, first-line treatment for NS NSCLC patients with pemetrexed-based combination treatment, with or without immunotherapy, followed by continuation maintenance (at least one arm or cohort). Parameters such as baseline characteristics, dose exposure, and safety outcomes (AE, SAE, death, dose delay or discontinuation, AE management, and hospitalization) are compared. **Result:** Using data from PRONOUNCE (n=182), PARAMOUNT (n=359), and KEYNOTE-021 (Cohort G, n=123) we describe the safety outcomes of pemetrexed/platinum-based combination therapy. Median age of patients from 3 studies was 61- 66 years. The majority of patients in PRONOUNCE and PARAMOUNT were male, whereas female in KEYNOTE-021G; with ECOG PS 1, and adenocarcinoma. The number of patients who completed 4 cycles of induction were 70.8%, 67.8%, 88.1%, and 71.0% in PRONOUNCE, PARAMOUNT, and KEYNOTE 021G Combo arm and Pem+Cb only arm, with median number of treatment cycles of 6, 8, 11, 8, respectively. All pemetrexed combinations with/without immunotherapy had a reasonable and manageable safety profile in our analysis (Table 1).

Table 1: The Safety Outcomes of Pemetrexed/Platinum +/- Pembrolizumab Treatment for NS NSCLC Patients in 3 Clinical Trials

	PRONOUNCE	PARAMOUNT	KEYNOTE-021 G	
	Pem+Cb with Pem M (Pem Arm)	Pem+Cis with Pem M (Pem Arm)[a]	Pemb+ Pem+Cb with Pemb+Pem M[b]	Pem+Cb with Pem M Alone
N	**182**	**359**	**59**	**62**
Patients received Pem Maintenance, n (%)	98 (54)	359 (100)	50 (85)	43 (69)
Subjects with ≥1 AE, n (%)	167 (91.8)	231 (64.3)	59 (100)	61 (98.4)
Drug-related	NA	155 (43.2)	55 (93.2)	56 (90.3)
Grades 3-5 AEs	37 (20.3)	32 (8.9)	32 (54.2)	32 (51.6)
SAE	73 (40.1)	68 (18.9)	24 (40.7)	17 (27.4)
SAE related to drug	NA	32 (8.9)	16 (27.1)	6 (9.7)
Discontinuation due to AE	13 (7.1)	36 (10.0)	7 (11.9)	8 (12.9)
Discontinuation due to drug-related AE	9 (4.9)	19 (5.3)	6 (10.2)	8 (12.9)
Hospitalization due to drug-related AE	59 (32.4)	30 (8.4)	1 (1.7)	1 (1.6)
Total deaths, n (%)	24 (13.2)	7 (1.9)	1 (1.7)	2 (3.2)
Drug-related	1 (0.5)	1 (0.3)	1 (1.7)	2 (3.2)

Abbreviations: AE=adverse event; BSC=best suitable care; Cb=carboplatin; N=total number of patients treated with at least one dose of pemetrexed; NA=not available; Pem=pemetrexed; Pemb=pembrolizumab; Pem M=pemetrexed maintenance; Pemb+Pem M=pembrolizumab with pemetrexed maintenance; SAE=serious adverse event

[a]In this abstract table, the safety data of PARAMOUNT were collected during the period of pemetrexed maintenance therapy only
[b]In Keynote-021 Cohort G combo arm, the pembrolizumab dose was 200mg/kg

Conclusion: This analysis provides a comprehensive safety overview of pemetrexed/platinum with or without immunotherapy in NS NSCLC. Ongoing phase 3 randomized studies of the combination could further inform the safety/efficacy of pemetrexed/platinum plus immunotherapy.

Keywords: safety profile, Immunotherapy, pemetrexed

P2.01-041 PEMETREXED PLUS PLATINUM CHEMOTHERAPY WITH OR WITHOUT IMMUNORESPONSES OF BEVACIZUMAB PLUS CISPLATIN FOR THE NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER PATIENTS WITH MALIGNANT PLEURAL EFFUSIONSTHERAPY IN NON-SQUAMOUS NSCLC: DESCRIPTIVE SAFETY ANALYSIS

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Background: To explore the efficacy and safety of intrapleural bevacizumab plus cisplatin for malignant pleural effusions (MPEs) of non-squamous non-small-cell lung cancer (NSCLC) patients. **Method:** We retrospectively analyzed 14 patients with MPEs who received intrapleural bevacizumab (200mg) plus cisplatin (60mg) from May, 2015 to March, 2017. Treatment response was assessed according to RECIST 1.1 **Result:** The patients included 6 (42.6%) men and 8 (57.1%) women, with a median age of 54 years (ranged, 41-71 years). Five (35.7%) patients had smoking history. Thirteen (92.9%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Driver gene alterations were detected in 4 (28.6%) patients, among them, 3 epidermal growth factor receptor mutations and 1 anaplastic lymphoma kinase arrangement. Four (28.6%) patients received first-line intravenous chemotherapy, and 10 (71.4%) had second or later line chemotherapy. In the management of MPEs, 8 (57.1%) patients achieved partial response (PR), 2 (14.3%) patients showed stable disease (SD) and 4 (28.6%) patients experienced progressive disease (PD). No one was seen complete response (CR). The overall response rate (ORR) and disease control rate (DCR) was 57.1% and 71.4%, respectively. There were 7 (50.0%) cases treated with bevacizumab and cisplatin as initial intrapleural therapy, another 7 (50.0%) patients as subsequent treatment. There were 4 (57.1%) PR for group with bevacizumab plus cisplatin as initial treatment and 4 (57.1%) PR for group with bevacizumab plus cisplatin as subsequent treatment. No significant difference was observed in the two groups (P=1.00). In addition, the adverse events we seen were myelosuppression (7.1%), nausea and emesis (28.5%), mainly in grade 1-2. No thrombosis or bleeding occurred in this study. **Conclusion:** Combined intrapleural therapy with bevacizumab and cisplatin was found to be effective for the non-squamous NSCLC patients with MPEs, and the adverse events were well tolerable.

Keywords: bevacizumab, Cisplatin, malignant pleural effusion

P2.01-042 PERIOPERATIVE CHEMOTHERAPY WITH PEMETREXED AND CISPLATIN FOR PULMONARY LCNEC: A CASE REPORT AND LITERATURE REVIEW

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Background: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is associated with poor prognosis, and its treatment strategy is still controversial, especially chemotherapy regimens. **Method:** Case Report: A 49-year-old Chinese male with primary pulmonary LCNEC treated by neoadjuvant and adjuvant chemotherapy with cisplation plus pemetrexed was presented in this paper. A suspected quasi-circular mass in the left lower pulmonary lobe and an enlarged mediastinal lymph node were found. The patient was diagnosed with adenocarcinoma with neuroendocrine differentiation based on CT guided percutaneous lung biopsy. EGFR gene mutation test showed negative results. Cisplatin and pemetrexed were administered as the neoadjuvant chemotherapy regimen. The primary lesion had remarkably reduced and the enlarged mediastinal lymph node had disappeared after two cycles of neoadjuvant chemotherapy. He was performed left lower lobectomy and mediastinal lymph node dissection. The lesion was confirmed as LCNEC based on postoperative histopathological analysis and immunohistochemical results. **Result:** The patient underwent four cycles of adjuvant chemotherapy with cisplation and pemetrexed for a month postoperatively, followed by postoperative adjuvant radiotherapy. The patient is still alive after a follow-up of 24 months, with no evidence of tumor recurrence. **Conclusion:** Cisplatin combined with pemetrexed is effective and safe for patients with pulmonary LCNEC.

Keywords: pemetrexed, Pulmonary tumor, large cell neuroendocrine carcinoma

P2.01-043 PD-L1 EXPRESSION, EGFR AND KRAS MUTATIONS IN FIRST-LINE THERAPY (1L) FOR NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: The association of PD-L1 expression, *KRAS* and *EGFR* mutations, and survival in NSCLC patients who received 1L therapy was examined. **Method:** 1L metastatic NSCLC patients diagnosed during 2001-2012 who had sufficient archival tumor tissue were selected from the Danish Lung Cancer Group Registry. Medical data from population-based medical registries and paraffin-embedded tumor tissue from pathology archives were retrieved. PD-L1 expression was assessed at two cut-offs (25% and ≥1%) using the Ventana IHC (SP263) assay, *KRAS* and *EGFR* genotyping was performed using PCR-based kits. Follow-up started at commencement of 1L therapy and continued to death, emigration, or 31/12/2014. Cox regression models were used to compute hazard ratios (HRs) and associated 95% confidence intervals (95%CI) for PD-L1, *EGFR*, and *KRAS*. **Result:** Among 491 patients, 280 (57%) were men and 334 (68%) were aged >60 years at diagnosis; 283 (58%) had adenocarcinoma, 152 (31%) had PD-L1 expression ≥25%, 23 (5%) had *EGFR* mutations, and 130 (26%) had *KRAS* mutations. In PD-L1 ≥25% tumors, 4% had *EGFR* and 30% had *KRAS* mutations. In PD-L1 <25% tumors, 16% had *EGFR* and 27% had *KRAS* mutations. Patients with a *KRAS* mutation had an increased risk of death and those with an *EGFR* mutation had a lower risk of death, but neither estimate was statistically significant (Table). Adjusted exploratory analyses indicated that tumor PD-L1 ≥25% was not associated with survival, however immune cell expression for

PD-L1 at the 1% threshold and increasing tumor infiltration with immune cells were both significantly associated with a survival benefit.

	No of deaths during follow-up / N (%)	Median Survival (months) (95%CI)	Adjusted HR* (95%CI)
% Tumor expression§			
PD-L1 < 25%	208/307 (67.8)	23.6 (18.1, 27.5)	ref.
PD-L1 ≥ 25%	101/152 (66.4)	23.3 (16.9, 29.4)	0.96 (0.76, 1.22)
EGFR§			
Wildtype	284/419 (67.8)	23.3 (18.4, 26.0)	ref.
Mutant	13/23 (56.5)	32.8 (18.2, 92.5)	0.75 (0.43, 1.32)
KRAS§			
Wildtype	193/309 (62.5)	24.7 (20.0, 29.1)	ref.
Mutant	95/130 (73.1)	19.4 (15.3, 26.4)	1.28 (0.99, 1.65)
% Immune cell expression§			
PD-L1 < 25%	264/387 (68.2)	21.8 (18.1, 25.1)	ref.
PD-L1 ≥ 25%	45/72 (62.5)	30.2 (17.3, 44.2)	0.86 (0.61, 1.20)
% Immune cells (1% threshold) §			
PD-L1 < 1%	92/122 (75.4)	16.5 (13.3, 20.2)	ref.
PD-L1 ≥ 1%	217/337 (64.4)	26.7 (23.2, 30.2)	0.62 (0.48, 0.80)
% Tumor with Immune Cells ('infiltration'; continuous)	309/459 (67.3)	23.6 (18.5, 26.4)	0.98 (0.97, 0.99)

*Adjusted for age, sex, and histology (adenocarcinoma versus other). § Excluding those with missing PD-L1, KRAS or EGFR status, respectively **Conclusion:** Immune cell expression of PD-L1 and tumor infiltration by immune cells are associated with survival among 1L lung cancer patients. These findings are based on a small cohort and further study is warranted.

Keywords: PD-L1, advanced NSCLC, first line therapy

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-044 THE CORRELATION BETWEEN ONE YEAR SURVIVAL AND THE AFFECTING FACTORS OF LUNG CANCER PATIENTS AT DR. MOEWARDI HOSPITAL SURAKARTA

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Background: Primary lung cancer is still becomes a major public health problem and become the most common cause of death due to cancer in the developing countries. Lung cancer's survival rate still low because the early symptoms of lung cancer mostly the same with other chronic lung disease such as tuberculosis and undetected metastases in most cases.Pleural effusion is the most common symptom of lung cancer in Indonesia. The Life expectancy is shorter in advanced lung cancer with the median of 4-6 month survival rate. **Method:** Objective: To determine the factors associated with 1 year survival of lung cancer patients. This study observed independent variables which assumed associated with a 1 year survival, i.e : age, gender, history smoking, performances status, histological types, managements and the presence of pleural effusion. Research design: This was a cohort retrospective study. The subjects were all lung cancer patients who were admitted in ward at Dr Moewardi hospital from January 1st,2015- December 31,2015. There were 105 participants consists of 85 men and 25 women. Statistical analysis were done using Relative Risk (RR) analysis, Chi-square test, Fisher's exact test and survival analysis. **Result:** The 1-year survival rate is 38.1%, Age {Chi-square test (p): 0.984: RR: 1.009 (95% CI: 0.435-2.340), Log rank test (p): 0.886, Gender {Chi-square test (P): 0.010: RR: 3.300 (95% CI: 1.303-8.359), Log rank test (p): 0.046, Smoking history {Chi-square test (p): 0.030: RR: 2.650 (95% CI: 1.082- (P): 0.301: RR: 3.368 (95% CI: 0.295-38.407, Log rank test (p): 0.080, Pleural Effusion {Chi-square test (p): 0.005: RR: 3.143 (95% CI: 1.386-7.127, Log rank test (p): 0.010, Performance status: Log rank test (p): 0,001,Histologycal types: Log rank test (p):0.039, Treatment: Log rank test (p): 0,000 **Conclusion:** Gender, Pleural effusion, Performance status, Histological types, and Treatment were correlated with a one year survival rate statistically while age and smoking history were not correlated

Keywords: lung cancer, pleural effusion, survival rate

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-045 THE EFFICIENCY OF APATINIB PLUS S-1 AS LATERLINE CHEMOTHERAPY FOR ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: There is no standard treatment strategy for patients with advanced non-small cell lung cancer (NSCLC) who experienced progression with three or more lines of chemotherapy. Apatinib, a new tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2), has been shown confirming antitumor activity and manageable toxicities in breast and gastric cancers. Clinical trials of apatinib on non-small cell lung cancer show that progression-free survival is improved, but the objective response rate is still low. However, It remains to be explored whether the combined treatment of apatinib plus S1 could be further effective on NSCLC. **Method:** We retrospectively assessed the efficacy and safety of apatinib plus S1 in patients with advanced NSCLC after the failure of second or third-line chemotherapy. The study group comprised 15patients who received oral apatinib, at a dose of 250 mg daily, and S1, at a dose of 40-60mg bid D1-14, repeat every 3 weeks, for progression after the failure of second or third-line chemotherapy for advanced NSCLC. Treatment was continued until disease progression. **Result:** Between Mar 30, 2016 and Jun 1, 2017, 15 patients were enrolled. In 15 patients, there were 12 patients available for efficacy and safety evaluation. 4/12 (33%) patients experienced dose reduction during treatment. Followed up to Jun 20, 2017, the median during time of treatment was 3 months. According to RECIST criteria, the disease control rate was 83%, 10/12 (partial response 50%, 6/12 and stable disease 33%, 4/10). The most frequent treatment-related adverse events were secondary hypertension (41.6%, 5/12), oral mucositis (50%, 6/12), hand-foot syndrome (33%, 4/12) and fatigue (33%, 4/12). Main grade 3 or 4 toxicities were hypertension (16.6%, 2/12), oral mucositis (8.3%, 1/12) and fatigue (8.3%, 1/12). **Conclusion:** Apatinib plus S1 exhibits superior activity and acceptable toxicity for the heavily pretreated patients with advanced non-small cell lung cancer.

Keywords: Non-small-cell lung cancer, Apatinib, chemotherapy

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-046 CLINICAL CHARACTERISTICS OF SURVIVAL WITH DE NOVO VERSUS RELAPSED METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Metastatic non-small cell lung cancer (mNSCLC) can present as *de novo* or relapsed disease. This study aimed to determine the clinical prognostic factors impacting post-metastatic survival, specifically comparing outcomes in *de novo* versus relapsed early stage populations. **Method:** Retrospective review of mNSCLC patients diagnosed between January 1999 and December 2013 in the Glans-Look Lung Cancer Database was conducted to identify relapsed early stage and *de novo* cases. Fisher›s exact and Wilcoxon rank-sum tests were used to analyze categorical and continuous factors, respectively. Survival outcomes were analyzed and compared via the Kaplan-Meier and log-rank tests. Cox regressions were used to determine the impact of *de novo* versus relapsed mNSCLC presentation on prognosis, while adjusting for multiple confounders. We excluded stage III patients. **Result:** 3039 *de novo* and 185 relapsed patients were identified. Median post-metastatic survival was significantly longer for relapsed vs *de novo*, 8.90 (CI: 6.24-12.06) versus 3.71 (CI: 3.48-3.98) months, ($p<0.001$). Relapsed patients also demonstrated significant survival gains since 1999-2004. Different patterns of smoking history, histology, systemic anti-cancer therapy (SACT) usage and number of extra-pulmonary sites existed between the relapsed and *de novo* cohorts. Multivariate analysis demonstrated that *de novo* disease, male gender, 'Never' smoking history, 'NOS' histology, and the presence of extra-pulmonary metastases were significant factors in predicting a worse prognosis. SACT receipt and 'Other' histology were associated with better outcomes. In the relapsed subset, squamous cell histology also boded inferior survival. (Table 1)

Table 1: Multivariable analysis of median post-metastatic survival for relapsed and de novo patients.	Relapsed N = 185		de novo N = 3039		All mNSCLC N = 3224	
	HzR [95% CI]	p value	HzR [95% CI]	p value	HzR [95% CI]	p value
Metastatic Presentation						
Relapsed (reference)	-	-	-	-	1.0	-
De novo					1.6 (1.3-1.8)	<0.001*
Year of Metastatic Disease Dx						
1999-2004 (reference)	1.0		1.0		1.0	
2005-2009	0.6 (0.4-0.9)	0.011*	1.0 (0.9-1.1)	0.303	1.0 (0.9-1.1)	0.672
2010+	0.6 (0.4-0.9)	0.009*	1.0 (0.9-1.1)	0.486	1.0 (0.9-1.1)	0.892
DFI						
≤ 12 months (reference)	1.0		-	-	-	-
≥ 13 months	1.0 [07-1.4]	0.982				
Gender						
Female (reference)	1.0		1.0		1.0	
Male	1.1 [0.7-1.5]	0.755	1.2 [1.1-1.3]	<0.001*	1.2 [1.1-1.3]	<0.001*
Smoking History						
Current (reference)	1.0		1.0		1.0	
Former	1.0 [0.7-1.4]	0.923	1.0 [1.0-1.1]	0.299	1.0 [1.0-1.1]	0.275
Never	0.9 [0.5-1.5]	0.595	1.2 [1.0-1.3]	0.005*	1.2 [1.0-1.3]	0.006*
Histology						
Adenocarcinoma (reference)	1.0		1.0		1.0	
NOS	2.0 [1.1-3.6]	0.027*	1.1 [1.0-1.2]	0.004*	1.2 [1.1-1.3]	<0.001*
Other	0.7 [0.6-0.8]	0.262	0.7 [0.6-0.8]	<0.001*	0.7 [0.6-0.8]	<0.001*
Squamous Cell	1.9 [1.3-2.9]	0.001*	1.0 [0.9-1.1]	0.8	1.1 [1.0-1.2]	0.204
Extra-Pulmonary Metastatic Sites						
0 (reference)	1.0		1.0		1.0	
1	1.6 [1.1-2.3]	0.015*	1.3 [1.2-1.4]	<0.001*	1.3 [1.2-1.4]	<0.001*
2+	2.6 [1.1-6.3]	0.038*	2.0 [1.8-2.2]	<0.001*	2.0 [1.9-2.2]	<0.001*
Systemic Treatment for Metastatic Disease						
No (reference)	1.0		1.0		1.0	
Yes	0.6 [0.4-0.8]	0.003*	0.4 [0.3-0.4]	<0.001*	0.4 [0.4-0.4]	<0.001*

CI confidence intervals, HzR hazard ratio, mNSCLC metastatic non-small cell lung cancer, * denotes significant result

Conclusion: Relapsed and *de novo* patients represent significantly different sub-populations within mNSCLC, with survival favoring relapsed patients. This finding may inform discussions around prognosis, reinforce the value of follow-up/surveillance of early stage patients, and provide support for screening initiatives aimed at reducing the burden of *de novo* disease.

Keywords: advanced NSCLC, de novo, relapsed

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-047 A PHASE 1 TRIAL OF DOSE ESCALATED BGB324 IN COMBINATION WITH DOCETAXEL FOR PREVIOUSLY TREATED ADVANCED NSCLC

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Background: AXL is a member of the TAM family of receptor tyrosine kinases that regulate multiple cellular responses including cell survival, proliferation, and migration. AXL expression is associated with a variety of human cancers including NSCLC, and is predictive of poor patient overall survival. AXL is associated with epithelial-to-mesenchymal transition (EMT) and is required to maintain invasiveness and metastasis. Importantly, AXL confers resistance to both chemotherapeutic agents as well as EGFR tyrosine kinase inhibitors. BGB324 is a selective clinical-stage small molecule AXL kinase inhibitor. We found in a colony formation assay with NCI-H1299 cells (AXL$^+$, EGFR wt) that BGB324 displayed anti-proliferative activity as single agent (IC50 348nM). In a 3D organotypic assay, BGB324 prevented 3D-growth, and formation of aggregates and migration. In a mouse xenograft NCI-H1299 model non-responsive to docetaxel, BGB324 treatment significantly enhanced the antitumor activity of docetaxel. This suggested that BGB324 could overcome acquired resistance in *in vivo* models of NSCLC and provided a translational rationale for combining AXL targeted therapy with docetaxel in NSCLC to enhance anti-cancer response **Method:** This is a multi-centre, open-label phase Ib study of BGB324 in combination with docetaxel in advanced NSCLC. The study consists of a dose escalation and expansion phase. BGB324 is administered as monotherapy for 1week after which BGB324 and Docetaxel are co-administered as a continuous treatment with 21day treatment cycles. It is anticipated that a maximum of two BGB324 dose levels will be evaluated, with up to 12 patients enrolled in the dose-escalation phase. BGB324 is administered orally with a loading dose/maintenance dose regimen with the first three doses (200mg or 400mg) in Cycle 1 serving as the 'loading' dose and a maintenance dose of either 100mg or 200mg daily thereafter. Docetaxel 75 mg/m^2 is administered as a one-hour IV infusion every 21 days. The BGB324 dose will be escalated in a standard 3+3 fashion until a MTD or RP2D is reached. DLT will be assessed using the NCI CTCAE version 4.03 during the first cycle of treatment (7-day lead-in plus 21 days of combination therapy). Efficacy endpoints include the response rate, progression-free survival and overall survival. Blood and archival tumor tissue samples are taken to assess the pharmacokinetic profile of BGB324 and docetaxel, and for the investigation of pharmacodynamic effects of BGB324, including tissue epithelial markers, mesenchymal markers, and AXL expression; circulating Gas6 (AXL ligand), and systemic immune response. Enrollment began in December 2016 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Targeted therapy, Axl, therapeutic resistance

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-048 EARLY CHANGES IN BODY COMPOSITION IN METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) ARE PREDICTIVE FOR POOR OVERALL SURVIVAL

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Background: Weight loss adversely affects prognosis in metastatic NSCLC. However, the pattern of changes in muscle mass and adipose tissue during first cycle of chemotherapy and their relation to survival is unclear. Therefore, we analyzed changes in muscle cross-sectional area (CSA), inter- and intramuscular adipose tissue (IMAT), subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) on CT-images after three weeks of chemotherapy in patients with metastatic NSCLC and their influence on overall survival (OS). **Method:** In this post-hoc analysis of a subset of the randomized controlled NVALT12 trial (NCT01171170 [1]), body composition was characterized by CSA and distribution of both muscle and adipose tissue at the third lumbar level on CT-images obtained at baseline and three weeks after start of chemotherapy. Changes in body composition parameters were related to OS with Kaplan Meier and log-rank test. Cox multivariate analysis was performed to assess the relative contribution of muscle and adipose tissue CSA and distribution to OS. **Result:** Data were available of 103 patients. Cox regression analysis showed that loss of muscle CSA and IMAT independently affected survival while change in SAT and VAT did not. 74 patients (72%) exhibited muscle loss (group 1) versus 29 patients (28%) who had stable or gain of muscle CSA (group 2). Groups were comparable regarding age, WHO PS, TNM status, and Charlson comorbidity index. Median OS (95% CI) was 10.0 (7.9-12.2) months in group 1 and 15.3 (11.1-19.5) months in group 2 (p=0.004). Among muscle losing patients two sub-groups were distinguished based on IMAT change. Loss of muscle mass combined with loss of IMAT (group 1a, n=33) also showed significant loss of SAT and lower survival rates compared to loss of muscle mass with preserved IMAT (group 1b, n=40). Median OS (95% CI) was 7.3 (5.0-9.5) months in group 1a compared to 12.9 (9.2-16.6) months (p<0.001) in group 1b. **Conclusion:** Early changes in body composition patterns during the first cycle of chemotherapy in metastatic NSCLC are predictive for OS and might be useful for more personalised supportive intervention during follow-up treatment. **Reference** 1. Dingemans AM, Groen HJ, Herder GJ et al. A randomized phase II study comparing paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches in patients with stage IV nonsquamous nonsmall-cell lung cancer: NVALT12 (NCT01171170) dagger. Ann Oncol 2015; 26: 2286-2293.

Keywords: Metastatic NSCLC, body composition changes, overall survival

P2.01-049 LONG PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL IN ADVANCED NSCLC PATIENTS WITH EGFR MUTATION AND COMPLETE RESPONSE WITH TKI TREATMENT

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Background: Lung cancer is the first cause of death by cancer worldwide. Around 70% of patients are diagnosed in advances stages. The EGFR mutations (EGFRmut) are present in 15-20% of cases of lung adenocarcinoma. Most frequent mutations are exon 19 deletions and L858R (90%); in those patients, the TKI treatment have higher response rates (RR) and longer progression free survival (PFS) compared versus chemotherapy. However, the long time OS is low and the complete responses (CR) are achieved in 1-3% only. Nevertheless, contributing factors to long term survival are still unclear. Our objective was to describe long PFS and OS associated factors in patients with TKI treatment. **Method:** We analyzed patients with EGFRmut NSCLC, who received TKI between 2011 and 2017 in the Thoracic Tumors Clinic at Instituto Nacional de Cancerologia, Mexico. EGFR mutational test was performed by RT-PCR (SCORPION/ARMS therascreen). We search factors associated with CR and Major responses (MR; defined as tumor size reduction > 80%) and correlated with PFS and OS. **Result:** One-hundred sixty patients were analyzed. Median age was 62y (SD ±12.8), female 66%, never smoking 82%, adenocarcinoma 98%, exon 19 deletions 60.6% and L858R 34.4%, uncommon mutations 5%. The RR were 56.3%; 12/160 (7.5%) patients had CR (Group1), 16/160 (10%) patients had MR and received local control with Radiotherapy (Group2) and 132/160 (82.5%) had non-CR without radiotherapy (Group3). In the total population PFS and OS was 15months (CI95% 8.2-21.9mo) and 27.9mo (21.8-32.2mo) respectively; in group3 PFS/OS was 8.77 (CI95% 7.66-9.88mo)/24.7mo (CI95% 20.8-28.8mo); in Group1 PFS/OS was 38.7mo (CI 95% 35.7-41.6)/47.8mo (CI95% 40.1-55.5mo) and Group2 PFS/OS 28.1mo (0.43-56.4mo)/OS 36.1mo (CI95% 11.6-60.7mo). We found significant differences in PFS and OS compared group1 vs Group3 (p=0.003 and p=0.0001, respectively) and Group2 vs group3 (p=0.009 and 0.007, respectively). Was not significant differences in PFS/OS between Group1 vs Group2 (p=0.09/0.9, respectively). All patients with CR are alive, except one patient who died due to pneumoniae. In the multivariate analysis were not found association with CR and TKI or mutation subtype (Exon 19 vs L858R). **Conclusion:** Patients treated with TKI who reach CR or MR followed by local control with radiotherapy have longer PFS and OS. These findings support the importance to optimize TKI treatment, in order to achieve CR as well as the importance of local control in residual lesions to improve survival outcomes.

Keywords: TKI response, advanced NSCLC, EGFR mutation

P2.01-050 PREDICTING RISK OF HOSPITALIZATION IN PATIENTS WITH NSCLC RECEIVING CHEMOTHERAPY USING THE LCSS 3-ITEM GLOBAL INDEX (3-IGI)

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Background: A leading factor of poor treatment outcomes and cost in cancer care is hospitalization. If hospitalization risk can be accurately predicted, preventive interventions can be effectively used and treatment regimen selection may be able to be refined. Currently, oncologists do not routinely use laboratory, molecular, PRO or imaging data to predict risk of hospitalization or its prevention. Prior research demonstrated that the 3-IGI (quality of life, activities, distress) of the LCSS at baseline, predicts survival more accurately than performance status and requires only two minutes for administration. **Method:** The objective was to determine if the 3-IGI measured at baseline accurately predicts cancer-related or treatment toxicity-related hospitalization risk. PROs were prospectively evaluated in 164 patients receiving chemotherapy for advanced NSCLC using the LCSS 3-IGI, with electronic assistance ("eLCSS-QL"). Patients were followed for hospitalization over three months. Hospitalizations were characterized as cancer-related, or treatment toxicity-related. **Result:** Characteristics: 57% men; 92% Stage IV; 73% first-line therapy; mean age 63; ECOG 1/2: 56%/42%. 77 hospitalizations occurred among 53 (33%) patients. Patients were placed into 3-IGI groups based on scores at baseline by thirds (tertiles; mean 3-IGI = 188 with 0=worst, 300=best; 33rd percentile <162, and 67th percentile > 239). Baseline 3-IGI significantly predicted risk of cancer-related hospitalizations (p<0.0001), but not treatment toxicity-related hospitalizations (27%, p=0.69). The table outlines marked differences in hospitalizations associated with baseline 3-IGI groups.

PERCENT OF HOSPITALIZATIONS BY 3-IGI GROUP AT BASELINE (p = 0.0001)

TIME FROM BASELINE:	LEAST-RISK GROUP	MEDIUM-RISK GROUP	HIGHEST-RISK GROUP
30-DAYS	0%	18%	23%
60-DAYS	10%	20%	39%
90-DAYS	12%	27% (HR 2.7)	41% (HR 4.6)

Additionally, in only those in the ECOG=1 group, the 3-IGI significantly identified cancer-related hospitalization risk (p=0.025). **Conclusion:** The 3-IGI of the LCSS significantly identifies risk of hospitalization in patients receiving chemotherapy for NSCLC, and is more accurate than ECOG PS. Interventions (including enhanced monitoring) focused on identifiable high risk groups is warranted to reduce hospitalization. These results may also help in appropriate regimen choice to reduce hospitalization. Such interventions could improve cancer care and reduce costs. Support: NIH/NCI R01 CA-157409

Keywords: LCSS, 3-IGI, Hospitalization

P2.01-051 RANDOMIZED STUDY OF PEMETREXED VERSUS ERLOTINIB AS MAINTENANCE THERAPY IN METASTATIC /LOCALLY ADVANCED EGFR MUTATION NEGATIVE NSCLC

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Background: Maintenance treatment of locally advanced or metastatic non small cell lung cancer (NSCLC) other than predominantly Squamous cell histology in patients whose disease has not progressed following 4 to 6 cycles of platinum based doublet therapy has been standard of care . Pemetrexed and Erlotinib both have been used as either continuous maintenance or switch maintenance therapy. **Method:** All patients of NSCLC other than the Squamous cell carcinoma , who have completed either 4 or 6 cycles of platinum and pemetrexed and have either CR /PR/SD on response assessment scan post induction treatment and willing to participate in study ,were randomized to receive either pemetrexed or erlotinib . Quality of life (QoL) questioners were collected every 8 weeks till disease progression or unacceptable toxicities. Patients were followed up till death. PFS and OS were calculated for each arm and indirectly compared. **Result:** Two hundred patients were randomized to receive either pemetrexed or erlotinib) from November 2014 to March 2017. Median age of cohort was 55 (28-79).One hundred and thirty two patients were male and 68 were female. PS was 0-1 in 195 patients. Sixty three percent were smokers (126/200). Majority of patients (62.5 %) has stable disease post completion of induction chemotherapy (125 /200).Median number of cycle of maintenance pemetrexed was 4 (4-6). Median PFS in pemetrexed arm was 4.46 month (95 % confidence interval (CI); 3.98 to 4.95) while in erlotinib arm median PFS was 4.5 month (95 % CI ; 3.98 to 4.95),(hazard ratio , 0.98 ; 95% CI , 0.714 to 1.369 , p value 0.945).Median OS from starting induction chemotherapy in pemetrexed arm was 16.56 months (95 % CI ; 14.83 to 18.29) while in erlotinib arm median OS was 18.33 months (95% CI ; 13.74 to 22.92),(hazard ratio , 1.23 ; (95 % CI ; 0.829 to 1.831 , p value 0.0302) **Conclusion:** Maintenance treatment with pemetrexed and erlotinib has similar PFS and OS in indirect comparison. QoL analysis in both arms is ongoing.

P2.01-052 DOES RADIOMICS IMPROVES THE SURVIVAL PREDICTION IN NON SMALL CELL LUNG CANCER?

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Background: Non small cell lung cancer (NSCLC) accounts for 85% of all the lung cancer worldwide. An accurate survival time prediction is important so that subject can plan his activities and also it aids physician in arriving at the best treatment plan. There have been multiple studies that are conducted to build the survival analysis model for lung cancer. The factors that are considered in most of the models includes age, gender, tumor size, weightloss, smoking history and TNM staging to arrive at the survival prediction. However, the current focus is to make the prediction of the survival analysis more personalized and accurate. With the advent of radiomics, which deals with extraction of quantifiable features from the CT images promises to aid in personalized medicine. The objective of this work is to validate the use of radiomic features and arrive at a radiomic signature, which has better prediction power. Also, to analyze the role of radiomic features in improving the accuracy of survival prediction in NSCLC. **Method:** The dataset consist of 237 subjects CT images with NSCLC with the follow up data of 5 years with different histologies (Adenocarcinoma-39;Large cell-102 and Squamous cell carcinoma-96). The data also contained, the clinical information such as age, gender, TNM staging and the survival status.

Furthermore, 432 radiomic features were extracted from the gross tumor volume of the CT images for all the corresponding subjects. Assessment was performed using cox regression model between different groups of features (clinical information, radiomic features and combination of clinical information and radiomics features) to arrive at the survival prediction model. Also, unique radiomic signature was identified with 16 features that has maximum influence on the survival model. **Result:** The results showed that the concordance Harrell's concordance index (c-index) for only clinical information was observed to be 0.56, with only radiomics features being 0.64 and with combination of radiomics features along with clinical information was observed to be 0.69. **Conclusion:** In this study we observed that the radiomic features along with clinical information aids in providing better survival prediction model for NSCLC. Also, a unique radiomic signature was obtained which is used as an input to the survival prediction model for improving the accuracy. The study also highlights the role of imaging features driving towards personalized treatment in NSCLC.

Keywords: NSCLC, Survival Analysis, Cox model

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-053 OUTCOME OF CLINICAL MANAGEMENT OF ELDERLY AND YOUNGER PATIENTS WITH NSCLC INSIDE A PRIVATE INSTITUTION (ONCOSALUD-AUNA)

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Background: Most non-small cell lung cancer patients (NSCLC) patients are older than 70 years and therefore their management is challenging as it may be complicated by an increased number of comorbidities and greater risk of treatment-related complications. For these reasons, elderly patients tend to be undertreated. Our objective was to evaluate the efficacy of treatment in this population in comparison with younger patients. **Method:** Retrospective study of patients with unresectable stage IIIB and stage IV NSCLC diagnosed between 2011 and 2014 at Oncosalud AUNA, a private specialized cancer center, which were treated with chemotherapy. Data was collected from clinical files. Type of treatment among young and elders (>70) was compared, as well as benefit from treatment, in terms of objective response rate (ORR), progression free survival (PFS) and 1-year overall survival (OS). **Result:** 83 patients were included (70.8% young, 29.2% elder). There were no significant differences in gender, among the 2 groups (male 56.1 vs 57.7% p= 1.00), histology (86% vs 82%, p=0.972), ECOG 2-3 (19% vs 30.8% p=0.383), metastatic disease (70.2% vs 69.2% p=0.16), brain metastases (15.8 vs 3.8%, p=0.16), for younger and elder, respectively. The both groups received same combinations treatment, the monotherapy in both groups was 7% vs 11.5% (p= 0.672). Carboplatin and pemetrexed was the most frequent chemotherapy regimen (56% vs 57% p=1.00) respectively. The cisplatin based regimens was (15.8% vs 7.7% p=0.489). The benefits of treatment were similar, regardless of age, ORR was 52.6% vs 46%(p 0.65). At 21 months of follow up, PFS was 5.5 vs 4.9 months (p=0.52), respectively. The 1-year OS was 19.2% and 5% respectively (p=0.199). **Conclusion:** In our clinical practice, the elderly tend to be treated the same. Treatment efficacy is similar among both groups. If medically fit, patients should be treated the same, regardless of age.

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-054 INCLUSION OF CENTRAL NERVOUS SYSTEM METASTASIS IN LUNG CANCER EARLY PHASE CLINICAL TRIALS

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Background: Central nervous system (CNS) metastases are commonly seen in lung cancer patients; up to 40% will have CNS involvement during the course of the disease. However, clinical trials often exclude this patient population due to the increased morbidity/mortality associated with CNS metastases, subsequent reduction of overall survival and poor CNS pharmacokinetics or uncertainty about CNS pharmacokinetics in humans. Therefore, we studied the effects of CNS metastases on the enrollment of lung cancer patients in early phase clinical trials. **Method:** Trials were extracted from ClinicalTrials.gov on April 1st, 2017. Completed and active trials from 2000-2016 were included in the analysis. Exclusion of CNS metastasis was treated as a binary variable and grouped as strict exclusion vs. allowed. Logistic regressions were used for statistical analysis. **Result:** 598 trials were reviewed, 308 (52%) were phase 2, 164 (27%) were phase 1, and 126 (21%) were combined phase 1/2 trials. 304 (51%) trials were conducted in the U.S., 82 (14%) in Asia, 74 (12%) in Europe and 138 (23%) internationally. Most trials were funded by industry (59%), followed by investigator initiated/institutional (23%) and NIH funded (18%). Patients with CNS metastasis were strictly excluded in 130 (22%) trials, allowed if controlled/asymptomatic in 156 (26%) and allowed with no prior treatment in 42 (7%) trials. Patient requiring steroids for their CNS metastasis were excluded in 156 (26%) trials. CNS criteria were not referenced in 114 (19%) trials and these were excluded from further analysis. Of the 194 trials that included survival as one of their end points, 121 (62%) excluded patients with CNS disease. On univariate analysis, the odds of CNS metastasis exclusion were significantly higher in immunotherapy trials (OR: 1.26, 95%CI: 1.07-1.50, p<0.006) and significantly lower in NIH funded trials (OR: 0.35 95% CI: 0.17-0.73, p<0.005). In multivariate analysis, U.S. based trials had higher odds of exclusion of CNS disease (OR: 1.18, 95%CI: 1.06-1.31, p<0.001) compared to European, Asian and International trials. 58 phase 1 trials were followed by phase 2 trials, when comparing exclusion criteria, no changes were made regarding CNS metastasis. **Conclusion:** Many patients with lung cancer and brain metastases are excluded from participation in early phase clinical trials. Broader inclusion of patients with CNS metastasis, or separate clinical trials for those with CNS disease would help determine the efficacy of novel agents for those with CNS metastasis and provide clinical trial options for this patient population.

Keywords: CNS Metastasis, advanced NSCLC, clinical trials

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-055 EXAMINING METABOLOMICS AS A PROGNOSTIC MARKER IN METASTATIC NON–SMALL CELL LUNG CANCER PATIENTS UNDERGOING FIRST-LINE CHEMOTHERAPY

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Background: The metabolome represents the endpoint of many cellular events; hence patients' baseline metabolomic profile may reveal specific prognostic markers of overall survival. In this study, we sought to characterize the serum metabolite signatures in patients with metastatic non-small cell lung cancer (mNSCLC) who underwent first-line therapy, using nuclear magnetic resonance (1H-NMR) spectroscopy and liquid chromatography mass spectrometry (LC-MS), and to explore their potential prognostic impact. **Method:** Serum samples were collected prospectively as part of a clinical trial in which patients were treated with systemic therapy including platinum-doublet chemotherapy. For each method of analysis, samples were divided into training (3/5) and validation (2/5) sets stratified by treatment received, stage (III vs. IV), and ECOG PS (0, 1, vs. ≥ 2). Exploratory analyses were performed to characterize the relationships between baseline lipid and polar levels and overall survival. Kaplan-Meier curves were used to estimate the distributions of time to event outcomes, and a Cox regression model was used to correlate marker levels while adjusting for baseline characteristics. **Result:** Using 1H-NMR, 16 out of 43 metabolites were significantly correlated with overall survival (OS) by univariate analysis (p < 0.025) and 4 metabolites were included in the final multivariate model. The median OS was 11.4 months in the low risk group vs. 6.6 months in the high risk group (HR=1.99, 95% C.I. 1.45 – 2.68; p<0.0001). Using LC-MS, 53 lipid species were correlated with OS by univariate analysis. Variables were then subjected to hierarchical cluster analysis resulting in 12 branches which were moderately to significantly correlated with lipid features. Principle component analysis (PCA) was performed and the first PC from each such branch was used (n=9). Using Cox regression modeling, median OS was 5.7 months vs. 11. 9 months for the low and high risk groups respectively, even after adjusting for baseline characteristics (HR: 2.23, 95% C.I. 1.55 – 3.20; p< 0.0001). **Conclusion:** Metabolite profiles from baseline pre-treatment serum samples have the potential to act as prognostic markers in patients with mNSCLC undergoing first-line chemotherapy. Serial metabolite measurements pre- and post-treatment may yield additional information and provide enhanced data for predicting clinical outcomes.

Keywords: metabolomics, non-small cell lung cancer, prognostic marker

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-056 USE OF CELL-FREE CIRCULATING RNA (CFRNA) EXPRESSION OF PD-L1 AND ERCC1 IN PLASMA TO MONITOR RESPONSE TO THERAPY IN NSCLC

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Background: There is an unmet need to evaluate tumor response by other means than radiology tests. Cell-free circulating tumor RNA (cfRNA) can be extracted from plasma of cancer patients (pts); measuring dynamic changes in gene expression and levels of b-actin; cfRNA (per ml of plasma) as a proxy for total cfRNA in metastatic patients has shown great potential for evaluating disease status and predicting outcome to anti-tumoral therapy in advance of imaging. We have previously shown that high levels of PD-L1 cfRNA expression correlates well with positive response to immunotherapies including nivolumab in pts with NSCLC. **Method:** Blood was drawn from pts at approximately 6-week intervals under various therapies, with CT scans at 3-month intervals. Total cfRNA was extracted from patient plasma and reverse transcribed to cDNA. Levels of b-actin, ERCC1 and PD-L1 were quantitated across multiple blood draws by RT-qPCR and correlated with pt response (PR/SD/PD), as determined by CT scans. **Result:** A total of 24 NSCLC patients were enrolled in a 1-year clinical study. Non-SCC comprised 87% (21/24). 19 pts completed the first two

cycles of therapy. 1 pt with PR had decreasing levels of cfRNA, 10 pts achieved SD with decreasing or no change while 6/8 pts with PD had increasing levels of cfRNA. CfRNA levels were predictive of disease status about 4 weeks in advance of imaging in 6/19 pts and matched with disease status in 8/19 pts (74%). Dynamic changes in PD-L1 expression correlated with response to nivolumab in 3/4 pts. In 2/4 pts with SD, PD-L1 remained undetected after therapy, whereas 1 patient continued to have PD despite loss of PD-L1. PD-L1 was undetectable in a pt initially with PD on nivolumab who achieved SD after one cycle of nivolumab plus radiation. Changing ERCC1 expression correlated with platinum-based therapy outcome in 8/8 patients. 4/4 patients with PD on pemetrexed/carboplatin had an increase in ERCC1. 4/4 patients with lower or decreasing levels of ERCC1 achieved PR or SD. In the only patient achieving PR, ERCC1 became undetectable during treatment. **Conclusion:** We found significant concordance between clinical response and changes in plasma cfRNA levels in NSCLC pts (74%). Levels of PD-L1 expression correlated with response in 3/4 pts treated with nivolumab . ERCC1 levels were predictive of outcome to platinum based therapy for 8/8 patients. ERCC1 and PD-L1 expression in cfRNA can be used to monitor response to platinum-based and immuno-therapy.

Keywords: liquid biopsies, cfDNA, PDL-1

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-057 ACTIVITY OF PEMETREXED ON WILD-TYPE AND UNKNOWN STATUS EGFR GENES WITH BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER

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Background: Brain metastases (BM) are a common cause of morbidity and mortality in patients with non-small-cell lung cancer (NSCLC). For patients with wild-type EGFR genes, therapeutic options for BM are even limited. Besides local therapy, pemetrexed is the preferred chemotherapy in NSCLC, but the efficacy of this treatment is uncertain. This study evaluated the efficacy of wild-type and unknown status EGFR patients with BM receiving pemetrexed based chemotherapy and analyze the prognostic factors. **Method:** We retrospectively studied 138 EGFR wild-type and unknown EGFR status patients with BM, who had received first line pemetrexed based chemotherapy between 2010 and 2015 at Zhejiang Cancer Hospital. Unknown EGFR status patients were treated with EGFR TKIs after progression. Patient follow-up by telephone was done until January 2016. Treatment response was evaluated and survival data were collected and analyzed. **Result:** Among the 138 patients, 49(35.5%) were EGFR wild type and 89(64.5%) were unknown EGFR status. And 80(58.0%) received whole-brain radiotherapy (WBRT), 19(13.8%) received stereotactic radiosurgery (SRS)/surgery, 10(7.2%) were treated with WBRT plus SRS/surgery, 29(21.0%) didn't receive any local therapy. The median overall survival (OS) from diagnosis of BM was 21.0 months for the whole cohort (95% CI, 17.2-24.8 months), the intracranial progression-free survival (iPFS) was 9.5 months (95% CI, 6.6-12.4 months) and extracranial PFS was 8.3 months (95% CI, 6.9-9.7 months). Patients with unknown EGFR status had a longer iPFS and OS than EGFR wild-type (11.7 vs. 7.6 months, P=0.23; 24.0 vs. 17.7 months, P=0.24). The combination of pemetrexed and platinum showed better iPFS than single agent of pemetrexed in patients, although it did not reach statistical significance (10.7 vs. 7.2 months, P=0.27). Patients with more than 6 cycles of chemotherapy tend to have longer iPFS and OS than those who received less than 6 cycles or 4 cycles (12.6 vs. 10.3 vs. 8.3 months, P=0.52; 47.9 vs. 27.9 vs. 19.2 months, P=0.18). **Conclusion:** Pemetrexed shows good tolerability and efficiency in EGFR wild-type and unknown EGFR status patients with brain metastases from advanced NSCLC, and have a good control of activity on brain localizations.

Keywords: brain metastases, pemetrexed, Non-small-cell lung cancer

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-058 PHARMACOKINETIC PARAMETER VARIABILITY OF DOCETAXEL BETWEEN INDIVIDUALS AND ITS RELATIONSHIP WITH HEMATOLOGICAL TOXICITY

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Background: Docetaxel is the commonly used chemotherapy drugs of various types of tumors. However, the major adverse effect of which is the dose-limiting hematologic toxicity. In clinical practice, 3/4 grade neutropenia and febrile (FN) is the severe side effects threatening the patient life. This research aims to analyze the variability of docetaxel's medicine area under the curve (AUC) between individuals and its relationship with hematological toxicity in advanced NSCLC, which sets up the mathematical model to predict its hematological toxicity by docetaxel AUC to lay the theoretical foundation for individual adjustment in future. **Method:** Select 32 patients with advanced NSCLC in Shandong Cancer Hospital that receiving docetaxel chemotherapy treatment from 2014-10 to 2015-12. Adopt Mycare® reagent kit to determine the blood concentration, and calculate the docetaxel AUC over model software of non-mixed effects. After standardized treatment, analyze the AUC variability between individuals, relationship of AUC with decreased amount of neutrophils before or after the chemotherapy, and the relationship of AUC with 3/4 grade neutropenia. And make the fitting with different methods to set up the mathematical model in relationship with decreased percentage of neutrophils after AUC prediction chemotherapy and incidence rate of 3/4 grade neutropenia **Result:** 1. The AUC of 32 patients in the first cycle after standardized treatment that use docetaxel is between 1.8ug.h/ml-4.7ug.h/ml in average of 3.32±0.12ug.h/ml. The difference between the maximum value and minimum one is 2.6 times. 2. AUC value has the tendency that increases as cycle number increases. However, the number of chemotherapy cycle has no statistical significance of AUC influence (F=0.186, P=0.824). 3. The model predicting the decreased percentage of neutrophils with docetaxel AUC is : $y1 = 1.4812x^2 + 3.0217x + 29.061$ (cycle 1), $y2 = 4.3981x^2 + 14.006x + 50.532$ (cycle 2), $y3 = 2.0683x^2 + 2.1257x + 19.604$(cycle 3), $y4 = 4.683x^2 - 19.273 + 61.398$ (cycle 4); The model predicting the incidence rate of 3/4 grade neutrophils is $y=19.383\ln(x)+2.4005$. (x=AUC). **Conclusion:** This research sets up the mathematical model to predict the decreased percentage of neutrophils and incidence rate of 3/4 grade neutropenia by docetaxel AUC, which provides basis for screening high-risk patients who may suffer seriously hematological toxicity and lay the theoretical foundation for individualized adjustment based on doxetaxel AUC. In addition, as the first cycle of doxetaxel AUC has important reference value, it suggests that all patients receiving docetaxel chemotherapy at the first time must receive AUC test.

Keywords: NSCLC, area under the curve, hematologic toxicity

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-059 BREAST METASTASIS FROM PULMONARY CANCER: A CASE REPORT. UNIVERSITY HOSPITAL "SHEFQET NDROQI" TIRANA ALBANIA 2008

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Background: Breast metastasis from the lung malignancy is very rare. An incidence of 0.1% to 1.6 %. The most commonly of primary malignant disease that metastasize to the breast are lymphoid tissue malignancy, malignant hemopoetic disease, and malignant melanoma. **Method:** In our experience we have had only one case with breast cancer metastazis from primary lung cancer. A 56-year-old female ex smoker, manifested a right breast mass and limphonods in the right axillar region.She was treated for primary lung cancer stage IIB befor 4 months.Although she was treated for right spontaneous pneumothorax six years ago through right posterolateral thoracotomy ,wedge bulectomy superior dexter ,fruotazh and pleural drainage.After 3 years she was treated and for metastasectomy left lung and lateral chest wall resection coste 6/7. **Result:** The patient underwent right local mastectomy and right axillary dissection. After histological and immunohistochemical analyses showed that breast mass was metastasis from a primary lung carcinoma **Conclusion:** A accuracy treatment and prognosis of the breast metastasis from primary lung cancer is differentiation from the primary brest cancer and is very important to do this diferentation.

Keywords: primary lung cancer, breast metastases, mastectomy,

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-060 OUTCOMES FOLLOWING GAMMA KNIFE RADIOSURGERY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER WITH BRAIN METASTASES

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Background: Gamma knife (GK) radiosurgery is a common treatment for brain metastases from non-small cell lung cancer (NSCLC). This study reports outcome results for patients with synchronous brain metastases and delayed brain metastases from NSCLC at Leeds Cancer Centre (LCC). **Method:** Data was obtained by retrospective case note review for 72 patients, who were all treated with GK from 2009 until 2014. Radical thoracic therapy (surgery, chemoradiotherapy or stereotactic ablative radiotherapy) was also undertaken for 58 patients. Statistical analysis using Kaplan-Meier curves was performed to estimate time to intracranial progression, survival from diagnosis of brain metastases, and overall survival. **Result:** Demographic data identified a median age of 65 years (range 43 – 83 years). For patients with delayed brain metastases (47 patients), TNM stage at diagnosis was stage I (7 patients), stage II (11 patients), stage IIIA (12 patients) or stage IIIB/IV (17 patients). Histology was majority adenocarcinoma (50%) or squamous cell carcinoma (22%). The median time to intracranial progression for all patients treated with GK was 9 months. In patients treated with radical thoracic therapy, of which 88% completed treatment, the median survival from diagnosis of brain metastases was 15 months for those with synchronous brain metastases (18 patients), and 14 months for those with delayed brain metastases (40 patients). In those with synchronous brain metastases, 83% received GK prior to radical thoracic therapy (median survival 18 months vs. 14

months for delayed GK). In those with intracranial progression following GK prior to death, 25% were treated with salvage GK with a median survival of 23 months. This compares to 18 months for those treated with salvage whole brain radiotherapy and 8 months for those not suitable for salvage treatment. The overall median survival for patients treated with combination radical thoracic therapy and GK at LCC was 21 months (median survival in synchronous brain metastases at diagnosis = 16 months vs. median survival in delayed brain metastases = 27 months). **Conclusion:** In conclusion, GK radiosurgery is an effective treatment for brain metastases in NSCLC. Beneficial effects are seen in patients with synchronous and delayed brain metastases, demonstrating its role in a wide subset of patients with advanced NSCLC. Use of GK, in combination with radical thoracic therapy, therefore has the potential to dramatically improve survival in patients who may not have previously been suitable for radical treatment.

Keywords: Gamma Knife, Brain mets, NSCLC

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-061 MODE OF LUNG AND AIRWAY METASTASIS OF NSCLC: REVIEW OF CHEST CT FINDINGS

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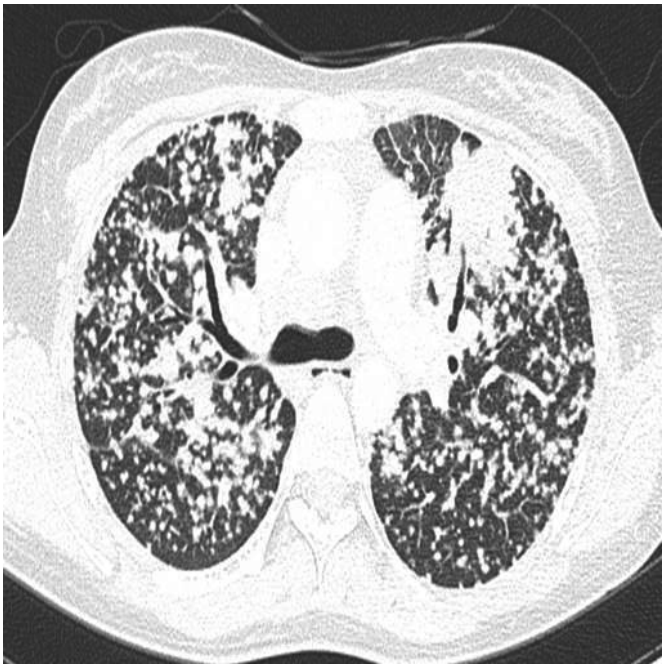
Background: NSCLC metastasize to lung parenchyma and airway, and occasionally they show characteristic CT findings according to the histological types and mutations. We will illustrate computed tomographic (CT) features of variable metastasis of lung parenchyma and air way of thorax depending on histologic types and mutations of NSCLC by the pattern approach. We are going to discuss about the early detection and the clues to radiologic diagnosis. **Method:** We used conventional chest CT protocol with ehnacement. *Contents:* 1) Hematogeneous metastasis -Scattered nodular metastasis (eg. the most common type) -Military metastasis (eg. EGFR mutant ADC) -Cavitary nodular metastasis (eg. ADC or squamous cell caricinoma) 2) Lymphangitic metastasis (eg. ALK mutant ADC) 3) Aerogenous metastasis (eg. mucinous ADC with airspace consolidation type) 4) Endobronchial metastasis (eg. squamous cell carcinoma) 5) Pulmonary thrombotic microangiopathy (eg. ADC)

Result:



miliary metastasis

Aerogenous metastasis

Conclusion: Knowing the CT findings according to the types of NSCLC and mutation will be helpful in differential diagnosis of metastasis in 'era of multicentric lung cancers or various secondary lung metastases in other primary sites'.

Keywords: metastasis, non small cell lung cancer, computed tomography

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-062 PRIMARY LUNG ADENOCARCINOMA IN THE YOUNG WITH MULTIPLE METASTASES: AN AUTOPSY REPORT OF 2 CASES

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide with tobacco use and increasing age as the strongest risk factors. We report 2 uncommon cases of primary pulmonary adenocarcinoma with multiple metastases in young non-smoker, immunocompetent males diagnosed post-mortem. **Method:** Tissue sections taken during autopsy were fixed in 10% neutral buffered formalin and embedded in paraffin. Some 5-micrometer sections were stained with hematoxylin-eosin, mucicarmine and immunohistochemical stains for morphologic and immunohistochemical evaluation. **Result:** Case 1: The patient was a 23 year-old, non-smoker male, non-reactive with HIV test, who presented with several months of shortness of breath, exertional dyspnea and easy fatigability. Imaging studies revealed massive pleural and pericardial effusion and was admitted as a case of tuberculosis. Pericardial biopsy and cytology of pericardial and pleural fluid showed atypical cells. The patient's condition progressed rapidly and he eventually died. On autopsy, the thoracic cavity was filled with a mass occupying the right hemithorax. The mass was a moderately differentiated adenocarcinoma that extensively infiltrated the left lung and other contiguous structures like the pericardium, ventricular wall, aorta and pulmonary trunk and peritoneal surface of the liver. IHC revealed the tumor cells as positive for CEA and CK7, but negative for CK20 and TTF-1. Mucicarmine stain was positive. Case 2: The patient was a 33-year old, non-smoker male, non-reactive with HIV test, who presented with progressive difficulty of breathing for 2 years and managed as a case of tuberculosis and pneumonia in a hospital and subsequently referred and admitted at our institution. Chest x-ray showed diffuse extensive hazy reticular densities and confluent densities in the left lung and managed as tuberculosis. His condition deteriorated rapidly and he eventually expired. Post-mortem examination revealed a mass located in the carina with several metastatic deposits in the mediastinum, peritoneum and retroperitoneum. The mass was a moderately differentiated adenocarcinoma of bilateral lung with extension to contiguous structures like the great vessels, pericardium, esophagus, distal trachea and with distant metastasis to adrenals. IHC revealed the tumor cells as positive for CEA, CK7 and TTF-1, but negative for CK20. Mucicarmine was focally positive. **Conclusion:** These cases are uncommon presentation of disseminated lung cancer. Clinicians should be wary in the clinical diagnosis of young, immunocompetent, non-smoker patients who present with difficulty of breathing and effusion. In such cases, a diagnosis of tuberculosis in a country with a high TB burden, might mask a greater evil in the form of an underlying lung malignancy.

Keywords: Autopsy, primary lung adenocarcinoma, young non-smoker

P2.01-063 OUTCOMES OF PATIENTS WITH OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER WHO WERE TREATED WITH RADICAL TREATMENT

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Background: Patients with oligometastatic non-small cell lung cancer (NSCLC) represent an indolent phenotype who may benefit from aggressive therapy and experience long-term overall survival (OS). Previous several small retrospective studies have showed that aggressive therapies for both the primary tumor and the metastases might be beneficial for patients with oligometastatic NSCLC compared with patients that did not receive aggressive treatment. The aim of this study was to determine the efficacy of aggressive treatment for patients with oligometastatic NSCLC. **Method:** We retrospectively analyzed 40 patients with oligometastatic NSCLC who were treated with aggressive treatments. Response rates, progression-free survival (PFS) and OS were evaluated. **Result:** Median age was 58 years, the majority of patients were male (67.5%), and have adenocarcioma histology (77.5%) and ECOG PS 0-1 (92.5%). Oligometastase locations were brain (55%), adrenal gland (22.5%), bone (15%), lung (5%), and other (2.5%). Oligometastatic disease was mostly limited: 80% of patients had metastases confined to one involved organ, and the majority of patients (57.5 %) presented with a solitary metastasis. Primary tumor treatments were concomitant chemoradiotherapy (60%), surgery (17.5%), chemotherapy (17.5%) and sequential radiotherapy (5%). On the other hand, metastase treatments were consisted of radiosurgery (77.5%), metastasectomy (17.5%) and radiosurgery and metastasectomy (5%). After agressive treatment objective response rate was 82.5%. At the median follow-up of 16.5 months, the median PFS and OS intervals were 15.5 (95% CI 9.3-21.7) and 21.9 (95% CI 13.5-30.2) months, respectively. **Conclusion:** Radically aggressive treatment for both the primary tumor and the metastases is reasonable and effective therapeutic option to provide long-term survival rates in selected patients with oligometastatic NSCLC. Further studies are needed, preferably prospective and randomized that analyze the efficacy and safety of aggressive ablative treatment for these patients.

Keywords: agressive treatment, non-small cell lung cancer, Oligometastatic disease

P2.01-064 CO-EXISTING MUTATIONS AND THEIR CLINICAL IMPLICATIONS IN NON-SMALL CELL LUNG CANCER: KOREAN LUNG CANCER CONSORTIUM (KLCC-13-01)

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Background: Non-small cell lung cancer (NSCLC) is a common type of cancer with typically poor prognosis. As individual cancers exhibit unique mutation patterns, identifying and characterizing gene mutations in NSCLC might help predict patient outcomes and guide treatment. The aim of this study was to characterize the mutational landscape of NSCLC and identify biomarkers to predict patient outcome. **Method:** Archived DNA was extracted from formalin-fixed, paraffin-embedded, mostly small biopsy samples of 162 patients. Targeted sequencing of genomic alterations was conducted using Ion AmpliSeq Cancer Hotspot Panel v2. **Result:** The median age of patients was 64 years (range; 32-83 years) and the majority had stage IV NSCLC at the time of cancer diagnosis (90%). Among the 162 patients, 161 patients (99.4%) had novel or hotspot mutations (range: 1-16 mutated genes). Hotspot mutations were found in 20 genes. Three of the most frequently found hotspot mutations were in *TP53* (82, 51.2%), *EGFR* (66, 40.8%), and *STK11* (19, 11.7%). Given that 72.7% (48/66) of EGFR mutant patients were treated with EGFR TKIs, there was a significant difference in overall survival between *EGFR* mutant and EGFR wild-type patients. In *EGFR* wild-type subgroup analysis, *TP53* status was associated with poor overall survival, while S*TK11* status was associated both poor progression-free survival and overall survival. **Conclusion:** These results suggest that targeted next-generation sequencing using small biopsy samples is feasible and allows for the detection of both common and rare mutations that have independent prognostic value.

Keywords: non-small cell lung cancer, targeted next-generation sequencing

P2.01-065 CLINICO-RADIOLOGICAL AND PATHOLOGICAL EVALUATION OF LUNG ADENOCARCINOMA WITH INFILTRATION ON THE COMPUTED TOMOGRAPHY OF THE CHEST

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Background: Invasive mucinous adenocarcinoma of the lung which is well known as poor prognosis is often difficult to distinguish from pneumonia on the chest Computed Tomography (CT). However, the characteristics of lung adenocarcinoma resemble to pneumonia on the chest CT are not known well. **Method:** We retrospectively reviewed 607 patients with lung cancer pathologically diagnosed with adenocarcinoma in Saiseikai Suita Hospital from April 2007 to March 2017. **Result:** Of the 607 patients, 9 cases showed infiltration like pneumonia without any masses or nodules on the chest CT. The patients included 3 males and 6 females, mean age of 69.89 years (range 32-82 years). Many cases relatively needed time from the point of first contact to the medical institution to diagnosis: the average was 142.9 days (range 8-385 days). Furthermore, some of the cases were treated as pneumonia at first. Most of the cases diagnosed with invasive mucinous adenocarcinoma pathologically, but there were 2 cases presenting no or few mucin. These 2 cases also have EGFR major mutation. One patient died within 2 months after diagnosis, but more than half of the cases were confirmed the existence over one year. **Conclusion:** It is important to take lung adenocarcinoma into consideration when we see infiltration on the chest CT scan. We suppose early diagnosis and treatment could lead to relatively good survival.

Keywords: infiltration, lung adenocarcinoma

P2.01-066 TARGETED THERAPY FOR LUNG CANCER: LIQUID BIOPSY OR TUMOR SAMPLING? A CASE-CONTROL STUDY

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Background: Liquid biopsy provides a valuable source to guide the targeted therapy for lung cancer. However, the comparison between the liquid biopsy or tumor sampling guided therapy was lacking. Here we performed a case-control study to compare the clinical outcome of these two strategies. **Method:** In this retrospective study, the admitted patients from Jan 2015 to Feb 2016 were screened through a pre-established database. Patients with metastatic, pathologically-confirmed, and treatment naïve non-small cell lung cancer who were prescribed with epithelial growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) from the guidance of liquid biopsy were enrolled (Liquid group). The mutation status in tumors was not mandatory. During the same period, patients medicated with TKI based on tumor samples were included in the Control group. They were enrolled in an age-, gender-, performance-matched manner. **Result:** We screened 536 patients and enrolled 26 patients in the Liquid group. Another 52 patients were enrolled in a 1:2 ratio in the Control group. In the Liquid group, a high consistence (84.6%) in EGFR mutation status between liquid and tumor was observed. The best response was partial response in 19 patients (73.1 %), and followed by stable disease in 6 patients (23.1 %). The median progression-free survival was 10.0 months (95%CI: 4.2-15.8 months). In the Control group, a similar disease control rate (81.2%, P=0.679) and comparable PFS (7.8 months, 95% CI: 7.1-10.4 months, P=0.798), HR=0.713, 95% CI: 0.321-1.195) was found. In the Liquid group, 3 of 4 patients with discordant results between tumor and liquid biopsy showed treatment responses favoring the liquid biopsy. **Conclusion:** This study provided direct evidence supporting the liquid biopsy for guiding the targeted therapy for lung cancer.

Keywords: PFS, Targeted therapy, liquid biopsy

P2.01-067 TREATMENT OF THE PATIENTS WITH ONCOLOGICAL EMERGENCIES WITH MASSIVE PLEURAL EFFUSION AT THE FIRST HOSPITAL VISIT

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Background: Massive pleural effusion may cause the oncological emergencies in the patients with advanced lung cancer. We describe here the treatment experience of patients with the massive pleural effusion at the first visit. **Method:** Three patients had massive pleural effusion at the first visit from April 2016 to March 2017. We report these 3 patients treated with carboplatin, pemetrexed, and/or bevacizumab. **Result:** All of 3 patients urgently received the continuous chest tube drainage for several days (Table 1). Pleural effusion was examined for cytology. Patient A received pleurodesis therapy because of negative fluid cytology, while she was examined by CT guided needle biopsy. Patient B and C revealed malignant adenocarcinoma cytology in pleural effusion. Both of two received additional biopsy for EGFR-mutation and ALK-translocation. Patient A waited the result of the pathology of adenocarcinoma, EGFR-mutation of negative, and ALK-translocation of negative for 24 days. She received the chemotherapy of carboplatin and pemetrexed with pregressive disease and died of locally advanced lung cancer after 1 course of chemotherapy followed 20 days best supportive care. Patient B and C quickly began the first line chemotherapy of carboplatin, pemetrexed, and bevacizumab without waiting the result of EGFR-mutation and ALK-translocation. Patient B received the six-course of chemotherapy

with partial remission, followed the one course of the maintenance chemotherapy of pemetrexed and bevacizumab, however, he died of brain metastasis 183 days after the first chemotherapy. Patient C received the six courses of chemotherapy, followed pemetrexed and bevacizumab maintenance therapy, and is living with partial remission more than 130 days.

Table 1

	Age	Sex	Pleural effusion cytology	Additional pathology	EGFR-mutation
Patient A	77	F	Class I	Dissemination, adenocarcinoma	wild
Patient B	60	M	Class IV	Lung, adenocarcinoma	wild
Patient C	69	F	Class IV	Dissemination, Adenocarcinoma	L858R

Table 1 continued

	Period to the first chemotherapy	1st line chemotherapy	Prognosis
Patient A	25 days	Carboplation, Pemetrexed	Dead, 58 days, Locally advancement
Patient B	8 days	Carboplatin, Pemetrexed, Bevaxizumab	Dead, 183 days Brain metastasis
Patient C	4 days	Carboplatin, Pemetrexed, Bevaxizumab	Alive, 130 days, PR

Conclusion: Carboplatin, pemetrexed and bevcizumab treatment was well-tolerable in the patients with the oncological emergencies of massive pleural effusion. We should start the first line treatment as soon as possible. Two weeks of waiting period are so long for the patients with advanced lung cancer.

Keywords: carboplatin, pemetrexed, bevacizumab, lung cancer, oncological emergencies

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-068 LOBECTOMY IMPROVE THE SURVIVAL OF NON-SMALL CELL LUNG CANCER PATIENTS WITH OCCULT MALIGNANT PLEURAL DISEASE FIRST DETECTED AT THORACOTOMY

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Background: To aim of this study was to determine the clinical and biological prognostic factors for occult malignant pleural disease (MPD) first detected at thoracotomy in patients with non-small cell lung cancer (NSCLC) and evaluate the results of surgical intervention. **Method:** A total of 123 patients diagnosed with MPD at consecutive 2894 thoracotomy from January 2006 to October 2016. Clinical and pathological characteristics were evaluated in 120 patients. Survival curves were estimated by the Kaplan–Meier method, and Cox regression analysis was performed to validate the selected risk factors. **Result:** With a median follow-up of 34 months, the 5-year overall survival of 120 patients was 28%. Multivariate analyses using the Cox proportional hazards model showed gender (p=0.066), T stages (p<0.001), N stages (p=0.032), pleural invasion in image (p=0.004), pleural effusion (p=0.027), surgery intervention (p=0.024) and EGFR status (p=0.001) were independent predictors of survival. The 5-year survival rate and median survival time (MST) for 21 patients with lobectomy were 71.6% and 62.6 months, compared with 25.6% and 40.0 months in 46 patients with sublobectomy. When 53 patients subjected to open-close surgery, their 5-year survival rate and MST were 23.4% and 30.2 months. There was significant prognostic difference between lobectomy and sublobectomy /open-close surgery (p=0.033/0.016), but no significant difference was found between sublobectomy and open-close surgery (p=0.679)

Conclusion: Lobectomy confers better prognosis compared to sublobectomy and exploratory thoracotomy for occult MPD patients with NSCLC.

Keywords: lobectomy, Malignant pleural disease, EGFR

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-069 RADIOLOGISTS' CONSIDERATIONS TO DETERMINE THE ORIGIN OF TUMOR ON CHEST CT: LUNG VS MEDIASTINUM

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Background: In daily practice of chest radiology, radiologists encounter various cases of tumor involving both mediastinum and lung parenchyme, and often undergo difficulty determining the origin of tumor. We retrospectively collected 10 cases of tumor and the determinants of 15 radiologists' decisions to inquire about the origin of tumor. There have been certain agreeable findings for the right expectations. Through the review of published articles, we re-estimated the findings that may be the factors providing appropriate diagnostic approach to the origin of tumor involving lung and mediastinum. **Method:** We retrospectively collected 16 cases of tumors involving the lung parenchyme and mediastinum. After excluding tumors with posterior mediastinum involvement, benign histology, and no histopathological confirmation, 10 cases were evaluated by 15 radiologists (6 residency trainees and 9 specialists in chest radiology). The inquiries included the expected origin of tumor and the determinants for the expectation. Then the review of collected determinants for each case was performed by 2 specialists in chest radiology (5 year and 22 years of experience in radiology) and the certain agreeable findings for the right expectations were analyzed. **Result:** Among the 10 cases of tumor, 8 cases were lung cancer (3 small cell lung cancer, 3 adenocarcinomas, 2 squamous cell carcinoma) and 2 cases were thymic carcinoma. The largest percentage of correct expectations was 87 % (9/9 of chest specialists and 4/6 residents) and the smallest percentage was 13 % (1/9 of chest specialist and 1/6 residents). For lung cancer, the determinants for the right expectation included open bronchus sign, involvement of middle mediastinum, and mediolateral displacement of mediastinum. On the other hand, findings such as epicenter of mass, irregular margin, angle of the mass with mediastinal contour, and pleural metastasis were not contributable. **Conclusion:** Findings helped to make the right expectations were open bronchus sign, involvement of middle mediastinum, and mediolateral displacement of mediastinum. Understanding the CT findings of tumor mass involving mediastinum and lung may be helpful to diagnosis.

Keywords: origin of tumor, lung cancer

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-071 EFFICACY OF THORACIC RADIOTHERAPY IN OLIGOMETASTATIC NON-SMALL-CELL LUNG CANCER HARBORING WILD-TYPE EGFR AFTER FIRST-LINE CHEMOTHERAPY

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Background: Evidence from retrospective and small prospective trials suggested that local therapy might be beneficial for patients with oligometastatic non-small-cell lung cancer (NSCLC). The purpose of this study is to analyze the efficacy of thoracic radiotherapy in oligometastatic NSCLC patients harboring wild-type EGFR that did not progress after first-line chemotherapy in Asian population. **Method:** We retrospectively reviewed 181 stage IV NSCLC patients harboring wild-type EGFR with three or fewer metastatic lesions after first-line chemotherapy with an Eastern Cooperative Oncology Group(ECOG) performance status(PS) score of 2 or less. All the patients treated with first-line therapy of four to six cycles of platinum doublet therapy and did not progress. Patients were classified into two regimens: 89 patients received

thoracic radiotherapy (arm A) with volumetric modulated arc therapy (VMAT) technology, 92 patients received maintenance treatment or observation only (arm B). Maintenance treatment used only one chemotherapy drug including gemcitabine or pemetrexed or docetaxel, and observation was defined as close surveillance without cytotoxic treatment. The progression-free survival (PFS) was defined as the interval from the date of treatment to the earliest date of disease progression or death. The overall survival (OS) was defined as the interval from the date of treatment to the date of death. PFS and OS were estimated by the Kaplan-Meier method and were compared by the log-rank test. **Result:** The median PFS of the thoracic radiotherapy arm was significantly longer than that of the maintenance treatment arm (7.5 vs. 4.3 months, p = 0.006). The median OS of the thoracic radiotherapy arm also slightly longer than that of maintenance treatment or observation arm (13.0 vs. 10.0 months, p=0.031). Multivariate analysis indicated that thoracic radiotherapy were independent predictors of PFS. Thoracic radiotherapy, ECOG PS (0-1) ,histology adenocarcinoma and no brain metastasis were correlated with longer OS. **Conclusion:** The thoracic radiotherapy could improve PFS and OS in oligometastatic unresectable NSCLC patients harboring wild-type EGFR that did not progress after first-line chemotherapy.

Keywords: Oligometastatic, thoracic radiotherapy, Non-small-cell lung cancer

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-072 LOCAL MANAGEMENT OF OLIGOMETASTASIS IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Stage IV NSCLC patients with oligometastasis may experience long-term survival when macroscopic tumour sites are treated radically. The aim of this abstract is to analyse our experience in local management of oligometastasis in NSCLC. **Method:** We retrospectively analysed 38 patients with oligometastatic NSCLC in terms of overall survival (OS), progression-free survival from diagnosis (SLP) and treatment (SLPT) of oligometastatic disease and the association with clinical features such as age, gender, histology, molecular profile, stage at diagnosis and metastatic sites. Kaplan Meier method was used. **Result:** We analysed 38 patients (25 men, 13 women). Mean age: 61 years (40-82). Histology: 60% adenocarcinoma, 8% squamous carcinoma, 13% large cell carcinoma, 19% NOS. 2 EGFR and 1 BRAF mutations. 60% patients (23/38) presented oligometastatic NSCLC at diagnosis, 34% after progression of early disease and 6% after response to initial systemic treatment for advanced disease. Mean number of metastasis: 1 (1-3). Most frequent location: brain (80%). 35% of patients (8/23) oligometastatic at diagnosis received local treatment for the primary tumour: 75% surgery, 25% radiotherapy. Systemic therapy was administrated in 65% of patients (15/23): 93% platinum-based chemotherapy, 7% EGFR-TKI. Table 1 shows local treatment for oligometastasis at diagnosis. No severe complications were observed.

Table 1	Brain (n=30, 80%)	Adrenal gland (n=4, 10%)	Lung (n=3, 8%)	Liver (n=1, 2%)
Surgery + Radiotherapy	87% (26/30)			
Surgery	10% (3/30)	50% (2/4)	67% (2/3)	
Radiotherapy			33% (1/3)	
No local treatment	3% (1/30)	50% (2/4)		100% (1/1)

With a median follow up of 23 months (95%CI 0.9-78.2m), median SLPT was 8.5 months (95%CI 5.3-11.7m), median SLP was 8.7 months (95%CI 6.1 – 11.3m) and median OS was 9.9 months (95%CI 0-32). Median OS of brain metastasis was 9.7 months (95%CI 6.5-12m) *vs* not reached in patients without brain metastasis (*p* 0.019). Median OS patients with oligometastatic NSCLC at diagnosis was 8.7 months (95%CI 5'9-11) *vs* not reached in the rest of patients (*p* 0.025). **Conclusion:** Data collected demonstrate that survival rate in patients with oligometastatic NSCLC is similar to that reported in literature. Cerebral metastasis significantly worsen the prognosis.

Keywords: Non-Small Cell Lung Cancer, Oligometastasis, Management

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-073 PROGNOSTIC FACTORS ANALYSIS OF NON-SMALL CELL LUNG CANCER WITH BRAIN METASTASES

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Background: There is a high incidence of brain metastases in non-small cell lung cancer, result in treatment failure. The usual outcome of untreated patients is very poor. How to improve living quality and extend the median survival is a hot item for clinical studies. Therefore, this study attempted to analyze the prognostic factors of the non-small cell lung cancer with brain metastases. **Method:** 145 patients who were diagnosed for brain metastasis from Non-small cell lung primary cancer by MRI at the Cancer Hospital affiliated to Fujian Medical University from January 2010 to December 2013 were retrospectively reviewed. A number of potential influencing factors which might affect prognosis were evaluated,including age,gender, pathological type,Karnofsky performance score (KPS),tumor and lymph node staging, internal from diagnosis of lung cancer to the development of BM,symptoms at BM diagnosis,number of BM,region of BM,maximum diameter of BM,peritumoral brain edema,radiation boost following WBRT and the treatments. Survival time was recorded from BM diagnosed to die or final follow-up. Survival rate was calculated by Kaplan-Meier method. Log-rank method was adopted to compare the difference of each inferior group in survival rate. The multi-variate analysis about survival was performed with Cox'S regression proportional model. Statistical significance was defined as P<0.05. **Result:** There were 145 patients in the research,median survival time (MST) from BM diagnosed was 13.0 months,6-month,1-year and 2-year survival rates were 82.8%, 52.4% and 25.8%, respectively. The univariate analysis showed KPS,the presence of extracranial metastases, symptoms at BM diagnosis , both side of the brain metastases , meningeal metastases and maximum diameter of BM had tendency to statistical differences(P value are 0.009,0.004,0.019,0.044,0.023,0.044,respectively). The multivariate analysis indicated that the presence of extracranial metastases, symptoms at BM diagnosis and meningeal metastases were closely related to the prognosis. **Conclusion:** Based on the results of our study, we confirmed that meningeal metastases, no extracranial metastasis and no Symptoms at BM diagnosis are independent prognostic factors in NSCLC with brain metastases.

Keywords: non-small cell lung cancer, brain metastases, prognostic factor

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

P2.01-074 WAIT AND SEE: A FAVORABLE ALTERNATIVE FOR R-M1A AND S-M1A NSCLC PATIENTS

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Background: Intrathoracic dissemination M1a disease has been reported to be a distinct lung cancer with favorable prognosis and contraindicated surgery may be beneficial to patients with NSCLC. This study aims to investigate treatments of r-M1a and s-M1a in real world and explore which kind of resection type of lung benefits s-M1a patients. **Method:** Patient characteristics, pathology, gene profiles and treatment were respectively collected for lung cancer patients who were diagnosed as r-M1a or s-M1a stage IV disease. Different therapies were evaluated by comparing progression free survival (PFS) and overall survival (OS) by Kaplan-Meier. A cox proportional hazards regression model was applied to evaluate the prognosis factors. Statistical analysis was performed in all subgroups. **Result:** Overall, 2304 consecutive lung cancer patients receiving thoracotomies at Guangdong general hospital were retrospectively analyzed. Eighty r-M1a patients (3.47% of all patients) and Seventy-three s-M1a patients (3.17% of all patients) were enrolled. Difference was observed in two groups among gene profiles and treatment. Compared to r-M1a group, s-M1a group contained more patients with EGFR mutation (18.3% *VS* 32.7%, P<0.001) and ALK overexpression (0.7% *VS* 1.3%, P=0.005), a higher proportion chemotherapy patients and lower local treated patients (19.0% *VS* 24.2%, 7.5% *VS* 0%, P=0.008). Median PFS of r-M1a and s-M1a patients in chemotherapy group (66, 43.14%), targeted therapy group (33, 21.57%), local treatment group (11, 7.19%) and wait-and-see group (43, 28.1%) were 14.7, 27.5, 39.3 and 44.1 months, respectively [95% confidence interval (CI),19.15-28.05; P<0.001. local treatment group *VS* wait and see group, P=0.924]. And median OS was 52.2, 47.9, 59.4 and 71.7 months, respectively [95% confidence interval (CI), 47.86-61.95; P=0.208]. In addition, no difference between lobectomy and limited resection was observed in patients with s-M1a in PFS [median 21.9 months, 95% confidence interval (CI),17.59 to 26.22; P=0.738] and OS [median 42.6 months, 95% confidence interval (CI),30.89 to 54.25; P=0.944]. Cox regression analysis revealed group (r-M1a *VS* s-M1a) and pathology were the independent prognostic factors. **Conclusion:** Wait and see strategy may be a favorable alternation for r-M1a and s-M1a patients with NSCLC. For s-M1a NSCLC patients, limited resection of lesions was recommended compared to lobectomy.

Keywords: non-small lung cancer, Intrathoracic dissemination, M1a disease

P2.01-075 GENOMIC CHANGES AND CLINICAL CHARACTERISTICS ASSOCIATED WITH WOOD-SMOKE EXPOSURE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Chronic wood smoke exposure (WSE) is related to obstructive pulmonary disease and represents an increased risk of lung cancer. WSE is asociated with EGFR-mutations and low frequency of KRAS mutations. WSE signaling networks show better response to EGFR-TKIs, improving response rate and overall survival in NSCLC patients. Next-generation sequencing (NGS) has facilitated parallel analysis of multiple genes for treatment selection and monitoring response to treatment. We evaluated genomic alterations in patients with WSE based on tumor profiling by massive parallel sequencing. **Method:** 52 patients with advanced lung cancer were evaluated. Fresh-frozen samples were used for DNA extraction with the Wizard Genomic DNA Purification Kit (Promega) including some formalin-fixed paraffin-embedded tissues (FFPE). The TruSeQ Cancer Panel (Illumina) was used for library construction in targeted sequencing of 48 genes spanning 212 amplicons in mutation hotspots. **Result:** WSE was more frequent in women (59% vs 41% p=0.038). We found diferent mutations in ATM (A1309H, G1679V, N1793I and T2749P), EGFR exon 7 (G288V), KDR (H267, Q1146S) and SMARCB1 (T72Q, G157A). WSE correlated with mutations in the genes KDR 89% *vs.* 11% (p=0.024), ATM 72% *vs.* 27% (p=0.040), SMARCB1 74% *vs.* 26% (p=0.020) and in exon 7 of EGFR 75% *vs.* 25% (p=0.034). Additionally, ATM mutations correlated with metastasis in CNS and bones 77% *vs.* 23% (p=0.006), also, patients with EGFR exon 7 presented major metastases in CNS and bones 67 *vs.* 33 % (p=0.084). SMARCB1 mutations were associated with worse overal survival (48 vs 5.6 months p=0.066). WSE patients carrying EGFR exon 7 mutations had better response showing either partial response or stable disease. **Conclusion:** Latin American patients of lung cancer and WSE present a distinctive mutation profile compared to non-WSE patients showing a positive correlation with KDR, ATM, EGFR exon 7, and SMARCB1 mutations.

Clinical and Pathological Characteristics Related to Wood Smoke Exposure in patients with NSCLC

Characteristics	WSE (-) % (n/N)	WSE (+) % (n/N)	*p*-Value
Gender			
Male	82 (9/26)	18 (2/26)	***0.038***
Female	41 (17/26)	59 (24/26)	
Age			
Mean (±SD)	62 (±14)	62 (±11)	0.957
< 60 years	56 (10/26)	44 (9/26)	
≥ 60 years	47 (16/26)	53 (17/26)	0.771
Tobacco-Smoking Exposure			
Non-smoker	29 (10/26)	71 (24/26)	***< 0.001***
Smoker	89 (16/26)	11 (2/26)	
Asbestos Exposure			
Absent	52 (26/26)	48 (24/26)	0.490
Present	0 (0/26)	100 (2/26)	
Disease Stage			
IIIB	70 (8/26)	30 (4/26)	0.287
IV	47 (18/26)	53 (22/26)	
ECOG PS			
0-1	96 (19/30)	78 (11/30)	0.627
2-3	50 (2/26)	50 (2/26)	
Histological subtype			
Adenocarcinoma	52 (26/44)	48 (21/44)	0.703
Carcinoma	37 (3/8)	63 (5/8)	
Histological histological subtype			
Papilar	0 (0/2)	100 (2/2)	
Acinar	43 (6/14)	57 (8/14)	0.340
Lepidic	67 (4/6)	33 (2/6)	
Solid	60 (6/10)	40 (4/10)	
Architectural Histological Grade			
Low	0 (0/2)	100 (2/2)	0.301
Intermediate	50 (10/20)	50 (10/20)	
High	60 (6/10)	40 (4/10)	
Metastasis CNS and bones			
Absent	50 (12/24)	50 (12/24)	0.542
Present	39 (7/18)	61 (11/18)	
Metastasis Lung and Pleura			
Absent	45 (10/22)	54 (12/22)	1.000
Present	45 (9/20)	55 (11/20)	
Metastasis Liver			
Absent	42 (16/38)	58 (22/38)	0.313
Present	75 (3/4)	25 (1/4)	
***EGFR* mutations**			
Negative	59 (13/22)	41 (9/22)	0.400
Positive	43 (13/30)	57 (17/30)	

Keywords: wood-smoke exposure, next-generation sequencing

P2.01: ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:00-16:00

PP2.01-070 FAACT- ANOREXIA CACHEXIA SCALE: CUT-OFF VALUE FOR THE ANOREXIA DIAGNOSIS IN NSCLC PATIENTS

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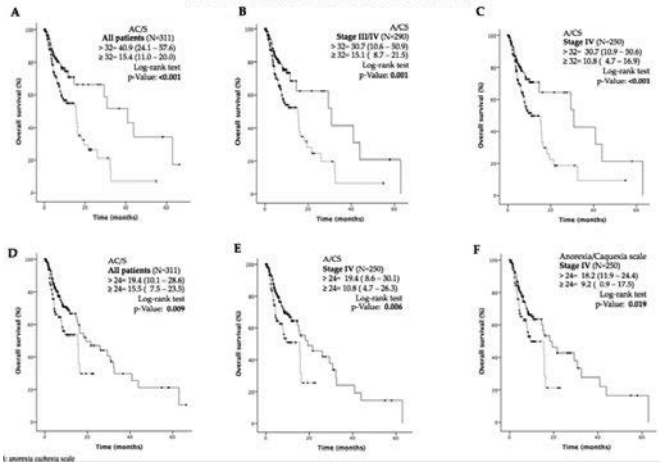
Background: Lung cancer has the highest death rate among cancer types and anorexia is reported by a high percentage of patients, but the prevalence values may vary according to form of diagnosis. Anorexia is associated with reduced food intake, weight loss and a negative affect in quality of life and worse outcome. There is no gold standard for anorexia diagnosis. The anorexia cachexia scale (AC/S) from FAACT instrument has been proposed as a tool for diagnoses anorexia but a validated cut-off value for NSCLC patients is required. This study validates a cut-off value of AC/S for anorexia diagnosis in NSCLC patients. **Method:** The AC/S were evaluated in Non-Small Cell Lung Cancer (NSCLC) patients to establish a cut-off value by ROC curve analysis and CutOff Finder program with the anorexia score from QLQ-C30 questionary as a standard reference and by X-tile based on survival. The cut-off value was associated with clinical parameters **Result:** Three hundred and twelve ambulatory NSCLC patients were evaluated, 67% with adenocarcinoma, 65% stage IV and 98% with ECOG ≤2. The mean of AC/S was 31 ± 9 and the identified cut-off value was 32.5, sensitivity 80.3% (85.7-73.3) and specificity 85% (90%-78.2). The proportion of anorexia based on cut-off value of 24 was 26% and with cut-off value of 32 was 50%. AC/S cut-off value 32 was associated significantly with clinical parameters, nutritional consumption and quality of life. Overall survival was determined in all patients, stage III/IV and stage IV. The overall survival was independently associated with the cut-off value of 32.

Figure 2. Kaplan-Meier curves for OS among all patients (A,D), only patients with advanced disease (B,E) and only patients with metastatic disease (C,F)among patients with AC/S based on cut-off 32 and 24.



Conclusion: Lung cancer patients with the score of ≤32 in AC/S for anorexia diagnosis is proposed, clinically useful and this cut-off can improve the identification of patients with a risk of complications of cancer related malnutrition. Future treatments and follow ups of cancer-related anorexia should be focus in this patients.

Keywords: anorexia, Anorexia cachexia scale (AC/S), NSCLC

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-001 DETECTION OF GENE FUSIONS IN NSCLC USING NGS FUSION ASSAY

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Background: ALK/RET/ROS and MET exon 14 skipping detection are important to guide of treatment in non-small cell lung cancer (NSCLC) patients. Next generation sequencing (NGS) platform has been implemented in the daily practice for the diagnosis. However, the validation of the NGS-based panel is still complicated and difficult. **Method:** We developed NGS-based fusion assay panel to detect 183 total fusion variants including ALK/RET/ROS as well as MET exon 14 skipping. The fusion call agreement between OCP-50 NGS assay and Nanostring was performed. The result was compared with the FISH and IHC results. This study describes the validation of the assay to define assay parameters, performance characteristics and reproducibility across laboratories. **Result:** For the 55 samples analyzed, the results are as follows;

	ALK Fusion			ROS1 Fusion		
	NGS(+)	NGS(-)	Total	NGS(+)	NGS(-)	Total
NS (+)	20	0	20	6	0	6
NS (-)	1	33	34	1	47	48
Total	21	33	54	7	47	54

	RET Fusion			METD14		
	NGS(+)	NGS(-)	Total	NGS(+)	NGS(-)	Total
NS (+)	5	0	5	0	0	0
NS (-)	0	49	49	2	52	54
Total	5	49	54	2	52	54

Conclusion: The results of our study will be of help in learning the process of establishing, validating and applying the fusion gene detection method in NSCLCs. Furthermore, NGS based OCP-50 assay for fusion detection is more accurate and reliable method for the diagnosis.

Keywords: non-small cell lung cancer, next generation sequencing, fusion

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-002 DIGITAL MULTIPLEXED DETECTION OF SINGLE NUCLEOTIDE VARIANTS (SNV) IN NON-SMALL CELL LUNG CANCER USING NANOSTRING TECHNOLOGY

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Background: Non-small cell lung cancer (NSCLC) is a heterogeneous disease characterised by somatic mutations in many genes, some of which are actionable drivers. Modern management of NSCLC requires the identification such driver variants to predict sensitivity to targeted drug therapies. Current methods for mutation detection exhibit varying diagnostic accuracies and limitations. In this study, we determined the utility of a novel high-throughput assay by NanoString for mutation testing in comparison to an alternate platform. This is the first presentation of this combination of NanoString technologies in NSCLC. **Method:** Mutational status was evaluated using the nCounter SPRINT Profiler and the Vantage 3D DNA SNV Solid Tumour Panel in a cohort of 174 fresh-frozen NSCLC tumours, utilising digital counting of unique barcoded probes to detect 104 SNV, multi-nucleotide variants (MNVs) and InDels from 25 genes of clinical significance. 5ng of tumour-derived gDNA was subjected to multiplexed pre-amplification and hybridisation of variant-specific probes to unique fluorescent barcodes. Positive variant calls required raw digital count levels above 200, with a raw-count fold-change above the reference DNA sample greater than 2.0 and a statistical significance of $p<0.01$. SNV calls by the nCounter assay were made by comparison to a previous study using MALDI-TOF mass spectrometry. An agreement analysis was performed for variants common to both platforms to determine positive, negative and overall percentage agreement (PPA, NPA and OPA). A subset of discordant cases were validated using ddPCR. **Result:** The nCounter SNV assay detected at least one variant in 102/174 (58.6%) cases. Seven (4.0%) cases harboured two SNVs. KRAS variants were detected in 79 (45.4%) cases, EGFR in 6 (3.5%), PIK3CA in 3 (1.7%), TP53 in 3 (1.7%). Overall agreement analysis revealed PPA, NPA and OPA of 96.0%, 93.2% and 94.8% respectively. 5/9 discordant samples were available for validation using ddPCR. 4/5 validated cases favoured the nCounter assay, with one case harbouring a KRAS G12V variant confirmed at a fractional abundance of 1.15%. **Conclusion:** This study found the performance of the nCounter SNV assay and a contemporary platform to be highly concordant. The advantages of this technology include low DNA input, digital data output, reduced turn-around-time (<24hr) and customisability for inclusion of novel variants. The nCounter SNV assay is a robust and sensitive method for translational cancer research.

Keywords: mutation profiling, single nucleotide variants, non-small cell lung cancer

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-003 A PRACTICAL PROGNOSTIC LNCRNA SIGNATURE FOR LUNG SQUAMOUS CELL CARCINOMA

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Background: This study aimed to develop and assess a practical prognostic lncRNA signature for squamous cell carcinoma of the lung (LUSC). **Method:** RNA expression profile and clinical data from 388 LUSC patients were accessed and download from the Cancer Genome Atlas (TCGA) database. Differential lncRNA expression was compared and analyzed between normal tissue and tumor samples. By univariate and multivariate Cox regression analyses, a seven-lncRNA signature was developed and used for the purpose of survival prediction in LUSC patients. We applied receiver operating characteristic analysis to assess the performance of our model. **Result:** Sixteen out of 1414 differentially expressed lncRNAs in the TCGA dataset were associated with the overall survival of LUSC patients. Risk score analysis was used to select 7 lncRNAs to be included in our model development and validation. The ROC analysis indicated that the specificity and sensitivity of this profile are high.

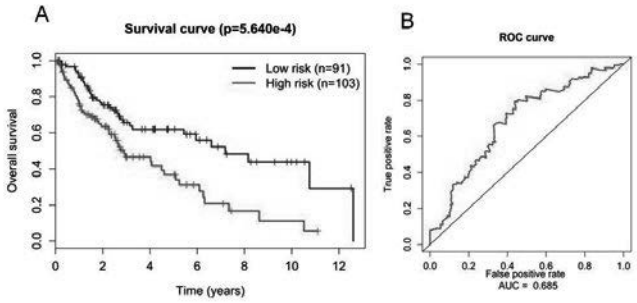

Figure 1. Kaplan-Meier and ROC curves for the 7-lncRNA signature in the validation set. (A) The differences between the high-risk (n=103) and low-risk (n=91) groups were determined by the log-rank test ($p<0.0001$). Five year overall survival was 36.8% (95% CI: 26.1%-51.8%) and 61.9% (95% CI: 51.4%-74.6%) for the high-risk and low-risk groups, respectively. (B) ROC curves indicated that the area under receiver operating characteristic of 7-lncRNA model was 0.685. **Conclusion:** The current study identified a seven-lncRNA signature that predicts the outcome of LUSC, offering potentially novel therapeutic targets for the treatment of squamous cell carcinoma of the lung.

Keywords: Lung Squamous cell carcinoma, lncRNA, prognostic signature

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-004 GENE MUTATIONAL FEATURE IN LUNG ENTERIC ADENOCARCINOMA BY THE NEXT GENERATION SEQUENCING

W. Wang[1], C. Xu[2], L. Lin[3], W. Zhuang[4], Y. Shao[5], Y. Tai[5], R. Chen[6], Y. Guan[6], X. Yi[6], Y. Chen[2], M. Wu[1], G. Chen[2]

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Background: Primary lung enteric adenocarcinoma is a rare type of invasive lung carcinoma. Its morphology and immunohistochemistry is close to colorectal carcinoma, but there is no associated primary colorectal carcinoma. The purpose of this study is to assess the gene mutational feature in lung enteric adenocarcinoma by the next generation sequencing. **Method:** From Feb. 2013 to Dec. 2016, 11 lung enteric adenocarcinoma patients (5 males and 6 females) received treatment from three medical centers: including Beijing, Zhejiang and Fujian. All the patients were diagnosed by pathology. Analysis was used by the next generation sequencing. **Result:** ALK/ROS1 primary point mutations were confirmed in 5 patients (71.42%, 5/7). MSH2/MSH6 point mutations were confirmed in 3 patient (42.86%, 3/7). There was no case with drive genes changed, such as EGFR mutation, ALK rearrangement, ROS1 rearrangement, RET rearrangement, MET amplification or 14 exon skipping mutation. The median overall survival (OS) of 11 lung enteric adenocarcinoma patients was 9.0 months, Subgroup analysis the median OS of ALK/ROS1 primary point mutation patients was 6.5 months, the median OS of MSH2/MSH6 primary point mutation patients was 26.0 months. **Conclusion:** ALK/ROS1 primary point mutations or MSH2/MSH6 point mutations are the most frequent feature of heterozygous mutation in our study. The MSH2/MSH6 subgroup of the median OS is longer. Further investigations will be required to validate our findings.

Keywords: NGS, Lung enteric adenocarcinoma, Gene mutation

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-005 13 CASES OF MOLECULAR FEATURES ANALYSIS IN PULMONARY MUCOEPIDERMOID CARCINOMA

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Background: The cases of pulmonary mucoepidermoid carcinoma (PMEC) are extremely rare. There is only limited data on treatment outcome for chemotherapy in PMEC, and less so for targeted therapy such as targeted therapy with icotinib. The aim of this study is to investigate the molecular characteristics of pulmonary mucoepidermoid carcinoma (PMEC). **Method:** From July 2013 to December 2016, 13 PMEC patients received treatment. All the patients were diagnosed by pathology. We retrospectively reviewed the clinical data and genetic state. **Result:** EGFR mutation rate was 15.38% (2/13), and 2 cases were both L861Q point mutations, the relationship between EGFR gene status and gender (P=1.000), age (P=1.000), smoking (P=0.848) and stage (P=1.000) were no significant, respectively; the positive rate of MAML2 fusion gene was 45.45%(5/11). the relationship between MAML2 fusion gene status and gender (P=0.521), age (P=0.521), smoking (P=1.000) and stage (P=0.924) were no significant, respectively. **Conclusion:** The most common form change of pulmonary mucoepidermoid carcinoma is EGFR gene L861Q point mutation, MALM2 fusion gene exist in the EGFR gene wild type patients. icotinib treatment may benefit from patients with EGFR L861Q point mutations and MALM2 fusion gene.

Keywords: mucoepidermoid carcinoma, EGFR gene, MAML2 gene

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-006 NOVOSV: IDENTIFY AND PARSE THE PATTERN OF CHROMOSOMAL STRUCTURAL VARIATION

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Background: With the development of High-throughput DNA sequencing technologies, several tools have been developed aim at searching structural variations. However, most of available structural variation predication tools can only identity the abnormal connections, a systematically parsing the pattern of structure variation to obtain the length and connection type of SVs is still tough work. **Method:** In this study, we present a tool, NovoSV, which can identify the abnormal connections precisely, and based on associated abnormal connections NovoSV will report the length and connection type of the structural variation. **Result:** NovoSV took a BWA mapped results as input and identified abnormal connections and pattern of chromosomal structure variations would be reported. For validation, NovoSV was applied to target sequencing data derived from 10 samples, NovoSV identified 8 abnormal connections, and 7 of these results could be validated by polymerase chain reaction (PCR). When applied to whole-genome sequencing data derived from 5 samples, NovoSV reported 46 SVs with their length and connection type. Of the 4 random selected identified results, 3 were validated by Sanger sequencing. **Conclusion:** NovoSV is an efficient tool for chromosomal variation detection, which can accurately identify abnormal connections and parse the pattern of chromosomal variations. NovoSV has been validated on GNU/Linux systems, and an open source PERL program is available.

Keywords: NovoSV, seeds of structure variation, NGS

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-007 MOLECULAR SPECTRUM OF STK11 GENE MUTATIONS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER IN CHINESE PATIENTS

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Background: STK11 is commonly mutated in non-small cell lung cancer (NSCLC). In light of recent experimental data showing that specific STK11 mutantion can acquire oncogenic activities due to the synthesis of a short STK11 isoform, The aim of this study is to investigate whether this new classification of STK11 mutants can help refine its role as a prognostic marker. **Method:** A total of 879 patients with NSCLC were recruited between July 2012 and December 2014. The status of STK11 mutation and other genes were detected by the next generation sequencing (NGS). **Result:** STK11 gene mutation rate was 0.91% (8/879) in NSCLC, including p.K269fs*18 (1 patient), p.K329stop (1 patient), c.464 plus 1G>T (1 patient), p.D194E (1 patient), p.D176V (1 patient), p.D53Tfs*11 (1 patient), p.D194A (1 patient) and p.Y118* (1 patient), and median overall survival (OS) for these patients was 22.2 months. Among them, all patients were STK11 gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=6) co-occurring EGFR mutations had a median OS of 29.0 months and 22.2 months respectively (P=0.73); patients with (n=5) or without (n=3) co-occurring TP53 mutations had a median OS of 29.0 months and 22.2 months respectively (P=0.95); patients with (n=3) or without (n=5) co-occurring KRAS mutations had a median OS of not reached so far and 13.8 months respectively (P=0.02); patients with (n=2) or without (n=6) co-occurring SMARCA4 mutations had a median OS of 14.0 months and 37.0 months respectively (P=0.11); patients with (n=3) or without (n=5) co-occurring KEAP1 mutations had a median OS of not reached so far and 14.6 months respectively (P=0.20). **Conclusion:** STK11 mutations represent a distinct subset of NSCLC. NGS showed that STK11 mutations commonly co-existed with other driver genes. Our results show that STK11 mutations delineate an aggressive subtype of lung cancer for which a targeted treatment through STK11 inhibition might offer new opportunities.

Keywords: Non-small-cell lung cancer, Prognosis, STK11 mutation

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-008 SNAI1-EXPRESSION CANCER-ASSOCIATED FIBROBLAST INDUCE EPITHELIAL-MESENCHYMAL TRANSITION OF LUNGCANCER CELLS THROUGH MIR-33B

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Background: Lung cancer patients often have poor prognosis, on account of high propensity for metastasis. Cancer-associated fibroblasts (CAFs) are the main type of stromal cells in lung cancer tissue, which are activated by tumor cells, play a significant role in tumor development. However, it is uncertain whether CAFs induce lung cancer cells metastasis and which pathway is involved. Snail1 is a transcriptional factor and its expression in the stroma associates with lower rates of survivors in cancer patients. Nevertheless, it has not been determined how Snail1 regulate the crosstalk between stromal and tumor cells when it expresses in stroma. Altered expression of microRNA (miRNA) correalates with lung carcinogenesis and metastasis. Our previous study of miRNAs showed that the level of miR-33b was obviously decreased in lung adenocarcinoma cell lines and lung cancer tissues, and when miR-33b was elevated, it can suppressed tumor cell growth and EMT in vitro and in vivo experiments. **Method:** (1) We co-culcured four different human lung cancer cells (A549, H1299, SPC-a-1, LTEP-a-2) with control medium, NFs and CAFs,then we examined lung cancer cells motility, migration, invasion, miR-33b expression level, relevant mRNAs and proteins expression levels. (2) A549 and H1299 cells was transfected with miR-33b mimics or with miR-NC prior to CAF stimulation, then subjected to wound healing assay, Transwell assay, qRT-PCR, immunoblotting assay. (3) Using coculture lung cancer cell lines with SNAI1 transfected CAFs models, we explore the role of Snail1 in CAFs cells. **Result:** (1) Cocultivation of CAFs with lung cancer cells induced downregulation of miR-33b in lung cancer cells and promoted epithelial cells epithelial-mesenchymal transition (EMT). (2) MiR-33b overexpression by transfecting cancer cells with miR-33b mimics reverted CAFs induced EMT. (3) Transfection of CAFs with SNAI1 enhanced CAFs modulation on lung cancer cells EMT when CAFs co-cultured with A549 and H1299 cells, whereas si-SNAI1 attenuated CAFs modulation role. **Conclusion:** The induction of cancer cells EMT by CAFs is a key mechanism underlying the acquisition of cancer cells aggressive propensity. And CAFs induce lung cancer cells EMT in a miR-33b-mediated manner. Expression of Snail1 in fibroblasts was essential for the induction effect of CAFs on lung cancer cells EMT.

Keywords: Snail1, cancer-associated fibroblasts, MiR-33b

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-009 METABOLOMIC ANALYSIS IN LUNG CANCER

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Background: Metabolomics measures low weight molecules, generally called metabolites, and it is an effective technique to understand how metabolism is changed by various factors, including environment and disease, particularly malignant disease. Body fluids, for example sputum or urine, harvested non-invasively havebeen used in remarkable recent developments of omics analysis technology, yielding highly precise results for diagnosis of oral cancer, breast cancer, and pancreatic cancer. 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 metabolomics as an aspect of lung cancer. **Method:** We obtained resected specimens from patients with lung cancer after obtaining informed consent for this study, and compared the metabolism profile of the normal tissue portion with carcinoma tissue in 80 patients in terms of various clinical aspects. Metabolomic analysis was performed by capillary electrophoresis / time-of-flight mass spectrometry (CE-TOFMS) of metabolites of the lung tissue and analysed

ionized tissue which contained the most main metabolites. **Result:** Analysis of serum and metabolite organization by CE-TOFMS revealed that the intermediate metabolite levels of several pathways changed markedly in lung cancer tissue. We can identify a characteristic metabolic marker in advanced lung cancer tissue 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 resected tissue 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 cheap cancer screening are expected in the future.

Keywords: metabolomics, lung cancer

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-010 ONCOGENIC ROLE OF PKP1 IN NON-SMALL-CELL LUNG CANCER.

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Background: Non-Small-Cell Lung Cancer (NSCLC) is often diagnosed at an advanced stage and carries a poor prognosis. Greater knowledge of the molecular origins and progression of lung cancer may lead to improvements in the treatment and prevention of the disease. Although it is well-known the importance of desmosomes in cell-to cell adhesion, several evidences suggest that some of their structural proteins may have additional and relevant roles in cancer development. In this regard, Plakophilin 1 (PKP1) is up-regulated in primary NSCLC tumors (SCC and AD) suggesting an oncogenic role in tumor development that it is probably beyond their role into cell-to-cell adhesion. **Method:** In order to gain greater insight into the multifuntional role of PKP1 in NSCLC tumours, we have generated functional models in that express different levels of PKP1 protein using siRNA, Crispr Cas9 system or lentivirus-vectors. We have carried out several phenotypical assays to demonstrate the PKP1´s role in tumor development into NSCLC cell lines (proliferation, cell cycle, apoptosis, wound healing, BrdU and colony assays, etc.) and an *in vivo* xenograph assays using CrispR-Cas9. **Result:** On the one hand, when we inhibit PKP1 in cell lines with high PKP1 protein basal level, we observe an increment in migration in the wound-healing assays. This PKP1-function formally can be considered a tumour-suppressor activity. On the other hand, we have also observed pro-oncogenic activity after PKP1 expression inhibition. In this way, after the knock-down or knock-out PKP1, we have observed cell-growth and cell-cycle arrest and higher levels of apoptosis. Additonally, when we over-express PKP1 in a cell line with no PKP1 protein basal level,we detect cell growth and S phase increment, and apoptosis reduction; gainning new evidences that support pro-oncogenic role of this protein. To determine the results of these apparently opposing tumoral activity, we have developed and *in vivo* xenograph assay using CrispR-Cas9. The tumoral burden dynamics in the model clearly indicate that, although the loss of PKP1 promotes cell-migration, overall the role of PKP1 is pro-oncogenic. Currently, we are performing a PKP1 immunoprecipitation and an expression array in order to elucidate PKP1 tumoral functions that could help us to explain these new pro-oncogenic activities that remain unknown. **Conclusion:** In conclusion, our results indicate PKP1 protein has a contribution in NSCLC development and it may be a potential useful for NSCLC diagnosis, prognosis and treatment.

Keywords: PKP1, oncogen, NSCLC

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-011 CLINICAL AND MOLECULAR FEATURES OF LUNG CANCERS WITH INCREASED FGFR1 MRNA AND/OR GENE COPY NUMBER

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Background: Lung cancer cell line data suggest FGFR1 status defined by FGFR1 mRNA levels and FGFR1 gene copy number can predict sensitivity to FGFR tyrosine kinase inhibitors (TKIs). **Method:** A phase II biomarker preselected trial of ponatinib, an FGFR1, FGFR2, and FGFR4 targeted TKI was designed. Patients with metastatic EGFR- and ALK-negative lung cancers (both NSCLC and SCLC) were pre-screened for FGFR1 mRNA levels by in-situ hybridization (ISH) and FGFR1 gene copy number by silver in-situ hybridization (SISH). Positivity criteria for ISH were defined as a score of 3 (Dot clusters seen in 1 to <10% tumor cells; otherwise >10 dots/cell in ≥ 10% tumor cells), or 4 (Dot clusters seen in ≥ 10% of tumor cells). Positivity for SISH was defined as an average of ≥ 4 FGFR1 signal clusters/nucleus or FGFR1/CEN8 ratio ≥ 2.0. Clinical factors including sex, histology, age and sites of metastases at diagnosis of stage IV disease, smoking status, status of other known molecular drivers, and response to initial platinum-doublet therapy for stage IV disease were collected. **Result:** From 11/2013 to 05/2017, the study has pre-screened 163 patient samples for FGFR1 ISH and SISH. Thirty-eight (23.3%) had insufficient tissue; four had incomplete clinical or FGFR1 information. Clinical variables according to FGFR1 ISH/SISH status (n=121) are summarized in **Table 1.** Impact of alternate positivity cut-points, outcomes of patients treated with ponatinib and survival analysis according to ISH/SISH subgroups will be presented.

Table 1. Clinical and molecular characteristics of FGFR1 ISH / SISH subgroups

	FGFR mRNA (ISH) and gene copy number (SISH)			
	ISH+/SISH+	ISH-/SISH-[1]	ISH+/ SISH-	ISH-/ SISH+
N	6	67	44	4
Median age at diagnosis	67 (56-73)	63 (42-85)	65 (32-89)	67 (52-70)
% Male	5/6 (83%)	33/67 (49%)	21/44 (48%)	2/4 (50%)
Histology				
Adenoca/adenosquamous	2/6 (33%)	50/67 (75%)	26/44 (59.1%)	3//4 (75%)
Squamous	1/6 (17%)	10/67 (15%)	10/44 (22.7%)	1/4 (25%)
Small cell / LCNE	3/6 (50%)	8/67 (12%)	8/44 (18.2%)	0/4 (0%)
Sites at stage IV diagnosis beyond lung				
Lymph node	5/6 (83%)	43/67 (64%)	37/44 (84%)	4/4 (100%)
Pleura / Pericardium	1/6 (17%)	24/67 (36%)	15/44 (34%)	1/4 (25%)
Bone	1/6 (17%)	26/67 (39%)	12/44 (27%)	1/4 (25%)
Brain	1/6 (17%)	11/67 (16%)	8/44 (18%)	1/4 (25%)
Liver	3/6 (50%)	8/67 (12%)	6/44 (14%)	1/4 (25%)
Adrenal	1/6 (17%)	6/67 (9%)	2/44 (5%)	0/4
Soft tissue	0/6	2/67 (3%)	5/44 (11%)	0/4
Smoking Hx				
Never smoker	1/6	8/67 (12%)	7/44 (16%)	0/4
>30 PY	4/6 (67%)	28/67 (42%)	19/44 (43%)	3/4 (75%)
Smokers who quit smoking < 15 years	4/5 (80%)	30/59 (51%)	18/34 (53%)[2]	2/4 (50%)
Molecular co-drivers (denominator = tested samples)				
EGFR mt	0/3	0/56	0/40	0/4
ALK	0/3	0/60	0/40	0/4
KRAS mt	0/3	29/54 (52%)	16/36 (47%)	1/4 (25%)
ROS1	0/3	0/42	0/28	0/4
MET/CEP7 > 5.0	0/3	0/44	0/26	0/4
MET exon 14	0/2	2/33 (6%)	1/21 (5%)	0/2
BRAF V600	0/2	0/46	0/32	0/4
HER2 mutation / amplification	0/1	2/45 (4%) (one mutation; one HER2/ CEP17 = 5.0	0/34	0/4
RET	1/3 (33.3%)	0/35	0/22	0/4
NTRK	Not tested	Not tested	1/1	Not tested
MEK	0/1	0/44	0/32	0/4
NRAS	0/2	0/44	1/32 (3.1%)	0/4
1st line platinum-doublet response				
PR/CR	4/5 (80%)	29/42 (69%)	22/31 (71%)	1/3 (33%)
SD	1/5 (20%)	7/42 (17%)	3/31 (10%)	1/3 (33%)
PD	0/5	6/42 (14%)	6/31 (19%)	1/3 (33%)

[1] 2 patients with ISH- / SISH inadequate counted as ISH- / SISH-

[2] 3 patients did not have smoking quit date

Conclusion: Although the numbers were small, the FGFR1ISH+/SISH+ subgroup had a greater percentage small cell histology, liver metastases at diagnosis and male sex compared to other FGFR1 subgroups. FGFR1 ISH and/or SISH positivity can overlap with other known oncogenic drivers suggesting that the initial cut-points for FGFR1 positivity used may be too low to identify a true FGFR1 addicted state.

Keywords: lung cancer, FGFR1, biomarker

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-012 THE EPIGENETIC ROLE OF LSD1+8A IN SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a neuroendocrine tumor which account for 15% of all lung cancers. SCLC is characterized by rapid progression which led metastasis to distant organs and represented poor prognosis. Although there were various molecular targeted therapies in SCLC that were already under investigation, results have been disappointing. The focus on biological pathways has recently shifted from genetic to epigenetic regulations. Histone methylation is one of the epigenetic mechanism which has pivotal role in gene expression, cell cycle and differentiation. Lysine-specific demethylase 1 (LSD1)/KDM1 is a histone modifier that is expressed in certain human cancers including SCLC. LSD1+8a is one of the isoform of LSD1 that was reported to be restricted in neural tissues and it plays critical role in neuronal differentiation. The aim of this study is to elucidate the epigenetic role of LSD1+8a in SCLC. **Method:** The expression of LSD1 and LSD1+8a mRNAs were analyzed by qPCR in several cancer cell lines. Neuroendocrine markers were detected by qPCR in several SCLC cell lines. The Pearson correlation test was performed to investigate the correlation between LSD1+8a and neuroendocrine markers. siRNA against specific to exon 8a was designed and knockdown LSD1+8a isoform specifically. Cell proliferation assays following knockdown of LSD1+8a were performed in LSD1+8a expressed SCLC cell lines. **Result:** LSD1 mRNA was expressed in majority of SCLC cell lines, interestingly LSD1+8a mRNA was detected in small subset of SCLC cell lines. There were positive correlations of LSD1+8a and neuroendocrine marker genes such as chromogranin A (CHGA), enolase2 (ENO2), neural cell adhesion molecule (NCAM) and synaptophysin (SYP) in human cancer cell lines. The suppression of LSD1+8a by siRNA drove to decrease expression of neuroendocrine marker genes in SCLC and inhibited cell proliferation in LSD1+8a expressed cell. **Conclusion:** LSD1+8a could play an important role in SCLC.

Keywords: SCLC, LSD1, LSD1+8a

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-013 INVESTIGATION OF GENOMIC AND TCR REPERTOIRE EVOLUTION OF AAH, AIS, MIA TO INVASIVE LUNG ADENOCARCINOMA BY MULTIREGION EXOME AND TCR SEQUENCING

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Background: Carcinogenesis may result from accumulation of molecular aberrations (molecular evolution) and escaping from host immune surveillance (immunoediting). It has been postulated that atypical adenomatous hyperplasia (AAH) represents preneoplastic lesion that may progress to adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and further to frankly invasive adenocarcinoma (ADC). However, due to lack of appropriate study materials, the molecular and immune landscape of AAH, AIS or MIA have not been well studied and the definition and management of these lesions remain controversial. **Method:** With the intent to delineate the pivotal molecular and immune events during early carcinogenesis of lung adenocarcinoma, we have collected 119 resected pre- and early neoplastic lung lesions including AAH (N=24), AIS (N=27), MIA (N=54) and ADC (N=14) from 53 patients including 41 patients presenting with multifocal lesions and 25 patients carrying more than one type of pathology. Two to five spatially separated regions from each lesion were subjected to whole exome sequencing and T cell receptor sequencing. **Result:** Mutation burden (average SNVs) was found to progressively increase from 1.32/Mb in AAH to 2.55/MB in AIS, 5.42/MB in MIA and 15.38/MB in ADC. Genomic heterogeneity has also become more complex with neoplastic progression with mean Shannon index of 1.53 in AAH, 1.78 in AIS, 1.56 in MIA and 1.79 in ADC. An increase in C>A transversions coincident with a decrease in A>G transitions and progressively increasing APOBEC enrichment scores (4.13 in AAH, 5.63 in AIS, 6.02 in MIA and 6.59 in ADC) were observed with neoplastic disease progression. Furthermore, phylogenetic analysis revealed varying evolutional processes in AAH, AIS, MIA and ADC with canonical cancer gene mutations in *KRAS*, *ATM*, *TP53* and *EGFR etc.* as key drivers in a subset of patients. TCR sequencing demonstrated a progressive decrease in T cell density (average percent T cells among all nuclear cells: 12% in AAH, 8% in AIS, 7% in MIA and 4% in ADC) and a progressive decrease in productive TCR clonality (average productive TCR clonality: 0.0434 in AAH, 0.0427 in AIS, 0.0399 in MIA and 0.0395 in ADC) suggesting suppressive T cell repertoire in more advanced diseases. **Conclusion:** Our results provide molecular evidence supporting the model of early lung carcinogenesis from AAH, to AIS, MIA and ADC and demonstrated that with disease progression, genomic landscape of lung neoplastic lesions has become progressively more complex along with progressive immunosuppressive TCR repertoire.

Keywords: Genomic evolution, Immune landscape, Preneoplastic lung lesions

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-014 SIMULTANEOUS GENE PROFILING OF ADVANCED NSCLC: SINGLE-MOLECULE QUANTIFICATION OF DNA AND RNA BY NCOUNTER3D™ TECHNOLOGY

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Background: Currently, assessment of several tumor drivers is critical for individualized treatment of non-small cell lung cancer (NSCLC). Tools for molecular profiling are based on DNA, RNA and protein (PCR, NGS, FISH, IHC). However, these tests have several disadvantages including hands-on-time and tissue mass requirements. Nanostring digital barcoding technology enables simultaneous assay of different analytes, DNA and RNA from a single sample with 3D Biology Technology. **Method:** The nCounter Vantage 3D SNV:Fusions Lung Assay was used to analyze a total of 36 formalin-fixed paraffin embedded (FFPE) samples from advanced NSCLC patients. Samples were known to harbor mutations (*EGFR, KRAS, NRAS, PIK3CA, BRAF, P53)* or gene-fusion rearrangements (*ALK, ROS1, RET, NTRK1*) as verified by sequencing (Ion Torrent, Gene Reader), nCounter Elements, IHC and/or FISH. Probes were designed to target 25 genes for SNVs (104 different point and InDel mutations) as well as four genes for fusion transcripts (*ALK, ROS1, RET, NTRK1*) including 33 specific variants. The 3D workflow requires pre-amplification of gDNA, whereas RNA does not require any enzymatic treatment. After hybridization, the analytes (DNA/RNA) are pooled for simultaneous, single-lane, digital counting in total turnaround of 3 days. A total amount of 5ng DNA and 150ng RNA from two4-micron FFPE-sections was used for the assay without microdissection. **Result:** A total of 72 analyses (DNA/RNA) were performed with an evaluation pass of 97.2% (70/72 analyses yielded results) and 89% concordant results (64/72). Sensitivity of the technique was 92.1%. Among 41 SNVs interrogated in this study 34 were successfully detected (two not evaluable). Five new mutations were found involving *NRAS, FBXW7, GNA11, FGFR2* and *KRAS* genes. Of those, only two were considered false positives as they were not confirmed by alternative sequencing and/or PCR. The remaining three were not assessable for test confirmation. For gene fusion analysis, 13 known positive samples were tested. All fusion transcripts were detected for *ALK* (n=5) *RET* (n=2) and *NTRK1* (n=1). For *ROS1* (n=5) there were 2 false negatives only detected by nCounter Elements target-specific assay. **Conclusion:** We have shown that the SNV detection chemistry can be successfully combined with fusion gene expression analysis by using the nCounter 3D™ single-workflow. The Nanostring nCounter Vantage 3D SNV:Fusions Lung Assay is highly efficient in detecting hotspot mutations as well as gene rearrangements. The assay is simple, features a brief hands-on time and requires low amounts of genomic material, supporting minimal use of precious samples.

Keywords: NSCLC, SNV, gene fusions

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-015 MUTATION PATTERNS IN A SWEDISH NON-SMALL CELL LUNG CANCER COHORT

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Background: Non-small cell lung cancer (NSCLC) is a heterogeneous disease with unique combinations of somatic molecular alterations in individual patients, as well as significant differences in populations across the world with regard to mutation spectra and mutation frequencies. Here we describe the mutational pattern and linked clinical parameters in a population-based Swedish NSCLC cohort. **Method:** The cohort consists of 354 patients treated surgically at the University Hospital in Uppsala between 2006 to 2010. DNA was extracted from either fresh frozen (n=200) or formalin fixed paraffin embedded (FFPE; n=154) tissues prior to library preparation with Haloplex capture probes and Illumina Hiseq sequencing. The gene panel covers all exons of 82 genes, that have been shown to harbor mutations relevant for NSCLC development, and utilizes a reduced target fragment length and two strand capture compatible with degraded FFPE samples. **Result:** In order to avoid a systematic technical bias between FFPE and fresh-frozen samples, we adapted the sequencing depth and the bioinformatic pipeline for variant calling to obtain uniform sequence coverage and mutational load across the two sample types. TP53 was the most frequently mutated gene in both adenocarcinoma (AdC; 47%) and squamous cell carcinoma (SqC; 85%). KEAP1 or NFE2L2 was mutated in 19% of AdC and 23% of SqC in a mutually exclusive fashion. In AdC, hotspot alterations in driver genes could be seen in KRAS (43%), EGFR (13%), ERBB2 (3%, exon 20 insertions), BRAF (2%) and MET (1%, exon 14 skipping). Mutations in STK11 were observed in 21% of AdC cases. In SqC, frequently mutated genes were MLL2 (26%), PIK3CA (20%), CDKN2A (15%) and DDR2 (4%). Survival analysis revealed a worse overall survival for AdC patients with a mutation in either TP53, STK11 or SMARCA4. In the KRAS-mutated group poor survival appeared to be linked to concomitant TP53 or STK11 mutations, and not to KRAS mutation as a single aberration. In SqC a worse overall survival could be observed for patients with MLL2 mutations. SqC patients with mutations in CSMD3 had trend for a better prognosis. **Conclusion:** Here we have evaluated the mutational status of a Swedish NSCLC cohort. Technical adaption allowed analysis across both FFPE and fresh-frozen samples. Overall, the high frequency of TP53 and KRAS mutations might be related to the large fraction of smokers. Poor prognosis was linked to mutations in TP53, STK11 or SMARCA4 in AdC and MLL2 mutations in SqC.

Keywords: Swedish NSCLC cohort, Mutational profiling, targeted next-generation sequencing

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-016 PULMONARY SARCOMAS: A COMPREHENSIVE GENOMIC PROFILING STUDY

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Background: Pulmonary sarcomas (PSRC) are uncommon primary thoracic malignancies that are often clinically aggressive. Comprehensive genomic profiling

(CGP) can identify biomarkers for both targeted and immunotherapy. We used CGP to analyze novel treatment options for patients with advanced PSRC. **Method:** CGP using hybridization-captured, adaptor ligation-based libraries for up to 406 genes plus select introns from 31 genes frequently rearranged in cancer was performed on 19 PSRC; 15 cases also underwent RNA sequencing for enhanced fusion detection in 265 of these genes. All classes of genomic alteration (GA) were assessed simultaneously: base substitutions, indels, rearrangements, and copy number changes. Clinically relevant GA (CRGA) are GA associated with drugs on the market or under evaluation in clinical trials. Tumor mutational burden (TMB) was determined on 1.1 Mb of sequenced DNA. **Result:** In this cohort were 10 sarcoma NOS, 5 pulmonary artery intimal sarcomas, 2 pleomorphic/MFH sarcomas, 1 primary IMT, and 1 primary SFT, including 1 stage I, 1 stage II, 9 stage III and 8 stage IV tumors. Patient median age was 52 years (range 33–81 years), with 7 female and 12 male patients. The mean GA per sarcoma was 5.7. Notable alterations not presently considered actionable affected *TP53* (53%), *CDKN2A* (32%), *CDKN2B* (27%), and *RB1* (21%). CRGA alterations were detected in *PDGFRA*, *RICTOR*, *CDK4* and *KIT* (11% each), and *EGFR*, *TSC2*, *ALK* and *BRAF* (5% each); 9 (47%) PSRC featured ≥1 CRGA. An *ALK* fusion was detected in an IMT localized only to the lung and diagnosed as a primary lesion. Inactivation of *SMARCA4* through mutation and loss of heterozygosity was found in 1 case. Mean TMB was 8.65 mutations/Mb (16% had TMB >10 mut/Mb, 11% had TMB >20 mut/Mb); cases with TMB >20 mut/Mb lacked characteristically targetable CRGA. All samples tested for MSI (n=7) were microsatellite stable. Assessment of therapeutic intervention and responses is ongoing. **Conclusion:** PSRC is an extremely rare primary lung malignancy characterized by a relatively high frequency of GA. CGP identified various potentially targetable alterations in this small series, particularly driver mutations or fusions in tyrosine kinases and cell cycle regulatory genes. Furthermore, characteristic genomic profiles can provide diagnostic insight, as for *SMARCA* loss or *ALK* fusions. This study also identified a significant number of PSRC with intermediate or high TMB, indicating potential immunotherapy options for these patients. Further study of CGP to help manage patient care and minimize suffering from this rare pulmonary malignancy appears warranted.

Keywords: Biomarkers, comprehensive genomic profiling, pulmonary sarcoma

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-017 ABERRANT EXPRESSION OF LONG NON-CODING RNAS FROM PSEUDOGENE LOCI HIGHLIGHTS ALTERNATIVE MECHANISMS OF CANCER GENE REGULATION

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Background: Less than half of lung adenocarcinoma (LUAD) patients harbour clinically actionable driver genes, emphasizing the need to explore alternative mechanisms of cancer gene deregulation. Long non-coding RNAs (lncRNAs) have emerged as important players in cell biology, and can be exploited by tumours to drive the hallmarks of cancer. Pseudogenes are DNA sequences that are defunct relatives of their functional protein-coding parent genes but retain high sequence homology. Interestingly, several lncRNAs expressed from pseudogene loci have been shown to regulate the protein-coding parent genes of these pseudogenes *in trans* due to sequence complementarity. We hypothesize that this phenomenon occurs more broadly than previously realized, and that these events provide an alternative mechanism of cancer gene deregulation in LUAD tumourigenesis that has clinical implications. **Method:** Illumina HiSeq reads were processed and aligned to the ENSEMBL annotation file in order to derive the most complete set of both protein-coding and non-coding genes. Two datasets were selected due to their paired nature, complete with both LUAD and non-malignant lung profiles (TCGA n=108, BCCA n=72). LncRNAs were filtered based on positional overlap within pseudogene loci, and a Wilcoxon sign-rank test was run to identify lncRNAs with significantly altered expression between paired tumour and normal tissues (FDR $p<0.05$). To identify lncRNAs that likely regulate protein-coding parent gene expression *in trans*, tumours were ranked by lncRNA expression, and protein-coding parent gene expression of top and bottom ranked tertiles was compared by Mann Whitney U-test ($p<0.05$). Survival analysis was performed using a Cox proportional hazard model. **Result:** Our analysis has identified 129 lncRNAs expressed from pseudogene loci that were significantly deregulated in LUAD in both datasets. Remarkably, many of these deregulated lncRNAs (i) were expressed from the loci of pseudogenes related to known cancer genes, (ii) had expression that significantly correlated with protein-coding parent gene expression, and (iii) protein-coding parent gene expression was significantly associated with survival. For example, *RP11-182J1.1* is a lncRNA expressed from a pseudogene to *EGLN1*, a previously described cancer gene involved in regulation of tumour hypoxia. *RP11-182J1.1* was underexpressed in LUAD and significantly positively correlated with *EGLN1* expression. In addition, *EGLN1* was significantly associated with patient survival (p=1.2e-08) emphasizing the clinical potential of these lncRNAs. **Conclusion:** This work uncovers evidence to suggest the lncRNA-pseudogene-protein-coding gene axis is a prominent mechanism of cancer gene regulation. Further characterization of this understudied gene regulatory mechanism could lead to novel therapies that silence oncogenes or reactivate tumour suppressor genes.

Keywords: non-coding RNA, genetics, gene regulation

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-018 GENOMIC PROFILING OF DRIVER GENE MUTATIONS IN 498 CHINESE NSCLC PATIENTS

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Background: Identifying genomic alterations of actionable driver genes in non-small cell lung cancer (NSCLC) such as *EGFR, ALK, ROS1* has been used as important evidences for firstline treatments. Patients with driver mutations received matched target drugs could have significantly longer progression free and overall survival. **Method:** FFPE tumor samples of 498 Chinese NSCLC patients including 279 males (56%) and 219 females (44%) with a median age of 60 were collected for next-generation sequencing (NGS)-based multi genes panel assay. Genomic alterations including single base substitution, short and long insertions/deletions, copy number variations, and gene rearrangement and fusions in selected genes were assessed. **Result:** Different histological subtypes of adenocarcinoma (417/498, 83.7%), squamous carcinoma (68/498, 13.7%), mixed carcinoma (6/498, 1.2%) and large cell carcinoma (7/498, 1.4%) were included in the Chinese NSCLC cohort. The top ranked genomic alterations in driver genes were *EGFR* (47.8%), *KRAS* (10.0%), *ALK* fusions (8.2%), *PIK3CA* (7.0%), *HER2* (6.2 %), *PTEN* (3.6%), *BRAF* (2.6%), *MET* (3.6%), *RET* fusions (1.6%), and *ROS1* fusions (0.8%), which counts up to 86.9% of the 498 patients with at least one driver mutation. In addition to common driver mutations, rare mutation types such as *EGFR-KDD, EGFR-RAD51, AMOTL2-NTRK1* and KIF13A-RET were also detected by deep sequencing assay. **Conclusion:** Our study revealed the landscape of driver gene mutations in 498 Chinese NSCLC patients. Comparing to the largest public NSCLC cohort from Foundation Medicine, mostly Western populations (N=6823, PMID: 27151654), we identified similar frequencies of some driver genes, but more *ALK* fusions (8.2% vs 3.9%), *EGFR* mutations (47.8% vs 20.0%) as druggable target genes, and less *KRAS* mutations (10.0% vs 32.0%) consistent with reported results. Totally 78.7% of the Chinese patietns harbored at least one mutaiton in the 8 core driver genes including *EGFR, ALK, BRAF, ERBB2, MET, ROS1, RET*, or *KRAS* (vs. 71% in the FMI cohort). Our findings demonstrated that genomic profiling of driver genes in NSCLC showed significant differences among racial or ethnic groups, which indicated different treatment options between Eastern and Western populations.

Keywords: Chinese NSCLC patients, next-generation sequencing, Genomic Profiling

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-019 UTILITY OF CIRCULATING TUMOR DNA (CTDNA) IN PROGNOSTICATION OF LUNG CANCER VS. OTHER CANCER TYPES

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Background: The detection of circulating tumor cells and the corresponding expression of tumor genes has been utilized as a prognostication tool for assessing therapeutic response to various anti-cancer therapies including immune cell therapy, chemotherapy and natural products-based anti-cancer therapy at the Lung Center of the Philippines (LCP) since 2014. Recently, circulating tumor DNA (ctDNA) has emerged as a new promising test for noninvasive detection of several cancers including lung cancer. This study aims to evaluate the utility of ctDNA in prognostication of lung cancer vs. other cancer types. **Method:** Blood sample from cancer patients (7.5 ml) were extracted for DNA and RNA using the QIAamp Circulating Nucleic Acid Kit, Qiagen, and subjected to two tests, 1) detection of EGFR mutation using the therascreen EGFR Plasma RGQ PCR Kit, and 2) detection of tumor gene expression level using an in-house two gene panel (i.e. EGFR and ERBB2). Three groups were compared, group A (Lung cancer, 7 cases), group B (Breast cancer, 7 cases) and group C (one case of Ovarian, one case of Colon and one case of Mixed Epithelial). The protocol is approved by the Technical and Ethics Review Board of the hospital. **Result:** Data show that in groups B and C, no EGFR mutation was detected while in group A, two out of 7 cases showed Exon 19 Deletion. The in-house two gene panel showed group A to have two cases of upregulated ERBB2 (i.e., 5-9.5 folds), group B to have three cases of upregulated ERBB2 (i.e., 1.6-6.5 folds) and one upregulated EGFR (i.e., 15.7 folds) and group C to have one case of upregulated ERBB2 (i.e., 7.4). ctDNA with therascreen for EGFR mutation detection has less sensitivity (i.e.2/17) as compared to ctDNA with in-house two panel for tumor gene expression (i.e., 7/17), although specific to detect EGFR-associated lung cancer. The data also suggest a possible preponderance of copy number-driven cancer as compared to mutation-driven cancer in these set of patient samples. **Conclusion:** ctDNA-based tumor detection can be useful as a prognostication tool however it should be in combination with a compatible detection platform that may indicate copy-number driven or mutation-driven cancer.

P2.02-020 MOLECULAR CHARACTERISTICS OF PATIENTS WITH PTEN MUTATIONS IN CHINESE NON-SMALL CELL LUNG CANCER

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Background: Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a known tumor suppressor in non-small cell lung cancer (NSCLC). Because of the rarity of those mutations, associated clinical features and prognostic significance have not been thoroughly described so far. The aim of this study is to investigate mutations and prognosis of NSCLC harboring PTEN mutations. **Method:** A total of 402 patients with non-small-cell lung cancer were recruited between July 2012 and December 2014. The status of PTEN mutation and other genes were detected by the next generation sequencing. **Result:** PTEN gene mutation was detected in 1.99% (8/402) NSCLC patients, including A333fs*10 (2 patients), D252N (1 patient), P38S (1 patient), Q171E (1 patient), S59* (1 patient), S10R(1 patient) and Y225Ifs*18(1 patient), and median overall survival (OS) for these patients was 19.7 months. Among them, 7 patients with co-occurring mutations had a median OS of 23.3 months, and OS of the 1 patient without complex mutations was 14.6 months. No statistically significant difference was found between the two groups (P=0.35). Briefly, patients with (n=5) or without (n=3) co-occurring EGFR mutations had a median OS of 33.6 months and 16.0 months respectively (P=0.33); patients with (n=4) or without (n=4) co-occurring TP53 mutations had a median OS of 14.9 months and 33.5 months respectively (P=0.18); patients with (n=2) or without (n=6) co-occurring DNMT3A mutations had a median OS of 17.8 months and 24.8 months respectively (P=0.27). **Conclusion:** Our results demonstrated that decreased PTEN gene mutation correlated with poor overall survival in non-small-cell lung cancer patients. PTEN gene mutation may define a subset of patients with lung cancer appropriate for investigational therapeutic strategies.

Keywords: PTEN mutation, Non-small-cell lung cancer, Prognosis

P2.02-021 PREVALENCE OF PTPRD GENE MUTATIONS IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: PTPRD, encoding protein tyrosine phosphatases receptor type D, is located at chromosome 9p23-24.1, a loci frequently lost in many types of tumors. Recently, PTPRD has been proposed to function as a tumor suppressor gene. The aim of this study is to investigate mutations and prognosis of non-small-cell lung cancer(NSCLC) harboring PTPRD mutations. **Method:** A total of 962 patients with NSCLC were recruited between July 2012 and December 2014. The status of PTPRD mutation and other genes were detected by next generation sequencing. **Result:** PTPRD gene mutation was detected in 0.64% (6/962) NSCLC patients, including V693F (1 patient), V330L (1 patient), T1103A (2 patients), D388Y (1 patient) and R1692G plus G1213V (1 patient), and median overall survival (OS) for these patients was 31.4 months. Among them, all patients were PTPRD gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=4) co-occurring EGFR mutations had a median OS of 41.0 months and 20.6 months respectively (P=0.06); patients with (n=4) or without (n=2) co-occurring TP53 mutations had a median OS of 27.6 months and 26.0 months respectively (P=0.79). **Conclusion:** PTPRD gene mutation coexist with other gene mutation in NSCLC. EGFR and TP53 gene accompanied may have less correlation with PTPRD mutation in NSCLC patients. Results of ongoing studies will provide more insight into effective treatment strategies for patients with PTPRD mutations.

Keywords: PTPRD mutation, Non-small-cell lung cancer, Prognosis

P2.02-022 ALTERNATIVE REGULATION OF CANCER-ASSOCIATED GENES THROUGH MODULATION OF LONG NON-CODING RNAS

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Background: Uncovering novel mechanisms of cancer-gene regulation may reveal new actionable targets to direct the treatment of patients who do not harbour targetable molecular drivers of lung cancer. Long non-coding RNAs (lncRNAs), are a class of transcripts that hold an emerging role in cell biology, particularly in gene regulation. These genes have since been implicated in cancer-associated phenotypes, and may represent attractive therapeutic intervention points; however, prediction of downstream regulatory targets of lncRNAs has been impeded due to their complex tertiary structure. Recently, a subset of lncRNAs has been shown to regulate the expression of neighbouring protein-coding genes in *cis*. Here we take a novel approach to identify lncRNAs deregulated in lung adenocarcinoma (LUAD) and examine their roles in the expression modulation of their cancer-associated protein-coding *cis*-partner genes. **Method:** RNA-sequencing was performed on 36 LUAD tumour samples with matched adjacent non-malignant tissue obtained via microdissection to 90% purity. Significantly deregulated lncRNAs and neighbouring protein-coding genes were identified by comparison of matched tumour and non-malignant normalized read counts (Wilcoxon Signed-Rank Test, FDR-BH<0.05). Fifty LUAD tumours with paired normal tissue from The Cancer Genome Atlas (TCGA) were used to validate these findings. Cox-Proportional Hazard analysis was performed on both datasets to assess survival associations of significantly deregulated lncRNAs. **Result:** Our approach revealed greater than 500 lncRNAs that were significantly deregulated between LUAD and matched normal tissues. Many of these lncRNAs have neighbouring protein-coding genes that also display deregulated expression patterns. Of particular interest are the protein-coding-target genes that have been previously implicated in cancer, including *OIP5*, which is involved in chromatin segregation, as well as *HMGA1*, which contributes to cell transformation and metastasis. In both of these cases, the neighbouring lncRNA is significantly underexpressed while the protein-coding gene is significantly overexpressed, suggesting a negative regulatory function of the lncRNA. Moreover, survival analyses revealed that patients with high expression of either *OIP5* or *HMGA1* had significantly shorter overall survival. Strikingly, patients with low expression of the lncRNA near *OIP5* also displayed poorer overall survival, illustrating the clinical opportunity that these genes present. **Conclusion:** Our results highlight the landscape of lncRNA deregulation in LUAD and uncover a role of these non-coding transcripts in the *cis*-regulation of neighbouring protein-coding genes, many of which have been described in cancer and predict patient survival. Further characterization of this alternative lncRNA-mediated cancer-gene regulatory mechanism may reveal novel therapeutic targets that may improve treatment for LUAD patients without well defined molecular drivers.

Keywords: gene regulation, non-coding RNA, epigenetics

P2.02-023 TARGETED GENE EXPRESSION PROFILING TO EVALUATE MINIMAL DIAGNOSTIC FFPE-BIOPSIES FROM NSCLC-PATIENTS

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Background: The molecular analysis of non-small cell lung cancer (NSCLC) is limited by the availability of only small biopsies or cytological specimens that are procured for diagnostic purpose. The nuclease protection method provides the possibility to analyze minimal amount of formalin fixed paraffin embedded (FFPE) tissue without previous extraction steps. We tested this technique and compared it to the traditional methods RNA sequencing (RNAseq) and immunohistochemistry (IHC). **Method:** The nuclease protection method (HTGmolecular) in combination with next-generation sequencing was used to measure gene expression of 549 immune-oncology genes in FFPE samples from NSCLC-patients. Standardized minimal tissue amounts were used for 12 samples (4 tissue circles, 4µm thick, 1 mm in diameter, from a tissue microarray). Of these tissue sections also two corresponding original tumor biopsy were analyzed. RNA sequencing data was available from a corresponding fresh frozen tissue as well as IHC annotation of the immune markers FOXP3, CDH1, CD20, CD44, CD3, CD4, CD8 and PD-L1 on the analyzed tissue cores. **Result:** Of the 12 core preparations, 9 samples were successfully analyzed and fulfilled the quality criteria in the first run, the three others in a second re-analysis. The mRNA expression profiles of 12 samples measured with HTG on minute FFPE samples and RNAseq from fresh frozen tissue showed most often good correlations (r=0.41-0.87). HTG based mRNA data correlated with IHC expression for 5 of 8 genes (PD-L1 r=0.76, CD44 r=0.75, CDH1 r=0.61, CD8 r=0.60, CD4 r=0.54). RNAseq data showed good correlations with IHC for only 3 of 8 genes (CD44 r=0.91, PD-L1 r=0.86, CD8 r=0.67). Also, the HTG data of the two biopsies demonstrated very good correlations to the corresponding tissue cores and the RNAseq data (r>0.91). Finally, technical replicates of 10 of the minimal tissue core samples measured in different laboratories revealed relatively good concordance (r=0.71-0.94). **Conclusion:** The applied nuclease protection technique opens the possibility to multiplex and analyze the immune profile of 549 genes in minimal diagnostic biopsies with a high success rate. This is of great value for clinical use or in NSCLC clinical studies where the amount of tissue often is a limiting factor in companion diagnostics.

Keywords: immune-oncology genes, minimal amount of FFPE tissue, Nuclease protection assay

P2.02-024 FALSE POSITIVITY DUE TO POLYSOMY IN FLUORESCENCE IN SITU HYBRIDIZATION

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Background: Pathologists may recognize the phenomenon of polyploidy in FISH, which may be misleading in interpretation of break apart fluorescence in-situ hybridization (FISH). The chance for single or split probe signals is likely to increase with the degree of polysomy. The aim of this study was to explore whether false positivity due to polyploidy occurs in practice. **Method:** A cohort of cases referred for study or patient care was collected from the archives. From the cases where the ALK and/or ROS1 in-situ hybridization test was repeated in our hospital the outcome of testing was compared. Additionally tumor DNA of an occasional case was tested by an orthogonal method (Ion Torrent Oncomine Focus Assay) for translocations. **Result:** Three cases with ALK FISH rearrangement elsewhere were diagnosed with polyploidy in the referral center. One case was reported with rearrangements in both the ALK and the ROS1 gene detected by FISH analysis. In the repeated FISH analysis the average number of co-localization signals in the tumor cell nuclei was 7.6 for ALK and 9.5 for ROS1 respectively (range 1 - 30). Moreover, the morphology of this case was a giant cell carcinoma, variant of pleomorphic carcinoma of the lung. Examination with an orthogonal method (Ion Torrent Oncomine Assay) revealed no translocations and the tumor cells were negative for ALK and ROS1 by immunohistochemistry proving the original report as false positive, supported by absence of response on crizotinib. In break apart FISH the 15% threshold for positivity was obtained in cells emphasizing that in cross sections of normal nuclei occasionally split signals or 3' probe signals may be present even in diploid nuclei. In the range of 15-20% the chance of false positive FISH is >1%.[1] However, in polyploid tumors the higher number of probe signals within one nucleus comes with an increased chance of split or 3' signals and a higher rate of false-positive results when maintaining a uniform threshold 15% irrespective of ploidy. Moreover, this may in case of ALK be an additional reason for discordancy with ALK immunohistochemistry, explaining the lack of response on targeted therapy in these patients.[2] 1. vLaffert *Lung cancer.* 2015;90:465 2. vdWekken. *Clin Cancer Res.*epub. **Conclusion:** In case of polysomy there is a increased chance of false positive in break apart FISH results. An addition technique should be used to confirm a positive FISH status in tumors with highly increased gene copy number due to polysomy.

P2.02-025 HISTOLOGICAL DIFFERENCE OF TUMOR-INFILTRATE LYMPHOCYTES IN NON-SMALL CELL LUNG CANCER

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Background: Lymphocytes play important roles in cancer immunity. Tumor-infiltrate lymphocytes (TILs) are seen in non-small cell lung cancer (NSCLC) and generally classified according to their localization (epithelial area and stromal area). The distribution and the number of TILs are quite different. Cancer cells have an ability to evade from cancer immunity, and the several mechanisms of the ability have been reported; decreased expression of tumor antigen, inhibition of immune response, induction of immunosuppressive cells, and secretion of immunosuppressive cytokines. We hypothesized that the mechanisms of evasion from cancer immunity would influence TIL representation. In this study, we investigated the differences of TILs in histological differentiation, since we considered that histological difference could affect cancer immunity. **Method:** We retrospectively investigated surgical specimens between 2009 and 2015. Consecutive 20 cases with minimally invasive adenocarcinoma (MIA), lepidic adenocarcinoma (Ad lepidic), acinar or papillary adenocarcinoma (Ad aci/pap), solid adenocarcinoma (Ad solid) and squamous cell carcinoma (Sq) were selected (total 100 cases). We checked all fields of the tumors in the slice with maximum tumor-diameter microscopically at 100-fold magnification. TILs in the field were judged as positive when more than 10 lymphocytes flocking in tumor epithelial area or stromal area were observed. TILs of the tumors were assessed as the rate of the TIL positive fields in all, and separately evaluated in epithelial area and stromal area. Then, analysis of variance was used to assess the histological differences of TILs. Significant difference was considered as p-value was less than 0.05. **Result:** The average rates of TIL positive fields in epithelial area of MIA, Ad lepidic, Ad aci/pap, Ad solid and Sq were 11.2 ± 20.4%, 15.8 ± 20.4%, 26.9 ± 20.9%, 52.4 ± 30.0% and 27.8± 28.8%, respectively. The rate of Ad solid was significantly higher than those of MIA, Ad lepidic and Ad aci/pap, and the rate of Sq was also significantly higher than those of MIA and Ad lepidic. The average rates of TIL positive fields in stromal area of MIA, Ad lepidic, Ad aci/pap, Ad solid and Sq were 41.9 ± 26.1%, 51.2 ± 28.3%, 57.6 ± 23.2%, 67.7 ± 25.4% and 67.8 ± 30.0%, respectively. The rate of MIA was significantly lower than Ad solid and Sq. **Conclusion:** TILs were significantly different representation depending on the histology. Especially in adenocarcinoma, the TILs differed according to the grade of differentiation. These results might show that highly differentiated lung adenocarcinoma has low expression of tumor antigen.

Keywords: Tumor-infiltrate lymphocyte, histology

P2.02-026 IMPACT OF PD-L1 EXPRESSION ON 18F-FDG-PET IN PULMONARY SQUAMOUS CELL CARCINOMA

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Background: 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with positron emission tomography (18F-FDG-PET) is clinically useful for the evaluation of cancer. The accumulation of 18F-FDG within tumor cells is implicated in the expression of glucose transporter 1 (GLUT1) and hypoxic inducible factor-1α (HIF-1α). Although anti-programmed death-1 (PD-1) antibody therapy is approved for non-small cell lung cancer (NSCLC), the predictive biomarkers remain unknown. It was recently reported that the expression of programmed death ligand 1 (PD-L1) was positively correlated with the expression of GLUT1 and HIF-1α. Based on these backgrounds, we investigated the relationship between the tumor immunity including PD-L1 expression and the degree of 18F-FDG uptake in surgically resected pulmonary squamous cell carcinoma (SQC). **Method:** One hundred and sixty-seven patients (153 men, 14 women) with SQC who underwent 18F-FDG PET were included in this study. Tumor sections were stained by immunohistochemistry for GLUT1, HIF-1α, PD-L1, CD4, CD8, and Foxp3. Relationships of clinicopathological and molecular biological features to the degree of FDG uptake and survival were analyzed. **Result:** The SUVmax of 18F-FDG was significantly correlated with the expression of PD-L1 (p=0.0224) and GLUT1 (p=0.0075). The PD-L1 expression was significantly correlated either with GLUT1 (p=0.0059), HIF-1α (p<0.0001) or CD8 (p=0.0006). Other pairs exhibiting significant correlation are as follows: GLUT1 and HIF-1α (p=0.0072), HIF1α and CD8 (p=0.0072), CD8 and Foxp3 (p<0.0001). Univariate analysis demonstrated that advanced stage (p=0.0027), elevated SUVmax (p=0.0233), and elevated PD-L1 expression (p=0.0157) were associated with unfavorable overall survival (OS). Multivariate analysis also revealed that advanced stage (p=0.0445), elevated SUVmax (p=0.0382), and elevated PD-L1 expression (p=0.0173) were independent prognostic factors predicting unfavorable OS. **Conclusion:** 18F-FDG uptake was significantly correlated with the expression of PD-L1 and GLUT1 in SQC. 18F-FDG PET may reflect the immune response in the tumor microenvironment involved in the regulation of PD-L1 expression.

Keywords: Squamous cell lung cancer, PD-L1, FDG-PET

P2.02-027 ARE INFLAMMATORY MARKERS PREDICTIVE OF NIVOLUMAB EFFICACY IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)?

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Background: Elevated neutrophile-to-lymphocyte ratio (NLR) is a systemic inflammatory marker that has been associated with poor prognosis in NSCLC (Bar-Ad, 2016). There is, however, limited data of the effect of inflammatory markers on Nivolumab efficacy. We assessed whether there is an association between NLR and efficacy of Nivolumab in NSCLC. We also evaluated the value of neutrophil count percentage (NCP). Finally, to establish if the effect was predictive of Nivolumab or prognostic of a therapeutic effect, we studied also NLR and NCP in a cohort of chemotherapy-treated NSCLC. **Method:** Data from NSCLC patients treated with Nivolumab (N=40) in routine clinical practice in our Hospital between January 2015 and May 2017 were retrospectively collected. Population was dichotomized according to whether they had NLR≥5 or <5. Cut-off for NCP was established at 80% using the minimum p-value method. The association between NLR or NCP and progression free survival (PFS) and overall survival (OS) was analyzed by log-rank, Kaplan-Meier method and Cox proportional models. A cohort of chemotherapy-treated NSCLC patients (N=54) were also analyzed. **Result:** In Nivolumab cohort, median age was 67. Thirteen patients (32.5%) were NLR≥5 and five (12.5%) were NCP≥80%. In chemotherapy cohort, median age was 69. Thirty-one patients (57%) were NLR≥5 and ten (18.5%) were NCP≥80%. In Nivolumab cohort, PFS and OS were longer with NLR<5 (log-rank p<0.0001). This effect was also observed with NCP<80% (log-rank p<0.0001 -PFS-, p=0.01 -OS-). In chemotherapy-treated patients, a similar effect was observed. Complete data of median PFS and OS, and Cox proportional models is shown in table 1.

Treatment	Inflammatory marker	Median PFS (months)	Cox proportional models median PFS	Median OS (months)	Cox proportional models median OS
Nivolumab	**NLR<5 ≥5**	6 2	HR 6.7 CI 95% 2.9-15.3 p<0.000001	25 10.5	HR 4.4 CI 95% 1.9-9.2 p<0.0000001
Nivolumab	**NCP<80% ≥80%**	6 1.5	HR 0.09 CI 95% 0.02-0.34 p<0.0000001	21 9.5	HR 0.2 CI 95% 0.09- 0.84 p=0.02
Chemotherapy	**NLR<5 ≥5**	15.5 6.5	HR 6.7 CI 95% 3.0-15.1 p<0.0000001	24 17	HR 8.9 CI 95% 3.6-21.9 p<0.0000001
Chemotherapy	**NCP<80% ≥80%**	4 2.5	HR 0.45 CI 95% 0.2- 0.9 p=0.03	14 9.5	HR 0.35 CI 95% 0.16- 0.75 p=0.007

Conclusion: Systemic inflammation biomarker NLR, and to a lesser extent NCP are prognostic, but not predictive, factors of Nivolumab efficacy in NSCLC. NLR<5 and NCP<80% are associated with improved PFS and OS in NSCLC regardless of treatment evaluated.

Keywords: Neutrophil-to-lymphocyte ratio, Neutrophil count percentage, Non-small-cell lung cancer

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-028 PROGNOSTIC VALUE OF COX-2 EXPRESSION DIFFERS DEPENDING ON CD8+ T LYMPHOCYTES AND PD-L1 EXPRESSION IN RESECTED LUNG ADENOCARCINOMA

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Background: Programmed cell death-1 ligand 1 (PD-L1), tumor infiltrating CD8-positive T lymphocytes (CD8+TILs), and cyclooxygenase-2 (Cox-2) has been used as a prognostic tool in lung adenocarcinoma. **Method:** We conducted a retrospective review of data from 170 patients who underwent pulmonary resection as the first treatment for clinical T1-2 N0 lung adenocarcinoma. We investigated the expressions of three biomarkers and *EGFR* mutation, and analyzed between expression levels and clinicopathological characteristics or prognosis. Then we classified tumors into four groups based on PD-L1 and CD8+TILs status, and evaluated the prognostic significance of Cox-2 expression according to tumor immune-microenvironment classification. **Result:** The high PD-L1 expression tumors showed a significantly larger number of CD8+TILs than low PD-L1 tumors, in contrast, the high Cox-2 expression tumors showed significantly fewer CD8+TILs than low Cox-2 tumors. A multivariate analysis showed that histological subtype, nodal metastasis, CD8+TILs count, and the PD-L1 expression were independent predictor of recurrence-free survival. Based on the classification of PD-L1 and CD8+TILs status, the prognosis in patients with low PD-L1 and high CD8+TILs was significantly better than other types. In patients with low PD-L1 and low CD8+TILs, the rate of *EGFR* mutation was significantly higher than other types and Cox-2 expression was a powerful predictor of prognosis. **Conclusion:** Clinical and pathological features in conjunction with tumor immune-microenvironment classification indicate that lung adenocarcinoma should be divided into different subgroups. The classification of PD-L1 and CD8+TILs status might predict the effect for immunocheckpoint inhibitors, *EGFR* tyrosine kinase inhibitors, and/or Cox-2 inhibitor.

Keywords: programmed cell death-1 ligand 1 (PD-L1), tumor infiltrating CD8-positive T lymphocytes, Cyclooxygenase-2 (Cox-2)

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-029 MORPHOLOGIC FEATURES OF LUNG ADENOCARCINOMA EXPRESSING PD-L1 PROTEIN IN SMALL BIOPSY SPECIMENS

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Background: In patients with resected non-small cell lung cancer, the relationships between PD-L1 expression and various clinicopathological characteristics have been examined. However, the association between cytological features and PD-L1 expression to the authors' knowledge remains unknown. In the current study, the authors used small biopsy specimens to investigate whether morphologic feature correlated with PD-L1 expression in patients with advanced and inoperable lung adenocarcinoma. **Method:** Archival slides from ninety patients with lung adenocarcinoma who underwent small biopsy between October 2014 and May 2017 at Incheon St. Mary's Hospital were reviewed. The small biopsy specimens were obtained from lung (52 cases), pleura (16 cases), lymph node (13 cases), brain (8 cases), and bone (1 cases). PD-L1 expression was detected by immunohistochemistry using the PD-L1 22C3 IHC assay. We examined the association of PD-L1 expression with pathological and molecular features (EGFR mutation, ALK and ROS-1 rearrangement) and was statistically correlated with histological characteristics. **Result:** PD-L1 expression in tumor cells was positive in 33 of 90 cases (36.7%). Higher PD-L1 expression (≥50%) was more frequent in marked nuclear pleomorphism (p<0.001), coarse chromatin pattern (p=0.006), predominant nucleoli (≥3μm)(p< 0.001), large nuclear diameter (>5 small lymphocytes) (p= 0.006), non-glandular feature (p<0.001) and atypical mitosis (p=0.034). There were no significant correlations between PD-L1 positivity and molecular features. In a multivariable logistic regression analysis, PD-L1 positivity was independently associated with prominent nucleoli (multivariable odds ratio, 6.688; 95% confidence interval [CI], 1.784–25.065; P = 0.005) and non-glandular feature (multivariable odds ratio, 4.539; 95% confidence interval [CI], 1.508–13.663; P = 0.007). **Conclusion:** Our study demonstrated that PD-L1 expression was associated with prominent nucleoli and non-glandular feature in lung adenocarcinoma, which might lead to a poor prognosis.

Keywords: Small biopsy, PD-L1, lung adenocarcinoma

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-030 BAVITUXIMAB IN COMBINATION WITH NIVOLUMAB ENHANCES TUMOR IMMUNE RESPONSE IN A 3D EX VIVO SYSTEM OF LUNG CANCER PATIENTS

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Background: Bavituximab is a chimeric monoclonal antibody that targets the membrane phospholipid phosphatidylserine (PS) exposed on endothelial cells and cancer cells in solid tumors. Our previous studies showed that bavituximab enhances the activation of CD8+ TILs that correlates with increased cytokine production by lymphoid and myeloid cells in lung cancer with low PD-L1 expression suggesting that the interruption of the PD-1/PD-L1 axis by nivolumab may enhance the bavituximab effect in tumors. **Method:** Fresh tumor tissues obtained from consented patients with NSCLC, urothelial carcinoma or renal cell carcinoma at the time of surgical resection were utilized in a proprietary 3D ex vivo tumor miscrosphere assay, where 3D tumor microspheres were treated with bavituximab or nivolumab alone or in combination at 10 mg/ml for 36 hours. At the end of the treatment, a multiplex human cytokine assay was used to simultaneously analyze the differential secretion of cytokines, including human IFNg, in culture media as a surrogate of TIL activation. In addition, gene expression analysis of microspheres was performed using the NanoString PanCancer Immune Profiling panel which contains probes to quantitate 770 immune function genes. **Result:** Preliminary results indicate the combination treatment with bavituximab and nivolumab led to increased expression of genes involved in M1 polarization of tumor associated macrophages in a subpopulation of lung tumors that closely correlated with release of cytokines such as MIP1b (CCL4) which is a chemoattractant for natural killer cells, monocytes and a variety of other cells involved in tumor immune response. **Conclusion:** This lung patient derived ex-vivo approach indicates that bavituximab in combination with nivolumab may enhance immune response. This response likely involves M1 polarization of tumor associated macrophages and suggests potential clinical implications in the treatment of lung cancer.

Keywords: biomarker, cytokine, miscrosphere assay

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-031 RELATIONSHIP BETWEEN PD-L1 EXPRESSION AND EGFR/HER2 SIGNALING IN NON-SMALL-CELL LUNG CANCER

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Background: Immunocheckpoint inhibitors targeting PD-1/PD-L1 axis have shown promising results in patients with non-small-cell lung cancer (NSCLC). It is well known that PD-L1 is induced by IFNg, however recent study shows that EGFR also affects PD-L1 expression in tumor cells. **Method:** We evaluated the expressions of PD-L1, EGFR, and HER2 in tumor tissues collected from patients with pStage IA–IIIA NSCLC using immunohistochemistry. Intensity scoring for staining was calculated with H-score (0-300). The relationships between their expression and clinicopathological characteristics were evaluated. For in vitro assay, the expression of PD-L1 was evaluated by flow cytometric analysis while cell signaling pathways were assessed with Phospho-Receptor Tyrosine Kinase (RTK) array in LC2/ad human lung adenocarcinoma cell line. **Result:** Of the total 91 tumors, 13 cases (14%) showed PD-L1 overexpression, 12 cases (13%) showed EGFR overexpression, and 35 cases (38%) showed HER2 overexpression in tumor cells. PD-L1 overexpression associated

with poor clinical outcome and was positively correlated with EGFR expression while inversely correlated with HER2. To assess the regulation mechanism of PD-L1 expression via EGFR/HER2 signaling, LC2/ad cells were treated with EGF with or without inhibition of EGFR or HER2, after which PD-L1 expression was evaluated using flow cytometry. Consistent with previous reports, PD-L1 expression was clearly enhanced by EGF, and either EGFR-tyrsine kinase inhibitor Gefitinib and siRNA for EGFR blocked EGF-induced PD-L1 overexpression in LC2/ad cells. On the other hand, we found that siRNA for HER2 could not block EGF-induced PD-L1 overexpression. We compared EGF-induced signaling with IFNg-induced one by RTK array, and found EGF stimulation activated AKT, MAPK, and S6 ribosomal protein while IFN-g activated STAT1. **Conclusion:** PD-L1 overexpression is associated with poor prognosis and is positively correlated with EGFR expression but inversely correlated with HER2 expression in NSCLC. The expression mechanism of PD-L1 is different between EGFR and HER2 signaling in LC2/ad cell line. Additionally, both EGF and IFNg enhance PD-L1 expression but via different pathway in NSCLC cell line LC2/ad.

Keywords: EGFR, PD-L1, non-small cell lung cancer

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-032 INTERPLAYING BETWEEN GAMMA-H2AX AND AUTOPHAGY IN A549 CELLS TREATED WITH CISPLATIN AND ETOPOSIDE

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Background: DNA damage-repair and autophagy may contribute to the efficacy of anticancer therapy. The gamma-H2AX is phosphorylated to repair DNA after the double stranded breakdown. Thus, this study was aimed to check the expression of gamma-H2AX and autophagy in cisplatin- and etoposide-treated lung cancer cell line. **Method:** A549 cells were cultured within Dulbecco's Modified Essential Medium with 10% of fetal bovine serum. Cisplatin and etoposide were treated into the cells with time and dose dependent manners. MTT assay and light microscopy were performed to determine the LD50 of these drugs. Western blotting was performed to define the expression of proteins related to LC3A/B-I/II, NBR1 and DNA damage(gamma-HA2X). **Result:** Based on MTT assay, LC50's were determined as the followings: LC50 of CDDP was 14.4 micromole/L and LC50 of etoposide was approximately 25 micromole/L. Chemoresistant cancer cell islets were defined the surviving cells under light microscopy with the treatment of cisplatin and etoposide. In 0-, 5-, 10- and 20-h time points, gamma HA2X showed increasing expressional pattern. This pattern was also similar in etoposide with the peak time point of 10 hour. LC3A/B-I/II and NBR1 expressions were increased by 25 micromole/L of CDDP and 100 micromole/L of etoposide whose patterns were also similar to gamma H2AX. **Conclusion:** Similar expressional patterns of DNA breakdowns (gamma H2AX) and autophagy(LC3A/B-I/II, NBR1) by cisplatin and etoposide may suggest the linkage between autophagy and DNA breakdown. Therefore, this tentative conclusion must be furthermore defined by the research for molecular networks in the chemoresistant lung cancer cells.

Keywords: Gamma-H2AX , autophagy, adenocarcinoma

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-033 THE ASSOCIATION OF PD-L1 EXPRESSION WITH CLINICAL CHARACTERISTICS AND EGFR AND ALK STATUS IN LUNG ADENOCARCINOMA

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Background: Programmed cell death-1 (PD-1) inhibitor is one of important medicines of immunotherapy for cancers. Programmed cell death ligand-1 (PD-L1) expression is a valuable predictor for selection of patients by PD-1 inhibitors therapy. However, the correlation of PD-L1 expression with clinicopathologic features, EGFR and ALK status, and prognosis of lung adenocarcinoma remain controversial. **Method:** 421 lung adenocarcinoma patients with identified EGFR and ALK status in tumor tissues were enrolled. Using tissue microarrays, PD-L1 expression was evaluated using clone SP263 antibody by immunohistochemistry (IHC) on Ventana Benchmark automated staining system. The association of PD-L1 expression with clinicopathologic characteristics, EGFR and ALK status and prognosis of lung adenocarcinoma were analysed. **Result:** A total of 404 patients were available for evaluation. The positve incidence of PD-L1 expression was 22.5% (91/404) (using a cutoff of ≥ 25%). Multivariate Logistic regression analysis showed PD-L1 expression was associated with advanced stage (ORR 2.190, 95% CI 1.313-3.651, $P = 0.003$), solid predominant subtype (ORR 3.594, 95% CI 1.826-7.073, $P < 0.001$), and wild-type epidermal growth factor receptor (EGFR) (ORR 1.895, 95% CI 1.091-3.291, $P = 0.023$), while it was not associated with ALK rearrangement. In multivariate analysis for OS by Cox hazard proportion model, patients with early stage (HR 2.495, 95% CI 2.003-3.106, $P < 0.001$) and EGFR mutations (HR 1.635, 95% CI 1.310-2.040, $P < 0.001$) had a significantly longer survival, while PD-L1 expression was not associated with OS of patients with lung adenocarcinoma (HR 0.847, 95% CI 0.655-1.094, $P = 0.203$). **Conclusion:** Positive PD-L1 expression in lung adenocarcinoma tissues was significantly associated with tumor advanced stage, solid predominant subtype, and wild-type EGFR, however, PD-L1 expression may not be a predictor of OS for patients with lung adenocarcinoma.

Keywords: PD-L1, lung adenocarcinoma

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-034 PD-L1 EXPRESSION CAN BE A PROGNOSTIC MARKER IN EGFR MUTANT NSCLC PATIENTS TREATED WITH ERLOTINIB

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Background: INF-gamma secreted by CD8+ lymphocytes upregulates PD-L1 expression in cancer cells. We recently identified STAT3 and YAP1 as compensatory mechanisms of resistance to EGFR tyrosine kinase inhibition in EGFR mutant cells. STAT3 and YAP1 up-regulate CCL5 (Rantes) and CXCL5, respectively, with both chemokines attracting the myeloid-derived suppressor cell. STAT3 stimulates DNMT1 by repressing STAT1 and retinoic acid-inducible gene-I (RIG-I) expression. STAT1 and RIG-I are key mediators in INF-gamma signaling. We assume that alterations in the INF-gamma signaling pathway could be present in EGFR mutant NSCLC. **Method:** Total RNA from 53 EGFR mutant NSCLC patients was reversed transcribed and analyzed by qRT-PCR. STAT3, YAP1, RIG-I, STAT1, PD-L1, DNMT1 and CXCL5 mRNA were examined with specific primers/probes in triplicates. Progression-free survival (PFS) and overall survival (OS) were estimated. **Result:** Fifty-three EGFR mutant NSCLC patients treated with erlotinib were analyzed, 72% were female, 62% never-smoked, 70% had exon 19 deletion and 36% brain metastases. A positive correlation was found between RIG-1 and STAT1 (r=0.42, p=0.003). An anti-correlation trend was noted between STAT3 and PD-L1, YAP1 and PD-L1 and DNMT1 and STAT1. Median PFS was 22, 12.9 and 8.6 months for patients with high, intermediate and low PD-L1 mRNA, respectively (P=0.04). Median PFS was numerically longer for patients with low levels of DNMT1, RIG1 STAT1 and CXCL5, although the differences were not statistically significant. A similar trend was observed for OS. **Conclusion:** PD-L1 mRNA could be a prognostic marker in EGFR mutant NSCLC patients. Down-modulation of PD-L1 indicates alterations in pattern-recognition receptors (PRRs), like RIG-1 or downstream interferon signaling factors. The dysregualtion of the pathway is multifactorial, and the role of STAT3 and YAP1 hyperactivation merits further research. DNMT1 overexpression ablates STAT1. Since the cyclin-dependent kinase 4 (CDK4) interacts with DNMT1, therapies with CDK4 inhibitors can directly neutralize the main defects in the INF-gamma signaling pathway.

Keywords: PD-L1, EGFR mutant NSCLC, INF-gamma signaling pathway

P2.02: BIOLOGY/PATHOLOGY -
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P2.02-035 PD-L1 IHC TEST ON CYTOLOGICAL CELL BLOCK SPECIMEN; POTENTIAL UTILITY AND PRACTICAL ISSUES

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Background: PD-L1 IHC test is an important biomarker for predicting the response of the immune checkpoint inhibitor against the PD1/PD-L1 axis. The FFPE tissue sample is an only validated specimen used in the clinical study, although it is sometimes difficult to obtain an enough tissue sample in advanced stage patients. Cytology specimen is an expected candidate. In this study, we evaluated the PD-L1 IHC expression on cytology cell block specimen (CB) and compared to the corresponding formalin-fixed-paraffin-embedded tumor tissue sample (FFPE-T). **Method:** Nine primary lung cancer patients who have both surgical resected FFPE-T and pleural effusion CB were recruited. CB was prepared as following; pleural fluid was centrifuged to collect the cell pellet, then fixed in formalin and embedded in paraffin. PD-L1 expression was evaluated using two clones (DAKO PharmDx kit, 22C3 and 28-8). Three pathologists (two certified, one path-trainee) and one cytotechnologist reviewed the slides independently. The proportion score of tumor cell (TPS) was evaluated and divided into 2-tier (positive, negative for 28-8) and 3-tier (no, low, high expression for 22C3) categories, according to the manufactural protocols. The correlation between CB and FFPE-T and the inter-observer agreement (kappa value) were calculated. **Result:** All samples were acceptable for PD-L1 evaluation. FFPE-T resulted in 2 positive, 7 negative (28-8); 3 low and 6 no expression (22C3), respectively. CB resulted in 5 positive, 2 negative (28-8); 3 low and 6 no expression (22C3), respectively. The TPS and tiered-category of CB did not correlate to those of FFPE-T, statistically. The concordant rate of tiered-category between FFPE-T and CB resulted in 4/9 (45.4%) for both clones. It can be explained by the heterogeneity of PD-L1 expression. The TPS and category judgment of two tests (28-8 and 22C3) within each observer were statistically correlated (R=0.588-0.951, p-value <0.001). The kappa value of the inter-observer agreement varied from 0.18 to 1.0,

depending on the experience and education. Two certified pathologists reached moderate (kappa=0.59 for 28-8) to high (1.0 for 22C3) agreement on CB, but low (0.05 and 0.14) on FFPE-T. The kappa value between certified pathologist and path-trainee/ cytotechnologist was 0.6/ <0.01 for FFPE-T, and 0.18/0.57 for CB, respectively. These results seem to be influenced by the recognition of appropriate target tumor cells. **Conclusion:** Our study suggested that the properly processed cytology sample has a potential clinical utility for PD-L1 evaluation. The difficulty of target cell recognition on cytology specimen seems to be one of the critical issues of standardization.

Keywords: cytology, cell block, PD-L1 IHC

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-036 THE EXPRESSION PATTERN OF CD26/DPP4 IN HUMAN LUNG CANCER

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Background: Lung cancer is the leading cause of death among cancers. Despite improved surgical and novel radiation improvements, the overall prognosis remains poor. CD26/dipeptidyl peptidase 4 (DPP4) is a ubiquitously expressed transmembrane exopeptidase on the cell surfaces of many different cells including malignancies of breast, colon, and mesothelioma. Phase I data in mesothelioma with a specific antibody showed tolerability in mesothelioma patients.Our group found previously that the activity of CD26/DPP4 of lung adenocarcinoma (Adeno-CA) patients is four times higher than in normal 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 biomarker for lung cancer and a target for inhibition to reduce lung cancer burden. burden. **Method:** To identify CD26/DPP4 by immunohistochemistry (IHC), we tested four antibodies from Abcam, R/D systems, and Cell signaling technology on multi-organ tissue micro array (TMA) and human lung Adeno-CA cell lines (A549, H460, Gon8, Mai9) derived from advanced stage (IV) of human Adeno-CA. We selected the antibody from Cell signaling technology against CD26/DPP4. For the analysis of CD26/DPP4 by IHC in lung cancer samples, TMAs constructed from non-small cell lung cancer patients were used. The cohort consisted of 475 patients (Adeno-CA: 223; Squamous carcinoma: 252). The intensity of the staining was scored from 0 to 3 in a blinded manner. To quantify CD26/DPP4 in the supernatant of human lung Adeno-CA cell lines *in vitro*, ELISA was performed. **Result:** IHC scores revealed that Adeno-CA expresses significantly more CD26/DPP4 compared to squamous carcinoma (p<0.0001). Consistent with our previous findings, early stage cancer (IA) scores significantly higher than other stages IIB (p=0.0012), IIIA (p=0.0019), and IV (p=0.02) among Adeno-CA samples. We could not find CD26/DPP4 expression on human Adeno-CA cell lines by IHC, but the secretion of the protein in supernatant stays high (A549: 20pg/ml; H460: 161pg/ml; Gon8: 74pg/ml; Mai9: 648pg/ml). **Conclusion:** CD26/DPP4 expression was significantly higher at early stages of Adeno-CA samples when compared to advanced stages, supporting our previous findings. From the human cell line data, we suggest that advanced cancer secretes CD26/DPP4 more actively than early stage cancers. CD26/DPP4 seems to be a substantial target for inhibition of human Adeno-CA.

Keywords: CD26/DPP4, lung, Cancer

P2.02: BIOLOGY/PATHOLOGY -
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P2.02-037 CD14⁺ CELL TUMOR MICROENVIRONMENT INFILTRATION CORRELATES WITH POOR OVERALL SURVIVAL IN PATIENTS WITH EARLY STAGE LUNG CANCER

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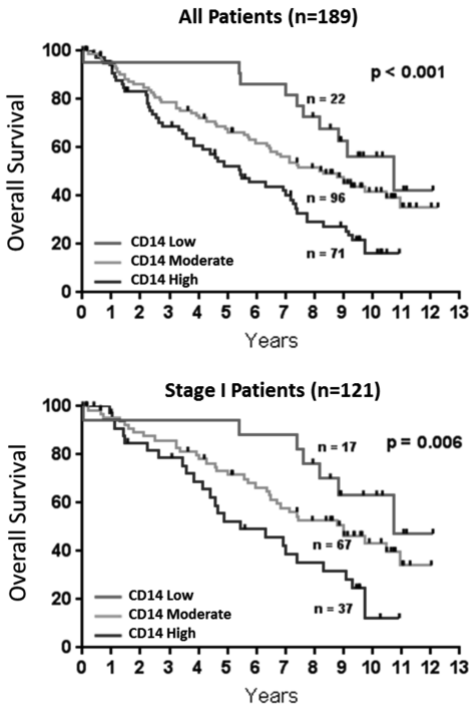
Background: Despite undergoing curative-intent therapy, patients with early stage non-small cell lung cancer (NSCLC) have reduced survival rates of 43-73% due to the risk of distant metastasis(1-3). This underscores the acute need to identify new biomarkers for improved prognostication and to better understand the underlying biology that drives poor outcomes. **Method:** Tumor tissue from 189 patients with NSCLC who underwent curative intent surgery was stained for CD14 by IHC and qualitatively scored for low, moderate, or high expression. CD14 expression groups for all patients and stage I patients alone were analyzed for overall survival. *In vitro* studies were performed utilizing a coculture system of human lung cancer cell lines and freshly isolated CD14⁺cells. **Result:** We found that the level of CD14⁺cells within the tumor microenvironment (TME) was strongly associated with overall survival in all patients (p<0.001) and stage I patients alone (p=0.006). Patients with high CD14 TME staining had a median overall survival of 5.5 years versus 8.3 years and 10.7 years for moderate or low CD14 staining, respectively. The intensity of CD14 TME infiltration was associated with an advanced stage at time of diagnosis (p=0.049) and more positive lymph nodes found at surgery (p=0.012). The potential advantages of TME CD14⁺cells were investigated through a coculture system. Tumor growth kinetics were not altered with coculture. Lung cancer cells cocultured with CD14⁺cells recovered more quickly after exposure to chemotherapy. This improved recovery was observed only after a 48 hour coculture of tumor cells and CD14⁺cells.



Conclusion: CD14⁺cells are a prognostic marker within the TME of patients with resected lung adenocarcinoma. Our data suggests crosstalk with the CD14⁺cell infiltration results in a tumor survival benefit that drives poor patient outcomes.

Keywords: CD14+ cells, tumor microenvironment, Prognosis

P2.02: BIOLOGY/PATHOLOGY -
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P2.02-038 IMAGING PLATFORM FOR THE QUANTIFICATION OF CELL-CELL SPATIAL ORGANIZATION WITHIN THE TUMOUR-IMMUNE MICROENVIRONMENT

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Background: The contribution of the tumour-immune microenvironment to tumour progression and patient outcome has become increasingly evident. Newly developed genomic tools have enabled the study of immune cell composition from bulk tumour data. However, such tools (e.g. CIBERSORT) do not provide the key spatial information that is crucial to understand tumour-immune cell interactions. To this end, we have developed a multispectral imaging platform that improves upon traditional analysis methods of cell segmentation and cell density calculations by further quantifying nearest-neighbour interactions (cell-cell spatial relationships). We apply this technology to investigate tumour-immune cell spatial relationships and their clinical significance to discover novel biological insights. **Method:** Whole tissue sections from 20 lung adenocarcinomas were stained for CD3, CD8, and CD79a and counterstained with haematoxylin. Multispectral images were acquired for five fields of view and analyzed to quantify cell types. Regions of Interest (ROIs) were then identified for the characterization of intra-tumoural and dense inflammatory regions. Image files including ROIs were analyzed in order to quantify cell-cell spatial relationships. Non-random patterns of immune cell distributions were identified using the Monte Carlo re-sampling method (500 iterations). Immune cell counts, densities, spatial relationships, and significant immune cell distributions were associated with clinical features by two-group comparison (Kruskal-Wallis p<0.001). **Result:** Our analysis generated 234 image files for analysis, including ROIs. Each field of view contained an average of 16,400 cells. The densities of intra-tumoural CD3+CD8+ and CD3+ T cells were significantly lower in recurrent cases, agreeing with literature reports. Following Monte Carlo analysis, non-random cell-cell spatial proximities emerged that were not observed at a cell density level. For example, an increased proximity of CD3+ T cells and B cells was observed in never smokers, while a decreased proximity was observed in ever smokers. **Conclusion:** While immune cell densities are of clinical prognostic importance, their spatial organization within the tumour architecture is of functional importance (e.g. the inhibition of cytotoxic T cell activity by adjacent PD-L1 expressing cells). In addition to cell densities, our platform is capable of quantifying

cell-cell spatial relationships, thereby providing further information for clinical associations and for the identification of novel prognostic interactions. This automated quantification could be used to complement visual diagnostics and improve prognostic interpretation of histology specimens.

Keywords: Immunology, Digital Pathology, tumour microenvironment

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-039 SPATIAL HETEROGENEITY OF IMMUNOLOGICAL MARKERS BETWEEN CORES AND COMPLETE NSCLC SECTIONS USING MULTISPECTRAL FLUORESCENT IHC

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Background: Immunotherapy with immune checkpoint inhibitors have revolutionised the management of solid organ malignancy including melanoma and NSCLC. Direction has turned to the tumour immune microenvironment (TIM) to explore predictive biomarkers. The spatial arrangement of immune infiltrative cells has the potential to better explain the TIM. Vectra multispectral immunohistochemistry (IHC) allows accurate definition of the TIM and may help detect mechanisms of immune evasion. **Method:** Multispectral fluorescent immunohistochemistry with a panel including CKAE1/3, CD8, FOXP3 and PD-L1 (clone E1L3N, Cell Signalling Technology) was used to analyse the TIM in six patients (pts) with resected NSCLC (full face section from block). Respective tissue microarrays were collected in triplicate from each specimen and underwent conventional IHC scoring for PD-L1, tumour infiltrating lymphocytes (TILs), CD8, FOXP3 and scored (0,1,2,3). The spatial arrangement of lymphocytes relative to tumour cells, stroma and PD-L1 expression was examined. **Result:** All six pts had adenocarcinoma histology, with the following level of PD-L1 expression: low(0-5%;n=2), intermediate(5-50%;n=2) and high(>50%;n=2) Figure1. In PD-L1^{hi} pts Vectra staining showed uniform staining of PD-L1 across the full face. CD8 lymphocytes were present mainly in tertiary lymphoid structures without evidence of clustering. In PD-L1^{lo} pts, one had heterogenous staining of TILs with dense stromal clustering (3:1 ratio of stroma to intratumoural). Neither patient (PD-L1^{lo}) demonstrated significant PD-L1 uptake on full section assessment. Of the PD-L1^{int} pts, although heterogeneity in PD-L1 expression was evident across the full face, the majority of tumour rich areas stained positively and TILs were uniform in the stroma. FOXP3 had low expression across all 6 patients <1% almost uniformly in the stroma.

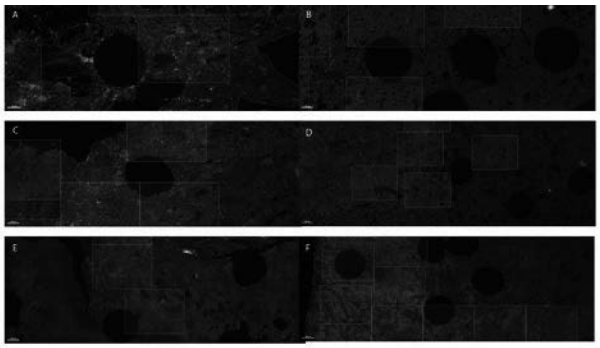

Figure 1 – Representative images of multispectral fluorescent immunohistochemistry in six NSCLC patients: (A) and (B) PD-L1 0-5%, (C) and (D) PD-L1 5-50% and (E) and (F) PD-L1 >50%

Conclusion: Although PD-L1 staining heterogeneity was limited in this small dataset, clear differences in immune-cell infiltrate were seen between full-face sections and limited cores. Multiplex Immunofluorescent IHC provides accurate quantification of immune infiltrates and spatial alterations within the TIM and may facilitate predictive biomarkers.

Keywords: pathology, PD-L1, multispectral immunohistochemistry

P2.02: BIOLOGY/PATHOLOGY -
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P2.02-040 CYTOLOGY CELL BLOCK IS SUITABLE FOR IMMUNOHISTOCHEMICAL TESTING FOR PD-L1 IN LUNG CANCER

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Background: PD-L1 immunohistochemistry (IHC) testing is usually performed on core needle biopsy or surgical resection tissue blocks, and tumor proportion score (TPS) ≥50% is used to select patients to treat with Pembrolizumab immunotherapy. In this study, we evaluate the results using cytology cell block for PD-L1 IHC assay. **Method:** A total of 1423 consecutive cases of non-small cell lung cancer (NSCLC), including 368 cytology cell blocks, 813 small biopsies and 242 surgical resections, were included in the study. 151 cytology cell blocks had known fixation status, which were either directly fixed in formalin, or in alcohol first then refixed in formalin. IHC used Dako PD-L1 IHC 22C3 pharmDx. The TPS of ≥ 50% tumor cells was defined as positive. A total of 100 viable tumor cells were required for adequacy. **Result:** Of the cytology cell blocks, 93% of the specimens had sufficient numbers of tumor cells, and the rate was equivalent to the rate of small biopsies (93%). All resection specimens were shown to be adequate for testing. PD-L1 expression was positive in 42.1% of cytology cell blocks, statistically comparable to small biopsies (36.3%, $P>0.05$), but higher than in surgical resections (28.5%, $p<0.05$). The fixative methods did not affect the immunostaining, since the PD-L1 positive rate was of 41.9% in formalin only group, *vs* 40.4% in alcohol plus formalin fixed cell blocks ($p>0.05$). The PD-L1 positive rate appeared lower in cell blocks from bronchoalveolar lavage (BAL) (27%) as compared to fine needle aspiration (FNA, 42%) and pleural/pericardial fluid (45%), although the difference did not reach statistical significance ($P>0.05$). **Conclusion:** Our results demonstrate that PD-L1 IHC performs well with cytology cell blocks. The rate of positive PD-L1 was comparable between cytology blocks and small biopsies. As cytology cell blocks are commonly available from lung cancer patients, they can provide valuable resource for PD-L1 testing and can help to avoid rebiopsies. However additional correlation with clinical response will be helpful to further validate the cytology specimens.

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P2.02-041 UPDATE ON PROSPECTIVE IMMUNOGENOMIC PROFILING OF NON-SMALL CELL LUNG CANCER (ICON PROJECT)

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Background: Given the rapidly changing therapeutic landscape for non-small cell lung cancer (NSCLC), a thorough understanding of the tumor immune environment is critical to the appropriate selection of patients and testing of immuno-oncology agents. We established a project aimed at defining the comprehensive and integrated immunogenomic landscape in NSCLC, including immune, genomic and clinical data from 100 surgically resected lung cancers. **Method:** Tissue samples were collected at the time of surgery, and blood samples before and after surgery up to 1-year. Tissue samples were subjected to tumor infiltrating lymphocyte (TIL) isolation and expansion; generation of PDX models,WES and in-silico neoantigen prediction, RNA sequencing, RPPA, CyTOF, T cell receptor sequencing, and multiplex immunofluorescence evaluation of immune cells and markers. Blood samples were processed for cfDNA, microRNA, and cytokine profiling. **Result:** 93 out of 131 enrolled patients with median age 67 years contributed samples to ICON; 44% males, 80% former smokers, 12% never smokers. Majority had adenocarcinoma (60%) and 26% SCC. 37 (40%) had stage I, 29 (31%) stage II, and 20 (22%) stage III disease; 14 patients received neoadjuvant chemotherapy. Median tumor size was 4.0cm and 79 (85%) underwent R0 and 9 (10%) R1 resection. TIL expansion was 68% successful. Phenotypic and functional analysis of TIL is ongoing. Preliminary analysis show suppression of intratumoral $CD8^+$ cells with low perforin levels and high $CD8^+PD1$ levels as compared to normal tissue; however tumor $CD8^+CD28$ co-stimulatory molecule expression was high. PDX success rate is 35%. IHC analyses show higher $CD8^+PD1$, CD3, $CD8^+BTLA$ expression in SCC than in adenocarcinoma or normal tissue. WES and RNA sequencing show that median mutation burden is 9.3/MB in adenocarcinomas and 11.2/MB in SCC. Other immunogenomic analyses are in process. **Conclusion:** The ICON is an ambitious multi-team project designed to integrate multiple levels of tumor related data. Preliminary analysis demonstrates the project to be feasible, with a high rate of prospective sample acquisition. Tumor profiles from ICON will serve as a reference for upcoming neoadjuvant single and dual checkpoint immunotherapy trials. **ICON Team:** A. Weissferdt, A. Vaporciyan, A. Futreal, T. Karpinets, C. Yee, C. Haymaker, L. Federico, M.-A. Forget, G. Lizee, A. Talukder, J. Roszik, H. Tran, M. Vasquez, E. Prado, C. Behrens, E. Parra, J. Rodriguez-Canales, J. Fujimoto, L. Vence, J. Roth, I. Meraz, E. Roarty, L. Lacerda, L. Byers, S. Swisher, W. William Jr., P. Sharma, J. Allison, B. Fang, H. Wagner, E. Bogatenkova, I. Wistuba, J. Heymach and C. Bernatchez

Keywords: cfDNA, immunogenomic landscape, TIL isolation

P2.02: BIOLOGY/PATHOLOGY -
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P2.02-042 CLINICAL SIGNIFICANCE OF THE TUMOR EXPRESSION OF PD-L1 USING FOUR IMMUNOHISTOCHEMISTRY ASSAYS IN NON-SMALL CELL LUNG CANCER. MULTICENTRE STUDY

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Background: PD-L1 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 investigated whether the PD-L1 expression in Non-small lung cancer is associated with specific clinical features or survival using four different antibodies. **Method:** PD-L1 status was assessed with IHC (AB clone SP142 and SP263 - Ventana, 22C3 and 28-8 - Dako) on archival FFPE surgical tumor specimens, arrayed on tissue microarrays (TMAs) with duplicate 1 mm cores from two institutions (Karolinska University Hospital and Nagasaki University Hospital). All patients (n = 682) 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%. Median overall survival was 74 months. PD-L1 28-8 was positive in 11% of cases (SCC (56%)/N-Sq-NSCLC(40%), Pearson Chi-square p<0.0001). PD-L1 positivity (>50%) 22C3/SP263/SP142 was 10%/13%/3%. All carcinoids were negative for PD-L1. In PD-L1-SP263 positive cases, the staining intensity and distribution had a homogenous pattern between the 2 TMA cores. In NSCLC, PD-L1 positivity for each antibody was associated with tumour 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). **Conclusion:** In this surgical series, the clone SP142 showed less PD-L1 expression in the tumour cells. PD-L1 expression was associated with tumour size, grading and only the clone SP263 showed association between its expression and survival ratio.

Keywords: non-small cell lung cancer, PD-L1

P2.02: BIOLOGY/PATHOLOGY -
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P2.02-043 MULTICENTRE ASSESSMENT OF PD-L1 IMMUNOHISTOCHEMISTRY: CHALLENGES FOR ESTABLISHING THE CONCORDANCE BETWEEN FOUR DIFFERENT ANTIBODIES

C. Ortiz -Villalón[1], H.H.n. Pham[2], A. Yoshikawa[2], A. Montero[1], A. Roden[3], C. Fernandez[4], L. Kis[1], L. De Petris[5], J. Fukuoka[2]

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Background: PD-L1 status in lung cancer may be a predictive biomarker for the use of PD1/PD-L1 inhibitors. Nonetheless, the reproducibility of PD-L1 staining using different antibodies and platforms is still a matter of debate. We investigated the performance of four different antibodies with two different platforms in two different institutions. **Method:** PD-L1 expression was assessed with IHC (AB clone SP142 and SP263 - Ventana, 22C3 and 28-8 - Dako) on archival FFPE surgical tumour specimens, arrayed on tissue microarrays (TMAs) with duplicated 1 mm cores from two institutions (Karolinska University Hospital and Nagasaki University Hospital). All patients (n = 682) underwent curative surgery between 1987 and 2015. PD-L1 staining was scored as positive if present in ³1% of tumor cells, independently of staining intensity. The slides were scanned and scored by seven experienced pathologists who estimated the expression of PD-L1 in the tumour and inflammatory cells. The statistical analyses were performed to compare the four different antibodies and the scoring of the pathologists on the tumour and inflammatory cells. **Result:** PD-L1 positivity ³1% of tumor cells using clones 28-8 / 22C3 / SP263 / SP142 was 32%/29%/33%/9%, respectively. All carcinoids were negative for PD-L1. SP142 showed a significantly lower mean score compared with other clones. PD-L1 positivity ³50% of tumour cells using clones 28-8 / 22C3 / SP263 / SP142 was 11%/10%/13%/3%, respectively. The pair comparison analysis in the tumour cells showed that the score from the highest agreement was between 28-8 and 22C3 (Kappa 0.75, CI95% 0.70-0.80) and the lowest concordance was between SP263 and SP142 (Kappa 0.21, CI95% 0.16-0.27). The evaluation of the concordance in the inflammatory cells and among the pathologists is ongoing. **Conclusion:** The present study shows a comparative analysis using four different antibodies. The clone SP142 shows significantly lower expression of PD-L1 in the tumour cells. The clones 28-8, 22C3 and SP263 showed an excellent concordance in the tumour cells with two different cut offs (>1% an >50%) showing a good reproducibility for the pathology assay. The highest agreement was between the clones 28-8 and 22C3. The lowest concordance was between the clones SP263 and SP142.

Keywords: NSCLC, PD-L1, Four antibodies

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-044 PULMONARY FINDINGS IN 7 AUTOPSY CASES OF PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Side effects of immune checkpoint therapy are milder than with standard chemotherapy. Pulmonary toxicity has been described in 5% of patients, most of which are low grade pneumonitis with varied radiologic and pathologic appearances.

Here we report lung pathology findings in 7 autopsy cases of patients who died while on immune checkpoint therapy. **Method:** Patient characteristics are shown in table 1. We evaluated tumor burden, the presence of tumor infiltrating lymphocytes (TIL), and type of lung injury. TIL were quantitated using a 4 tier system (0 -3+ = none, mild, moderate, extensive)

Table 1. Summary of demographic and clinical information

Case	Age	Sex	Immune Tx	Pneumonitis	Chest Imaging
1	38	WM	3 mo	Yes	GGO, multifocal
2	65	WM	9 mo	No	Bilateral pleural effusion
3	54	WF	single dose	Yes	Bilateral reticular opacities
4	30	BM	4 mo	No	GGO, patchy
5	59	WM	7 mo	No	Pulmonaryemboli and tumor
6	72	WM	25 mo	Yes	GGO, bilateral, diffuse
7	68	WM	5 mo	Yes	GGO, bilateral, diffuse

Result: Residual viable tumor with little or no therapy effects was present in all 7 cases. The 4 cases where pneumonitis was diagnosed clinically had at least focal DAD. The majority of tumors had at least scattered TIL present, while one tumor had a large number TIL.

Table 2. Summary of autopsy findings

Case	Tumor	TIL	LVI	DAD	Pneumonia	Tumor necrosis
1	ACA in 5 lobes	1+	Yes*	Focal	No	<5%
2	MM in LLL, LUL	3+	No	Focal RLL	No	None
3	ACA in 4 lobes	1+	Yes	LUL, RUL, LLL	LLL, RLL, LUL	None
4	MM in 4 lobes	1+	Yes	No	No	None
5	MM in RUL	1+	No	No	No	None
6	SCC in RLL, LL, LUL	2+	Yes	RUL, RML, RLL	No	10% and fibrosis
7	SCC in 5 lobes	1+	Yes	LUL, LLL	No	20-30%

ACA: adenocarcinoma; MM: Malignant melanoma; SCC: squamous cell carcinoma; *extensive LVI **Conclusion:** The majority of patients with clinical diagnosis of pneumonitis had DAD at autopsy and variable amount of viable tumor in the lungs and at least a few tumor infiltrating lymphocytes. Additional studies are pending to further characterize the phenotype of the TIL and to determine PD1 and PDL1/PDL2 expression on the tumor cells.

Keywords: Pneumonitis, immune therapy, autopsy

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-045 PD-L1 ASSESSMENT IN CYTOLOGY SAMPLES

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Background: Pembrolizumab therapy for non-small cell lung cancer requires patient selection using PD-L1 immunohistochemistry (IHC). FDA approval was based on staining of resections or core biopsies. There is only limited data on PD-L1 expression in fine needle aspiration (FNA) specimens including EBUS of mediastinal lymph nodes. **Method:** Immunohistochemistry (IHC) was performed on an automated platform (Ventana Benchmark Ultra) using clone 22C3 (Dako) and the Optiview detection system (Ventana Medical Systems) on formalin fixed paraffin embedded FNA cell blocks (n:49), cell blocks from aspirated fluids (n:14), core biopsies (n:21) and 4 transbronchial biopsies. The cohort included of 18 squamous cell carcinomas, 56 adenocarcinomas (ACA), 2 adenosquamous carcinoma, 1 NUT-1 carcinoma, 7 NSCLC and 2 melanomas (age: 24-89, mean: 66, median: 69; 43 female and 45 male). Membranous PD-L1 staining of any intensity and extent was recorded in at least 100

tumor cells (tumor proportion score). The tumors were grouped as: no staining (< 1%), low expression (1-49%) and high expression (50% or more). **Result:** Twenty (23.3%) tumors showed no staining, 26 (30.2%) low expression and 40 (46.5%) high expression. Of the 56 adenocarcinomas 21 (37.5%) showed high expression, while of the 18 squamous cell carcinomas 7 (39%) showed high PD-L1 expression. The other tumors with high expression included one adenosqaumous carcinoma and 11 poorly differentiated carcinomas. One EBUS biopsy also had PDL1 assessed on a transbronchial biopsy of the primary tumor showing similar staining (30% versus 20%). **Conclusion:** PD-L1 immunohistochemistry appears to be feasible using formalin fixed cell blocks of fine needle aspirates and aspirated fluid specimens containing adequate number of viable tumor cells. High PD-L1 expression was seen in approximately half the tumors, which is greater than has been observed in resections/core biopsies, this finding merits further study. High expression of PD-L1 was seen in both squamous cell carcinoma and adenocarcinomas.

Keywords: Immunohistochemistry, PD-L1, cytology

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-046 ASSESSMENT OF PDL1 AND IMMUNOPROFILING USING MULTIPLEX QUANTITATIVE IMMUNOFLUORESCENCE IN LUNG CANCER: CLINICAL IMPLICATIONS

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Background: Understanding of the "profile" of PD-L1 expression and its interplay with immune cells will provide important insights into lung cancer pathogenesis, and immunotherapeutic strategies targeting this important immune checkpoint protein. The aim was to investigate the correlation between multiplex immunofluorescence (mIF) expression of PD-L1, density and nature of tumor infiltrating immune cells in non-small cell lung carcinomas (NSCLC), and correlate those profiles with clinical and pathological variables including patient outcome. **Method:** We studied 194 stage II/III patients that underwent pulmonary resection, including 98 adenocarcinoma (ADC), 59 squamous cell carcinoma (SqCC), 15 large cells carcinomas (LCC) and 22 neuroendocrine carcinomas (NEC), primary tumors. Formalin-fixed and paraffin embedded (FFPE) tissue microarrays were constructed with five 1.5 mm cores representative of histologic patterns found in each tumor. mIF was performed using the Opal 7-color fIHC Kit™, scanning in the Vectra™ multispectral microscope and analyzed using the inForm™ software (Perkin Elmer, Waltham, MA). The markers studied were grouped in two 6-antibody panels: Panel 1, AE1/AE3 pancytokeratins, PD-L1 (clone E1L3N), PD-1, CD3, CD8 and CD68; and Panel 2, AE1/AE3, Granzyme B, CD45RO and CD57, FOXP3, and CD20. General linear model was used to evaluate the interaction among primary vs metastatic tumors, histologic type and TAICs and Cox's proportional hazard model for overall survival (OS). **Result:** Fifty-eight % out of 164 tumors were positive for PDL-1+ expression (5% cut-off) in malignant cells (EA1/EA3+). Significant higher levels of PD-L1+ expression were detected in NEC compared with other histologies (ADC, SqCC and LCC) (P=0.006). In the same way, we observed higher densities of cytotoxic T lymphocytes (CD3+CD8+) in NEC when compared with the lowest expression in SqCC (P=0.02). Large cell carcinomas presented high levels of memory/regulatory T cells (CD3+FOXP3+CD45RO+) compared with other histologic types but the difference didn't achieve statistical significance. No difference was found for CD3+PD-L1+, CD68+PD-L1+, natural killer T lymphocytes (CD3+CD57+) and B lymphocytes (CD20+) among the histologic types. Difference between primary and metastatic tumors was found only for naive/memory T lymphocytes (CD3+ CD45RO+) (P=0.04). High CD3+FOXP3+CD45RO+ and CD3+PDL1+ expression were independent favorable prognostic factor for DFS and OS adjusted by smoking, primary vs metastatic, and histologic type [HR 2.68, 95% (CI 1.37–5.24), P=0.004; HR 2.11 (CI 1.07-4.18, P=0.03]. **Conclusion:** High abundance of CD3+PD-L1+ cells and memory/regulatory T cells CD3+FOXP3+CD54RO are favorable prognostic factors for resected NSCLC, highlighting the importance of comprehensive assessment of both tumor and immune cells. *Supported by CNPQ P246042/2012-5 e CNPQ 301411/2016-6; FAPESP 2013/10113-7.*

Keywords: immune cells, lung cancer, PD-L1

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-047 COMPARISON OF PD-L1 IMMUNOHISTOCHEMISTRY ASSAYS AND RESPONSE TO PD-L1 INHIBITORS

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Background: The FDA has approved different companion and complementary PD-L1 assays for selection of patients for different PD-L1 inhibitors. As a result, laboratories intending to implement FDA approved assays face significant operating and capital expenses. Several studies have demonstrated technical concordance between different PD-L1 assays, but their clinical validity in terms of the response to treatment has not entirely been explored. The aim of our study is to prospectively assess the staining performance of laboratory developed tests (LDT) for Ventana SP263 (nivolumab) and Dako 22C3 (pembrolizumab) clones on formalin fixed paraffin embedded samples, and to investigate the association between PD-L1 assays and response to PD-L1 inhibitors. **Method:** 189 sequential lung tumor samples from patients with advanced NSCLC were prospectively stained with Ventana SP263 and Dako 22C3 clones. Both antibodies were optimized for use on the automated Ventana BenchMark ULTRA platform, and validated against corresponding FDA approved assays. Scoring algorithms for staining of the tumor cells approved by matched FDA assays were applied to all samples. Best overall response (BOR) for 43 patients treated with either nivolumab or pembrolizumab were assessed using RECIST v.1.1 and correlated with PD-L1 expression with SP263 and 22C3 using cut off points of 1%, 5% and 10%, 1-49% and 50%. **Result:** Ventana SP263 and Dako 22C3 LDTs showed good agreement with a concordance correlation coefficient of 0.86 (95% CI 0.82-0.90). Comparing the assays using the cutoffs of 1%, 5% or 10% for SP263 and the two cutoffs of 1% and 50% for 22C3 showed an association between the two assays as well (p<0.0001). There were no differences in BOR between pembrolizumab and nivolumab (p=0.12). For SP263, BOR was associated with a cut off point of 10% (Fisher's p=0.030); while the 1% (Fisher's p=0.09)and 5 % (Fisher's p=0.054) cut off points were not associated with response. In contrast, for 22C3, BOR was associated with a cut off point of 1% (Fisher's exact test p-value = 0.006), 5% (p 0.006) and 10% (0.006) **Conclusion:** Similar to FDA approved assays, Ventana SP263 and Dako 22C3 LDT, if properly validated, demonstrate good concordance, but are not interchangeable. Dako 22C3 is more sensitive assay and its expression shows better association with therapeutic response. Larger studies evaluating associations of alternative staining assays and a response to specific therapy are needed.

Keywords: PD-L1 assay response

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-048 SURVIVAL CORRELATION BETWEEN TP53 GENE AND PD-L1 TUMOUR EXPRESSION IN RESECTED NON-SMALL CELL LUNG CARCINOMA

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Background: Tumour suppressor gene TP53 mutation is common in human cancers, especially playing an important role in lung cancer tumourgenesis. Some clinical studies have shown that TP53 alterations in non-small cell lung carcinoma (NSCLC) carry a worse prognosis and may relatively more resistant to chemotherapy and radiation. We conducted this study to evaluate the impact of TP53 assessed by limited targeted profiling, correlating with PD-L1 tumour expression and clinicopathological variables in resected NSCLC. **Method:** NSCLC patients who underwent curative resection between 1998 and 2006 at our institution were included. PD-L1 status was assessed using Ventana SP142 antibody on archival FFPE surgical tumour specimens, arrayed on tissue microarrays (TMAs) with triplicate 0.6 mm cores. PD-L1 was scored as positive if membranous staining was present in >1% of tumour cells aggregated across the replicate cores to address heterogeneity. In collaboration with the Lung Cancer Genomics Ireland Study, a targeted panel of 49 genes was assessed by Sequenom MassArray including TP53 and genes in MAPK and PI3K pathways. Clinicopathological data was obtained from hospital electronic database. **Result:** Seventy-two patients were included, of which 40 (58.0%) were males, with a median age of 66.0 years (range: 51.0 – 82.6). 54.2%, n=39 with adenocarcinoma histological subtypes, 45.8%, n=33 were ex-smoker and 42.9%, n=30 had Stage IB disease. Most patients had T2 stage (71.4%, n=50), N0 nodal disease (55.2%, n=37) and grade 2 differentiation (65.7%, n=46). Presence of TP53 mutation was identified in 22 patients (30.5%). Five patients had co-presence of TP53 mutation and PD-L1 positivity. There was no correlation between PD-L1 positivity with TP53 status, KRAS, PTPN11, PHLPP2, PIK3CA, MET and PIK3R1. The median disease-free survival in TP53 mutation with PD-L1 positivity was not reached. In univariate/unadjusted analysis, co-presence of TP53 mutation and PD-L1 positivity appear to have superior disease-free survival over TP53 wild-type and PD-L1 negativity, HR 0.17 (95%CI 0.01-0.78, p=0.018). A trend was seen with overall survival but not statistically significant (TP53 mutant, PD-L1 positive vs TP53 wild-type, PD-L1 negative: NR vs 23.1 months, HR 0.34 (95% CI: 0.0.5-1.11, p=0.079). Independent PD-L1 positivity appears to be associated with better prognosis: DFS HR 0.36 (95% CI 0.11-0.90, p=0.0272) and OS HR 0.47 (95% CI 0.19-0.98, p=0.0427). **Conclusion:** In our cohort, co-presence of TP53 mutation and PD-L1 expression was not associated with poorer survival among resected NSCLC patients. Independently, PD-L1 expression was associated with better survival, a finding which warrants further investigations as potential biomarker.

Keywords: TP53, PD-L1 expression

P2.02-049 IMMUNOHISTOCHEMICAL APPROACH IN PREDICTING PRIMARY LUNG CANCER OUTCOME: A SINGLE CENTER STUDY

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Background: The death rate from lung cancer in Uzbekistan during 1990 to 2000 increased from 2.1 to 3.1 per 100,000 and in 2016, it reached 3.8 per 100,000 with steady rising. The most prevalent type of lung neoplasm in Uzbekistan is squamous cell carcinoma, whereas in other countries, adenocarcinoma of the lung is considered to be more frequently diagnosed than squamous cell carcinoma. Important key factors in cancer evaluation are diagnosis and prognosis. The aim of this study is directed to determine biological characterization of lung cancer by means of immunohistochemistry, which would be a crucial step towards to therapy. **Method:** Study consisted 564 patients (mean age 58; range, 34-82 years) with primary lung cancer registered at National Cancer Register in the period from 2000 to 2010. All patients were clinically diagnosed, resected, reviewed by a pathologist and followed for at least 72 months. Two different types of oncoproteins were chosen for this analysis: p53, a tumor suppressor gene; and VEGF, vascular endothelial growth factor for detecting the prognostic value of VEGF and its possible association with p53-gene mutation. Overall cancer-specific survival and cancer-free survival or the risk of recurrence was defined from the date ofoperation to the date of recurrence or last follow-up. **Result:** Among the 564 patients, immunoreactivity for VEGF was negative, weakly, moderately and strongly positive in 96 (17%), 141 (25%), 225 (40%) and 102 (18%) cases, respectively. Abnormalities in p53 expression were found in 220 (39%) of 564 carcinomas. A strong, statistically significant association was found between the presence of a p53 gene mutation and expression of VEGF ($P<0.001$). Tumors with high p53 expression showed significantly higher VEGF, also high expression of p53 correlated with mediastinal and lymph node metastasis. Survival and post-operative relapse time were shorter in patients with high p53 expression. Median follow-up was 34 months (1-72 months). The median time to recurrence was 9 months; the recurrence rate was 310 of 564 (55%). With 5-year follow-up on all patients, actual 5-year survival was 58%. **Conclusion:** *P53* overexpression was an indicator of poor prognosis; in addition, it is generally believed that tumors with p53 alterations are more resistant to cancer chemotherapeutic agents than those without *p53* mutation. Our study showed that among 40% p53 positive cases have patients with 18% VEGF overexpression, which is the further assay for future studies, the next step will be to examine the capability of target therapy in this group of patients.

Keywords: primary lung cancer, p53, VEGF

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-050 WEIGHTED GENES CO-EXPRESSION NETWORK ANALYSIS OF LUNG CANCERS CONCERNING PATIENTS OVERALL SURVIVAL AND CANCER STAGE

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Background: Among the factors influence the prognosis of patients, cancer metastasis or cancer stage when first diagnosed at hospital is the most important. This article aims at finding the significant gene networks related with lung cancer patients' overall survival and cancer stage by analyzing big data of gene expression with the algorithm of weighted gene coexpression network analysis (WGCNA). **Method:** A dataset containing 188 lung cancer patients synthesized from TCGA were applied for WGCNA to find the most significantly related modules with overall survival and cancer stage. Then GO and KEGG analysis were performed for further analysis. **Result:** *(See next page.)*

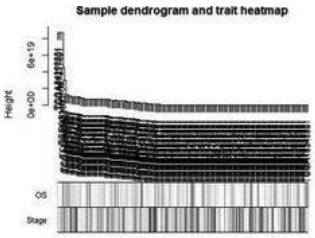

Figure 01

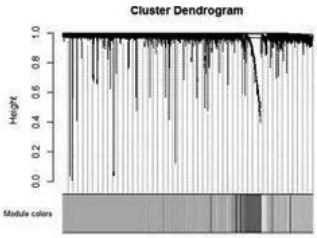

Figure 02

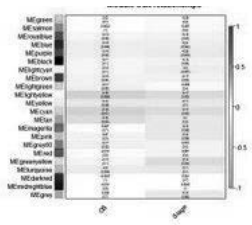

Figure 03

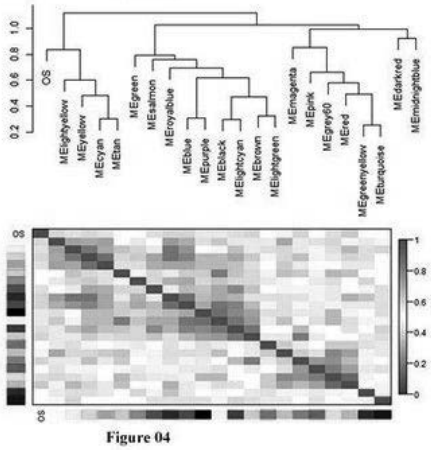

Figure 04

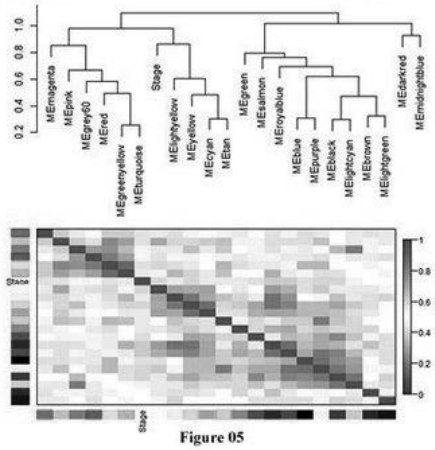

Figure 05

Figure 01: Sample dendrogram and trait heatmap. White meant a low value, red a high value, and grey a missing entry.

Figure 02: Cluster dendrogram. Different colors represent different modules.

Figure 03: Module-trait relationships. The more close to red, the module was more positive related with the corresponding trait, and on the contrary , the more close to green, the module was more negative related with corresponding trait.

Figure 04: Visualization of the eigengene network representing the relationships among the modules and the clinical trait OS. Upper pannel shows a hierarchical clustering dendrogram of the eigengenes in which the dissimilarity of eigengenes.The lower heatmap shows the eigengene adjacency .

Figure 05: Visualization of the eigengene network representing the relationships among the modules and the clinical trait Stage. Upper pannel shows a hierarchical clustering dendrogram of the eigengenes in which the dissimilarity of eigengenes . The lower heatmap shows the eigengene adjacency .

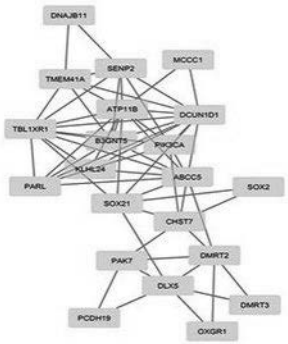

Figure 06

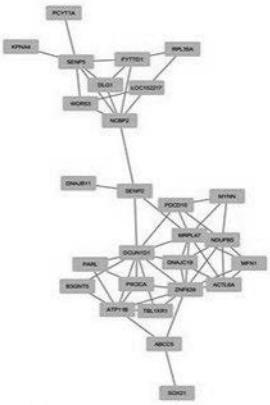

Figure 07

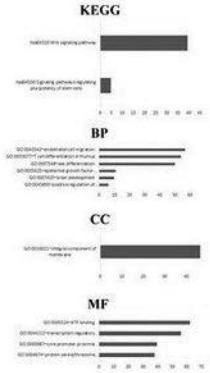

Figure 08

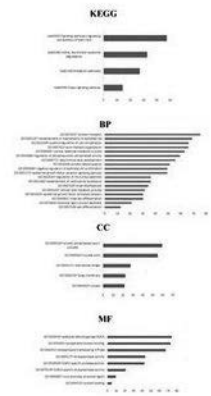

Figure 09

Figure 06: Gene co-expression network of light yellow related with OS. Figure 07: Gene co-expression network of light yellow related with Stage. Figure 08 : GO and KEGG analysis of light yellow related with OS. Figure 09 : GO and KEGG analysis of light yellow related with Stage.

A co-expression network concerning overall survival or cancer stage was constructed respectively. And the significant core genes were determined. The related pathways were also identified. **Conclusion:** Not only have we testified the present classical points concerning cancer progression and patients survival, but also some new discoveries have been identified.The genes of TBL1XR1, ATP11B, DCUN1D1 and ABCC5 played significant roles in deteriorating lung cancer patients overall survival. WNT pathway was significantly related with the patients overall survival. The genes of DUUN1D1, MRPL47, NDUFB5, DNAJC19, PIK3CA, ACTL6Aand ZNF639 promote lung cancer progressing, and lung cancer stage progress was also related with signaling pathways regulating pluripotency of stem cell.

Keywords: lung cancer, overall survival, WGCNA

P2.02-051 BEVACIZUMAB PREVENTS GROWTH OF ESTABLISHED NON-SMALL CELL LUNG CANCER BRAIN METASTASES IN HEMATOGENOUS BRAIN METASTASIS MODEL

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Background: Patients with non-small cell lung cancer are at high risk of developing brain metastases. The mainstay treatment for patients with brain metastasis is surgical excision, whereas radiation is used for multiple brain metastases. Regardless of the treatment, brain metastasis is associated with poor prognosis and the diminished quality of life. Here, we established experimental brain metastasis model allowed interrogation of the brain-specific requirements for cancer cell metastasis and evaluated antitumor efficacy of bevacizumab (BEV), a humanized monoclonal antibody targeting VEGF. **Method:** To produce brain metastases model, we transfected secreted NanoLuc (Nluc) genetic reporter vectors into NCI-H1915 cell line, which was established from a brain metastasis derived from a primary human lung carcinoma and injected into internal carotid artery of SCID mice with external carotid clamped with microclamp. Mice whose Nluc activities in plasma (Relative Light Unit; RLU/5μl) were detected 16 days after inoculation of NCI-H1915 cells were randomly allocated to control and BEV treatment groups (n=9). HuIgG or BEV (5 mg/kg) was intraperitoneally administered once a week (Day 1, 8, 15). Antitumor activity was evaluated by measuring Nluc activity (RLU/whole brain) in supernatant of brain parenchyma homogenized with cell lysis buffer on Day 22. Statistical analysis was performed using the Wilcoxon test. **Result:** Large metastatic nodules were macroscopically observed in brain on Day 22 in 6/9 mice in the control group, whereas those were not observed in any mice treated with BEV. Nluc activity in brain parenchyma homogenate (RLU, mean ± SD) in the BEV group (3.12E+9 ± 3.04E+9) was significantly lower than that in the control group (1.88E+10 ± 2.03E+10, $p<0.05$). Meanwhile, the weight of parenchyma (mg, mean ± SD) on Day 22 of control and BEV, was 417 ± 27.5 and 398 ± 15.6, respectively and there was no significant difference between them ($p>0.05$). **Conclusion:** In the secNluc-transfected H1915 hematogeneous metastasis model, BEV showed remarkable activity in reducing Nluc activity in brain parenchyma as well as emergence of visible legion. These results suggested BEV has efficacy against established hematogenous lung cancer brain metastasis lesions in the xenograft model and it may be one of the treatments for brain metastases from lung cancer.

Keywords: brain metastasis, NSCLC, Bevacizumab

P2.02-052 A CLINICALLY-VALIDATED UNIVERSAL COMPANION DIAGNOSTIC PLATFORM FOR CANCER PATIENT CARE

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Background: The increase in targeted therapies and associated companion diagnostics (CDx) has led to the need for efficient determination of therapeutic eligibility from a single assay. Comprehensive genomic profiling (CGP) provides a solution, but due to the complexity and number of assays available today, standardization of validation has become critically important. We present here the first NGS-based universal CDx platform developed and performed in compliance with FDA 21 CFR part 820. The assay interrogates 324 genes, and is anticipated initially to have eight CDx indications (Table 1). The versatile assay design will facilitate streamlined development of future CDx indications. **Method:** DNA extracted from FFPE tumor tissue underwent whole-genome shotgun library construction and hybridization-based capture, followed by sequencing using Illumina HiSeq 4000. Sequence data were processed using a proprietary analysis pipeline designed to detect base substitutions, indels, copy number alterations, genomic rearrangements, microsatellite instability (MSI), and tumor mutational burden (TMB). **Result:** Concordance with FDA-approved CDx are shown in Table 1. Clinical validity was established such that the concordance between CGP and approved CDx were statistically non-inferior to that of two runs of approved CDx. For analytical validity, limit of detection (LoD) was at allele frequency 4% for known substitutions and indels. LoD was 16% tumor content for copy number amplifications, 30% for homozygous deletions, 11% for genomic rearrangements, 12% for MSI, and estimated 20% for TMB. Positive percent agreement (PPA) with an orthogonal NGS platform was 95.8% in substitutions and indels. PPA with FoundationOne was 98.3% across all variant types. Within-assay reproducibility was measured with PPA 99.4%.

Companion diagnostic	Indicated use	PPA	Comparator CDx assay
EGFR exon 19 deletions and L858R	erlotinib, afatinib or gefitinib in NSCLC	98.1% (106/108)	cobas® EGFR Mutation Test v2
EGFR T790M	osimertinib in NSCLC	98.9% (87/88)	cobas® EGFR Mutation Test v2
ALK rearrangements	crizotinib in NSCLC	92.9% (78/84)	Ventana ALK (D5F3) CDx Assay Vysis ALK Break-Apart FISH
KRAS	cetuximab or panitumumab in CRC	100% (173/173)	therascreen® KRAS PCR
ERBB2 (HER2) Amplifications	trastuzumab, pertuzumab and ado-trastuzumab-emtansine in breast and gastric cancer	89.4% (101/113)	Dako HER2 FISH PharmDx®
BRAF V600E/K	vemurafenib, dabrafenib, trametinib in melanoma	99.4% (166/167)	cobas® BRAF V600 PCR
BRCA1/2	rucaparib in ovarian cancer	N/A	N/A: Novel CDx that was previously validated in PMA P160018

Conclusion: Rapid expansion of targeted therapies and CDx has necessitated a new approach and urgency to defining performance standards. We developed a universal CDx assay and established a robust approach for demonstrating clinical and analytical validity to support and accelerate the use of CGP for routine clinical care.

Keywords: companion diagnostic, molecular testing, NGS

P2.02-053 THE PROGNOSTIC VALUE OF 18 CIRCULATING MARKERS OF INFLAMMATION, ENDOTHELIAL ACTIVATION AND EXTRACELLULAR MATRIX REMODELLING IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The aim of the study was to assess the prognostic value of 18 proteins as markers of inflammation and fibrosis (Table 1) in surgically treated non-small cell lung cancer patients and how the chronic obstructive pulmonary disease (COPD) as co-morbidity affected the prognostic significance. **Method:** Blood samples were collected from 207 lung cancer patients with an early-stage disease before surgery. 55,6% of the lung cancer group had COPD and the majority of these (86%) had moderate COPD (GOLD 2). We grouped the lung cancer patients with moderate, severe and very severe COPD (GOLD 2,3 and 4) in one group, and the lung cancer patients with mild (GOLD 1) or no COPD in another group. Serum levels of 18 proteins were measured by enzyme immunoassays. The proteins were selected because most were previously known to be associated with lung cancer and its prognosis, some with COPD. **Result:** Higher soluble tumour necrosis factor (TNF) receptor type 1 (sTNFR1) level was associated with better overall survival (OS) and progression-free survival (PFS) for lung cancer patients with COPD (OS p=0.006 and PFS p=0.030) and without COPD (OS p=0.040). High level of C-reactive protein (CRP) was significantly associated with poor overall survival regardless of COPD status. Higher osteoprotegerin (OPG) level was significantly associated with better PFS (p=0.014) and OS (p=0.027) in patients with lung cancer and COPD. In lung cancer patients with COPD, only CRP was significantly increased compared to patients without COPD of those three proteins. **Conclusion:** Whereas high levels of sTNFR1 and OPG, members of the TNF receptor superfamily, were associated with better prognosis, high level of CRP was associated with worse prognosis. This illustrates the complex role of inflammation and TNF-related molecules, particularly in the prognosis of non-small cell lung cancer, at least partly influenced by COPD as co-morbidity.

Keywords: proteins, lung cancer, copd

P2.02-054 THYMIDYLATE SYNTHASE PROMOTES EPITHELIAL-TO-MESENCHYMAL TRANSITION AND AGGRESSIVENESS IN NSCLC

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Background: Thymidylate synthase (TS) is a nucleotide metabolism enzyme and a chemotherapeutic target. TS overexpression is associated with worst prognosis in NSCLC and is important for the pathological progression of tumors. We investigated the role of TS in epithelial-to-mesenchymal transition (EMT), a developmental process that allows the cancer cells to acquire features of aggressiveness like motility and chemoresistance. **Method:** Immunohistochemistry (IHC) on TS and EMT markers was performed in tissues from 61 NSCLC patients. EMT and cancer stemness markers were quantified in cultured NSCLC cell lines by western blotting. Migration assays were conducted using an automated wound-healing real-time quantification system. Spheres-forming assays were performed by growing cells in low-adherence plates. In addition, cells were stably infected with a lentiviral reporter plasmid in which the expression of m-Cherry fluorescent protein was driven by the full-length promoter sequence of the TS gene (TYMS). **Result:** A significant association between TS mRNA expression and the markers of EMT was found ($p<0.01$). This was confirmed at the protein level in cultured cell lines, and TS was found up-regulated following EMT induction by TGF-Beta. In addition, a strong association between TS and the powerful EMT driver ZEB1 was found by western blotting and validated by IHC in tissue specimens from NSCLC patients ($p=0.02$). Importantly, TS showed to regulate EMT, as a shRNA-mediated knockdown of TS could reduce in vitro the levels of ZEB1 and of other EMT markers, suppress the cells' migratory and spheres-forming abilities and the chemoresistance. Furthermore, following infection with the fluorescent promoter reporter, we could FACS-sort two populations with distinct mesenchymal and epithelial-like phenotypes (TS-prom^{high} and TS-prom^{low}, respectively) from NSCLC cells. Sorted cells, in fact, displayed differential expression of EMT markers (E-Cadherin, Vimentin and ZEB1), migratory ability and spheroids-forming properties (all $p<0.001$), while no differences were observed using a GAPDH promoter reporter as control. **Conclusion:** All together, these data indicated an unprecedented role for TS in governing cancer differentiation and aggressiveness. The lentiviral promoter reporter may lead to the identification of the regulatory elements and the transcription factors linking TS to EMT. With regards to possible translational implications, the cancer EMT status could be tested as a predictor of the response to TS-inhibiting drugs in NSCLC, and eventually used as a stratification criterion. In the longer run, these data could inspire the development of conceptually novel anti-TS agents that better suppress tumor's growth and aggressiveness.

Keywords: Thymidylate Synthase, Epithelial-to-mesenchymal transition, NSCLC

P2.02-055 STRATIFIN REGULATES STABILIZATION OF RECEPTOR TYROSINE KINASES VIA ACTIVATION OF UBIQUITIN-SPECIFIC PROTEASE 8 IN LUNG ADENOCARCINOMA

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Background: Receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR) and hepatocyte growth factor receptor (MET) are the best-known therapeutic targets in lung adenocarcinoma. Previously, we have revealed that stratifin (SFN, 14-3-3 sigma) acts as a novel oncogene, accelerating tumor initiation and progression of lung adenocarcinoma and interacts with ubiquitin-specific protease 8 (USP8) (IJC 2011, Mol Cancer 2015). USP8 is one of the deubiquitination enzymes that stabilize specific protein substrates by removing ubiquitin from the proteins, and is known to target receptor tyrosine kinases (RTKs). In this study, we investigated the molecular mechanism underlying the binding of SFN to USP8 in lung adenocarcinoma cells, as the role of this interaction in RTK stabilization was considered a promising avenue for identifying a useful therapeutic target for lung adenocarcinoma. **Method:** Expressions of USP8 and SFN in human lung adenocarcinoma tissues (n=193) were examined by immunohistochemistry and statistically analyzed with clinicopathological features of patients. Functional analysis of USP8 and SFN such as cellular proliferation assay, apoptosis assay, and wound healing assay was examined after siRNA-USP8 or SFN transfection. Regulation mechanism of USP8 and SFN on RTKs stabilization was demonstrated using co-immunoprecipitation, western blot analysis, and immunofluorescence. **Result:** USP8 specifically bound to SFN in lung adenocarcinoma cells. Both USP8 and SFN showed higher expression in human lung adenocarcinoma than in normal lung tissue, and their expression was mutually correlated. Expression of SFN, but not that of USP8, was significantly associated with histological subtype, pathological stage, and patient's prognosis. *In vitro*, USP8 binds SFN at the early- and late-endosome in immortalized adenocarcinoma *in situ* (AIS) cells. Moreover, USP8 or SFN knockdown led to down-regulation of tumor cell proliferation, RTK expression, and expression of downstream factors including AKT and STAT3, as well as accumulation of ubiquitinated RTKs leading to lysosomal degradation. Additionally, transfection with mutant USP8 and mutant SFN, which are unable to interact each other, reduced the expression of RTKs and their downstream factors, indicating that interaction with SFN is important for USP8-mediated stabilization of RTKs via deubiquitination. **Conclusion:** RTKs are regulated by ubiquitin-lysosome system, and aberrant stabilization of RTKs contributes to the proliferative activity of many human cancers, including NSCLC. Here, we demonstrate SFN induces aberrant activation of USP8 and subsequently protects RTKs from lysosomal degradation, resulting in hyperactivation of these signaling pathways. SFN may be central to the development of a useful therapeutic strategy for both early and advanced lung adenocarcinomas.

Keywords: SFN, Adenocarcinoma, RTK

P2.02-056 REGULATORY VARIANTS IN CANCER-RELATED PATHWAY GENES PREDICT SURVIVAL OF PATIENTS WITH SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER

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Background: We conducted this study to identify genetic variants in cancer-related pathway genes which can predict prognosis of NSCLC patients after surgery, using a comprehensive list of regulatory single nucleotide polymorphisms (SNPs) prioritized by RegulomeDB. **Method:** A total of 509 potentially functional SNPs in cancer-related pathway genes selected from RegulomeDB were evaluated. These SNPs were analyzed in a discovery set (n=354), and a replication study was performed in an independent set (n=772). The association of the SNPs with overall survival (OS) and disease-free survival (DFS) were analyzed. **Result:** In the discovery set, 76 SNPs were significantly associated with OS or DFS. Among the 76 SNPs, the association was consistently observed for 5 SNPs (*ERCC1* rs2298881C>A, *BRCA2* rs3092989G>A, *NELFE* rs440454C>T, *PPP2R4* rs2541164G>A, and *LTBP4* rs3786527G>A) in the validation set. In combined analysis, *ERCC1* rs2298881C>A, *BRCA2* rs3092989, *NELFE* rs440454C>T, and *PPP2R4* rs2541164G>A were significantly associated with OS and DFS (adjusted HR IaHRJ for OS = 1.46, 0.62, 078, and 0.76, respectively; $P = 0.003$, 0.002, 0.007, and 0.003 respectively; and aHR for DFS = 1.27, 0.69, 0.86, and 0.82, respectively; $P = 0.02$, 0.002, 0.03, and 0.008, respectively). The *LTBP4* rs3786527G>A was significantly associated with better OS (aHR = 0.75; $P = 0.003$). **Conclusion:** Our results suggest that five SNPs in the cancer-related pathway genes may be useful for the prediction of the prognosis in patients with surgically resected NSCLC.

Keywords: Lung cancer; polymorphism; RegulomeDB; Survival

P2.02-057 EXPRESSION OF MGAT4A AND MGAT5 ARE CORRELATED WITH POORER OUTCOME IN ADVANCED LUNG ADENOCARCINOMA

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Background: Protein glycosylation is a post-translational modification that is altered in cancer. However, it is yet unclear if there is a correlation between different glycosylation patterns of N-glycan and clinicopathological features. Therefore, we aimed to investigate differing glycosylation in advanced non-small cell lung cancer tissues by lectin expression assays and N-acetylglucosaminyltransferase gene expression analysis. **Method:** Formalin-fixed and paraffin-embedded biopsy specimens were obtained from 62 patients with lung adenocarcinoma (ADC) (2009-2011) who were diagnosed at Nihon University Itabashi Hospital. Tumor cells were excised and collected by laser microdissection, and each solubilized glycoprotein and mRNA was extracted. Expression levels of 44 lectins were analyzed by lectin array using a lectin chip. mRNA expression levels of mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase (*MGAT3*), mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme A (*MGAT4a*), mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase (*MGAT5*), fucosyltransferase (*FUT*)*7*, and *FUT8* were analyzed by qRT-PCR. **Result:** Expression levels of *Datura stramonium* lectin (DSA), *Solanum tuberosum* lectin (STL), and *Aspergillus oryzae* lectin (AOL) were significantly higher in drug-resistant ADCs than drug-sensitive ADCs ($P = 0.036$, 0.0005, and 0.035, respectively). qRT-PCR showed that overexpression of *MGAT4a* and *MGAT5* was detected in 7/62 (11.3%) and 3/62 (4.8%) of ADCs, respectively. The prognosis of patients with *MGAT4a* and/or *MGAT5* positive ADC was worse than those with negative ADC ($P = 0.018$, log-rank). **Conclusion:** The results of the study suggested different glycosylation of N-glycan in lung ADC tissues. *MGAT4a* and/or *MGAT5* overexpression, in particular, may correlate with a poorer response to standard chemotherapy and poorer outcome in advanced lung ADCs.

Keywords: advanced lung adenocarcinoma, Prognosis, N-glycosylation

P2.02-058 ENDOGENOUS ARGINASE 2 AS A BIOMARKER FOR PEGYLATED ARGINASE 1 TREATMENT IN SQUAMOUS CELL LUNG CARCINOMA XENOGRAFT MODELS

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Background: Arginine depletion induced by PEGylated arginase 1 (BCT-100, PEG-BCT-100 or rhArg1peg5000) has shown promising anticancer effects among arginine auxotrophic cancers that are deficient in argininosuccinate synthetase (ASS1) and ornithine transcarbamylase (OTC). High endogenous arginase 2 (ARG2) was previously found in human lung cancers. Although high ARG2 does not induce immunosuppression nor affect disease progression, it may potentially affect the efficacy of PEGylated arginase 1 treatment. ARG2 was highly expressed in H520 squamous cell lung carcinoma (lung SCC) xenograft while undetectable in SK-MES-1 lung SCC xenograft. We postulated that high endogenous ARG2 expression might hamper anticancer effect of PEGylated arginase 1 in lung SCC. **Method:** The *in vivo* effect of PEGylated arginase 1 was studied using 2 lung SCC xenograft models (SK-MES-1 and H520). Protein expression, arginine concentration and apoptosis were investigated by Western blot, ELISA and TUNEL assay respectively. **Result:** PEGylated arginase 1 (60 mg/kg) suppressed tumor growth in SK-MES-1 but not in H520 xenograft. ASS1 was highly expressed in SK-MES-1 xenograft while expression of OTC remained low in both xenografts. Serum arginine level was decreased significantly by PEGylated arginase 1 in both xenograft models. On the other hand, intratumoral arginine level was reduced by PEGylated arginase 1 treatment in SK-MES-1 xenograft only. In H520 xenograft, intratumoral arginine level in control arm was already very low which could not be further lowered in PEGylated arginase 1 treatment arms. G1 arrest was indirectly evidenced by downregulation of cyclin A2, B1, D3, E1 and CDK4 with PEGylated arginase 1 in SK-MES-1 xenograft only. Moreover, suppression of proliferation factor Ki67 and activation of apoptosis were induced by PEGylated arginase 1 in SK-MES-1 xenograft only. **Conclusion:** PEGylated arginase 1 treatment was effective in lung SCC xenograft with low endogenous ARG2 expression. High endogenous ARG2 level may explain low intratumoral arginine level in lung SCC xenograft. ARG2 may serve as an additional predictive biomarker, other than ASS1 and OTC, in PEGylated arginase 1 treatment in lung SCC. Acknowledgment: This research was supported by Hong Kong Anti-Cancer Society, HKSAR.

Keywords: PEGylated arginase 1 (BCT-100), Endogenous arginase 2, squamous cell lung carcinoma xenograft models

P2.02-059 GENOMIC MUTATION PATTERNS DETECTED WITH CANCER PANEL CAN PREDICT POSTOPERATIVE PROGNOSIS IN CLINICAL STAGE I ADENOCARCINOMA

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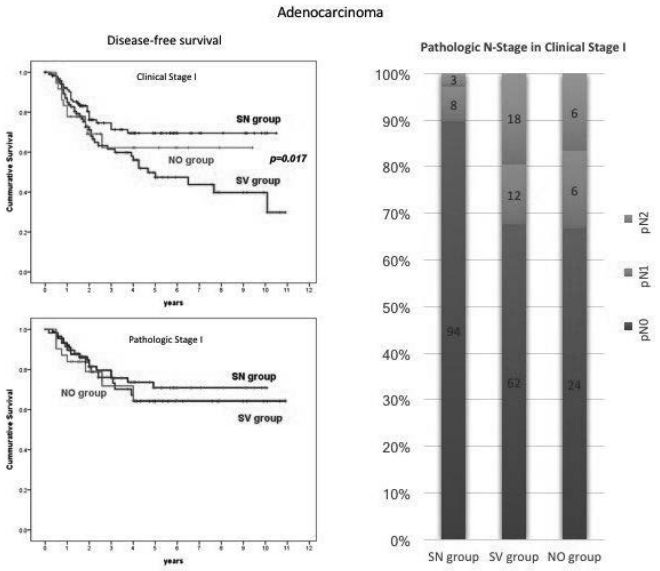
Background: Recent development of cancer panels based on target sequencing technology can detect genomic mutations which are useful to choose target agents for advanced stage lung cancer. We investigated if the result of panel-detected mutation patterns can predict prognosis of early stage lung cancer. **Method:** Among the 350 cases whose postoperative tissues were tested with cancer panel, we selected 338 cases excluding 9 recurrent tumors and 3 cases who received neo-adjuvant treatment. The mean age was 60.7+/-11.4 years (Male 197, female 141). Adenocarcinoma (293) was the most common followed by squamous cell (26), larger cell (5) and others (14). We classified the mutations patterns into three group; SN group (n=126) where a single nucleotide mutation (*EGFR, KRAS, NRAS, CTNNB1*) was detected, SV group (n=117) where a structural variation (SV) (indel, fusion, splicing) was present, and NO group (n=95) where no significant mutation was found. We investigated the association of mutation patterns with various clinical variables and their impact on the prognosis. **Result:** The mutation was rarely found in squamous cell cancer and the SVs were more frequently found in never-smoked patients. The 5 year overall survival was 73.8+/-3.1% and the 5 year disease-free survival was 46.3+/-3.2%. The disease-free survival of SV group was inferior to that of SN group (p=0.029). When we selected only adenocarcinoma patients and stratified them by clinical stage, the SV group showed poorer disease-free survival to that of SN group in clinical stage I (p=0.017). However, when stratified by pathologic stage, there was no difference. When we investigated discrepancies between clinical and pathologic stages, up-stage from clinical stage I to pathologic N2 was more frequently found in SV group.



Conclusion: Our observation suggests that if structural variations are detected in clinical stage I adenocarcinoma, more aggressive mediastinal lymph node evaluation is mandatory and a different treatment strategy may be investigated.

Keywords: mutation patterns, cancer panel, Prognosis

P2.02-060 PROGNOSTIC SIGNIFICANCE OF EDIL3 EXPRESSION AND CORRELATION WITH MESENCHYMAL PHENOTYPE AND MICROVESSEL DENSITY IN LUNG ADENOCARCINOMA

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Background: Epidermal Growth Factor-like repeats and Discoidin I-Like Domains 3 (EDIL3), is a secreted glycoprotein associated with endothelial cell surface and extracellular matrix. Overexpressed EDIL3 can contribute to carcinogenesis by promoting cancer vascularization and epithelial–mesenchymal transition. Therefore, EDIL3 might be a good candidate target for developing novel cancer anti-angiogenic therapy. Although the associations among EDIL3, mesenchymal phenotype, and angiogenesis have been observed in several malignancies, no study has examined the relationships among EDIL3, mesenchymal phenotype, and angiogenesis or the prognostic significance of EDIL3 expression in non-small cell lung carcinoma (NSCLC) patients. We examined the prognostic significance of EDIL3 expression and its correlations with mesenchymal phenotype and microvessel density in NSCLC. **Method:** A total of 268 NSCLC specimens were evaluated retrospectively by immunohistochemical staining for EDIL3, epithelial–mesenchymal transition (EMT) markers (e-cadherin, β-catenin, and vimentin), and CD31 to measure microvessel density. we performed real-time qRT PCR for EDIL3 expression **Result:** EDIL3, e-cadherin, β-catenin, and vimentin were expressed in 16%, 22.8%, 3.7%, and 10.1% of the specimens, respectively. The mRNA level of EDIL3 in tumor was correlated with the level of EDIL3 protein expression using immunohistochemistry. In lung adenocarcinoma patients, EDIL3 expression was significantly correlated with mesenchymal phenotype (low e-cadherin expression and high vimentin expression) and increased microvessel density ($P < 0.001$, $P = 0.001$, and $P = 0.023$, respectively). In lung squamous cell carcinoma patients, EDIL3 expression was significantly correlated with mesenchymal phenotype (low e-cadherin expression and high vimentin expression) ($P = 0.021$ and $P = 0.002$, respectively). In lung adenocarcinoma patients, EDIL3 was an independent prognostic factor for overall survival in a multivariate analysis (hazard ratio: 2.552, $P = 0.004$). **Conclusion:** EDIL3 is significantly correlated with mesenchymal phenotype, angiogenesis, and tumor progression in lung adenocarcinoma.

Keywords: non–Small-Cell Lung Cancer, epithelial–mesenchymal transition, Epidermal Growth Factor-like repeats and Discoidin I-Like Domains 3

P2.02-061 TWO NOVEL PROTEIN-BASED PROGNOSTIC SIGNATURES IMPROVE RISK STRATIFICATION OF EARLY LUNG ADC AND SCC PATIENTS

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Background: The development of robust, feasible and clinically useful molecular classifiers for early stage NSCLC patients to assess the risk of developing post-resection recurrence is an unmet medical need. Here we identified and validated the clinical utility of two different histotype-specific protein-based prognostic signatures to stratify the five-year risk of lung cancer recurrence or death in patients with either early lung adenocarcinoma (ADC) or early squamous cell carcinoma (SCC). The signatures are based on the immunohistochemical detection of three and five proteins, for ADC and SCC respectively **Method:** A total number of 562 lung cancer patients were included in this study (n=350 for ADC and n=212 for SSC). A training cohort was used to assess the value of the prognostic signatures based on immunohistochemical (IHC) detection (n=239 ADC and n=117 SSC). The prognostic signatures were developed by Cox regression analysis and were comprised of three and five proteins, respectively for ADC and SCC. Overfitting and optimism were quantified and calibrated by internal validation by applying shrinkage and bootstraping combination. The performance of the models was externally validated in a second cohort of 111 and 95 patients with stage I-II lung ADC and SCC, respectively. **Result:** The prognostic indexes (PIs) generated by the models were significant predictors of five-year outcome for disease-free survival: [P<0.001, HR=2.88 (95% CI, 1.77-4.69)] for ADC and [P<0.001; HR=2.97 (95% CI, 1.84-4.79)] for SCC; and overall survival: [P<0.001, HR=4.04 (95% CI, 2.30-7.10)] for ADC and [P=0.006; HR=1.86 (95% CI, 1.20-2.88)] for SCC, independently of other clinicopathological parameters. The prognostic ability of both PIs was externally validated in the second cohort of early stage lung cancer patients (P<0.05). The molecular classifiers added significant information to pathological stage. Combined models including both PIs and the pathological stage (CPIs) improved the risk stratification in both cases (P<0.001). Moreover, using the CPI value we were able to select the group of stage I-IIA patients who could obtain a benefit from platinum-based adjuvant chemotherapy treatment (P<0.05) in both histological subtypes. **Conclusion:** This study identifies and validates two protein-based prognostic signatures that accurately identify early lung cancer patients with high risk of recurrence or death. More importantly, the proposed models may be valuable tools to identify the subset of stage I-IIA patients for whom adjuvant chemotherapy could be beneficial.

Keywords: early lung cancer risk stratification, Adenocarcinoma and Squamous carcinoma, prognostic signatures

P2.02-062 THE MICRORNAS ASSOCIATED WITH RECURRENCE AND METASTASIS OF STAGE I LUNG ADENOCARCINOMA

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Background: Up to 30% stage I non-small cell lung cancer (NSCLC) patients undergone the tumor resection suffer from recurrence within 5 years. Applicable prognostic biomarkers are required to identify those with high risk of relapse after the surgery, for modified adjuvant therapy to potentially improve survival. This study aims to identify the microRNAs (miRNAs) that associate with recurrence and metastasis of stage I lung adenocarcinoma (ADC). **Method:** Two groups of stage I lung ADC patients were enrolled, with 40 cases for each. For the patients in the group RM, the tumor recurrence and/or metastasis occurred within 2 years after the surgical resection. For the patients in the group NRM, the tumor recurrence and/or metastasis had not reappeared for 5 years after the surgery. The tumor tissues were enriched from formalin-fixed and paraffin-embedded tissue sections, and the total RNAs were extracted. The Agilent human microRNA microarrays were used to generate miRNA profiles and explore the aberrantly expressed miRNAs in the samples investigated. The interesting differentially expressed miRNAs between the two groups were then validated by quantitative reverse transcription polymerase chain reaction (qRT-PCR) in an independent cohort of 80 cases of stage I lung ADC, which was also divided into two groups, the RM and NRM. **Result:** The miRNA expression profiling revealed that a panel of miRNAs were differentially expressed between the group RM and group NRM. Cluster analysis showed that this panel of miRNAs could distinguish patients in the group RM from those in the group NRM. Moreover, according to target gene prediction and KEGG pathway analysis of these miRNAs, predicted target genes of 2 miRNAs (miR-3621 and miR-2467-3p) in the panel are involved in the non-small cell lung cancer pathways. The expression of these miRNAs were tested subsequently by qRT-PCR in the tumor samples of the independent cohort, using miR-191 as an internal reference. The preliminary data showed that among them, the mean relative expression fold change ($2^{-\Delta Ct}$) of miR-2467-3p in the group RM was significantly lower than that in the NRM (p = 0.014). **Conclusion:** Our finding suggests that a panel of miRNAs may be regarded as candidate biomarkers for prognosis of early stage lung ADC. Among them miR-2467-3p was aberrantly down-regulated in the tumor tissues of patients in the group RM; accordingly, miR-2467-3p (and its predicted target genes) may play a role in recurrence and/or metastasis of stage I lung ADC after the surgical resection.

Keywords: Prognostic biomarkers, microRNA, stage I lung adenocarcinoma

P2.02-063 ONCOGENIC MICRORNAS ASSOCIATED WITH POOR PROGNOSIS ARE UP-REGULATED ON THE AMPLICON IN SQUAMOUS CELL LUNG CARCINOMA

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Background: Squamous cell carcinoma (Sq) is second major histological subtype of lung cancer. Unlike in the case of adenocarcinoma (Ad), Sq has only few molecular target drug. MicroRNA (miR) is a major part of post-transcriptional regulators functioning as tumor suppressor genes or oncogenes. MiR will regulate target molecules related to carcinogenesis and malignancy in Sq. **Method:** Using The Cancer Genome Atlas dataset including copy number variation, RNA sequence, miR sequence, clinicopathological feature from 484 lung cancer cases, the correlation between genomic copy number and expression of miR was analyzed. 245 samples of Sq and 239 samples of Ad were included. The raw counts of each mature miR fragments with different precursor were merged and calculated from miR-seq isoform files by R project (http://www.r-project.org/) Segmented copy number variation datasets were processed with R package CNTools of Bioconductor project. Independent two-group Mann-Whitney U test was used to compare different expression between Sq and Ad. MiR expression according to copy number variation was analyzed using Pearson correlation coefficient r-score. To identify the miR target sites of mRNAs, targetscan-Perl scripts were used (http://www.targetscan.org/). **Result:** From 1,001 mature miR fragments, 34 miRs were identified as the candidates especially for Sq distinguished from Ad. Furthermore, four miRs were up-regulated in amplified regions and independently associated with poor prognosis in Sq. Moreover, those who had the tumor with high expression in three of four miR simultaneously showed worst prognosis. To explore miR-mRNA network, we also predicted the target genes for each miR. From 734 common target genes, three showed positive correlation with the expression of three miRs. Among them, the expression of 109 mRNAs inversely correlated with that of 3 miRs. From 109 mRNA, the expression of 24 mRNAs inversely correlated with that of all the 3 miRs and only 2 mRNA expression showed low levels in Sq compared with Ad or normal tissues. **Conclusion:** Three miRs up-regulated in Sq were associated with poor prognosis through the regulation of two common target genes.

Keywords: Squamous cell carcinoma, micro RNA

P2.02-064 A NOVEL 5-MIR SIGNATURE SHOWS POTENTIAL AS A DIAGNOSTIC TOOL AND AS A PREDICTIVE BIOMARKER OF CISPLATIN RESPONSE IN NSCLC

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Background: MicroRNAs are a class of small non-coding RNAs that range in size from 19-25 nucleotides. They have been shown to regulate a number of processes within tumour biology, including metastasis, invasion and angiogenesis. More recently, miRNAs have been linked to chemoresistance in solid tumours, including lung cancer. Their role in cisplatin resistance has yet to be determined. **Method:** MicroRNA expression within a panel of age-matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines was profiled using the 7th generation miRCURY LNA arrays (Exiqon) and subsequently validated by qPCR. Significantly altered miRNAs within the CisR sublines were manipulated using antagomirs (Exiqon) and Pre-miRs (Ambion) and functional studies were carried out in the presence and absence of cisplatin. To examine the translational relevance of these miRNAs, their expression was examined in a cohort of chemo-naïve patient-matched normal and lung tumour tissue and serum from NSCLC patients of different histologies. A xenograft model of cisplatin resistance was carried out in which $1x10^3$ H460 PT or CisR cells were injected into 5-7week old NOD/SCID mice. Tumour volume was measured over time and harvested once the tumour mass measured $500mm^3$ and formalin-fixed and paraffin embedded (FFPE). Expression of the 5-miR signature was analysed within FFPE

murine tumours and compared between PT and CisR tumours. **Result:** Profiling and subsequent validation revealed a 5-miR signature associated with our model of cisplatin resistance (miR-30a-3p, miR-30b-5p, miR-30c-5p, miR-34a-5p, miR-4286). Inhibition of the miR-30 family and miR-34a-5p reduced clonogenic survival of CisR cells when treated cisplatin. Expression of the miRNA signature was significantly altered in both adenocarcinoma (AD) and squamous cell carcinoma (SCC) relative to matched normal lung tissue and between SCC and AD tissue. miR-4286 was significantly up-regulated in SCC sera compared to normal control and AD sera. Similarly to the cell line expression of the miRNAs, the miR-30 family members and miR-34a-5p were up-regulated in the CisR xenograft FFPE tissue relative to PT. **Conclusion:** A novel miRNA signature associated with cisplatin resistance was identified *in vitro*, genetic manipulation of which altered clonogenic response to cisplatin. The 5-miR signature showed both diagnostic and prognostic biomarker potential across a number of diagnostically relevant biological media.

Keywords: microRNA, Cisplatin resistance, Biomarkers

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-065 RANBP9 IS A NOVEL PROGNOSTIC AND PREDICTIVE BIOMARKER FOR NSCLC AND AFFECTS CELLULAR RESPONSE TO CISPLATIN AND PARP INHIBITORS

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Background: We have previously demonstrated the involvement of Ran Binding Protein 9 (RanBP9) in the DNA Damage Response (DDR) in Non Small Cell Lung Cancer (NSCLC) cells. Here, we investigate its role in response to DNA-damaging agents *in vitro* and as prognostic and predictive biomarker for NSCLC patients. **Method:** First, by IHC, we evaluated RanBP9 expression in tumor vs normal adjacent tissue (NAT). Then, we generated A549 RanBP9 WT and KO NSCLC cells using CRISPR/Cas9. We treated A549 RanBP9 WT and KO with cisplatin (CDDP) and PARP inhibitors. We assessed response to treatment by measuring cell toxicity, apoptosis and proliferation. Finally, we determined the expression of RanBP9 in cohort of NSCLC patients previously enrolled in the TAILOR trial. **Result:** In the present study, we report that significant overexpression of RanBP9 is a common event in lung cancer, as shown by an extensive immunohistochemical analysis of RanBP9 levels in 148 lung tumors of different histotypes and their normal adjacent tissue ($p<0.02$ - 0.001). RanBP9 expression was maintained/acquired in the nodal metastasis from 30 NSCLC patients, indicating its potential involvement in tumor aggressiveness. We also show that RanBP9 KO A549 NSCLC cell lines display a reduced DDR and higher levels of apoptosis upon cisplatin treatment both *in vitro* and *in vivo*. Accordingly, a retrospective analysis of 134 NSCLC patients revealed that higher levels of RanBP9 are associated with tumor stage ($p<0.0001$), and low response to platinum compounds as first-line treatment (PFS, $HR_{(RanBP9\ positive\ versus\ negative)}$ 1.71, 95% CI 1.142 - 2.563, p = 0.0093; OS $HR_{(RanBP9\ +\ vs\ -)}$ 1.942, 95% CI 1.243-3.033, p=0.0036). Finally, we show that ablation of RanBP9 is associated with overactivation of Poly(ADP-ribose) Polymerase (PARP) and increases sensitivity to PARP inhibitors. Moreover, that use of PARP inhibitors enhances cisplatin anti-neoplastic efficacy in the absence of RanBP9. **Conclusion:** We identified RanBP9 as a novel predictive biomarker of response to genotoxic treatments in NSCLC patients. We also report that RanBP9 affects the response of NSCLC cells to PARP inhibitors *in vitro*. Our results open new avenues for the treatment of NSCLC patients based on their level of expression of RanBP9.

Keywords: PARP inhibitors, RanBP9, Cisplatin

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-066 IDENTIFICATION OF CRUCIAL GENE TARGETS IN THE IN SITU ENVIRONMENT OF CANCER BY GOOGLE NETWORK RANKING

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Background: The vast majority of cancer driver genes in non-small cell lung cancer (NSCLC) are characterized by activating mutations or high gene copy number amplifications. To identify tumorigenic genes without any genomic aberrations remains difficult. Network analysis of gene expression provides the possibility to describe the relations of genes to each other and by that to estimate their importance. **Method:** To analyze gene networks of NSCLC we applied the PageRank algorithm that was established by Google primarily to order the importance of websites. Data from NSCLC cancer tissue (n=1002) and normal lung (n=110) were retrieved from the cancer genome atlas (TCGA) and the highest expressed genes (n=16000) were ranked according to their importance in normal lung tissue as well as in NSCLC tissue. Subsequently, the difference in rank between normal and cancer was analyzed. Four comparative categories were defined and were analyzed with respect to their cellular function (GO annotation) and survival. Additionally, organ specific (n=163), housekeeping (n=68) and lung cancer related genes (n=62) were compared in the networks. **Result:** Genes with the highest importance (top 100) in normal lung tissue were connected with cellular metabolic processes or membrane transport. In cancer, most genes (top 100) were related to cell cycle and mitosis, chromosomal localization and DNA processing. There was no overlap between the two lists. Organ specific genes increased in average in their rank ($p<0.001$) while housekeeping genes decreased ($p<0.001$). Notably, cancer related genes did not significantly change their relevance in the network. Among the genes (top 100) that increased rank from normal to cancer, many were related to antigen processing and presentation. **Conclusion:** The PageRank algorithm provides the possibility to unbiasedly evaluate the importance of genes in the gene expression network of cancer. Surprisingly, not traditional cancer related genes but several hitherto not recognized genes were identified to be of regulatory importance and may be target for therapy. Once again, our results indicate the significance of the immune response in changes related to cancer.

Keywords: RNA-seq, NSCLC, Network

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-067 LKB1 LOSS IS ASSOCIATED WITH DNA HYPOMETHYLATION IN HUMAN LUNG ADENOCARCINOMA

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Background: Lung cancer is the leading cause of cancer-associated mortality in the United States. LKB1 loss, for which there are no targeted therapies, occurs in 30% of lung adenocarcinomas. Our group has developed an RNA-based genetic signature for LKB1 loss and applied it to samples in the Cancer Genome Atlas (TCGA). Our studies have identified a novel role for LKB1 in regulation of DNA methylation and histone acetylation/methylation. While global demethylation has been noted in many cancers, LKB1-deficient lung tumors display a greater degree of demethylation compared to tumors that express functional LKB1. **Method:** RNA-Seq results the TCGA lung adenocarcinoma provisional dataset were analyzed using a genetic classifier for LKB1 loss; samples were separated into wildtype and loss cohorts. Approximately 420 of the samples classified were also characterized using Illumina 450k methylation arrays. We used this data to analyze differentially methylated CpGs. Motif analysis of common transcription factor binding sites near hypomethylated CpGs was accomplished using HOMER. To assess transcription factor localization and binding *in vitro, we* used a retroviral gene expression system to restore LKB1 function in previously deficient lung cancer cell lines and a CRISPR/Cas9 approach to knock out LKB1 in wildtype cell lines. **Result:** We observed that LKB1 loss is associated with widespread demethylation of CpG islands throughout the genomes of TCGA samples. Of approximately 138,000 differentially methylated probes, 131,000 are significantly hypomethylated in LKB1 loss (adj. p-value cutoff = .01). We observed that DNMT1, which maintains methylated CpG sites, is downregulated following LKB1 loss. HOMER motif analysis of common transcription factor binding sites in the top 5000 hypomethylated sites implicated several transcription factors that are associated with hypomethylated CpGs—most notably FOXA1/2/3, Nur77, CEBPB, and KLF5; the FOXA family and KLF family have been described as pioneering transcription factors in genomic demethylation. Fractionation and Western blot of A549 cells show that inducing LKB1 expression attenuates FOXA1 and FOXA3 chromatin binding as well as overall expression of FOXA1 and FOXA2. **Conclusion:** These results have broad implications for gene regulation in LKB1-loss lung tumors and a full understanding of these changes might uncover drug targets specific for these tumors. LKB1's association with global demethylation suggests that therapeutics targeting methylation such as decitabine may have different effects on LKB1 loss and LKB1 WT tumors, a hypothesis which we are currently testing. We are also continuing to study FOXA1/2/3 and KLF5 to determine the mechanism by which LKB1 regulates its demethylation program.

Keywords: epigenetics, LKB1

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-068 BRG1 AND P53 EXPRESSION IN RESECTED STAGE I – III NON-SMALL CELL LUNG CANCER

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Background: Evidence suggests a striking significance of BRG1 in non-small cell lung cancer (NSCLC) development and prognosis including its ability to modulate NSCLC response to commonly used chemotherapy. The human SW1/SNF (switching defective/ sucrose non-fermenting) family of chromatin remodeling complexes are composed of multi-subunit proteins among which are the BRG1 and INI-1. Both BRG1 (SMARCA4) and INI-1 (SMARCB1, BAF47, SNF7) are implicated in different cancers.

We aimed at identifying the frequency of the SW1/SNF protein components loss and the significance in NSCLC. Given that inactivating BRG1 mutations could coexist with TP53 alterations in NSCLC cell lines, we also included the tumor suppressor protein p53 in our analysis. **Method:** We analyzed the expression of the SW1/SNF subunits (BRG1 and INI-1) and p53 proteins from resected stage I – III NSCLC using the immunohistochemistry. Mouse monoclonal anti-p53 (DO-7, Dako Omnis) and anti-INI-1 (MRQ-27, Cell Marque) antibodies were used for p53 and INI-1 protein detection respectively. BRG1 was detected using the rabbit monoclonal anti-BRG1 antibody (EPNCIR111A, Abcam). Clinical data were obtained from the Glans-Look lung cancer database and patients diagnosed of NSCLC from 2003 to 2006 were included in the study. **Result:** A total of 150 cases were identified, {Adenocarcinoma n =82 (54.7%), Squamous cell carcinoma n = 50 (33.3%), Large cell carcinoma n = 7 (4.7%) and others n = 11 (7.3%: Adenosquamous, Bronchioalveolar and Giant cell carcinomas)}. The BRG1 protein was absent in 6% (9/150) of cases with the overall highest number (3.3%) seen in adenocarcinoma. Whereas, normal INI-1 protein was expressed in all samples. Within NSCLC subtypes, the rate of BRG1 loss was highest in the large cell carcinomas at 28.1% (2/7) and lowest in squamous cell subtype at 2% (1/50) while only 6.1% (5/82) of adenocarcinoma showed BRG1 loss. The frequency of aberrant p53 protein expression (including overexpression, cytoplasmic and complete expression loss) was at 63% (95/150) and 6 (2 large cell and 4 adenocarcinoma) of the 95 abnormal p53 cases (6.3%) had BRG1 loss. **Conclusion:** BRG1 loss seems to be a low occurrence in NSCLC. Although a high rate of BRG1 inactivating mutations were previously reported in NSCLC cell lines, the present result suggests that these mutations may still result in the expression of possibly an abnormal BRG1. BRG1 loss appears to coexist with p53 abnormality in NSCLC. Additional multivariate and outcome analysis will be presented.

Keywords: SW1/SNF complex, BRG1, p53, NSCLC

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-069 TARGETING NEUROPILIN-1 IN NSCLC

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Background: Neuropilin-1 (NP1) is expressed by a wide variety of human tumour cell lines and diverse human neoplasms, and is implicated in mediating the effects of VEGF on the proliferation, survival and migration of cancer cells. It is extensively expressed in tumour vasculature, where NP1 over-expression is associated with tumour progression and poor clinical outcome. In this study, we examined the effects of targeting NP1 in NSCLC both *in vitro* and *in vivo*. **Method:** A panel of NSCLC cell lines (H460, H647, A549 and SKMES) were screened for NP1 at the mRNA and protein levels by RT-PCR and Western blotting, respectively. Cellular expression and localisation of NP1 was further examined by immunocytochemistry, while a panel of retrospective resected lung tumours and matched normal tissues were stained by immunohistochemistry. The effects of targeting NP1 on cell proliferation (BrdU ELISA), apoptosis (FACS, HCS) and downstream survival signalling pathways (Western Blot) were examined under normoxic and hypoxic (0.1% O_2) cell growth using anti-NP1 neutralising antibodies. Cell survival was assessed in response to treatment of NSCLC cells with a range of chemotherapeutic agents in combination with NP1 neutralising antibodies. Using a human xenograft model, tumour growth studies were carried out in nude mice following subcutaneous injection of NP1 over-expressing cells relative to empty vector controls. **Result:** All lung cancer cell lines examined expressed NP1 with the exception of the H460 cell line. Immunocytochemistry analysis confirmed cellular expression and localisation of this receptor, particularly in the leading edges of migrating cells, suggesting a possible role in cell migration. In a small cohort of resected NSCLC patients, tumour expression of NP1 was high relative to their matched normal lung tissues in adenocarcinoma, squamous cell and large cell neuroendocrine carcinomas. Cell proliferation and apoptosis were significantly altered in NSCLC cells expressing NP1. While hypoxia induced the expression of NP1, treatment of cells with NP1 neutralising antibodies reduced hypoxia-mediated cell proliferation and decreased expression of PI3K and MAPK signalling pathways. In a preliminary study, treatment with NP1 neutralising antibodies sensitised NSCLC cells to the cytotoxic effects of chemotherapy. *In vivo*, H460 cells over-expressing NP1 significantly increased tumour growth in NOD/SCID mice relative to empty vector controls. **Conclusion:** These data suggest a role for the Neuropilin-1 receptor in promoting cell survival and tumour growth in NSCLC and may offer potential as a therapeutic biological strategy in lung cancer.

Keywords: Cell survival, NSCLC, Neuropilin

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-070 C-MET AS A BIOMARKER IN PATIENTS WITH SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER

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Background: c-MET protein overexpression has been proposed as potential prognostic as well as predictive biomarker for targeted therapy in non-small cell lung cancer (NSCLC), albeit its role in the clinical setting has not been firmly established yet and no clear cut-off value exists for immunohistochemistry (IHC) score. **Method:** We designed a retrospective cohort study, consisting of 725 patients with surgically removed non-small cell lung cancer. IHC was conducted in tissue microarrays (TMA) from lung tumors and healthy tissue adjacent to the tumor, using a specific antibody against human c-MET (MET PharmDx). IHC staining was quantified using H-scores (range 0-300). Association between c-MET H-score and overall survival (OS) as well as progression-free survival (PFS) was explored. **Result:** c-MET H-score over 20 had a significant protective impact on OS in the multivariate analysis in the whole study population, both as continuous variable (p=0.014), as well as dichotomous variable with HR=0.79 (95%CI: 0.64-0.97, p-value = 0.022). The prognostic effect of c-MET H-score over 20 was stronger in patients who received adjuvant treatment with a HR=0.61 (95% CI: 0.40-0.93, p-value=0.022). In the subgroup of adenocarcinoma and squamous cell carcinoma patients with stage IIA-IIIB disease, the prognostic impact of c-MET was significant even in the univariate analysis (HR=0.60, 95% CI: 0.43-0.83, p-value=0.002). **Conclusion:** c-MET H score > 20 is a positive prognostic biomarker for OS in early stage NSCLC. This benefit seems to be strongly correlated to adjuvant chemotherapy, therefore rendering c-MET H-score > 20 a possible predictive biomarker for platinum-based adjuvant chemotherapy in early stage NSCLC.

Keywords: c-Met, non-small cell lung cancer, early stage

P2.02: BIOLOGY/PATHOLOGY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.02-071 PROSPECTIVE MOLECULAR STUDY OF 22 GENES BY NGS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) IN ARGENTINA: A SINGLE INSTITUTION EXPERIENCE

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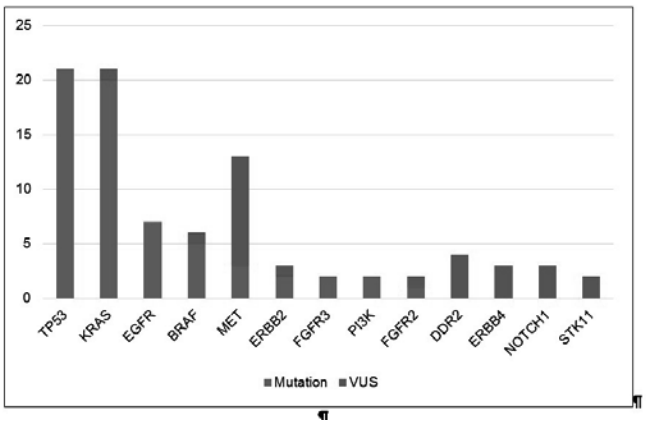
Background: Next generation sequencing has contributed to understanding the biology of NSCLC and to improve therapy selection. The prevalence of other oncogenic alterations beyond EGFR, ALK and KRAS in Argentina remains unknown. The aim of this study was to characterize the genomic lanscape of NSCLC tumors from 45 patients in our institution by NGS. **Method:** Prospective observational study. We included 45 patients, over 18 years old, with diagnosis of NSCLC and adequate tumor sample. DNA was purified from FFPET samples. Targeted NGS was done with Colon and Lung Cancer Research Panel v2 (Ion Torrent™ AmpliSeq™ technology) for 22 genes with Ion 520 chip, sequenced in Ion S5 Next Generation Sequencing Systems. **Result:** Forte five patients were included in the analysis, 19 female (42%) and 26 male (58%). Median age was 57 years old (range 34-89). Most patients had lung adenocarcinoma 43 (96%), 1 squamous (2%) and 1 adenosquamous histology (2%). A total of 28 patients (62%) had stage IV lung cancer, 18% stage III, 4% stage II and 16% stage I. From 43 evaluable samples, 65 mutations were detected: TP53 n=21, KRAS n=20, EGFR n=9, BRAF n=5, MET n=3, ERBB2 n=2, FGFR3 n=2, PI3K n=2, FGFR2 n=1. Of these, 10 are associated with clinical benefit with approved targeted therapies. Two samples had novel EGFR mutations and 2 had EGFR co-activating mutations (Del19 + L858R; and G719C + S768I). KRAS and TP53 co-mutations were present in 50% of KRAS mutant samples. We encountered 26 variants of unknown significance. In our population, 37 samples (86%) had EGFR Q787Q (c.2361G>A) polymorphism.



Conclusion: The distribution of oncogene mutations in patients with NSCLC in our institution in Argentina is similar to other western countries with the exception of higher KRAS mutant patients in this cohort. An ongoing larger trial will provide further information for our country and the region.

Keywords: NGS, NSCLC, Argentina

P2.02-072 RELIABILITY OF SMALL BIOPSY SAMPLES FOR TUMOR PD-L1 EXPRESSION IN NON-SMALL-CELL LUNG CANCER

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Background: Programmed death 1 immune checkpoint inhibitor antibody has been effective in patients with PD-L1 positive advanced NSCLC. However, surgically resected specimens or core-needle biopsy samples were used to estimate drug potency in past clinical trials.The aim of this study is to prospectively investigate small sample reliability for NSCLC to determine the PD-L1 expression status. **Method:** We prospectively enrolled patients who underwent diagnostic biopsy by any procedures (under rigid bronchoscopy, flexible bronchoscopy, CT & US-guided core-needle, excisional method) from March 2017 to March 2018 (ongoing study). Pathologically confirmed non-small cell lung cancer (NSCLC), PD-L1 expression was evaluated in our institution using companion diagnostic PD-L1 immunohistochemistry: PD-L1 IHC 22C3 pharmDx (Daco) with autostainer Link 48, detecting a driver mutation in parallel. We evaluated: 1) the total number of tumor cells and sample size; 2) compared PD-L1 expression for each procedure using tumor proportion score: TPS (<1%, 1~49%, 50%≦), 3) the concordance rate of PD-L1 expression status by biopsy and surgical materials; and 4) the efficacy of administration for PD-1 immune checkpoint inhibitor antibody. **Result:** During the first three months 44 cases of PD-L1 expression were evaluated. 33 cases were sampled by bronchoscopy (6 under rigid scope with BF 1T260, 17 TBBs using 1T260/P260F in 4/13 cases, 10 TBNAs), and 7 cases were CT-guided core-needle biopsy. The TPS (<1%, 1~49%, 50%≦) was 8/6/10 for TBB, 3/4/2 for TBNA, and 4/0/3 for CT-guided. Four cases harboring EGFR mutation showed a lower PD-L1 expression (<10%). **Conclusion:** Utilizing smaller samples to evaluate PD-L1 expression, and the frequency of TPS were comparable to past clinical trials using larger samples. Smaller samples might be an accurate alternative to assess PD-L1 expression. Current data will be updated at the conference.

Keywords: NSCLC, PD-L1 expression, diagnostic biopsy

P2.02-073 CYTOPLASMIC MISLOCALIZATION OF ECT2 PROTEIN IS ASSOCIATED WITH POOR PROGNOSIS IN LUNG ADENOCARCINOMA

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Background: Lung cancer is the most lethal malignancy in worldwide. We have previously compared genetic abnormality profiles in early-stage lung adenocarcinoma using array-comparative genomic hybridization (CGH) and found that Epithelial cell transforming sequence 2 (ECT2) amplification and overexpression a new prognostic marker in early-stage lung adenocarcinoma (Cancer Science, 2014). ECT2 is an oncogene that is overexpressed in several types of human cancer and has tumorigenic activity. ECT2 is localized in the nucleus of normal cells, and its function is associated with cytokinesis. In cancer cells, ECT2 exists in not only nucleus but also cytoplasm. However, cytoplasmic ECT2 is thought to promote tumor growth and invasion. In the present study, we aimed to explore the expression of cytoplasmic ECT2 and to assess its functional and prognostic significance in lung adenocarcinoma. First, we examined the subcellular localization of the ECT2 protein in lung adenocarcinoma cells. Subsequently, we investigated the biological significance of cytoplasmic ECT2 that mediated its phosphorylation state. Finally, we examined the clinicopathological attributes of cytoplasmic ECT2 in terms of patient outcome. **Method:** ECT2 expression was evaluated in an immortalized lung epithelial cells (PL16B) and eight lung adenocarcinoma cell lines Calu-3, A549, RERF-LC-KJ, NCI-H1650, PC-9, NCI-H23, NCI-H1975, and HCC827 using Immunoblotting, RT-PCR, Immunofluorescence, and Immunohistochemistry. In order to assess the clinicopathologic characteristics of cytoplasmic ECT2, we examined 50 cases of surgical specimens lung adenocarcinoma by immunohistochemistry. Twenty fresh scraping samples of lung adenocarcinoma were also used to evaluate the expression of Phosho-ECT2 (T790). The Kaplan–Meier method and Cox regression analyses represent the prognostic significance of cytoplasmic ECT2 in lung adenocarcinoma. **Result:** We found that ECT2 expressed in eight lung adenocarcinoma at variable degree levels. In PL16B cells, ECT2 was localized in the nucleus, whereas in lung adenocarcinoma cell lines ECT2 distributed in both the cytosol and the nucleus. Importantly, overexpression of ECT2 leads to aberrant cytoplasmic localization in lung adenocarcinoma cells. We also found that cytoplasmic ECT2 was phosphorylated and accumulated at the cell membrane in lung adenocarcinoma cell lines and surgical specimens. The phosphorylated form of ECT2 was reported to correlate with malignant attributes of lung adenocarcinoma and our clinical analysis showed that cytoplasmic ECT2 expression was significantly associated with poor outcome (OS; P=0.002, DFS; P=0.001), and was an independent prognostic factor in lung adenocarcinoma. **Conclusion:** We demonstrate that aberrant localization of ECT2 to the cytoplasm is a specific feature of lung adenocarcinoma, and provide a new potential prognostic biomarker in lung adenocarcinoma.

Keywords: lung adenocarcinoma, prognostic marker

P2.03-001 SURVIVORS AND ADVERSE EVENTS AFTER FIRST-LINE TARGET THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS IN TAIWAN

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Background: Some patients with advanced non-small cell lung cancer (NSCLC) show prolonged disease stabilization on treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib, erlotinib and afatinib provide remarkable response rates and survival in NSCLC patients harboring epidermal growth factor receptor-activating mutations, and are therefore standard first-line treatment in these patients, given the long-term exposure of such patients to EGFR-TKIs, from those observed in patients, to evaluate the efficacy and antitumor activity and toxicity, this study aimed to compared reasons severe adverse events (AEs) and survivors for NSCLC patients treated with these three EGFR-TKIs. **Method:** We conducted this retrospective study at a single teaching hospital in southern Taiwan from January 2014 to December 2015, the patients with advanced or metastatic EGFR mutation-positive NSCLC who received gefitinib, erlotinib, or afatinib as first-line treatment, used the Kaplan-Meier method to estimate survival, the data was analyzed by using SPSS 20.0 software. **Result:** Of the 192 patients diagnosed with stage IIIB and IV NSCLC(Non-squamous) in the study period, the analysis 88 (45.8%) had EGFR-activating mutations, of the 37 males, 51 females, median age was 63 years (range, 29-94 years). Sixty-two patients (70%) never smoked. 84 (95%) had adenocarcinoma,and received first-line therapy with gefitinib (n = 55, 63%), erlotinib (n = 10, 11%), and afatinib (n = 23, 26%).Rash and diarrhea were the most common drug-related toxicities, encountered in 68.2% and 53.4% of patients, The overall response and disease control rates were 58 and 80 %(Table 1), respectively, and the median progression-free survival and overall survival were 16 and 23 months, respectively.

Table 1. Response to first-line Target therapy with epiderma growth factor receptor-mutated non-small cell lung cancer

	Number of patients (%)	
Complete response	0	0%
Partial response	51	58%
Stable disease	19	22%
Progressive disease	9	10%
Stationary	2	2%
Not evaluable	7	8%
Response rate (%)	51	58%

Conclusion: First-line target therapy a preferred standard treatment in advanced NSCLC harboring sensitive EGFR mutations. treatment with TKI was feasible and lead to prolonged overall survival.

P2.03-002 IMPACT OF EGFR-TYROSINE KINASE INHIBITORS FOR POSTOPERATIVE RECURRENT NON-SMALL CELL LUNG CANCER HARBORING EGFR MUTATIONS

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Background: It is unclear whether there is a difference in the efficacy of treatment by EGFR-TKI between patients with postoperative recurrent non-small cell lung cancer

(NSCLC) and those with stage IV NSCLC harboring EGFR mutations. **Method:** The records of NSCLC patients harboring EGFR mutations who were treated with gefitinib or erlotinib were retrospectively reviewed, and the treatment outcomes were evaluated. Moreover, we performed an immunohistochemical analysis of PD-L1 expression in tumor lesions of the postoperative recurrence group. **Result:** In 205 patients, both the progression-free survival time (9.4 versus 16.9 months) and the median survival time (24.7 versus 37.4 months) were significantly longer in the postoperative group than stage IV group. Additionally, multivariate analysis identified that postoperative recurrence was as an independent predictor of the PFS and OS, as well as performance status and smoking status. The PFS durations were 15.7 and 16.6 months for the high PD-L1 expression and low PD-L1 expression groups, respectively, and a significant difference was not observed ($P = 0.73$). **Conclusion:** The findings of this study provide a valuable rationale for considering postoperative recurrence as a predictive factor for favorable PFS and overall survival in patients with NSCLC harboring activating EGFR mutations receiving EGFR-TKI.

Keywords: Epidermal growth factor receptor mutations, Postoperative recurrence, PD-L1 expression

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-003 COST EFFECTIVENESS OF GEFITINIB FOR LUNG ADENOCARCINOMA PATIENTS WITH MUTANT EPIDERMAL GROWTH FACTOR RECEPTOR

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Background: Tyrosine kinase inhibitor such as Gefitinib rather than conventional chemotherapy is the standard of care for advanced lung adenocarcinoma (LA) with mutant epidermal growth factor receptor (mEGFR). However, its cost-effectiveness is less clear. The aim of our study is to compare the cost and effectiveness of 1st line gefitinib vs platinum-based chemotherapy for clinical stage IV LA via this population-based propensity score (PS) matched analysis. **Method:** We identified eligible patients diagnosed within 2011 through a comprehensive population-based database containing cancer and death registries, and reimbursement data in Taiwan. The primary duration of interest (DOI) was two years within diagnosis. Effectiveness was measured as survival whereas direct medical cost was measured from the health care sector's perspective. In supplementary analysis (SA), we estimated the cost-effectiveness under potential unmeasured confounder(s) and the cost-effectiveness if the DOI was three years. **Result:** Our study population constituted 240 patients [Table 1]. Within 2 years, gefitinib was both more effective [mean overall survival 1.48 vs 1.47 life-year] and cost-saving [mean 78770 vs 82684, 2015 US dollars] when compared to chemotherapy. In SA, our results was sensitive to potential unmeasured confounder(s) but remained cost-effective when DOI was 3 years.

Table 1. Patient characteristics of the propensity-score matched final study population

		Gefitinib		Platinum-based chemotherapy		standardized difference (rounded)
		number	(%)	number	(%)	
age	<65	76	(63.33)	75	(62.5)	0.017
	>=65	44	(36.67)	45	(37.5)	
gender	female	60	(50)	60	(50)	0
	male	60	(50)	60	(50)	
residency	non-north	55	(45.83)	56	(46.67)	0.017
	north	65	(54.17)	64	(53.33)	
comorbidity	without	62	(51.67)	64	(53.33)	0.033
	with	58	(48.33)	56	(46.67)	
smoking history	no	79	(65.83)	79	(65.83)	0
	yes	41	(34.17)	41	(34.17)	
performance status	0-1	113	(94.17)	113	(94.17)	0
	2	7	(5.83)	7	(5.83)	

Conclusion: 1st line gefitinib was cost-effective for clinically stage IV LA with mEGFR from health care sector's perspective when compared to platinum-based chemotherapy.

Keywords: lung adenocarcinoma, mutant epidermal growth factor, gefitinib

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-004 RECURRENT RESPONSE TO ADVANCED NSCLC WITH ERLOTINIB DEVELOPING CENTRAL NERVOUS SYSTEM FAILURE DURING GEFITINIB OR ICOTINIB TREATMENT

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Background: Approximately one-third of non-small-cell lung cancer (NSCLC) patients harboring EGFR mutations develop central nervous system (CNS) metastases as the progressive pattern during EGFR-TKIs treatment. We design this study to evaluate the feasibility and efficacy of erlotinib as the subsequent therapy when intracranial tumor progression occurs during gefitinib or icotinib treatment. **Method:** The study reviewed the clinical data of patients with advanced NSCLC who received erlotinib treatment after CNS progression of gefitinib or icotinib in Cancer Hospital Chinese Academy of Medical Sciences from June 2012 to July 2016. **Result:** In 29 eligible patients, the objective response and disease control rates of erlotinib for intracranial lesions (ICLs) were 10.3% and 86.2%, and for extracranial lesions (ECLs) were 0% and 93.1%, respectively. The median progression-free survival (PFS) of patients treated with erlotinib was 6.28 months (HR 1.729, 95% CI 2.887–9.663) and the median overall survival (OS) was 11.73 months (HR 2.394, 95% CI 7.036–16.422). Synchronous ICLs and ECLs progression in initial EGFR-TKIs treatment (HR 2.467, 95% CI 1.029-5.915, P=0.043) was found to be an independent adverse prognostic factor for PFS of erlotinib. The patients who received ≥ 2 lines of treatment before erlotinib had a poorer PFS (HR 3.340, 95% CI 1.369-8.152, P=0.008) and OS (HR 2.563, 95% CI 1.025-6.412, P=0.044). The median intracranial progression-free survival (iPFS) for initial EGFR-TKIs was 14.22 months (range, 0.56-35.12 months) and showed no significant difference in PFS and OS of erlotinib re-treatment in subgroup analyses. As for safety profile, the most common adverse events of erlotinib were hematological (44.8%), gastrointestinal reaction (20.7%) and rash (37.9%) in grade 1/2. **Conclusion:** Erlotinib can be used when intracranial tumor progression occurs during gefitinib or icotinib treatment. The progressive pattern of initial EGFR-TKIs and multiple prior treatments may influence the survival of patients with erlotinib re-treatment. Prospective studies are needed to confirm these results.

Keywords: brain metastases, Non-small-cell lung cancer, Epidermal growth factor receptor tyrosine kinase inhibitor

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-005 OVERALL SURVIVAL RESULTS FROM A PROSPECTIVE, MULTICENTER PHASE II TRIAL OF LOW-DOSE ERLOTINIB AS MAINTENANCE IN NSCLC HARBORING EGFR MUTATION

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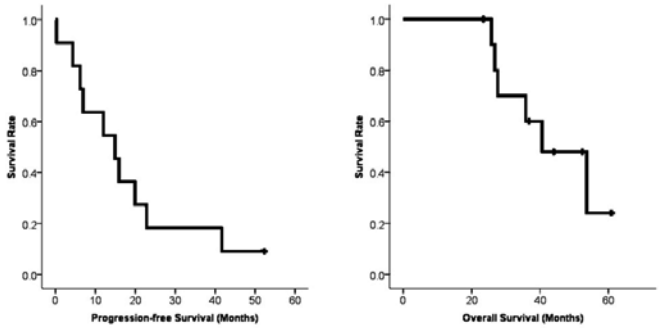
Background: Maintenance therapy with full-dose erlotinib for patients with advanced non-small cell lung cancer (NSCLC) has demonstrated a significant overall survival (OS) benefit. However, 150 mg/day of erlotinib seems too toxic as maintenance therapy. This study aimed to evaluate the efficacy and safety of low-dose erlotinib (25 mg/day) as maintenance treatment after platinum doublet chemotherapy in NSCLC harboring epidermal growth factor receptor (EGFR) mutation. **Method:** Activated EGFR-mutation-positive NSCLC patients who did not progress after first-line platinum-doublet chemotherapy, ≥20 and ≤85 years old, with performance status (PS) 0–3 were included in this study. Low-dose erlotinib (25 mg/day) was administered until disease progression. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), OS, and safety. The required sample size was 40 patients. **Result:** The study was stopped early, after achieving only 28% of planned enrollment, due to poor accrual. Between April 2011 and May 2014, 11 patients (male/female, 5/6; median age, 72 years; PS 0/1, 8/3; stage IV/relapse after surgery, 9/2; exon 19 deletions/L858R, 7/4) were enrolled and accessible in this study. Partial response (PR) was observed in 6 patients (56%). Median PFS was 14.9 months [95% confidence interval (CI), 2.7–27.1 months] and median OS was 40.6 months [95% CI, 24.7-56.5 months] (Figure 1). Toxicities were generally mild. Only one patient developed grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation. Eight patients developed grade 1 skin rash. No treatment-related deaths were observed. Ten patients progressed, and recurrences included brain metastases (n=3), pulmonary metastasis (n=3), local recurrence (n=2), local recurrence plus brain metastasis (n=1), and bone metastasis (n=1).

Figure 1 Progression-free survival and overall survival



Conclusion: The study was stopped early due to poor accrual. However, our study suggests that maintenance therapy with low-dose erlotinib might be useful and tolerable in selected NSCLC patients harboring EGFR mutation.

Keywords: EGFR mutation, Low-dose erlotinib, maintenance treatment

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-006 HOW MANY YEARS OF LIFE HAVE WE LOST IN BRAZIL DUE TO THE LACK OF ACCESS TO ANTI-EGFR TKIS IN THE NATIONAL PUBLIC HEALTH SYSTEM?

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Background: Lung cancer is the fourth most common cancer in Brazil with 28,220 new cases in 2017. It is the main cause of cancer-related deaths with 23,393 deaths in 2013. In the 2000s, better understanding of molecular pathways led to the development of targeted treatments. The introduction of EGFR tyrosine kinase inhibitors (TKI) led to significant improvements in Response Rate and Progression-Free Survival for patients with activating mutations. Nevertheless, this treatment is not available in the Brazilian Public Health System based upon its costs andthe absence of Overall Survival gain in randomized clinical trials. The aim of this study was to assess the potential number of life-years lost and the cost associated with lack of treatment. **Method:** We estimated the number of eligible cases for treatment using epidemiological data from the National Cancer Institute (INCA) plus the national database on the frequency of EGFR gene mutations since July 2010 (gefitinib approval in Brazil). We based the differences in survival between patients treated with EGFR TKIs and chemotherapy using the curves of The Lung Cancer Mutation Consortium. The costs of TKI treatment were based on the national reference ($1,200 monthly) and was compared with the amount reimbursed by the Brazilian Public Health System for chemotherapy ($350 monthly). **Result:** The number of eligible cases for EGFR TKIs in the Brazilian Public Health System is around 2,224 patients each year. Since gefitinib approval, the estimated number of years of life lost due to the lack of access to EGFR TKIs was 2,668 annually. Considering only drug acquisition costs, we need nearly 150 million dollars to incorporate TKIs into the public health care system. The cost per incremental life-year gained over chemotherapy was 585 dollars. Although our analysis does not consider quality-of-life, the cost of one life-year gain is lower than three times the Brazilian GDP per capita (approximately 35,000 dollars). **Conclusion:** The lack of access to EGFR TKIs cost more than 18,676 years of live in Brazil in the past 7 years. Treatment would also be cost-effective.

Keywords: public health, health policy, Target therapy

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-007 LOXOPROFEN PREVENTS EGFR-TKI-RELATED SKIN RASH IN NON-SMALL CELL LUNG CANCER PATIENTS: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background: Skin rash is the most common adverse event induced by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). The efficacy of tetracycline for EGFR-TKI-related skin rash has been reported. However, a skin rash is often observed despite the use of tetracycline. Some studies have reported that skin rash is caused by a type of inflammation. Hence, there is a possibility that loxoprofen, a non-steroidal anti-inflammatory drug, can prevent these skin rashes. **Method:** We conducted a single-center, retrospective study to investigate the efficacy of loxoprofen for EGFR-TKI-related skin rash. The patients had non-small cell lung cancer and received EGFR-TKIs at the Chemotherapy Research Institute, Kaken Hospital from October 2011 to March 2017. We divided them into two groups: those who received EGFR-TKIs along with loxoprofen (loxoprofen (+) group; n = 12) and without loxoprofen (loxoprofen (–) group; n = 37), and investigated the incidence of EGFR-TKI-related skin rash. **Result:** There was no significant difference in the baseline characteristics between the groups. Grade 1 and 2 EGFR-TKI-related skin rash were more common in the loxoprofen (–) group than in the loxoprofen (+) group (grade 1; 90% versus 60%, P = 0.007, grade 2; 50% versus 0% P = 0.043, log-rank analysis). Multiple regression analysis indicated that the use of loxoprofen was a predictive factor that reduced the incidence of grade 1 skin rash (P = 0.0046).

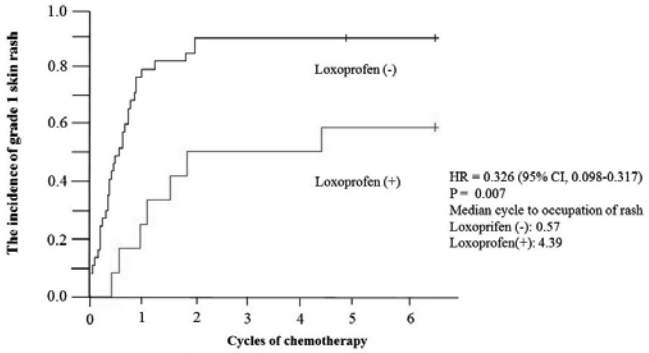

Figure 1. The incidence of grade 1 EGFR-TKIs related skin rash in two groups tested by Kaplan–Meier log-rank. Patients in Loxoprofen (+) group (n=12), in loxoprofen (-) (n=37).

Conclusion: Our study showed that loxoprofen combined with EGFR-TKIs could prevent skin rash, decreasing the risk by more than 65%. Our results suggest that loxoprofen can prevent and treat EGFR-TKI-related skin rash. Thus, we conclude that loxoprofen could be a new treatment option for EGFR-TKI-related skin rash.

Keywords: Loxoprofen, skin rash, EGFR-TKIs

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-008 PHASE I/II STUDY OF INTERMITTED ERLOTINIB IN COMBINATION WITH DOCETAXEL IN PATIENTS WITH RECURRENT NSCLC WITH WILD-TYPE EGFR: WJOG 4708L

T. Kimura[1], T. Kawaguchi[2], S. Kudoh[2], Y. Chiba[3], H. Yoshioka[4], K. Watanabe[5], T. Kijima[6], Y. Kogure[7], T. Oguri[8], N. Yoshimura[9], T. Niwa[10], T. Kasai[11], H. Hayashi[12], A. Ono[13], H. Tanaka[14], S. Yano[15], S. Nakamura[16], N. Yamamoto[17], Y. Nakanishi[18], K. Nakagawa[12]

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Background: Erlotinib (ERL) is modestly active to non-small cell lung cancer (NSCLC) with wild type *epidermal growth factor receptor (EGFR).* We hypothesized that an intermittent delivery of erlotinib and docetaxel (DOC) would increase efficacy. **Method:** This was a multi-center, single-arm phase I/II study in patients with wild type *EGFR* NSCLC who failed one prior chemotherapy. The phase I was designed a standard 3+3 dose escalation design to determine feasibility, the maximum tolerated dose (MTD) and phase II recommend dose (RD) of ERL on days 2 to 16, in combination with a fixed dose of 60mg/m^2 DOC on day 1. The phase II primary endpoint was objective response rate (ORR) by independent review committee. This study required 41 patients with expected ORR of 30% and threshold ORR of 10% (one-sided α= 0.025; β=0.1). The target number was 45 patients assuming the loss of follow-up cases. All eligible patients had ECOG performance status of 0/1 and adequate organ functions. **Result:** Between Mar 2009 and Dec 2010, 12 patients were enrolled in the phase I, and between May 2011 and Feb 2015, 46 patients in the phase II. Five patients were excluded from per protocol set, because of deviation of entry criteria. Planned dose escalation was completed without reaching a MTD. The RD was determined as 150 mg/dose of ERL. In the phase II, the ORR was 17.1% (95%CI, 7.2-32.1). The median progression free survival and median overall survival were 3.48 months (95%CI, 3.06-4.50) and 11.27 months (95%CI, 8.61-16.56), respectively. Gender, smoking status, or concomitant drugs which influence the ERL metabolism had no significant differences in ORR, or disease control rate. All 46 patients were evaluable for toxicity. The grade 3 non-hematological toxicities included 9 (19.6%) febrile neutropenia, 7 (15.2%) appetite loss, 3 (6.5%) oral mucositis and 3 (6.5%) infections. The grade 4 hematological toxicities were 31 (67.4%) neutropenia. Two treatment related deaths were observed; interstitial lung disease, and pleural infection. **Conclusion:** Intermittent dosing of ERL plus DOC is clinically feasible, but has no statistically significant improvement of ORR, in patients with recurrent NSCLC with wild type *EGFR*.

Keywords: wild-type EGFR, Erlotinib, docetaxel

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-009 CLARIFICATION OF MECHANISMS OF ACQUIRED RESISTANCE FOR AFATINIB USING PLASMA SAMPLES

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Background: It is important to clarification of mechanisms of acquired resistance for epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) to determine the next treatment. *EGFR* T790M and hepatocyte growth factor (HGF) over expression has been observed in 50 to 60% of lung cancer patients who acquired resistance to the first generation EGFR-TKIs. However mechanisms of acquired resistance for the second generation EGFR-TKI, afatinib have not be clear. **Method:** We analyzed plasma T790M and HGF in twenty lung adenocarcimona patients treated with afatinib. Seven patients treated with afatinib as the first EGFR-TKI treatment and thirteen patients treated as EGFR-TKI re-challenge after acquired resistance for first generation EGFR-TKI. EGFR mutations in plasma DNA were detected using the mutation-biased PCR and quenched probe system. HGF level in plasma was measured by enzyme-linked immunosorbent assay. **Result:** In patients treated with afatinib as the first line treatment, no patients detected plasma T790M before afatinib treatment, but one of seven patients detected plasma T790M at the time of acquired resistance. Five of seven patients detected elevation of plasma HGF level when they had progressive disease. In patients treated with afatinib as EGFR-TKI re-challenge, ten of thirteen patients detected plasma T790M before afatinib treatment and nine of them had also T790M positive at the time of acquired resistance for afatinib. Two of three patients who had not detected plasma T790M before afatinib treatment become plasma T790M positive at the time of acquired resistance. Six patients who detected T790M treated with osimertiib and five of them demonstrated partial response (PR). **Conclusion:** T790M might be also major mechanism of acquired resistance in afatinib. Elevation of plasma HGF level might be detected more high frequency at the time of acquired resistance for afatinib than first generation EGFR-TKIs.

Keywords: EGFR-TKI, liquid biopsy, Acquired resistance

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-010 UPDATED SURVIVAL OUTCOMES OF NEJ005/TCOG0902, A RANDOMIZED PII OF GEFITINIB AND CHEMOTHERAPY IN EGFR-MUTANT NSCLC

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Background: North East Japan Study Group (NEJ) 005/ Tokyo Cooperative Oncology Group (TCOG) 0902 study has demonstrated that first-line concurrent (C) and sequential alternating (S) combination therapies of EGFR tyrosine kinase inhibitor (gefitinib) plus platinum-based doublet chemotherapy (carboplatin/pemetrexed) offer promising efficacy with predictable toxicities for patients with *EGFR*-mutant NSCLC (ASCO2014, Ann Oncol 2015). However, overall survival (OS) data were insufficient because of the lack of death events in the primary report. **Method:** Progression-free survival (PFS) and OS were re-evaluated at the final data cutoff point (March 2017) for the entire population (N = 80). **Result:** At the median follow-up time of 35.6 months, 88.8% of patients had progressive disease and 77.5% of patients had died. Median PFS was 17.5 months for the C regimen and 15.3 months for the S regimen (p = 0.13). Median OS time was 41.9 with the C regimen and 30.7 months with the S regimen (p = 0.036). Updated response rates were similar in both groups (90.2% and 82.1%, respectively; p = 0.34). Patients who had common mutations showed no significant differences in PFS according to type of mutation. Patients with Del19 displayed relatively better OS (median: 45.3 and 33.3 months for C and S regimens) than those with L858R (31.4 and 28.9 months). No severe adverse events including interstitial lung disease have occurred during the follow-up period since the primary report. In an exploratory analysis, there was no significant difference in post progression survival and overall survival between patients with progression of target or non-target lesions and those progressed with new lesions. **Conclusion:** This updated analysis has confirmed that PFS is improved with first-line combination therapies compared to that with gefitinib monotherapy, and the C regimen in particular offers an overall survival benefit of 42 months in the *EGFR*-mutated setting. Our on-going NEJ009 study will clarify whether this combinational strategy can be incorporated into routine clinical practice.

Keywords: NEJ005, EGFR, gefitinib

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-011 CORRELATION AND PROBLEMS OF RE-BIOPSY AND LIQUID BIOPSY FOR DETECTING T790M MUTATION

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Background: T790M mutation test by the approved in vitro diagnostic agent (cobas v2.0) is essential for the use of osimertinib and opportunities for re-biopsy are increasing. **Method:** Success rate and T790M mutation detection rate were retrospectively investigated in 22 cases of 18 patients who took resistance to the 1st and 2nd generation EGFR-TKI at the Saga University Medical School Hospital and underwent re-biopsy. T790M with plasma DNA was examined by MBP-QP, a highly sensitive detection system developed in our laboratory, and cobas v2.0. **Result:** All patients were adenocarcinoma and the mutation status was 8 patients of del 19 and 10 patients of L858R. Re-biopsy sites were 7 bones, 4 primary sites, 3 cases of liver, pleura, lymph nodes, and 2 other sites, respectively, and surgical excision was 31.8%, median time to biopsy from informed consent was 10.5 days (range:1-39). The success rate was 95.5% and the T790M detection rate by cobas v2.0 was 52.3% for all cases, and there was no significant difference between 55.6% for del 19 and 50.0% for L858R. The plasma T790M detection rate using MBP-QP collected at the same time was 65.0% for all cases and there was no significant difference between 55.6% for del 19 and 72.7% for L858R. We experienced one case of atypical angina as a serious complication. Case presentation: ≪No.1≫ First biopsy as re-biopsy (bone): cobas method was negative and MBP-QP method was positive and could not be administered with osimertinib. Second biopsy as re-biopsy (liver): both cobas method and MBP-QP method were positive and could be administered with osimertinib and had a remarkable response. ≪No.2≫ Axillary lymph node biopsies were performed twice, but cobas method was negative and MBP-QP method was positive, and osimertinib could not be administered. Thereafter, hepatic metastasis was biopsied, but both cobas method and MBP-QP method were negative. When plasma specimens by cobas method were tested after insurance approval, plasma T790M was positive, and osimertinib could be finally administered. Although it was effective for axillary lymph node metastases, it had no effect on liver metastases. **Conclusion:** The sensitivity of the test method and the tumor heterogeneity between individuals may influence the detection of T790M mutation. In order to reliably administer osimertinib to patients with indication, it is desirable to establish an appropriate time and site for re-biopsy, and establish examination methods.

Keywords: T790M mutation, re-biopsy, liquid biopsy

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-012 CHARACTERIZATION OF THE EFFICACIES OF OSIMERTINIB AND NAZARTINIB AGAINST CELLS EXPRESSING EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS

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Background: A significant subgroup of non-small cell lung cancers harbor epidermal growth factor receptor (*EGFR*) mutations. Third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) were developed to overcome *EGFR* T790M-mediated resistance to first- and second-generation EGFR-TKIs. Third-generation EGFR-TKIs, such as osimertinib and nazartinib, are effective for patients with *EGFR* T790M mutation. However, there are no direct comparison data to guide the selection of a third-generation EGFR-TKI for patients with different *EGFR* mutations. We previously established an in vitro model to estimate the therapeutic windows of EGFR-TKIs by comparing their relative efficacies against cells expressing mutant or wild type *EGFRs*. The present study used this approach to characterize the efficacies of third-generation EGFR-TKIs and compare them with those of other EGFR-TKIs such as erlotinib and afatinib. **Method:** We evaluated the drug sensitivity and EGFR downstream signals of human lung cancer cell lines (PC9, H3255, H1975, PC9ER, BID007) and Ba/F3 cells harboring clinically relevant EGFR mutants for first (erlotinib), second (afatinib) and third (osimertinib and nazartinib) generation EGFR-TKIs with MTS assay and western blotting. An in vitro model of mutation specificity was created by calculating the ratio of IC50 values between mutated and wild type EGFR. **Result:** Among various mutation types, sensitivities to EGFR-TKI were different. For classic *EGFR* mutations, exon 19 deletion and L858R, with or without T790M osimertinib showed lower IC50 values and wider therapeutic windows than nazartinib. Afatinib, osimertinib and nazartinib inhibited the phosphorylation of EGFR, AKT, and ERK for human cell lines and Ba/F3 cells harboring these *EGFR* mutations. For uncommon EGFR mutations, G719S or L861Q, afatinib showed lowest IC50 values. For G719S+T790M or L861Q+T790M, the IC50 values of osimertinib and

nazartinib were around 100 nM, 10 to 100 fold higher than those of classic+T790M mutations. On the other hand, osimertinib and nazartinib showed similar efficacies in cells expressing *EGFR* exon 20 insertions. For C797S mutations, no EGFR-TKIs demonstrated efficacy. **Conclusion:** The present study provides fundamental osimertinib and nazartinib sensitivity/resistance data in cells expressing a range of EGFR mutations, including uncommon EGFR mutations. The findings highlight the diverse mutation selective sensitivity pattern of EGFR-TKIs. These data may help to inform the selection of EGFR-TKIs for non-small cell lung cancer patients harboring *EGFR* mutations.

Keywords: EGFR tyrosine kinase inhibitors, EGFR uncommon mutations, lung cancer

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-013 UNCOMMON MUTATION TYPES OF EGFR AND RESPONSE TO EGFR TYROSINE KINASE INHIBITORS IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is the standard therapy for advanced lung adenocarcinomas with common EGFR mutations. However, the efficacy of EGFR-TKIs in patients with these uncommon EGFR mutations (other than exon 19 deletions or exon 21 L858R mutation) remains undetermined. **Method:** Seven hundred and fifty-five non-small cell lung cancer (NSCLC) patients with EGFR mutation analyses for TKI therapy were identified between October 2010 and December 2015 in East of China. And 66 patients bearing uncommon EGFR mutations were included to collect data from TKI response and prognosis. **Result:** Rare sensitive mutations (G719X, L861Q, S768I), primary resistant mutation (Ex20 ins), and complex mutations (G719X + L861Q, G719X+S768I, 19 del+T790M, 19 del+L858R, L858R+S768I, and L858R+T790M) of EGFR were identified in 37 (56.1%), 9 (13.6%), and 20 (33.3%) patients, respectively. TKI treatment in patients harboring uncommon EGFR mutations exhibited a tumor response rate of 28.8% and a median progression-free survival (PFS) of 4.8 months. Importantly, patients with complex EGFR mutations had significantly longer PFS when compared with the remaining sensitizing rare mutations or Ex20 ins (8.6 versus 4.1 versus 3.1 months; p=0.041). Furthermore, complex EGFR mutations were independent predictors of increased overall survival in NSCLC patients (Hazard Ratios=0.31; 95% confidence intervals: 0.11-0.90; p=0.031). Among them, patients harboring Del-19 compound L858R mutations showed a tendency to have higher response rate and improved median PFS than those regarding patients with other complex mutations patterns (66.7% verse14.3%, p=0.021; 10.1 verse 8.6 months, p=0.232). **Conclusion:** Personalized treatment should be evolving in different types of uncommon EGFR mutations. And complex mutations of EGFR may benefit more from EGFR-TKIs than other uncommon mutations in Chinese NSCLC patients.

Keywords: Epidermal growth factor receptor, uncommon mutation, Tyrosine kinase inhibitors

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-014 A PHASE I STUDY OF AFATINIB FOR PATIENTS AGED 75 OR OLDER WITH ADVANCED NSCLC HARBORING EGFR MUTATIONS

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Background: The efficacy and safety of afatinib therapy among elderly (aged 75 or older) populations diagnosed with EGFR-mutated non-small cell lung cancer (NSCLC) has not been evaluated yet. This phase I trial was conducted to determine the maximum tolerated dose (MTD), recommended phase II dose of afatinib in elderly patients with advanced NSCLC harboring EGFR mutations. **Method:** The study used a standard 3+3 dose escalation design. Patients aged 75 years or older advanced NSCLC harboring EGFR mutations were enrolled. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 and adequate organ function. The doses of afatinib, which was given once daily, were planned as follows: level 1, 20 mg/body; level 2, 30 mg/body; level 3, 40 mg/body. Dose-limiting toxicity (DLT) was defined as grade 4 hematologic or grade 3 non-hematologic toxicity. DLT was evaluated during day1-28. **Result:** From February 2015 to October 2016, 15 patients were enrolled from 3 participating institutions. Patient characteristics were: male/female 3/12; median age 79 (range 75-87); Performance status 0/1 2/13. Six patients have been treated at level 1, 3 and three patients have been treated at level 2, respectively. At level 1, 1 of 6 patients showed DLTs. The patient grade 3 rush, grade 3 anorexia, and grade 3 infection was observed. At level 2, none of 3 patients experienced a DLT. At level 3, 2 to 6 patients were observed DLTs. One patient developed grade 3 diarrhea, another patient developed grade 3 diarrhea and grade 3 anorexia. Most frequent adverse events (AEs, any grade) were diarrhea, paronychia, rush, and nausea. Most patients at level 3 required dose reduction in three months. No treatment-related deaths were observed at either level. An objective response was 73.3%. **Conclusion:** We considered level 3 was the MTD and recommended phase II dose level was 3. Clinical trial information: UMIN000016441.

Keywords: lung cancer, afatinib, elderly

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-015 EFFICACY OF EGFR-TKIS FOR EGFR MUTATNT NSCLC PATIENTS WITH CENTRAL NERVOUS SYSTEM METASTASES: A RETROSPECTIVE ANALYSIS

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Background: Central nervous system (CNS) is a common site of metastases of non-small cell lung cancer (NSCLC). The prognosis for patients with brain metastases and/or leptomeningeal metastases is extremely poor. NSCLC harboring epidermal growth factor receptor (EGFR) mutation generally shows good response to tyrosine kinase inhibitors (TKI). However, the efficacy of EGFR-TKI in patients with CNS metastases is unclear. And the data on the occurrence of leptomeningeal metastases in the patients with brain metastases after use or EGFR-TKI remain limited. **Method:** We retrospectively evaluated clinical outcome and background of EGFR mutant NSCLC patients with CNS metastases who received EGFR-TKI for the first line drug therapy between January 2008 and December 2014 in the facilities belong to Niigata lung cancer treatment group. **Result:** A total of 104 eligible patients were enrolled. The response rate was 62%. The median time to treatment failure was 7.8 months. The median survival time (MST) was 24.0 months. The response rate of CNS was 37%. The median CNS-progression free survival (PFS) was 13.2 months. There was no statistical significant difference in TTF, overall survival (OS) and CNS-PFS between patients with exon 19 deletion and those with exon 21 L858R point mutation (mTTF 8.3 vs. 7.8 months, MST 26.1 vs. 24.9 months, mCNS-PFS 14.4 vs. 12.4 months) or between patients treated by Gefitinib and those treated by Erlotinib (mTTF 8.4 vs. 6.3 months, MST 26.0 vs. 20.2 months, mCNS-PFS 13.8 vs. 13.2months). Brain radiotherapy prior to EGFR-TKI prolonged TTF (11.2 vs. 6.8 months) and tended to prolong CNS-PFS (15.6 vs. 11.1 months), but was not significantly associated with OS (MST 26.1 vs. 24.0 months). There was no significant difference in treatment outcome between patients who received stereotactic irradiation and those who received whole brain irradiation as brain radiotherapy prior to EGFR-TKI. Leptomeningeal metastases (LM) were primarily found in 8 of 104 patients (8%), and those occurred subsequently during the clinical course in 19 patients (18%). Median time to occurrence of LM in the patients who had LM subsequently was 14.5 months. There was no significant difference in OS between patients who had LM subsequently and those without LM during the course (MST 28.1 vs. 24.9 months). MST from diagnosis of subsequent LM was 3.7 months. **Conclusion:** EGFR-TKI showed favorable effect for EGFR mutant NSCLC patients with CNS metastases. A longer TTF and CNS-PFS were observed with prior brain radiotherapy. Prognosis after occurrence of LM was poor.

Keywords: brain metastases, EGFR TKI, Leptomeningeal metastases

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-016 CLINICAL UTILITY OF LIQUID BIOPSY FOR DETECTING EGFR T790M MUTATION IS VERY LIMITED

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Background: Osimertinib, a third-generation EGFR tyrosine kinase inhibitor targeting EGFR T790M acquired resistance mutation, has demonstrated strong clinical activity. Therefore, we have to do a second biopsy to detect T790M when the tumor has progressed. On the other hand, liquid based assays are expected as minimally invasive methods for detecting resistance mutations. Recently, liquid-biopsy for detecting EGFR T790M mutation has been approved by the Japanese ministry of health, labor and welfare. The aim of this study is to assess the clinical utility of liquid biopsy for detecting EGFR T790M mutation. **Method:** Seventeen consecutive patients who underwent cobas® EGFR Mutation Test ver.2 for liquid biopsy from January to April 2017 were enrolled. Patient information and examination results were collected from electronic medical records and analyzed retrospectively. Concordance between liquid biopsy and tissue or cytological specimen was assessed in patients who underwent re-biopsy at the same time as liquid biopsy. **Result:** Median age: 70 (51-82); Women: 10 (58.8%); Never smoker: 12 (70.6%); Adenocarcinoma: 17 (100%); Stage IV: 16 (94.1%); Primary EGFR mutation: exon19 deletion = 11 (64.7%), exon21 L858R = 5 (29.4%), exon18+20 mutations = 1 (5.9%). Two patients (11.8%) were positive for T790M mutation in plasma. Tissue biopsy or cytology was done in 8 cases at the same time as liquid biopsy. Only one patient of four patients who were positive for T790M in tissue or pleural effusion was positive for T790M in plasma (sensitivity: 25%). One patient of two patients who were positive for T790M

in plasma was negative for T790M in spinal fluid. **Conclusion:** There is no doubt that liquid biopsy is a minimally invasive and very convenient method. However, at least currently, liquid biopsy cannot replace tissue biopsy in clinical setting because of its sensitivity. In order to deliver the appropriate medication to the patient, it is necessary to selectively use well the tissue biopsy and liquid biopsy.

Keywords: liquid biopsy, T790M, re-biopsy

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-017 CLINICAL FEATURES AND TREATMENT WITH AFATINIB IN PATIENTS WITH SQUAMOUS CELL LUNG CANCER WITH SENSITIVE EGFR MUTATIONS

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Background: As LUX-Lung8 has shown significant improvements in the progression-free survival and the overall survival with afatinib when compared with erlotinib, afatinib could be an additional option for the second-line treatment of patients with squamous cell lung cancer. The selection process of patients on the basis of EGFR mutations would likely result in a population with a greater sensitivity to afatinib. However squamous cell lung cancer is not routinely examined for EGFR mutation status because of the low frequency of positive results and the poor clinical response of squamous cell lung cancer with EGFR sensitive mutations to gefitinib, compared to that of adenocarcinoma. We reviewed clinical features of squamous cell lung cancer with EGFR mutations at our hospital and their responses to EGFR-tyrosine kinase inhibitors. **Method:** The medical records of this retrospective review were taken from patients with histological or cytological proven squamous cell lung cancer from April 2008 to May 2017 at NTT Medical Center Tokyo. The patients were tested for EGFR mutation status with PNA-LNA clamp method. The electronic medical records were reviewed to obtain clinical and demographic data, including gender, age, smoking history, clinical stage of lung cancer, treatment, and survival. Based on the chest CT findings, the patients were categorized into three groups according to the underlying pulmonary disease; normal lungs, emphysematous lungs and fibrotic lungs. The differences among the categorized groups were then compared. **Result:** Of 441 patients with squamous cell lung cancer, 23 patients (5.2%) were tested EGFR mutation status. Of 23 patients, we identified 5 (21.7%) patients with an EGFR mutation (Exon 19 deletion 3, L858R 2). All patients with EGFR mutation were female and never-smokers. EGFR mutations were identified in 4 (44.4%) of 9 patients with normal lungs, 1(8.3%) of 12 with emphysema, and 0 (0%) of 2 with pulmonary fibrosis. Of the 5 patients with EGFR mutation, 2 patients received gefitinib and 2 patients received afatinib. Although the two patients treated with gefitinib did not respond to treatment (SD 1, PD 1), the two patients treated with afatinib responded well (PR 2). **Conclusion:** Squamous cell carcinoma patients with sensitive EGFR mutations had a prognosis comparable to patients with adenocarcinoma. Selecting an afatinib treatment for patients on the basis of the underlying pulmonary diseases(normal lungs) and the smoking status (never smoker) for the EGFR mutation test would likely result in a population with a greater sensitivity to afatinib.

Keywords: Squamous cell lung cancer, EGFR, afatinib

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-018 DIAGNOSTIC YIELD OF FINE-NEEDLE ASPIRATION AND CORE-NEEDLE BIOPSY IN ASSESSMENT OF EGFR AND ALK MUTATION STATUS IN NON–SMALL CELL LUNG CANCER

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Background: The identification of specific molecular drivers of pathogenesis is now crucial for treatment with targeted therapies in NSCLC. It is reported that ALK-rearrangement shows an intratumor heterogeneity in mixed adenocarcinomas and adenosquamous carcinomas, while EGFR-mutation is generally homogeneously expressed. Because of this intratumor heterogeneity, there is concern about underestimation of molecular markers in biopsy. Thus, we compared the diagnostic yields of fine-needle aspiration (FNA), core-needle biopsy (CNB), and surgical resection sample for EGFR-mutation and ALK-rearrangement. **Method:** This retrospective study was approved by institutional review boards, and informed consent was waived. Diagnostic yields of EGFR-mutation pyrosequencing tests and ALK-rearrangement FISH studies performed during a 6 year period (Jan 2010 - Dec 2016) were investigated stratified by the 3 tissue sampling methods: FNA, CNB and surgical resection. The diagnostic yields of positive results of EGFR-mutation and ALK-rearrangement tests were compared according to the tissue sampling methods. **Result:** Among the 1617 EGFR-mutation pyrosequencing tests, the number of surgical resection sample, CNB, and FNA was 996, 262, and 359, respectively, and the positive results were 41.7% (95% confidence interval 38.6–44.8), 40.8% (35.1–46.9), 38.2% (33.3–43.2), respectively. On the other hand, in a total of 221 ALK-rearrangement FISH studies, positive results of surgical resection sample (n = 60), CNB (n = 87), FNA (n = 74) were 45% (95% confidence interval 33.1–57.5), 44.8% (34.8–55.2), 31.1% (21.7–42.3), respectively. **Conclusion:** Diagnostic yields of FNA, CNB and surgical resection samples were not significantly different in EGFR-mutation pyrosequencing tests, and this probably reflects known intratumor homogeneity of EGFR-mutation. In the ALK-rearrangement FISH study, the diagnostic yield of FNA was lower than that of surgical resection or CNB samples. This difference is presumably due to intratumor heterogeneity, and caution should be made as it may cause underestimation of ALK-rearrangement in biopsy samples.

Keywords: non-small cell lung cancer, EGFR and ALK mutation, Underestimation in biopsy samples

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-019 SIZING CAPILLARY ELECTROPHORESIS WITH PCR TO DETECT VARIOUS EGFR EXON 19 DELETIONS IN NON-SMALL CELL LUNG CANCER

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Background: This study points out an issue of PCR-based methods to detect exon 19 deletions. PCR methods are used for clinical examination, because they are useful, rapid and cost-effective to detect *EGFR* mutations. Exon 19 deletions are most important among *EGFR* mutations to dictate *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) therapy in non-small cell lung cancer (NSCLC), and have various species. The sensitive PCR methods select major exon 19 deletions, but cannot detect unusual variants. We investigated the clinical significance of minority exon 19 deletions. **Method:** A series of 73 NSCLC patients, which were treated with *EGFR*-TKI for recurrent disease after they had undergone surgery from 1992 to 2004. In all cases, Microdissenction and direct sequence were performed. Scorpion Amplification Refractory Mutation System (ARMS) and cobas version 2.0, as sensitive PCR methods, were performed in 47 patients along with sizing capillary electrophoresis for the exhaustive detection of exon 19 deletions. **Result:** *EGFR* mutations were detected from 35 patients (47.9%), which were one exon 18 mutation, 23 exon 19 deletions, and 11 exon 21 mutations in all 73 cases. The catalog of somatic mutation in cancer (COSMIC) database included 174 different exon 19 deletions in 4190 submitted cases at December 2014. E746_A750 deletion was most common deletion of exon 19, accounting for 70% of the total exon 19 deletions (2931/4190). Predicted frequency of exon 19 tested by Scorpion-ARMS was 81.6% (3419/4190), and that of cobas version 2.0 had 82.5% (3457/4190) in the detection of various exon 19 deletions. In clinical samples of this study, Scorpion-ARMS and cobas version 2.0 failed to detect four exon 19 deletions, in two squamous cell carcinomas (*EGFR*-TKI effects were stable disease and no assessable patient) and two papillary adenocarcinomas (*EGFR*-TKI effects were stable disease and no assessable patient). One of papillary adenocarcinoma had minority deletion 'T751_I759 deletion and insertion S', which had long stable disease for 43.4 months in *EGFR*-TKI therapy. Sizing capillary electrophoresis was able to detect this deletion. **Conclusion:** This study suggests sizing capillary electrophoresis is necessary for the exhaustive detection of exon 19 deletions, and may identify tumors responsive to *EGFR*-TKIs therapy, especially those with unusual deletions.

Keywords: EGFR Tyrosine Kinase Inhibitors, PCR-based methods, Exon 19 deletions

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-020 PEMETREXED CONTINUATION MAINTENANCE VERSUS CONVENTIONAL PLATINUM-BASED DOUBLET CHEMOTHERAPY IN EGFR-NEGATIVE LUNG ADENOCARCINOMA: RETROSPECTIVE ANALYSIS

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Background: Although targeted therapy and immuno-oncology have shifted paradigm in treating lung cancer, platinum-based combination is still the standard of care for advanced lung cancer patients, especially for those without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase translocation. Based on the JMDB study conducted by Scagliotti et al., pemetrexed/platinum combination is a preferred treatment for nonsquamous non-small cell lung cancer (NSCLC). However, which chemotherapeutic regimen is better for patients with EGFR-negative nonsquamous NSCLC remains unclear. Thus, the object of this study was to compare pemetrexed-based chemotherapy to non-pemetrexed-based chemotherapy for EGFR-negative advanced nonsquamous NSCLC. **Method:** A total of 183 patients with EGFR-negative nonsquamous NSCLC who were treated with platinum-based doublet between January 2009 and December 2016 were retrospectively enrolled for this study. Progression-free survival (PFS) and overall survival (OS) of different treatment regimens were analyzed and compared. **Result:** Drugs combined with platinum as first-line chemotherapy were as follows: pemetrexed (n = 97, 53%), gemcitabine (n = 52, 28%), paclitaxel (n = 24, 13%), and docetaxel (n = 10, 6%). Among 97 patients in

the pemetrexed group, 50 (52%) received continuation maintenance chemotherapy with pemetrexed after 4 cycles of combination. In the non-pemetrexed group, 7 (8%) patients received switch maintenance chemotherapy with erlotinib (n = 5) or pemetrexed (n = 2). Median PFS and OS of all patients were 5.1 months (95% confidence interval [CI]: 3.8-5.9 months) and 15.3 months (95% CI: 8.9-18.4 months), respectively. Median PFS was significantly higher in the pemetrexed group compared to that in the non-pemetrexed group (7.2 vs 4.1 months, p < 0.05). In addition, median OS showed an increasing tendency in the pemetrexed group compared to that in the non-pemetrexed group but it was not statistically significant (19.5 vs 14.3 months, p = 0.06). Multivariate analyses showed that the use of pemetrexed-based regimen was independently associated with better PFS, but not with better OS. **Conclusion:** Although sample size was relatively small, our data suggest that pemetrexed-based treatment was more beneficial compared to non-pemetrexed based treatment for EGFR-negative advanced nonsquamous NSCLC. Further large-scale studies are needed to confirm our findings.

Keywords: pemetrexed, chemotherapy, Platinum

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-021 A PHASE I STUDY EVALUATING THE COMBINATION OF AFATINIB, CARBOPLATIN AND PEMETREXED AFTER FAILURE OF 1ST GENERATION EGFR-TKIS

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Background: Despite the high response rate in patients with *EGFR*-mutation positive NSCLC, treatment with EGFR-TKIs is not curative and eventually there is disease progression. In patients with acquired resistance to 1st generation EGFR-TKIs, previous studies have demonstrated that afatinib had some clinical activity. We previously reported that the combination of gefitinib, pemetrexed and carboplatin showed promising antitumor efficacies in *EGFR*-mutated lung cancer patients. In this phase I trial, we assessed the safety and efficacy of afatinib combined with pemetrexed and carboplatin in NSCLC patients who acquired resistance. **Method:** Patients with *EGFR*-mutation positive metastatic NSCLC, who had received 1st line gefitinib or erlotinib and developed disease progression were eligible. Patients received pemetrexed 500 mg/m^2 and carboplatin AUC=5 on day 1 in all cohorts, and afatinib at doses of 20, 30 and 40 mg/body from day 8 to 18 of 21-day cycle. DLT was assessed after the first cycle, and doses were escalated in cohorts of 3 to 6 patients. **Result:** Eleven patients were enrolled to this trial and 9 patients were evaluable for safety and efficacy. At an afatinib dose of 30mg/body, 3 patients experienced DLT (grade 3 diarrhea, grade 3 hypokalemia, grade 4 thrombocytopenia, grade 3 amylase elevation and grade 3 gamma-glutamyl transferase). The overall response rate was 20% (95% C.I. 5.7 to 51) and median progression free survival was 16.2 months (95% C.I. 4.7 to not reached). **Conclusion:** The MTD of afatinib is 20mg/body in combination with pemetrexed 500 mg/m^2 and carboplatin AUC=5 on day 1 every 21 days. This combination demonstrated activity in EGFR mutation positive NSCLC with acquired resistance to 1st line EGFR-TKIs.

Keywords: EGFR-TKI, afatinib, combination therapy

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-022 IMPACT OF EGFR MUTATION ON CLINICAL OUTCOME OF NINTEDANIB PLUS DOCETAXEL IN PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER (NSCLC)

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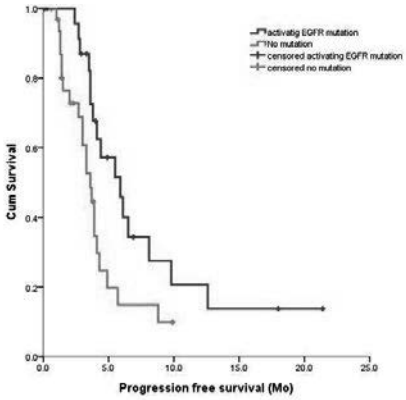
Background: Anti-angiogenic agents have been reported to have clinical activity EGFR mutant NSCLC with/without EGFR Tyrosine kinase inhibitor (TKI). We reported clinical outcomes of nintedanib plus docetaxel in refractory NSCLC according to EGFR mutation status during a Korean nintedanib NPU program. **Method:** Patients with NSCLC were eligible if they failed at least one prior systemic treatment. Docetaxel was administered either 75mg/m^2 or 37.5mg/m^2 on D1, D8 q every 3weeks plus nintedanib 200mg orally twice daily. Nintedanib treatment was continued until disease progression or unacceptable toxicity after 4-6 cycles of combination therapy. **Result:** 62 patients were enrolled. 28 patients with activating EGFR mutation (17 in exon19 deletion, 8 exon21 L858R/L861Q, 1 exon 18 G719X, 1 in exon20 duplication, 1 in exon19 deletion and exon20 T790M) progressed after EGFR-TKI, 25/28 patient also progressed after platinum doublet chemotherapy were enrolled. Only for 2 patients EGFR mutation status were unknown. Patients were heavily pretreated, with 38.7% patients receiving nintedanib plus docetaxel as ≥ 4th line therapy. 5 patients had received bevacizumab. For patients with response assessment reported objective response rate was 30.6% and median PFS and OS were 3.9 months (95% CI 3.4-4.4) and 11.7months (95% CI 5.2-18.1) respectively in overall patients. Based on EGFR mutation status, objective response rate was 52.1% *vs* 24.1% (EGFR mut(+) *vs* EGFR mut (-), *p*=0.47) and median PFS was 5.9 *vs* 3.6 months (EGFR mt(+) *vs* EGFR mt(-), *p*=0.031). No treatment related death was reported. Common grade 3/4 adverse event were neutropenia (33.8 %), and reversible elevated liver enzyme(9.7%). 10 patients in 150mg twice daily and 2 patients with 100mg twice daily administered grade 3 adverse events.



Conclusion: Nintedanib plus docetaxel was well-tolerated and had clinical activity in refractory NSCLC. Specifically, EGFR TKI resistant EGFR mutant NSCLC may be a good candidate for nintedanib plus docetaxel.

Keywords: EGFR mutation, nintedanib, docetaxel

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-023 CHARACTERISTICS OF NSCLC PATIENTS TREATED IN FIRST LINE TREATMENT WITH TYROSINE KINASE INHIBITORS (TKI) - REAL DATA FROM THE CZECH REPUBLIC

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Background: From October 2013 there is a possibility to treat patients with NSCLC and with activated epidermal growth factor receptor (EGFR) mutations with three TKI (afatinib, erlotinib, gefitinib) in the Czech Republic. We have tried to find differences among patient groups treated with single TKI in 1st line of treatment. **Method:** Only patients with EGFR mutations and in which 1st line treatment started in October 2013 and later were included in analysis. With respect to defined inclusion criteria. We analysed 287 patients (gefitinib - 138 patients, afatinib - 102 patients, erlotinib - 40 patients.). Descriptive statistics and frequency tables were used to characterize the sample data set. Statistical significance of differences among three TKI inhibitors subgroups was assessed using the Fisher's exact test or Kruskal-Wallis test for continuous variables. Overall survival (OS) was defined as the time from 1st line TKI inhibitor treatment initiation to the date of death due to any cause. Progression-free survival (PFS) was defined as the time from 1st line TKI inhibitor treatment initiation to the date of first documented progression or death due to any cause. OS and PFS were estimated using Kaplan-Meier method and all point estimates include 95% confidence intervals (95% CI). All statistical tests were performed at a significance level of α=0.05. **Result:** Between these three groups of patients there was no statistically significant difference in sex (p=0.972), in age (p=0.031), in smoking habits (p=0.877), in type of EGFR mutation (p=0.437), in adenocarcinoma proportion (p=0.07). Between these three groups, there was statistically significant difference according to performance status (< 0.001), patients treated with afatinib have better PS in common. Between these three groups, there was no statistically significant difference according to disease control (CR+PR+SD) (p=0.626) and in response to treatment (CR + PR) (p = 0.791). There was no statistically significant difference in PFS survival (p=0,015) and in overall survival ((p=0.046). There was no statistically significant difference in the occurrence of adverse events (p=0.002). **Conclusion:** We have not found any important difference in basic characteristic of patients treated in 1st line treatment with TKI (sex, age, smoking, histology and type of EGFR mutations). We have not found any important difference in response to treatment, in disease control, PFS, in overall survival and in occurrence of adverse events. We found a significant difference in PS segmentation at treatment initiation – patients treated with afatinib have better PS than others.

Keywords: tyrosine-kinase inhibitors, advanced NSCLC, activated epidermal growth factor receptor (EGFR) mutations

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-024 PHASE II TRIAL OF AZD9291 IN SECOND-LINE TREATMENT AFTER ACQUIRED RESISTANCE WITH T790M MUTATION DETECTED FROM CIRCULATING TUMOR DNA

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Background: Administering the best treatment after acquiring resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) requires the knowledge of the resistance status. In this trial, the treatment efficacy of osimertinib (AZD9291) was assessed in patients with non-small-cell lung carcinoma (NSCLC) harboring T790M resistance mutation, which was detected in the circulating tumor DNA (CtDNA) without re-biopsy of the tumor tissue. **Method:** To prove 60% response rate of osimertinib compared to 30% as null hypothesis, and considering 10% drop out rate, 19 subjects were recruited. To extract CtDNA, 15 mL of peripheral blood was withdrawn and centrifuged immediately before storage. Cobas® v2 RUO (Roche diagnostics) and PANA mutyper® (Pangene, Korea) were used to detect the EGFR mutations from CtDNA. Osimertinib was prescribed as an 80 mg tablet once in a day irrespective of the food intake. **Result:** Eighty patients with acquired resistance to prior EGFR TKIs were screened for T790M resistance mutation, and the CtDNA of 21 subjects (26.3%) showed T790M mutation. T790M mutation was detected by both PANA mutyper® and Cobas® in 13 cases, T790M was detected only by PANA mutyper® in 4 cases, and only by Cobas® in 4 cases. Nineteen subjects (age: 64.4 ± 11.6 years old, 14 women, 5 men) were enrolled in this prospective single arm trial from September 2016 to April 2017. Prior EGFR TKIs were afatinib (n=3), erlotinib (n=4), gefitinib (n=10), erlotinib and afatinib (n=1), and gefitinib and afatinib (n=1). Twelve subjects had exon 19 deletion of EGFR gene, 4 had L858R point mutation, one showed exon 19 deletion and L858R, 1 had G719X, and 1 case showed no activating mutation. The response to osimertinib was evaluable in 15 subjects; 4 subjects dropped out from this trial before response evaluation. Among the 15 subjects (efficacy analysis set), partial remission was observed in 10 cases (66.7%). **Conclusion:** Assuming 40% of screened patients are harboring T790M mutation, sensitivity of CtDNA testing is 65% using both tests, and 53% with either test. Toxicity and survival analyses will be followed. (ClinicalTrials.gov Identifier: NCT02769286)

Keywords: Epidermal growth factor receptor, osimertinib, Circulating Tumor DNA

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-025 PREVALENCE OF EGFR T790M MUTATION IN NSCLC PATIENTS AFTER AFATINIB FAILURE, AND SUBSEQUENT RESPONSE TO OSIMERTINIB

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Background: In patients with *EGFR*-mutant non-small-cell lung cancer (NSCLC), progression inevitably occurs after 9 to 14 months of treatment with EGFR tyrosine kinase inhibitors (TKIs). *EGFR* T790M mutations have been identified as the most common mechanism of acquired resistance. Analyses assessing the frequency of acquired T790M mutations have mainly been conducted in patients receiving the first-generation EGFR TKIs erlotinib and gefitinib, however limited data is available on the prevalence of this mutation after failure of the ErbB family blocker afatinib. This retrospective analysis aimed at determining the prevalence of *EGFR* T790M mutation in patients who had benefitted from afatinib therapy, but ultimately developed progression. Another objective was the assessment of response to the subsequent treatment with the third-generation EGFR TKI osimertinib, which is the treatment of choice for patients who have developed T790M mutations. **Method:** The analysis included consecutive patients with stage IV adenocarcinoma of the lung and sensitizing *EGFR* mutations who had progressed on first-, second- or third-line afatinib treatment after experiencing at least 3 months of disease stabilization. Mutation status was assessed using liquid biopsy or both liquid biopsy and tissue re-biopsy. Patients with confirmed T790M mutation received osimertinib. **Result:** T790M mutations were found in 27 of 48 patients, corresponding to a prevalence rate of 56.3%. The concordance rate between liquid biopsy and re-biopsy was 80%. In the total cohort, the objective response rate (ORR) obtained with afatinib was 89.6%, and in the patients who developed T790M mutation, 92.6%. Complete responses (CR) occurred in 25.0% and 37.0%, respectively, and partial responses (PR) in 64.6% and 55.6%, respectively. In the patients who received osimertinib after the discovery of T790M mutations, ORR was 81.5%, with CR and PR rates of 22.2% and 59.3%, respectively. **Conclusion:** The prevalence of acquired T790M mutations as assessed in this cohort was consistent with the mutation rates reported for patients who progressed on first-generation EGFR TKI treatment. T790M mutation appears to be the main mechanisms of acquired resistance to afatinib. The development of this mutation was not affected by any baseline characteristics. These real-world data confirm that for patients with advanced, *EGFR*-positive NSCLC who progressed on afatinib and developed T790M mutations, osimertinib therapy elicited excellent response rates, with a substantial proportion of patients achieving complete remissions.

Keywords: osimertinib, afatinib, NSCLC, EGFR T790M

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-026 MANAGING EGFR T790M MUTATION IN ADVANCED NON-SMALL CELL LUNG CANCERS IN THAILAND

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Background: Acquired Resistance to EGFR-TKI is inevitable to occur to most of NSCLC treated by first generation TKI such as Gefitinib or Erlotinib. There have been many secondary resistance mutations discovered to date including, L747S, D761Y, T790M and T854A . But in our series, the most common secondary resistance mutations was T790M type and was studied in details as to the occurrence, the treatment and the response to the treatment. **Method:** 42 patients from our own series of advanced Non-small cell lung cancer(NSCLC) , were identified as having EGFR mutations for which TKI was used for the treatment initially. Resistance to first generation TKI was found due to Mutation T790M in exon 20 of EGFR gene . A total of 21 patients 50%(from 42) harbored T790M mutation. Interestingly enough, only 5 cases from classical mutated exon19 EGFR (5/22) , 6 cases from classical mutated exon 21 L858R (6/7) and 10 cases from non –classical mutated exon 19 and 21(10/13). The treatment of those who harbored T790M was uniformly given: 1. Multi-targeted method , Bevacizumab and Afatinib second generation TKI 2.Osimertinib, third generation TKI to all patients when failed Afatinib. **Result:** At one year time, all 21 patients survived the treatment. Beyond one year with closed follow-up, the results showed, 1. All 5 cases from classical mutated exon 19 and 6 cases from mutated exon 21 survived the disease and continued the treatment with Osimertinib. 2. 1 case from non-classical mutated exon 19 and 21 survived The overall success rate was 5+6+1 = 12/ 21 = 57% All 9 cases who failed the treatment showed progression of cancer . **Conclusion:** Patients who harboured T790M mutation from classical mutated exon 19 and exon 21 EGFR continued to respond to the treatment very well clinically. Obviously, Osimertinib was specific for T790M mutation and no further acquired resistance mutation in their cancer cells. But for those who failed Osimertinib treatment they must have additional acquired resistance mutation along with T790M. Future Plan : Consider Immune Checkpoint Treatment

Keywords: EGFR T790M mutation, Osimertinib Treatment

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-027 COMPARATIVE LONGITUDINAL TOXICITY ANALYSIS OF EGFR MUTATED NSCLC TREATED WITH EITHER PEMETREXED CARBOPLATIN OR GEFITINIB

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Background: Toxicity analysis in randomized studies is classically reported as maximum grade toxicity occurring during the course of treatment. Unfortunately, the duration of toxicity is neglected. Patients receiving targeted therapy like gefitinib frequently have low grade continuous toxicities. Longitudinal toxicity analysis may be a more appropriate method of quantifying and comparing toxicity. **Method:** EGFR mutated NSCLC patients treated with gefitinib or pemetrexed-carboplatin as a part of randomized study were selected for this analysis. Patients were evaluated on the 7th day after the start of therapy and then on days 15, 21, 42, 63, 84,105 and then subsequently every 2 months till progression. Toxicities in accordance with CTCAE version 4.02 occurring during each visit were documented at each visit. Three toxicities were selected for this analysis and these were diarrhea, skin rash and fatigue. R software was used for analysis. Maximum grade toxicity and longitudinal time -toxicity analysis was performed. Toxicities were compared between the 2 arms using both methods. **Result:** Among the 290 patients, half each were randomized to gefitinib and pemetrexed-carboplatin arm respectively. Any grade diarrhea was seen in 22 % of patients receiving gefitinib as opposed to 12% receiving pemetrexed-platinum (p-0.12%). Similar higher proportion of toxicity was seen in gefitinib arm for skin rash (33% versus 13%, p-0.00).The proportion of fatigue in gefitinib and pemetrexed -platinum arm were similar (6% versus 9%, p-0.59). The longitudinal time-toxicity analysis revealed that both rash and diarrhea were higher and more sustained in gefitinib arm. The difference area under the curve for rash and diarrhea were 10 units (p-0.192) and 21.89 units (p-0.09) respectively. The fatigue was similar in both arms (p-0.779) **Conclusion:** Longitudinal time -toxicity analysis provides information which is clinically relevant and might impact patients quality of life and hence should be performed in patients receiving targeted therapies.

Keywords: longitudinal time- toxicity analysis, toxicity analysis in randomized studies, EGFR mutated NSCLC

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-028 THIRD GENERATION EGFR INHIBITOR AST2818 (ALFLUTINIB) IN NSCLC PATIENTS WITH EGFR T790M MUTATION: A PHASE1/2 MULTI-CENTER CLINICAL TRIAL

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Background: AST2818 (Alflutinib) was designed to inhibit EGFR active mutations as well as the T790M acquired resistant mutation. The purpose of this study was to determine the safety and antitumor activity of AST2818 in EGFR T790M positive non-small cell lung cancer (NSCLC) patients after the first-generation EGFR-TKIs treatment failure. **Method:** Patients with histologically diagnosed, EGFR T790M mutant stage IV NSCLC were considered eligible, and they should have documented disease progression on EGFR-TKIs. In a 3+3 dose-escalation design, AST2818 was orally administered every day on a 21-day cycle at doses ranging from 20mg to 240 mg (NCT02973763). AST2818 was then explored in a dose-expansion cohort at doses ranging from 40 to 240 mg every day. Plasma samples were collected to evaluate pharmacokinetics of AST2818. EGFR T790M mutation in tissue samples was detected by amplification refractory mutation system. The primary endpoint was to determine dose limiting toxicity and objective response rate (ORR). Adverse events (AEs) were evaluated by CTCAE 4.03, and efficacy was assessed per RECIST v1.1 every 6 weeks. **Result:** From December 27, 2016 to August 21, 2017, 17 patients received at least one dose of AST2818 across four cohorts (20mg, 40mg, 80mg and 160 mg QD). Maximum tolerated dose has not been reached. The most common treatment-related AEs were grade 1 proteinuria (25%, 3/12). Other AEs included fatigue and prolonged Q-T interval, etc, all less than 10% and grade 1 or 2. The first 12 patients had been evaluated with an ORR of 58.3% (7/12) and a disease control rate of 91.7% (11/12). Profound and sustained tumor regression had already been observed at 20mg cohort. AST2818 plasma exposure, measured as Cmax and AUC 0-24h showed a dose-proportional increase.

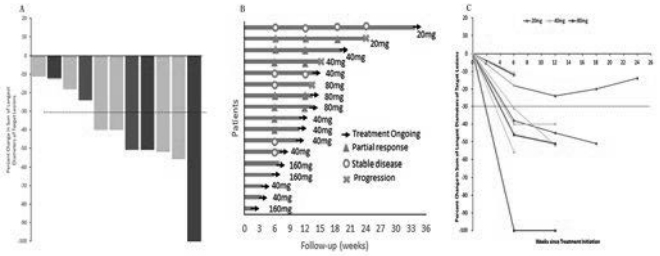

Figure 1 Efficacy of AST2818 based on RECIST. One patient didn't have target lesion and was not included in part A and part C.

Conclusion: AST2818 was well tolerated and had promising clinical activity with durable disease control in EGFR T790M mutant NSCLC after first-generation EGFR-TKIs treatment failure.

Keywords: Targeted therapy, Third generation EGFR TKI, EGFR T790M mutant NSCLC

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-029 A CASE OF A PATIENT HARBORING AN EGFR INSERTION OF EXON 20 AND LONG LASTING CLINICAL RESPONSE TO AFATINIB

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Background: Lung cancer remains a leading cause of mortality worldwide. Evolution in molecular biology has expanded and the identification of somatic mutations in the epidermal growth factor receptor (EGFR) as a clinically relevant oncogene also selected a subgroup of patients. Most commonly described as activating mutations, both deletion of exon 19 and L858R point mutation in exon 21 account for nearly 90% of all EGFR mutated patients. These patients usually benefit from tyrosine kinase inhibitors (TKIs). On the other hand, some patients harboring specific EGFR mutations – such as exon 20 insertions – do not benefit from the same strategy. **Method:** We describe a case report of a patient with advanced lung cancer. A female, 39-year-old patient was first diagnosed in late 2015 when she presented with dyspnea and lower back pain. Biopsy of the primary lung mass as well as a bone lytic lesion both revealed an adenocarcinoma. PET-CT showed extensive lymphangitic carcinomatosis, bone and cervical lymph node involvement. She underwent 5 cycles of cisplatin-pemetrexed with a good radiologic partial response and very good clinical response. During chemotherapy, the first molecular test (Cobas Z 480 Roche) became available showing an insertion of exon 20 in the EGFR gene. **Result:** Patient then requested an alternative treatment given that she was not inclined to accept maintenance with chemotherapy. We then proposed a short trial with afatinib, even though the chances of response were very low. She was started on afatinib PO 40mg/day on March 14th, 2016. Three weeks later the patient developed a grade 3 diarrhea and the drug was withheld until her symptoms resolved. She resumed afatinib PO at 30mg/day on April 20th, 2016. Her first radiologic evaluation two months later showed stable disease and she was kept on treatment and reported to feel healthier. Her second evaluation on November 2016 then showed a partial response, mainly in the bone and she was continued on oral TKI. New imaging studies on March 2017 revealed a progression of her disease only 12 months later. **Conclusion:** There is a lack of data addressing patients harboring rare and unique EGFR gene mutations. Most exon 20 insertions identified in patient samples have not been tested against reversible EGFR TKIs. Extrapolations from the few tested mutations might not apply for other exon 20 mutations. It is imperative that patient-derived cell lines of common EGFR exon 20 insertion mutations are developed to enhance our preclinical understanding on these tumors.

Keywords: NSCLC, EGFR, Targeted therapy

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-030 CUMULATIVE SMOKING DOSE AFFECTS THE CLINICAL OUTCOMES OF EGFR-MUTATED LUNG ADENOCARCINOMA PATIENTS TREATED WITH EGFR-TKIS

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Background: EGFR-mutated lung cancer patients are mostly found in never smoker but at least one third of the patients are ever smokers. Clinical outcomes are known to be variable according to the smoking history among EGFR-mutated lung adenocarcinoma patients when treated with EGFR-TKIs. The aim of this study is to investigate whether cumulative smoking dose affects the clinical outcomes such as progression-free survival (PFS) and overall survival (OS) in EGFR-mutated lung adenocarcinoma patients treated with EGFR-TKIs **Method:** We retrospectively analyzed 142 advanced or recurrent lung adenocarcinoma patients who harbored activating EGFR mutations (exon19 deletion or exon 21 L858R) and had received gefitinib, erlotinib or afatinib. Detailed smoking histories and smoking dose were obtained from all patients. The patients were classified into 4 groups by cumulative smoking dose (never smoker, ≤10 pack-years (PYs), 11-30 PYs and > 30 PYs). PFS and OS were analyzed according to smoking subgroups by Kaplan- Meier curves. **Result:** Among 142 EGFR-mutated patients, 91(64.1%) were never-smokers, 12(8.5%) were minimal smokers with ≤10 PYs, 22(15.5%) were moderate smokers with 11-30 PYs, and 17(12%) were heavy smokers with more than 30 PYs. Cumulative smoking dose was inversely associated with median PFS in dose-dependent manner with statistical significance. (11.8 months, 10.9months, 7.4 months, 3.9 months. $p < 0.05$). Kaplan-Meier curves of OS showed statistically significant negative association between cumulative smoking dose and median OS. (33.6months, 26.3months, 20 months, 8.9months: $p<0.001$) However, minimal smoker group less than 10 PYs showed very similar clinical outcomes of PFS and OS with never smoker group. In the multivariate analysis adjusted for age, sex, performance status, stage, and time point of EGFR-TKI treatment, cumulative smoking dose was an independent predictive factor for the disease progression (hazard ratio, 3.29; 95% confidence interval(CI), 1.68-6.45 p <0.001) and short OS(HR 4.3, 95% CI 2.1-8.7 p<0.001) to EGFR-TKIs. **Conclusion:** Cumulative smoking dose inversely affects the duration of response and survival to EGFR-TKIs in EGFR-mutated lung adenocarcinoma patients. Profiling of smoking-related gene signatures might be valuable for therapeutic decision besides EGFR mutation test in lung adenocarcinoma patients.

Keywords: lung adenocarcinoma, EGFR-TKIs, Cumulative smoking dose

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-031 EFFICACY OF GEFITINIB AND RADIOTHERAPY COMBINATION IN LUNG ADENOCARCINOMA

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Background: Combinations of gefitinib and radiotherapy have been observed to have synergistic and anti-proliferative effects on lung cancer in vitro, but clinical studies were limited. In clinical setting, patients who presented with respiratory difficulties like SVCS, radiotherapy should be given immediately to address the emergency while waiting for the results of EGFR mutation test. **Method:** We did a preliminary study to evaluate the efficacy of gefitinib and radiotherapy combination in lung adenocarcinoma in Persahabatan National Respiratory Refferal Hospital Jakarta Indonesia. Subjects were consecutively recruited between January 2013 to December 2016 **Result:** Thirty one lung adenocarcinoma with EGFR mutations were enrolled. Most of them were male (51.61%) with median age of 54.5 years

old (range 38-70 years old). Epidermal Growth Factor Reseptor (EGFR) mutation characteristics were on exon 21 L858R (61.30%); exon 21 L861Q (16.12%) and exon 19 deletion (22.58%). Radiotherapy were given at doses between 30-60 Gy. Among these subjects, Progression Free Survival (PFS) were 185 days (CI95%; 123.69-246.30), 1 year survival rate (1-ysr) was 45.2%. and overall survival (OS) are 300 days (CI95%;130.94-469.06). There were no grade 3/4 hematological and non hematological toxicities recorded. The most frequent Grade 1 and 2 non hematological toxicities were skin rash, diarrhea, paranochia and monoliasis and might be related to TKI. **Conclusion:** The combination of TKI with radiation may be considered in subjects with respiratory distress.

Keywords: Radiotherapy, gefitinib, lung adenocarcinoma

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-032 EFFICACY AND SAFETY OF OSIMERTINIB AS THIRD-LINE OR LATER THERAPY FOR T790M-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Advanced lung adenocarcinoma with epidermal growth factor receptor (EGFR) gene mutation in exon 18 to 21 is sensitive to EGFR tyrosine kinase inhibitors (TKI) such as gefitinib, erlotinib, and afatinib. However acquired resistance to EGFR-TKI develops after initial treatment, primarily due to T790M mutation. In March 2016, the Japanese Ministry of Health, Labour and Welfare approved osimertinib for the patients with advanced non-small cell lung cancer harboring a T790M mutation. In the same year, patients with a T790M secondary mutation were reviewed at Hiratsuka Kyosai Hospital for a period of 9 months. All patients were previously treated with an EGFR-TKI (with or without or prior/subsequent chemotherapy). **Method:** Data were obtained retrospectively by analysis of the medical records of patients who underwent molecular diagnostic testing for T790M mutation. All patients had stage IV adenocarcinoma. **Result:** A total of 8 patients with T790M mutation were identified. Molecular testing was performed using re-biopsy specimens of the primary tumor, metastatic lymph node, or circulating DNA in the plasma of patients. Seven out of 8 patients received osimertinib 80mg once daily. All patients treated with osimertinib received other treatments previously, including EGFR-TKI and standard chemotherapy. The overall response rate (ORR) was 87%. Most common adverse events included diarrhea (28.6%), rash (14.2%), nausea (14.2%). Adverse events of Grade 3 to 4 severity were not reported. **Conclusion:** These findings suggest that third-line or later osimertinib for advanced lung adenocarcinoma with T790M results in high ORR and managed tolerability. The use of molecular testing may improve treatment outcome in these patients.

Keywords: osimertinib, T790M, EGFR-TKI

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-033 PROPENSITY SCORE-ADJUSTED SURVIVAL ANALYSIS OF NON-SMALL CELL LUNG CANCER PATIENTS WITH ACQUIRED RESISTANCE TO EGFR-TKI

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Background: Non-small cell lung cancer (NSCLC) patients with activating epidermal growth factor receptor (*EGFR*) mutations are treated with EGFR-tyrosine kinase inhibitors (TKIs). However, most patients acquire resistance to EGFR-TKIs and receive subsequent treatments. To determine the optimal treatment for patients with TKI-resistance, we retrospectively examined the outcomes in advanced or recurrent NSCLC patients and analyzed the efficacy of the prevalent treatment options for those with TKI-resistance, using propensity score modeling. **Method:** *EGFR*-mutated NSCLC patients who acquired resistance to EGFR-TKIs during their first-line EGFR-TKI therapy were assigned to the TKI-resistant group based on the response of progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors. Patients with wild-type (WT) *EGFR* were assigned to the EGFR-WT group. By multivariate analysis of the two groups, a propensity score for chemotherapy use was calculated for each patient using logistic regression model. TKI treatment-free survival (TFS) was defined as «the overall survival (OS) - total progression-free survival (PFS) of every EGFR-TKI therapy». **Result:** A total of 415 patients with NSCLC were screened for *EGFR* mutations in the National Center for Global Health and Medicine, from April 2007 through March 2012. Of these, 158 (39%) patients harbored *EGFR* mutations, and 101 of these patients with activating *EGFR* mutations developed TKI-resistance. Seventy-five patients with *EGFR*-mutations who acquired TKI-resistance received a second-line chemotherapy or other EGFR-TKIs. Fifty-seven patients (75%) in the TKI-resistant group received ≥2 lines of EGFR-TKI treatments (beyond PD). Of the 252 *EGFR*-WT patients, 139 patients who received first-line chemotherapy or EGFR-TKIs formed the EGFR-WT group. OS was significantly longer in the TKI-resistant group compared to the EGFR-WT group (median, 43.8 vs 14.8 months, $p<0.001$). TFS did not significantly differ between the two groups (median, 16.6 vs 14.4 months, $p=0.83$). TKI-resistant patients receiving three or two lines of EGFR-TKIs had a better total PFS than those receiving a single line of EGFR-TKI (median, 28.2 vs 21.1 vs 9.0 month, $p<0.001$). In the propensity score-adjusted multivariate analysis, TFS was significantly associated with the post-operative recurrence (hazard ratio [HR] 0.40, $p<0.000$) and the use of chemotherapy (HR 0.32, $p=0.005$). Total PFS of EGFR-TKIs significantly correlated with the post-operative recurrence (HR 0.27, $p=0.02$) and sequential use of other EGFR-TKIs (HR 0.25, $p=0.03$). **Conclusion:** The use of chemotherapy prolonged the TFS in TKI-resistant NSCLC patients to the same extent as that seen in EGFR-WT patients. In TKI-resistant patients with *EGFR* mutations, sequential use of different EGFR-TKIs improved the total PFS of EGFR-TKIs.

Keywords: EGFR, EGFR-TKI, acquired resistance

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-034 EGFR EXON 19 DELETION IS ASSOCIATED WITH FAVORABLE OVERALL SURVIVAL AFTER FIRST-LINE ICOTINIB THERAPY IN ADVANCED NSCLC PATIENTS

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Background: Although previous studies demonstrated that the PFS of geftinib, erlotinib and afatinib as first line treatment is superior to chemotherapy in advanced NSCLC patients harboring activating EGFR mutation, the efficacy of icotinib therapy as first line therapy has not yet been elucidated. **Method:** Patients with IIIB/IV NSCLC and a confirmed activating mutation of EGFR (exon 19 deletion or exon 21 L858R substitution) received oral icotinib (125 mg, three times per day) until disease progression or unacceptable toxic effects. The primary outcome was overall survival (OS), and the second endpoint were progression-free survival (PFS), objective response rate(ORR), disease control rate(DCR). **Result:** 1615 patients with advanced NSCLC receiving icotinib from Oct. 2012 to Apr. 2016 were screened in four cancer centers in Qingdao city, P R.China, and 79 patients with intact follow-up data received icotinib in first-line setting and were enrolled.Of them, the number of women and men were 51 (64.56/%) and 28 (35.44/%) respectively. 27 (34.18%)patients were with EGFR exon 19 deletion, and 52(65.82%) patients with exon 21 L858R mutation. The median follow-up period at the time of analysis was 24.50 months. The objective response rate(ORR) was 45.57% (36/79) , and the disease control rate(DCR) reached 89.87%(71/79). One (1.27%) patient had CR, and 35(44.30%) patients had PR, 35(44.30%) patients had SD, 8(10.13%) patients with PD. The median PFS and OS were 13.61 months and 31.11 months respectively of overall population. The median PFS was 12.30 months in EGFR exon 19 mutation subgroup and 14.00 months in exon 21 mutation subgroup respectively($p=0.441$). The exon 19 mutation group had a significantly longer median overall survival than exon 21 mutation group (34.72 months, vs. 28.66 months,log-rank $p=0.006$, hazard ratio, 0.31 95% CI, 0.13 to 0.71). Meanwhile, there is significant difference of overall survival during different ECOG PS subgroups(ECOG PS 0-1 versus ECOG PS 2-3,32.59 months versus 20.59 months,$p=0.002$,HR 3.09,95%CI, 1.46 to 6.52). **Conclusion:** The study illustrate that icotinib is effective as first-line treatment for patients with advanced NSCLC and sensitive EGFR mutation. The patients harboring EGFR exon 19 deletion mutation yield similar PFS, but longer OS compared to those harboring exon 21 L858R mutation.

Keywords: epidermal growth factor receptor mutation, icotinib, non–small cell lung cancer

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-035 OSIMERTINIB IN RELAPSED EGFR-MUTATED NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES: RESULTS FROM THE TREM-STUDY

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Background: Osimertinib, an irreversible EGFR-TKI with activity also against the resistance mutation T790M, has a high brain permeability surmising intracerebral efficacy in T790M-negative cases. We assessed the efficacy of osimertinib in T790M-positive and –negative patients. **Method:** The TREM-study is an investigator initiated phase 2, single-arm, multi-center clinical trial conducted in five Northern European countries. Patients with advanced EGFR-mutated NSCLC with progression after at least one EGFR-TKI were assigned to treatment with osimertinib 80 mg daily until radiological progression or death. Both T790M-positive and –negative patients were enrolled, as well as patients with stable and asymptomatic brain metastases. The primary endpoint was objective response rate (ORR) according to RECIST 1.1.

Secondary endpoints were progression free survival (PFS), duration of response (DoR), disease control rate (DCR) and overall survival (OS). We here present data from a subset of patients with brain metastases at study entry. **Result:** Of 147 included patients, 34 presented with CNS-metastases at inclusion. This subset of patients had poorer performance status at baseline than the full study cohort (31 % with ECOG 2 in the CNS-subgroup vs 17 % in the full study cohort) and the median age was lower (61.5 vs 65 years), otherwise similar to the full cohort in terms of baseline characteristics. 69 % (20/29) were T790M-positive and 31 % (9/29) negative. 5 patients had unknown T790M-status. 28 patients were evaluable for response. ORR was 39 % (11/28) and DCR 75 % (21/28). For T790M-positive patients ORR was 53 % (9/17) and DCR 88 % (15/17), in T790M-negatives 13 % (1/8) and 38 % (3/8) respectively. Median DoR in T790M-positive patients was 14.7 months (95 % CI 6.4-22.9) and 5.5 months in one T790M-negative patient. Two patients had ongoing responses after 15.9 and 17.5 months at data cutoff. Median PFS in the CNS-subgroup was 7.2 months (95 % CI 4.1-10.3 months) vs 9.7 months (6.3-13.1) in patients without CNS metastases, p=0.300, regardless of T790M-status. In the CNS-subgroup PFS in the T790M-positive patients was 10.1 months (7.9-12.3) vs 2.0 months (0.9-3.2) in the T790M-negative patients, p<0.001. Of 18 patients who had progressed at cutoff, 7 had CNS as site of progression (4 T790M-negative, 2 unknown and only one T790M-positive). **Conclusion:** Although a limited number of patients in this subgroup analysis, our results show that osimertinib has similar efficacy in patients with CNS disease as without, whereas the benefit in T790M-negative patients may be substantially lower.

Keywords: brain metastases, EGFR, T790M

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-036 COMPARING THE EFFICACY/TOXICITY OF OSIMERTINIB AND FIRST LINE EGFR-TKI BY INDIVIDUAL PATIENT ANALYSIS

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Background: Osimertinib is a third generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which showed its efficacy for T790M resistant mutation in patients with advanced and recurrent non small cell lung cancer (NSCLC). The efficacy and toxicity of osimertinib comparing to previous EGFR-TKIs are not fully elucidated. Since every patient receiving osimertinib has received previous EGFR-TKI therapy, we compared the efficacy and toxicity of those agents in the same patients. **Method:** We retrospectively reviewed medical records of patients with T790M mutation positive advanced and recurrent NSCLC, who had disease progression after previous EGFR-TKI, the standard first line therapy, and started osimertinib between April 2016 and March 2017 at National Caner Center Hospital. Progression free survival (PFS) of osimertinib, and 1st line EGFR-TKI PFS of the same patients were calculated by Kaplan-Meier method. Objective response rate (ORR) was assessed according to RECIST version 1,1. Adverse events (AEs) were also reviewed to evaluate the difference of safety profiles between osimertinib and previous EGFR-TKIs. **Result:** A total of 46 patients with T790M positive NSCLC received osimertinib after the failure of first line EGFR-TKI treatment. At May 2017, the median follow-up time since the start of osimertinib was 7.8months. The median age was 65 (range 36-82), the median number of treatment received before osimertinib was 3 (range 1-9), and the median wash out time of 1st line EGFR-TKI till the start of osimertinib was 14.0 months. The median PFS of osimertinib is not reached. The median PFS of first line EGFR-TKI was 15.2 months. ORR of osimertinib and first line EGFR-TKI was 56.0% and 65.2%, respectively. The most frequent AEs of any grade of osimertinib were rash, dry skin, paronychia, and diarrhea (39.4%, 35.8%, 32.1%, and 30.2%, respectively). Rash, paronychia, and diarrhea over grade 2 was 6.5%, 6.5%, and 0% with osimertinib, compared to 0%, 12.5%, and 4.1% with gefitinib, and 41.7%, 8.3%, and 0% with erlotinib. The incidence of pneumonitis with osimertinib treatment was 10.9% (5 cases) in any grade, and 6.5% (3 cases) in grade 3 to 4, though 2 of them (1 case in grade 1 and 1 in grade 3) had received nivolumab as the prior chemotherapy. Except for pneumonitis, there was no AE leading to permanent discontinuation related to osimertinib. **Conclusion:** Osimertinib showed the efficacy and feasibility even in practical use. Adverse effect of osimertinib was generally better tolerated than previous EGFR-TKIs, except for pneumonitis.

Keywords: osimertinib, EGFR-TKI, T790M mutation

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-037 OSIMERTINIB IN RELAPSED EGFR-MUTATED, T790M-NEGATIVE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS: RESULTS FROM THE TREM-STUDY

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Background: The resistance mutation T790M emerges in around 60 % of EGFR-TKI treated NSCLC patients. Osimertinib is approved only in T790M-positive patients. We assessed the efficacy of osimertinib in both T790M-positive and -negative patients and here present results from T790M-negative patients. **Method:** In this investigator initiated, multicenter, single-arm, phase 2 clinical trial conducted in five Northern European countries, patients with progression on at least one previous EGFR-TKI and with measurable disease by RECIST 1.1 were assigned to treatment with 80 mg of osimertinib daily until radiological progression or death. Rebiopsy for assessment of mutational status was done after inclusion. Plasma samples were collected for translational research purposes (not analyzed yet). The primary endpoint was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints were progression free survival (PFS), duration of response (DoR), disease control rate (DCR) and overall survival (OS). **Result:** T790M-status was assessable in rebiopsies from 120 of 147 included patients. Of these, 42 patients (35 %) were T790M-negative in tissue. 55 % (23/42) of the T790M-negative patients had exon 19 deletion at diagnosis as opposed to 71 % of the T790M-positives, other baseline factors were similar between the two groups. ORR in the T790M-negative group was 19 % (7/36) including one patient with complete response. In the T790M-positive group, ORR was 52 % (37/71), no complete responses. DCR was 64 % (23/36) and 87 % (62/71), respectively. All responses were confirmed. Median DoR was 11.0 months (95 % CI 3.0-19.1) in the negatives and 12.0 months (8.7-15.2) in the positives, p = 0.887. In the T790M-negative group, median PFS was 5.5 months (2.6-8.3) vs 10.8 months (8.2-13.4) in the T790M-positive group, p = 0.009. Subgroup analyses were performed in the T790M-negative group and there was significant higher median PFS in patients without CNS-metastases (5.6 vs 1.6 months, p = 0.007), in patients with duration of previous TKI-treatment over median (15 months) vs under (9.7 vs 3.5 months, p = 0.044) and in patients with one previous line of TKI vs two or more lines (7.3 vs 2.0 months, p = 0.007). **Conclusion:** T790M-negative patients who respond have similar DoR as T790M-positive patients. T790M-negative patients without CNS-metastases and with durable response on first EGFR-TKI could benefit from osimertinib.

Keywords: clinical trial, EGFR, T790M

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-038 EARLY SERUM TUMOR MARKERS AFTER 14 DAYS OF TYROSINE KINASE INHIBITOR TARGET THERAPY PREDICTS OUTCOMES IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: The aim of the study was to demonstrate whether early variations in the levels of serum 4 tumor markers (TMs), carcinoembryonic antigen [CEA], cancer antigen [CA]125, CA19-9, and CA15-3), after TKI target therapy were associated with treatment response and progression-free survival (PFS) in patients with lung adenocarcinoma. **Method:** Patients with stage IIIB-IV lung adenocarcinoma taking epidermal growth factor receptor (EGFR) TKIs or anaplastic lymphoma kinase (*ALK*) inhibitors were enrolled prospectively from June 2012 to February 2015. According to the variations of percentage of change in 4-TM levels (4-TM_{pc}), we divided patients into ascending (increases in 4-TM_{pc} over the 7th- 14th day) and descending (decreases in 4-TM_{pc} over the 7th- 14th day) groups. **Result:** In all, 184 patients were enrolled, and 89% had at least one of the pre-treatment evaluable TMs and were further analyzed. A good response to the TKI target therapy was accurately predicted in the descending group, as determined using receiver operating characteristic curve analysis (an area under the curve, 0.83). The kappa value between type of 4-TM_{pc} and measurable radiographic lesions was 0.762. Multivariate Cox hazards model analyses demonstrated that the type of 4-TM_{pc} and mutation status were the strongest predictors of PFS (descending versus ascending, hazard ratios [HR] 0.30, 95% confidence interval [CI], 0.19–0.47; sensitive mutation versus wide type, HR 0.30, 95% CI, 0.19–0.48). **Conclusion:** Type of 4-TM_{pc} 14 days after TKI target therapy is associated with an image response and PFS, without regarding mutation status, in patients with advanced lung adenocarcinoma.

Keywords: tyrosine kinase inhibitor, Adenocarcinoma, tumor marker

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-039 COMPASSIONATE USE OF OSIMERTINIB: ARGENTINE EXPERIENCE

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Background: EGFR is one of the most commonly mutated proto-oncogenes in lung cancer. The frequency of these mutations varies from approximately 10% of lung adenocarcinomas in North American and European populations to 50% in Asia. The leucine to arginine substitution at position 858 (L858R) in exon 21 and short

in-frame deletions in exon 19 are the most common sensitizing mutations, comprising approximately 90% of cases. Approximately 50% of EGFR TKI resistance is due to a second site mutation, the T790M mutation occurring within exon 20. **Method:** To describe the "real life" experience in our country regarding the compassionate use of Osimertinib in patients with diagnosis of lung cancer with EGFR mutation and progression to tyrosine kinase inhibitors with detectable T790M mutation. We also include patients with de novo T790M mutation. We evaluated demographic data, the diagnostic method of resistance, sites of disease progression, toxicities and treatment efficacy. **Result:** We analyzed 17 patients from 10 different centers in Argentina in the period between January 2016 and May 2017. Median age: 61 years old, female 76%, PS: 0-1: 86%, non-smokers: 59%, histology: 15 adenocarcinoma and 2 undifferentiated, 14/17 with stage IV at diagnosis. EGFR mutations: Exon 19: 9 patients, 3 patients with evidence of T790M de novo, the remainder between exons 21 and 18. At the time of diagnosis, 13 patients start treatment with tyrosine kinase inhibitors, and the median time of response was 17 months. The most frequent site of progression was lung/pleura (85%) and liver (21%). Re-biopsy was performed in 13/17 patients. The major difficulty for successful biopsy was the site or the complexity of the procedure to be performed. A liquid biopsy was performed in 6 of 17 patients, 4 were positive. ORR with Osimertinib was 68%. The most common side effects were diarrhea: 31% (only 1 patient with grade 3), rash 18%. One patient had liver toxicity (grade 3 hepatitis). **Conclusion:** Osimertinib showed better adhesion and tolerance profile than tyrosine kinase inhibitors. Osimertinib offers an excellent toxicity profile with overall response rates similar to those described in publications.

Keywords: osimertinib, T790M, EGFR

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-040 EGFR T790M MUTATION DETECTION AND OSIMERTINIB TREATMENT RESPONSE EVALUATION BY LIQUID BIOPSY IN ADVANCED NSCLC PATIENTS

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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 accounts for about 50% of these resistance cases. Droplet digital PCR (ddPCR) and cobas enables quantification of specific mutated ctDNA. In this study, these methods were used to detect and evaluate the ctDNA response after Osimertinib treatment. **Method:** In the screening period of ASTRIS (D5160C00022) study in single center, tumor and blood samples from 69 stage IIIB- NSCLC patients defined as acquired resistance to first generation EGFR TKIs (Gefitinib, Elortinib or Ecotinib) were collected. The cobas® Mutation Test v2 kit was used to detect EGFR mutations in FFPE or plasma samples. Plasma T790M mutation of both Osimertinib naïve and treated patients were quantified by Droplet digital PCR (ddPCR). **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 the FFPE tissue cobas testing as gold standard, the sensitivity and specificity of plasma ddPCR to detect T790M mutation was 66.7% and 63.6%. Taking all testing methods into account, the T790M positive rate was 52.2%. In all of the plasma cobas positive cases, T790M mutation was detected by ddPCR. In 10 tumor biopsy cobas negative cases, 3 were positive defined by ddPCR. In 23 patients received Osimertinib treatment, the OOR was 60.9%, quantification of T790M after 6 weeks of treatment decreased to very low level, no association was observed between response status and T790M mutation decrease. **Conclusion:** ddPCR is more sensitive in plama ctDNA testing and should be performed even tumor tissue biopsy yielded negative results in certain cases. Osimertinib significantly decreased plasma T790M level, but not associated with clinical response.

Keywords: lung adenocarcinoma, T790M, osimertinib

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-041 THE CONCENTRATION OF AVITINIB IN CEREBROSPINAL FLUID AND ITS EFFICACY AND SAFETY IN NSCLC PATIENTS WITH T790M MUTATION

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Background: Avitinib is an oral, potent, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor selective for T790M resistance mutations. We report the safety, the intracranial/extracranial efficacy, and the blood brain barrier (BBB) penetration rate of Avitinib in non-small cell lung cancer(NSCLC) patients with EGFR T790m mutation. The data come from Peking Union Medical College hospital-a single center of the Phase 1, open-label, multicenter study (NCT02330367). **Method:** NSCLC Patients with acquired EGFR T790m (+) were enrolled. Patients were orally administered with dose escalating from 150 mg to 300 mg twice daily for 28-continuous-day cycles until disease progression. Blood (2mL) and cerebrospinal fluid (CSF) samples (2ml) were collected for concentration analysis on day 29 in available patients with brain metastases (BM). Tumor response was assessed on day 29 and then every 8 weeks. **Result:** Sixteen patients were included. Nine patients had asymptomatic BM, and all the nine patients had more than 3 BM lesions. The most frequent adverse events were the elevated hepatic transaminases (10/16, 62.5%) and diarrhea (5/16, 31.3%), Most were mild and reversible. 9 Patients (56.3%) achieved Partial Response (PR), 6 (37.5%) achieved Stable Disease (SD). Median Progress Free Survival (PFS) was 247 days (95%CI: 154.8-339.2), and the Median Overall Survival (OS) was 536 days (95%CI: 363.6-708.4). Of the 7 evaluable BM patients, the median intracranial PFS was 142 days (95% CI 31.1-252.9), with two patients progressed first in intracranial disease, while five patients had concurrent intracranial and extracranial progression after avitinib treatment. The cytologic analysis of CSF showed one meningeal metastases who accepted intrathecal injection with methotrexate and dexamethasone later. The blood and CSF analysis of 5 BM patients showed the BBB penetration rate were 0.046%-0.146% (Table).

patients	CSF Con. (ng/ml)	Plasma Con. (ng/ml)	Per.%	Intracranial PFS (days)	Extracranial PFS (days)
1	0.106	231	0.046	566	566
2	0.425	291	0.146	60	177
3	0.487	631	0.077	142	142
4	4.05	2940	0.138	138	138
5	1.72	1890	0.091	28	28
6	24	227	10.6[1]	218	218
7				308	350
8				550[2]	252

[1]Her BBB was broken by postocular metasatses. [2]He accepted brain radiotherapy before avitinib, and he also accepted chemotherapy with pemetrexed plus carboplatin plus endostatin after progression from avitinib. He was excluded from the analysis of intracranial PFS. **Conclusion:** Avitinib is well tolerated and efficacious in EGFR T790m(+) NSCLC patients. Its concentration in CSF is low, and the penetrability of BBB is weak. The median intracranial PFS for asymptomatic BM is relative short comparing to extracranial disease. Further studies are proceeding.

Keywords: concentration in cerebrospinal fluid, T790M mutation, EGFR TKI

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-042 EGFR MUTATION AND ERLOTINIB EFFICACY IN TURKISH ONCOREGISTRY

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Background: The aim of this registry was to collect demographic, diagnostic, treatment, and outcome information about Turkish patients with non-small cell lung cancer (NSCLC). **Method:** It was designed as a multicenter, cross-sectional, non-interventional study conducted on new and previously diagnosed lung cancer cases applied to 28 medical oncology outpatient clinics between 2012 and 2015. A total of 3790 male (85,5%) and female (14,5%) patients >18 years were included. **Result:** Mean age of patients was 60,4 (SD:±9,2) years. 79,4% of patients had smoking history and 19,6% of patients had familial cancer history. 63,5 % of patients were at stage IIIB and IV. 47,1% of total patients had adenocarcinoma and 42,2% had squamous cell carcinoma. In patients with no smoking history, adenocarcinoma histology was more dominant; 58,7% adenocarcinoma vs 30,6% squamous cell carcinoma. EGFR testing rate increased throughout the years but dependent to late market access of TKIs for EGFR mutation positive patients the testing rate for total patients is only 14,4%. EGFR mutation positivity rate in tested patients is 21,75% and 58,5% of these patients had exon 19 deletion. Overall survival of stage 4 patients was 15.9 months. For patients tested positive for EGFR mutation, erlotinib significantly improved the overall survival to 34,5 months (erlotinib users) vs 30,2 months (non-users) (p=0,043). **Conclusion:** In this multicenter, cross-sectional, non-interventional study we had an overall picture of Turkish NSCLC patients. 63,5% of NSCLC patients were at stage IIIB-IV and EGFR mutation positivity rate was 21,75%. For EGFR mutated patients, erlotinib is an effective treatment option and significantly improves overall survival.

Keywords: non-small cell lung cancer, Erlotinib, EGFR mutation

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-043 A PHASE 1B STUDY OF ERLOTINIB AND MOMELOTINIB FOR TKI-NAÏVE EGFR-MUTATED METASTATIC NON-SMALL CELL LUNG CANCER

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Background: In this study (NCT02206763), momelotinib, an inhibitor of Janus kinases 1 and 2, was administered in combination with erlotinib, a tyrosine kinase inhibitor (TKI) in patients with TKI-naïve epidermal growth factor receptor (EGFR)-mutated metastatic non-small cell lung cancer (NSCLC), to determine the maximum tolerated dose and safety of momelotinib in combination with erlotinib. As previously reported, dose limiting toxicities (DLTs) of grade 3 diarrhea (n=1) and grade 4 neutropenia (n=1) without fever were seen at dose level (DL) 2B and trial enrollment was halted. Here, we report the final results. **Method:** Patients received oral erlotinib 150 mg QD (including 11-31 day run-in). Momelotinib was administered orally in a standard 3+3 dose-escalation design: DL1, momelotinib 100 mg QD; DL2A, 200 mg QD; and DL2B, 100 mg BID. DLTs were evaluated in the first 28 days. Plasma samples were collected for PK/PD analyses. **Result:** Eleven patients enrolled: 3 in DL1, 3 in DL2A, and 5 in DL2B. The median duration of exposure to momelotinib was 40 weeks (range 2.4-63.1) and median number of cycles was 10 (range 0.6-15.8). Treatment was discontinued for progressive disease (n=7), adverse event (n=3), and patient decision (n=1). The objective response rate was 54.5% (90% CI: 27.1%–80.0%) and all responses (n=6) were partial responses; 4 patients had stable disease and 1 patient had progressive disease. The median duration of response was 7.1 (90% CI: 4.4–9.6) months. The median progression-free survival was 9.2 (90% CI: 6.2–12.4) months. The estimated median overall survival was not reached. The most common treatment-emergent adverse events (TEAEs) were decreased appetite, dry skin, and fatigue (7 patients each) and diarrhea (6 patients). In addition to the patient with grade 4 neutropenia (DLT), decreased neutrophil count was recorded in 4 additional patients (grade 1-2 [n=3], grade 3 [n=1]); median time to first neutrophil abnormality was 0.5 (range 0.5–3.7) months. Momelotinib-related TEAEs of interest (one patient each) included grade 1 sensory peripheral neuropathy, grade 1 paresthesia, and reactivation of hepatitis B. There was one momelotinib-related serious adverse event, grade 3 pneumonitis. There was no PK interaction between momelotinib and erlotinib. **Conclusion:** The combination of momelotinib and erlotinib had more toxicity than expected at DL2B. Neutropenia was common. Although the small number of patients in this phase 1 study limits our ability to make a definitive conclusion regarding efficacy, the response rate and progression-free survival was similar to previous reports with erlotinib alone.

Keywords: Targeted therapy, non-small cell lung cancer, chemotherapy

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-044 OSCILLATE - PHASE 2 TRIAL OF ALTERNATING OSIMERTINIB WITH GEFITINIB IN PATIENTS WITH EGFR-T790M MUTATION POSITIVE ADVANCED NSCLC

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Background: Activating mutations of the epidermal growth factor receptor (EGFR) are key drivers of non-small cell lung cancer (NSCLC) in approximately 10-15% of Western patients and 30-35% of Asian patients. Patients with common activating mutations (L858R and del19) typically have objective tumour response rates (OTRR) of 56-74% and median progression free survival (PFS) of 9-13 months with first-generation EGFR tyrosine kinase inhibitors (TKI) such as erlotinib or gefitinib. The most common mechanism of acquired resistance to first generation EGFR TKI is the T790M mutation (50-60% of cases). Osimertinib is an irreversible EGFR TKI effective against the T790M resistance mutation with OTRR of 51-71% in T790M positive disease. However, acquired resistance invariably develops, and median PFS is approximately 10 months. Mechanisms of resistance include C797S mutations and loss of T790M. Novel strategies that prevent or delay resistance to osimertinib are likely to enhance its durability of response and clinical benefit in EGFR-T790M positive NSCLC. **Method:** DESIGN: Open-label, single arm, multi-centre, phase 2 trial with safety run in. ELIGIBILITY: Adults with advanced, EGFR mutated NSCLC, acquired resistance to first or second generation EGFR TKIs, and mutation of T790M. ENDPOINTS: PFS rate at 12 months, feasibility of alternating osimertinib and gefitinib, time to progression and PFS time, objective tumour response rate, overall survival and adverse events. Tertiary correlative objectives include changes in plasma cfDNA levels for activating EGFR mutations and T790M over time, their relationships with OTRR and the mechanism of resistance. TREATMENT: Osimertinib 80mg daily for 8 weeks (2 cycles), then gefitinib 250mg daily for 4 weeks alternating with osimertinib 80mg daily for 4 weeks (i.e. alternating 4 weekly cycles of each drug) until disease progression or prohibitive toxicity. STATISTICS: A total of 45 participants provides 90% power, with a 1-sided type 1 error rate of 10%, to distinguish the observed proportion alive and progression free at 12 months from true rates of 45% (not worthy of pursuit) and 65% (worthy of pursuit) using a Simon, 2-stage, minimax design allowing for 4 ineligible or inevaluable participants. ASSESSMENT: CT scans 8-weekly until disease progression. Plasma collections at baseline and at the start of each 4-week cycle. OSCILLATE is an investigator-initiated cooperative-group trial led by ALTG, in collaboration with NHMRC Clinical Trials Centre, University of Sydney, with support from Astra-Zeneca. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: osimertinib, T790M, EGFR

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-045 UPDATED RESULTS OF PHASE II, LIQUID BIOPSY STUDY IN EGFR MUTATED NSCLC PATIENTS TREATED WITH AFATINIB (WJOG 8114LTR)

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Background: Liquid biopsy has been approved as an optional method to detect clinically relevant *EGFR* mutations in NSCLC. WJOG8114LTR is a prospective, multi-institutional study of liquid biopsy in *EGFR* mutated NSCLC patients. Previously, we reported that complete molecular response at 4 weeks could be an early surrogate marker of durable efficacy. Here, we report updated results. **Method:** Chemotherapy naïve, advanced NSCLC patients with EGFR-sensitizing mutation received afatinib monotherapy (40 mg/body) until progressive disease (PD) or unacceptable toxicity. Plasma DNA was obtained from patients at baseline, weeks 2, 4, 8, 12, 24, 48, and at PD. Three types of clinically relevant *EGFR* mutations (exon 19 deletion, exon 20 T790M and exon 21 L858R) will be analyzed using plasma DNA with multiplexed, pico-droplet digital PCR assay (RainDrop® system, RainDance Technologies, Billerica, MA). Complete molecular response (CMR) was defined as mutant allele event/frequency of exon 19 deletion or exon 21 L858R below the cutoff for the positivity by digital PCR in plasma. This study was registered at UMIN (ID: 000015847). **Result:** Fifty-seven patients were registered in the study. Efficacy of afatinib was comparable to previous reports (overall response rate: 78.6%, and median progression-free survival (mPFS): 14.2 months). At baseline, 62.5% of patients (35/56) were positive for *EGFR* mutation in plasma. Among those, CMR rate at 2, 4, 8, 12, 24 weeks was 60.6%, 87.5%, 93.8%, 87.1%, and 83.3%, respectively. About 40% of patients who achieved CMR at any time point maintain CMR at 48 weeks and had durable progression-free survival (more than 400 days). At the time of analysis, 17 patients experienced disease progression, and 14 plasma samples were collected. Of those, 8 (57.1%) were positive for mutation in plasma. In five patients, plasma progression was observed prior to radiological progression. Exon 20 T790M was detected in five patients (detection rate: 62.5%). **Conclusion:** Among *EGFR* mutated NSCLC patients, liquid biopsy was a useful method to predict durable efficacy and progression. Applicability of liquid biopsy should be explored in further study.

Keywords: EGFR, liquid biopsy, afatinib

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-046 LYMHOCYTE-TO-MONOCYTE RATIO AND MEAN PLATELET VOLUME AS PROGNOSTIC FACTOR IN EGFR MUTANT NSCLC TREATED WITH EGFR TKI

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Background: EGFR mutation is a strong predictor of the response to EGFR-TKI, but 10-30% of EGFR-TKI naive patients do not respond to the first line EGFR TKI therapy. Inflammation plays an important role in the initiation, progression, invasion and metastasis of cancer. Recentry study has demonstrated that hematological markers of inflammation such as LMR (lymphocyte to monocyte ratio), RDW (red cell distribution width), and MPV (mean platelet volume) are valuable biomarker in various types of human cancers. The purpose of the present study is to analyze whether hematological markers of inflammation is a prognostic factor in EGFR mutant NSCLC treated with EGFR TKI. **Method:** We retrospectively analyzed 75 advanced or recurrent NSCLC patients with common EGFR mutation treated with EGFR-TKI between 2008 to 2017 at the University of Tokyo hospital. Patients with de novo T790M mutaion, systemic corticosteroids or active infection were excluded from the analysis. We analyzed whether the hematological markers of inflammation before the TKI therapy impact the PFS of TKI therapy. The following variables were included: LMR, RDW, MPV, EGFR mutation subtype (Exon19 deletion of L858R) , ECOG performance status, age and gender. The PFS was estimated by the Kaplan-Meier method and were compared by the log-rank test. Prognostic factors for PFS were assessed by Cox's proportional hazards regression model. Statiscital analysis was performed using the survival package in the R software. **Result:** Low LMR and high MPV were associated with shoter PFS (log-rank test, p=0.000057 and p=0.03 respectively), but RDW was not associated with PFS. In the multivariate analysis, low LMR (hazard ratio (HR) 2.9; p=0.00015), high MPV (HR 1.7; p=0.039), and poor PS (HR 2.0; p=0.046) were independent risk factors for shoter PFS. **Conclusion:** Low LMR and high MPV are independent risk factors for shorter PFS in patients treated with EGFR-TKI.

Keywords: EGFR mutation, inflammation, biomarker

P2.03-047 THE MAIN TREATMENT FAILURE PATTERN FOR COMPLETELY RESECTED STAGE II–IIIA (N1–N2) EGFR-MUTATION POSITIVE LUNG CANCER

S. Xu[1], W. Zhong[2], Y. Zhang[1], W. Mao[3], L. Wu[4], Y. Shen[5], Y. Liu[6], C. Chen[7], Y. Cheng[8], L. Xu[9], J. Wang[10], K. Fei[11], X. Li[12], J. Li[13], C. Huang[14], Z. Liu[15], S. Xu[16], K. Chen[17], S. Xu[18], L. Liu[19], P. Yu[20], B. Wang[21], H. Ma[22], H. Yan[2], X. Yang[2], Y. Wu[23], Q. Wang[1]

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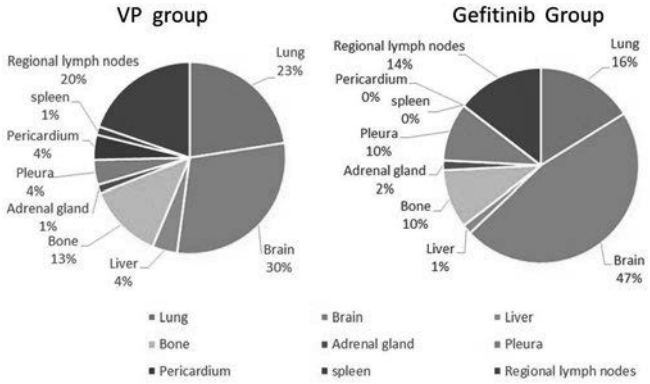
Background: ADJUVANT (CTONG 1104) is the first randomized trial shows significantly prolonged disease-free survival (DFS) in completely resected stage II-IIIA (N1-N2) epidermal growth factor receptor (EGFR)-mutation positive non-small-cell lung cancer (NSCLC) through adjuvant gefitinib compare with vinorelbine plus cisplatin (VP). Further we aim to analyze the treatment failure pattern in ADJUVANT study. **Method:** In the ADJUVANT trial, a total of 222 patients with completely resected stage N1–N2 EGFR-mutation positive NSCLC were randomized 1:1 into gefitinib group (250mg, QD, 24 months) or vinorelbine (25mg/m^2 Day 1/Day 8) plus cisplatin (75mg/m^2 Day 1) group (every 3 weeks for 4 cycles) respectively. Any recurrence or metastases occurred during the follow-up period was defined as treatment failure. Recurrent pattern in both group were analyzed with follow-up data (until Mar 9th 2017) integrated. **Result:** At the Data cut-off date for the primary analysis of DFS, 124 progression events (55.9% maturity overall) had occurred; 114 patients had disease recurrence,10 patients died before disease recurrence. Analysed recurrent pattern include lung, brain, liver, bone adrenal gland, pleura, pericardium, spleen and regional lymph nodes metastasis. Even no significant differences were found, highest proportion of patients in both group(18.9% for VP and 26.1% for gefitinib, p=0.199) surfer brain metastasis with lung metastases being the second common recurrent site. Time to brain metastases showed no significantly difference between the two groups (not reach vs 40.8m, p>0.05). Among the 29 brain metastases patients with gefitinib, the brain metastases occurred in 17 patients during the gefitinib treament, and 12 patients relapse after the gefitnib termination.



Conclusion: Compared with other site metastases, lung, brain and regional lymph nodes metastases account for major proportion of recurrence in ADJUVANT study. (NCT01405079)

Keywords: epidermal growth factor receptor (EGFR) mutation, non-small-cell lung cancer (NSCLC)

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-048 MIXED RESPONSE OF NON-SMALL CELL LUNG CANCER HARBORING THE EGFR T790M MUTATION TO OSIMERTINIB

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Background: Although patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations respond well to EGFR tyrosine kinase inhibitors (TKIs), most progress after approximately 1 year. At the time of progression, the EGFR T790M mutation is detected in more than half of these tumors. NSCLC harboring the T790M mutation shows a high response rate to osimertinib. However, the heterogeneous nature of NSCLC may limit the efficacy of osimertinib to those lesions with the T790M mutation, and a subset of patients may show a mixed response (MR), whereby some lesions shrink while others progress at the first evaluation. Previous study showed that about 20% of NSCLC patients exhibit MR to systemic therapies including EGFR-TKI. However, little is known about characteristics of MR to osimertinib. **Method:** To determine the frequency of a MR, we retrospectively reviewed patients treated with osimertinib for NSCLC harboring the EGFR T790M mutation at the National Cancer Center Hospital. **Result:** Between April and December 2016, 45 patients (median age 65 [36-82] years, 19 [42%] males) who had NSCLC with the T790M mutation received osimertinib. The median numbers of previous chemotherapies and EGFR-TKI therapies received by the patients were 1 and 2, respectively. All measurable tumor lesions showed a response to therapy in 35 (77%) patients and progression in three (7%) patients. A MR was seen in seven (16%) patients. Of these seven patients, the re-biopsy specimens in which T790M was detected were derived from the primary lesion in six and a metastatic lymph node in one patient. Two types of MRs were seen among these seven patients: (1) the tumor including the re-biopsy site responded, while the other lesions progressed (five patients), and (2) the tumor including the re-biopsy site progressed (two patients). The most frequent progressive sites were liver and lung metastasis (four patients, respectively). Three patients continued to receive osimertinib after the MR, one of whom underwent drug-eluting bead transarterial chemoembolization (DEB-TACE) for progressive liver metastasis and achieved disease control on osimertinib for an additional 4 months after the MR. **Conclusion:** A MR to osimertinib was seen in 16% of patients with NSCLC harboring the EGFR T790M mutation. This suggests that resistance mechanism of 1st line EGFR-TKI may differ by the site in same patient. Since benefit of osimertinib is mainly seen in T790M mutation, addition of local therapy may be beneficial for patients who develop a MR to osimertinib.

Keywords: EGFR, Mixed Response, T790M

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-049 PULMONARY ADENOID CYSTIC CARCINOMA WITH EGFR ACTIVATING MUTATION AND RESPONDS WELL WITH TYROSINE KINASE INHIBITOR

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Background: Adenoid cystic carcinoma (ACC) is an rare form of malignant neoplasm that arises from secretory glands in salivary glands of the head and neck but cases primary from respiratory tract is rare. Epidermal Growth Factor Receptor activating mutation is common in lung adenocarcinoma in Asian and responded well with Tyrosine Kinase Inhibitor. **Method:** We present the case of a 48 year old female complaining chest pain and shortness of breath. **Result:** The patient was referred to the hospital due to chest pain and shortness of breath since 4 months. Initial CXR showed pulmonary mass and chest CT scan showed giant pulmonary mass but no nodes enlargement. Lobectomy were performed and histopathology evaluation showed adenoid cystic carcinoma. The patient underwent radiotherapy chemotherapy. Four months later the symptoms increased and tumor grow. EGFR mutation were done and positive for activating mutation (exon 19 deletion) and Gefitinib were started. The patient was stable for 1 year with gefitinib with minor side effects. **Conclusion:** EGFR mutation testing should be considered in a rare pulmonary mass such as adenoid cystic carcinoma.

Keywords: adenoid cystic carcinoma, EGFR mutation, tyrosine kinase inhibitor

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
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P2.03-050 THE EFFICACY OF EGFR TYROSINE KINASE INHIBITORS IN ADVANCED NON-SMALL CELL LUNG CANCER HARBORING G719X MUTATION

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Background: Few uncommon EGFR mutations existed in NSCLC patients, such as G719X mutation on 18 exon. The best treatment option for G719X mutation is unclear, and it is usually excluded from clinical trials using EGFR TKI therapy. Here we studied the clinical data of patients harboring G719X mutation in real world and their sensitivity to EGFR TKIs. **Method:** Between January 2011 and December 2016, we retrospectively collected the clinical data of stage IIIB/IV NSCLC patients harboring G719X mutation at Peking Union Medical College Hospital. **Result:** A total of 830 NSCLC patients were found to harbor common sensitive EGFR mutations (417 patients harbored 19 exon deletion,413 patients harbored 21 L858 mutation, respectively), while 27 (27/857, 3.15%) patients harbored G719X mutation on 18 Exon, using amplification refractory mutation system (ARMs). 19 (19/27, 70.4%) patients with G719X mutation were treated with EGFR TKIs, 11 (57.9%) with Gefitinib, 5 (26.3%) with Icotinib, and 3 (15.8%) with Erlotinib, respectively. The median age was 58.3 years (range from 30 to 79 years). There were 11(57.9%) females, and 6 (31.6%) patients with history of heavy smoking. 3 (15.8%) patients had baseline central nervous systemic metastasis. 11(57.9%) patients had unique G719x mutation,

while 8 patient had compound mutations (5 patients had G719+20s768I, 2 patients had G719+L861Q, and 1 patient had G719+19del). 9 (47.4%) patients gained PR, 7 (36.8%) patients gained SD, and 3 (15.8%) achieved PD, the ORR was 47.4%, and the DCR was 84.2%. The median PFS was 8.8 months (95% CI: 0.932-16.67). The median PFS of first-line TKI therapy was longer than second-line TKI therapy (10.8months vs. 4.0months respectively), but it didn't got statistical significance (p=0.226). The median OS was 15.3 months (95%CI: 12.3-18.3), with 6 patients still alive. There were no intolerant adverse effect associating with EGFR TKIs. **Conclusion:** These results suggest that EGFR TKI therapy is effective in patients with G719X mutations. EGFR TKI could be a treatment choice better than chemotherapy for patients harboring G719X mutation.

Keywords: EGFR TKI, non-small cell lung cancer, EGFR G719X mutation

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-051 THE IMPACT OF EGFR MUTATIONS. TREATMENT WITH ITKS IN NON SMALL CELL LUNG CANCER PATIENTS

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Background: Patients with advanced stage of non small cell lung cancer (NSCLC) have been historically treated with a limited number of cycles of first-line chemotherapy, with platinum-doublets as the most commonly used regimen, after which, those with tumour response or stable disease are observed for evidence of disease progression; progression is followed by second-line therapy in proper patients. In patients with advanced NSCLC harboring EGFR mutations, the use of EGFR TKIs in first-line treatment has shown a large PFS benefit with almost no toxicity when compared with chemotherapy. For patients with lung adenocarcinoma and activating EGFR mutations who received EGFR TKIs median overall survival (OS) ranges between 24 and 30 months contrasts with the plateau of 10 months reached with first line platinum-based chemotherapy in populations not selected by molecular profiling. **Method:** We analyze all patients attended in our hospital with NSCLC, who had received EGFR-TKI since 2010 to 2015 when hoarbouring EGFR mutation. For descriptive purposes, continuous variables were summarized as arithmetic means, medians and standard deviations, and categorical variables were reported as proportions with 95% confidence intervals (95% CI). PFS and OS were measured from the day of EGFR TKI treatment to the date of progression or death, respectively, and analyzed with the Kaplan-Meier technique. **Result:** The amount of patients were 46. Six types of EGFR gene mutations were found: delection in exon 19, exon 18 (G719), exon 20 (T790 and S768I) and in exon 21 (L861Q and L858R). Two patients were combinations of G719 and L861Q, the third was a combination of G719 plus S768I, and the fourth was a combination of delection in 19 exon and T790 mutation. 13 patients (24.5%) could recieve second and furthers lines of therapy after EGFR ITKs, including: chemotherapy, immunotherapy and second generation EGFR TKIs. PFS was 9,98 months [4,7-15,25; IC95%.] OS was 23,45 months [11,26-35,6; IC 95%] **Conclusion:** The outcome of this study is to describe patient population receiving EGFR-TKIs. As expected most of them harbored the common sensitizing EGFR mutations L858R and delection in exon 19;both were higher in women and specially L858R mutation in non smokers. Nowadays treatment of patients with advanced NSCLC should be individualized, based on the molecular and histological features of their tumour. When harbouring an activating EGFR mutation, first-line treatment should be with an EGFR TKI.

Keywords: EGFR, ITK, NSCLC

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-052 LOCAL ABLATIVE THERAPY FOR OLIGOPROGRESSIVE, EGFR-MUTANT, NON-SMALL CELL LUNG CANCER (NSCLC) AFTER TREATMENT WITH OSIMERTINIB

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Background: EGFR tyrosine kinase inhibitors (EGFR-TKIs) improve progression-free survival (PFS) in patients with *EGFR*-mutant NSCLC, but disease progression limits efficacy. Retrospective studies show a survival benefit to local ablative therapy (LAT) in patients with oligoprogressive disease (progression at a limited number of anatomic sites). **Method:** This is a prospective study of LAT in patients with oligoprogressive *EGFR*-mutant NSCLC. Patients with no prior EGFR-TKI therapy (cohort 1) or progression after 1st/2nd generation EGFR-TKIs with acquired T790M mutation (cohort 2) receive osimertinib. Upon progression, eligible patients with <= 5 progressing sites undergo LAT and resume osimertinib until disease progression. Patients previously treated with osimertinib qualifying for LAT upon disease progression are also eligible for treatment (cohort 3). Primary endpoint: evaluation of safety and efficacy of reinitiation of osimertinib after LAT (assessed by PFS2). Additional goals are assessment of mechanisms of resistance to osimertinib by multi-omics analyses of tumor, blood, and saliva. **Result:** Between 04/2016 and 06/2017, 18 patients were enrolled (cohort 1: 11, cohort 2: 4, cohort 3: 3). Median age was 57 (range 36-71). The most common adverse events (AEs) on osimertinib treatment were rash, diarrhea, thrombocytopenia, and alanine transaminase elevation with most of the AEs being grade 1 or 2. Among evaluable patients, confirmed objective response rates prior to LAT in cohorts 1 and 2 were 66.7% (6/9) and 75% (3/4), respectively, with 11.3 months median PFS (95% CI: 3.4-11.3 months) in cohort 1 and 8.9 months in cohort 2 (95% CI not defined due to the small number of patients). To date, 7 patients had progressive disease, 6 of which had oligoprogression and subsequently underwent LAT (cohort 1: 2; cohort 2: 1; cohort 3: 3). Three patients were treated with combination of surgery and radiotherapy (RT), 2 patients with surgery, and 1 patient with RT. Whole exome sequencing (WES) and RNA-seq were performed on tumor tissues obtained pre-treatment and upon progression on osimertinib. *MET* amplification, transformation to small cell lung cancer, and EGFR C797S mutation were identified as mechanisms of resistance to osimertinib. One patient with *MET* amplification was referred for a clinical trial of osimertinib and savolitinib, a MET inhibitor, upon second progression on osimertinib re-challenge, and had a response to treatment. **Conclusion:** Patients with *EGFR*-mutant NSCLC and oligoprogression after EGFR-TKI therapy can be safely treated with LAT. In select patients, this approach could potentially maximize duration of EGFR-TKI treatment and prevent premature switching to other systemic therapies.

Keywords: Local ablative therapy, EGFR mutated non-small-cell lung cancer, Oligoprogressive disease

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-053 A FIVE-YEAR AUDIT OF EGFR AND ALK TESTING AT A TERTIARY CARE CENTRE IN NORTH INDIA: MORE SENSITIVE METHODS DO MAKE A DIFFERENCE!

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Background: Detection of targetable driver mutations in NSCLC may depend on the method employed. We carried out an audit to determine whether the EGFR mutation (EGFR-M) and ALK rearrangement (ALK-R) detection rate is dependent upon on the testing method used. We also sought to assess if EGFR-M and ALK-R was associated with baseline demographic characteristics. **Method:** Retrospective analysis of NSCLC patients who underwent testing for EGFR-M and ALK-R from January 2012 till May 2017. Methods used for EGFR-M were Real time ARMS PCR and gene sequencing while Break Apart FISH and D5F3 immunohistochemistry(IHC) were used for ALK-R testing. **Result:** Of the 599 patients tested for EGFR-M, 541 (90.3%) had interpretable results with an overall prevalence of 21.4%(n=116). Real time ARMS-PCR and gene sequencing yielded 95.9% and 81.9% interpretable results respectively. ALK-R testing was done in 462 patients of whom 431 (93.3%) had interpretable results, of which 8.6%(n=37) were positive. D5F3 IHC and Break Apart FISH yielded 94.7% and 82% interpretable results respectively. Mean age was 59.2 and 54.0 years respectively for EGFR-M and ALK-R patients with 54.3% and 45.1% being females. Mutations in exon 19 were the most common (n=81, 69.8%) followed by exon 21 L858R (n=30, 25.9%). 87/116 (75%) and 19/37 (51.4%) of EGFR-M and ALK-R patients received EGFR-TKIs and crizotinib respectively. Table shows differences in prevalence of EGFR-M and ALK-R prevalence in relation to gender, smoking status, histology and testing method used.

Table 1 Smoking, gender and histologic profile of the patients tested for EGFR mutations and ALK rearrangements

	EGFR-M positive (n=116)	ALK-R positive (=37)
Overall	21.4%	8.6%
Adenocarcinoma only	23.8%	9.5%
Females vs. males	37.1% vs. 14.3%	12.5% vs. 6.8%
Non-smokers vs. smokers	34.6% vs. 11.9%	11.6% vs. 6.5%
Female non smokers	39.9%	12.4%
Male non-smokers	26.1%	10.5%
Male smokers	11.1%	6.3%
Females with adenocarcinoma	40.7%	13.3%
Method used for testing	23.1% Real time ARMS PCR vs. 17.8% gene sequencing	9.0% D5F3 IHC vs. 4.9% Break Apart FISH

Conclusion: Real time ARMS-PCR and D5F3 IHC are more sensitive methods for detecting EGFR-M and ALK-R respectively. Prevalence of a targetable driver in North

Indian NSCLC patients ranges from 52.3% amongst female non-smokers to 17.4% of male smokers which are very encouraging results from both the patients and the treating oncologists perspectives. Higher percentage of EGFR-M patients receive targeted therapy as compared to ALK-R.

Keywords: lung cancer, PCR, driver mutation

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-054 EGFR MUTATION WITH ACQUIRED C-MET POSITIVE REVEALS POTENTIAL IMMUNOTHERAPEUTIC VULNERABILITIES

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Background: There are few effective strategies for C-MET positive advance non-small-cell lung cancer(NSCLC) patients with epidermal growth factor receptor(EGFR) inhibitor resistance.The efficacy of PD-1 blockade immunotherapy and even the status of PD-L1 expression in such population is unclear. **Method:** Patients diagnosed as advanced NSCLC synchronously tested for *EGFR* status, expression of PD-L1 and C-MET at the Guangdong Lung Cancer Institute (GLCI) from 2015 to 2017 were collected.PD-L1 expression on tumor cells and immune cell was evaluated using a three-tiered grading system. C-MET positive was define as immunohistochemistry staining (2+/3+) in ≥ 50% of tumor cells. A chi-squared test was used to assess the relationships between C-MET positive and PD-L1 expression. **Result:** A total of 487 eligible cases were selected including 166 *EGFR* mutant and 321 wild type patients.In the general population(n=487),the difference of PD-L1 expression were observed between C-MET positive group and C-MET negative group (65.3% vs 31.7%, P=0.001),which was in accordance with the result from the Cancer Genome Atlas (TCGA) dataset (n=512,P<0.001).Furthermore,among the *EGFR* mutant patients (n=166), PD-L1 expression was showed in 58.1% of C-MET positive group and 28.5% of C-MET negative group,*P value* <0.001. Subsequently,T790M negative was identified in 55%(47/86) of *EGFR* TKI resistant patients (n=86).In this subgroup,a significant increase of PD-L1 expression was demonstrated in C-MET positive group compared to C-MET negative group(66.7% vs 34.6%,P=0.027).Finally, clinical efficacy of immunotherapy was further confirmed in 2 C-MET positive advanced lung adenocarcinoma patients with remarkable response to PD-1 blockade immunotherapy who had disease progression after C-MET inhibitors.

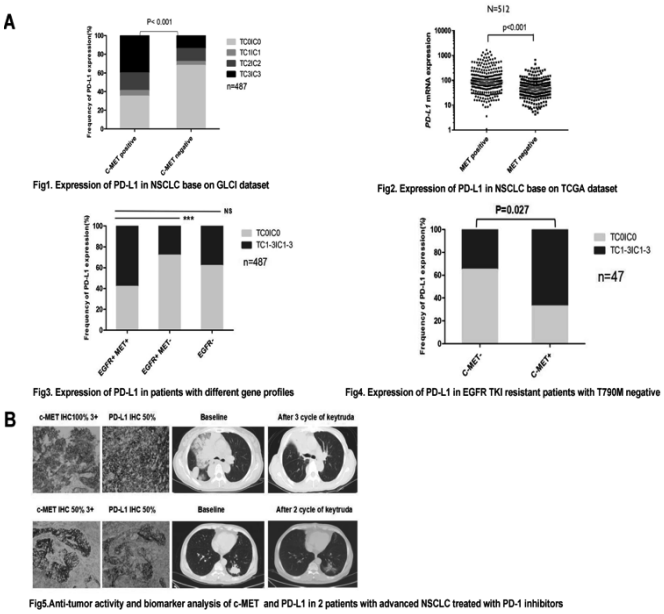

Fig1. Expression of PD-L1 in NSCLC base on GLCI dataset

Fig2. Expression of PD-L1 in NSCLC base on TCGA dataset

Fig3. Expression of PD-L1 in patients with different gene profiles

Fig4. Expression of PD-L1 in EGFR TKI resistant patients with T790M negative

Fig5.Anti-tumor activity and biomarker analysis of c-MET and PD-L1 in 2 patients with advanced NSCLC treated with PD-1 inhibitors

Conclusion: C-MET positive maybe associated with high PD-L1 expression in advanced NSCLC providing therapeutic insight into targeting the PD-1/PD-L1 pathway in EGFR inhibitor-resistant NSCLC with C-MET positive and *T790M* negative.

Keywords: c-Met, non-small cell lung cancer, programmed cell death ligand 1(PD-L1)

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-055 COMPARISON OF AFATINIB VERSUS ERLOTINIB FOR ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS WITH RESISTANCE TO EGFR-TKI

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Background: Afatinib, an irreversible ErbB-family blocker, has shown activity for patients with advanced non-small-cell lung cancer (NSCLC) after failure of gefitinib or/and erlotinib in LUX-LUNG1 trial; however, efficacy data of EGFR-TKI re-challenge with afatinib is insufficient. **Method:** We retrospectively reviewed medical record of the patients with advanced NSCLC harboring EGFR mutation whose disease progressed after the treatment with gefitinib or erlotinib and received EGFR-TKI re-challenge at Kyoto University Hospital between Apr 2008 and Mar 2017, and compared the efficacy of afatinib after the failure of gefitinib or erlotinib and erlotinib after the failure of gefitinib. **Result:** Sixty-two patients were identified, including 13 patients with afatinib and 49 patients with erlotinib. Patient characteristics, such as age, sex, ECOG-PS and smoking status, were not significantly different between the treatment groups. In the afatinib group, 8 patients had received erlotinib as their initial EGFR-TKI and 5 patients had received gefitinib. In the erlotinib group, all patients had received gefitinib as their initial EGFR-TKI. EGFR T790M mutation status was unknown in all patients when EGFR-TKI was re-administrated. Overall response rate (ORR) was 12.7% and disease control rate (DCR) was 54.5% in the entire population. ORR in the afatinib group and the erlotinib group were 7.7% and 14.3%, respectively (p=0.513), and DCR in the afatinib group and the erlotinib group were 61.5% and 52.4%, respectively (p=0.561). Median progression-free survival was 2.4 months in the entire population (95% confidence interval [CI], 1.8-3.3), and 3.9 months in the afatinib group and 2.3 months in the erlotinib group, respectively (hazard ratio [HR] = 0.698 (95% CI, 0.351-1.285), p=0.258). **Conclusion:** Re-challenge with EGFR-TKI demonstrated clinical benefit as previously reported. No significant difference was observed between the efficacy of afatinib after the failure of gefitinib or erlotinib and that of erlotinib after the failure of gefitinib.

Keywords: Erlotinib, Rechallenge, afatinib

P2.03: CHEMOTHERAPY/TARGETED THERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-056 PRIMARY DOUBLE EGFR MUTATIONS T790M AND MUTATION IN EXON 19 OR 21 IN SLOVAKIAB NSCLC PATIENTS - UPDATED SURVIVAL DATA

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Background: Primary EGFR dual mutations comprising T790M and exon 19 or 21 mutation (SM, sensitizing mutations) are rare in the Caucasian population, and there are only limited data about the treatment results with EGFR-TKIs in this setting. In 2016 we published results of the Slovakian retrospective study, in which six cases of the primary EGFR dual mutations T790M and SM were found among 3883 patients with NSCLC tested for EGFR mutations. Here we present the treatment results with updated PFS and OS data. **Method:** In this retrospective multicentre study the databases of the molecular/genetic diagnostic centres were searched for patients with primary dual EGFR mutations T790M and SM. Data about treatment results in these patients were obtained from the databases of the participating institutions and patient files. Kaplan-Meier survival analyses were done with MedCalc software, v. 17.5. **Result:** Patients' characteristics and the treatment results are in the Table. PS was improved after two months of treatment in patients with initial PS over 1, and remained unchanged in those with PS 1. There were no unexpected AEs. Median PFS was 16 months, 95%CI: 12 - 23 months, median OS: 26 months, 95%CI: 18 - 26+ months. Table: Characteristics of patients with primary dual EGFR mutations T790M and SM (sensitizing mutation), and results of treatment with EGFR-TKIs

Gender (M/W)	Age (yrs)	Smoking status	PS	NSCLC histology	Stage	T790M + SM
W	57	Never	3	AC	IV	Del 19
W	64	Never	1	AC	IV	Del 19
W	71	Never	1	AC	IV	Del 19
W	72	Ex	2	AC	IV	Del 19
W	72	Never	1	NOS	IV	Del 19
W	75	Never	1	AC	IV	Del 19

Gender (M/W)	Age (yrs)	Treatment line/TKI	Response	PFS (mo)	OS (mo)
W	57	1st/afatinib	PR	12	28+
W	64	2nd/ erlotinib	SD	16	18
W	71	1st/afatinib	SD	10	17+
W	72	1st/gefitinib	SD	54+	54+
W	72	1st/erlotinib	PR	20	26
W	75	1st/afatinib	SD	24	25

Conclusion: Results in our group of patients with primary dual EGFR mutations T790M and SM treated with first or second generation ERGFR TKIs are comparable with results seen in NSCLC patients with the SM only. The quantitative analysis of these mutations using either the recent tumour tissue or the blood sample is available at present. It might be useful in decision making about the use of the first – second, or the third generation EGFR-TKI, based on the prevailing mutation.

Keywords: T790M, exon 19 mutations, dual mutations, EGFR-TKIs

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-057 EFFECTIVENESS OF ICOTINIB ON UNCOMMON EGFR EXON 20 INSERT MUTATIONS: A763_Y 764INSFQEA IN NON-SMALL-CELL LUNG CANCER

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Background: Clinical features of epidermal growth factor receptor (EGFR) mutations: L858R, deletions in exon 19, T790M, G719X, and L861Q in non-small-cell lung cancer (NSCLC) are well-known. The clinical significance of other uncommon EGFR mutations, such as A763_Y764insFQEA, is not well understood. This study is aimed to improve the understanding of A763_Y764insFQEA, and the clinical response to icotinib of NSCLC patients with such an uncommon mutation. **Method:** Six cases of EGFR exon 20 A763_Y764insFQEA mutation and twelve cases of EGFR exon 20 other insert mutation NSCLC patients were retrospectively analyzed until the progress of the disease or the emergence of the side effects and clinical efficacy was observed after months of followed-up. **Result:** Six cases with EGFR exon 20 A763_Y764insFQEA and twelve cases of EGFR exon 20 other insert mutation NSCLC patients mutation manifested the median PFS (9.0months vs 1.2months, P<0.001). Clinical efficacy of icotinib with advanced NSCLC harboring EGFR exon 20 mutations between A763_Y764insFQEA and other insert mutation (ORR:33.33%, DCR: 100% vs ORR: 0, DCR: 16.16%). **Conclusion:** EGFR exon 20 A763_Y764insFQEA mutation of clinical benefit from icotinib is remarkable, and it close to the common mutation of clinical benefit. It illustrates the value of in-depth molecular testing with NGS of EGFR wild type NSCLC patients.

Keywords: icotinib, uncommon mutation, exon 20

P2.03: CHEMOTHERAPY/TARGETED THERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.03-058 TIGER-3: A PHASE 3 RANDOMIZED STUDY OF ROCILETINIB VS CHEMOTHERAPY IN EGFR-MUTATED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Rociletinib, an oral, irreversible tyrosine kinase inhibitor (TKI), selectively targets activating mutations in *EGFR* and the acquired resistance mutation T790M and demonstrated antitumor activity in the phase 1/2 TIGER-X study (NCT01526928). Initial results are reported from the TIGER-3 study (NCT02322281) of rociletinib vs chemotherapy in EGFR TKI-resistant patients with *EGFR*-mutated NSCLC. **Method:** Eligibility criteria included: metastatic or unresectable, locally advanced, *EGFR*-mutated NSCLC; radiological progression on most recent TKI therapy; ≥1 line of platinum doublet chemotherapy. Patients were not selected based on T790M status. Patients (N=900) were to be randomized (1:1:1) to rociletinib 500 or 625 mg BID or investigator's choice of chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel). The primary endpoint was investigator-assessed progression-free survival (PFS) (RECIST v1.1); objective response rate (ORR) was a secondary endpoint. The rociletinib dosing groups were combined and compared with chemotherapy in a step-down procedure (patients with a centrally confirmed T790M mutation, followed by all randomized patients). **Result:** TIGER-3 enrollment was halted upon discontinuation of rociletinib development in NSCLC in 2016; therefore, target enrollment was not achieved. TIGER-3 enrolled 75 patients in the rociletinib groups [500 mg BID, n=53; 625 mg BID, n=22] and 74 in the chemotherapy group. Median age was 62 years, 69.1% had ECOG Performance Status of 1, 39.6% were Asian, 58.4% were female, and median number of prior therapies was 3. PFS and ORR data are presented in the Table. The most common adverse events (all grade; grade ≥3) in the rociletinib group were diarrhea (62.7%; 2.7%), hyperglycemia (58.7%; 24.0%), nausea (37.3%; 4.0%), fatigue (37.3%; 8.0%), and decreased appetite (37.3%; 0%) and in the chemotherapy group were nausea (27.4%; 5.5%), anemia (24.7%; 2.7%), and fatigue (24.7%; 9.6%).

Outcome	Centrally Confirmed T790MPositive		Centrally Confirmed T790MNegative		Intent-to-Treat Population*	
	Rociletinib† (n=25)	Chemotherapy (n=20)	Rociletinib† (n=36)	Chemotherapy (n=41)	Rociletinib† (n=75)	Chemotherapy (n=73)
Median PFS, mo (95% CI)	6.8 (3.7–12.2)	2.7 (1.3–7.0)	4.1 (2.5–4.6)	1.4 (1.3–2.7)	4.1 (2.8–5.5)	2.5 (1.4–2.9)
HR (95% CI)	0.570 (0.285–1.140); P=0.105		0.532 (0.322–0.878); P=0.011		0.609 (0.423–0.875); P=0.006	
Confirmed ORR, n (%) [95% CI]	9 (36.0) [18.0%–57.5%]	3 (15.0) [3.2%–37.9%]	3 (8.3) [1.8%–22.5%]	2 (4.9) [0.6%–16.5%]	13 (17.3) [9.6%–27.8%]	6 (8.2) [3.1%–17.0%]

*Includes patients with undetermined T790M mutation status. †Rociletinib 500 mg BID and 625 mg BID dose groups were pooled for the analysis. CI, confidence interval; HR, hazard ratio.

Conclusion: Incomplete enrollment precluded hypothesis testing. However, the data show a trend toward longer PFS and higher ORR with rociletinib.

Keywords: non-small cell lung cancer, EGFR Inhibitor, T790M

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-001 BALTIC: A PHASE 2, OPEN-LABEL STUDY OF NOVEL COMBINATIONS OF IMMUNOTHERAPIES OR DDR INHIBITORS IN PLATINUM-REFRACTORY ED-SCLC

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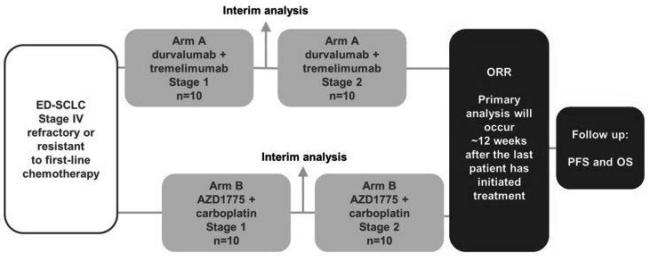
Background: Immunotherapy and DNA damage repair inhibitors have the potential to play a role in the treatment of patients with extensive-disease small cell lung cancer (ED-SCLC), due to high mutation load and genomic instability in this disease setting. Durvalumab, a selective, high-affinity, engineered human IgG1 mAb blocks PD-L1 binding to PD-1 and CD80. Tremelimumab is a selective human IgG2 mAb targeting CTLA-4. Durvalumab plus tremelimumab demonstrated clinical activity and manageable tolerability in a Phase 1b study in NSCLC (NCT02000947). AZD1775, a small-molecule inhibitor of DNA damage checkpoint kinase WEE1, potentiates genotoxic chemotherapies. AZD1775 plus carboplatin showed antitumor activity and acceptable safety in a Phase 2 study in platinum-refractory p53-mutated ovarian cancer (NCT01164995). **Method:** BALTIC (NCT02937818) is a Phase 2, open-label, multicenter, multi-arm, exploratory, signal-searching study to assess the preliminary activity of novel treatment combinations in patients with platinum-refractory/resistant ED-SCLC. Inclusion criteria include disease progression during, or within 90 days of completing, first-line platinum-based chemotherapy; WHO/ECOG performance status of 0/1; and life expectancy ≥8 weeks. Each study arm is independent and will open sequentially to enroll up to 20 patients. The study will open initially with two arms. Patients will receive durvalumab 1500 mg + tremelimumab 75 mg i.v. q4w for 4 doses, followed by durvalumab monotherapy 1500 mg i.v. q4w (Arm A); and oral AZD1775 225 mg bid for 2.5 days from Day 1 + carboplatin AUC 5 on Day 1 i.v. q3w (Arm B). Treatment will continue until confirmed disease progression or discontinuation. Further arms will be added to assess other combinations once tolerable dosing regimens have been established. The primary endpoint is investigator-assessed ORR (RECIST v1.1). Secondary endpoints include duration of response, disease control rate, time-to-response, PFS, OS, pharmacokinetics, safety and tolerability. Gene expression levels and biomarkers will also be explored. Recruitment is ongoing.



Result: Section not applicable **Conclusion:** Section not applicable

Keywords: Immune checkpoint inhibitors, DNA damage repair inhibitors, SCLC

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-002 CASPIAN: PHASE 3 STUDY OF FIRST-LINE DURVALUMAB ± TREMELIMUMAB + PLATINUM-BASED CHEMOTHERAPY VS CHEMOTHERAPY ALONE IN ED-SCLC

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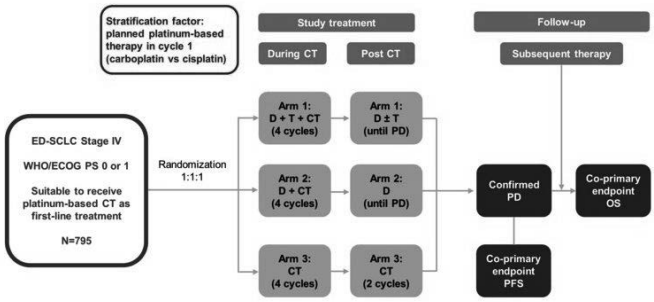
Background: New therapies are urgently needed for patients with extensive-disease small cell lung cancer (ED-SCLC). High mutation burden in SCLC suggests a potential role for immune checkpoint blockade. Durvalumab is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Tremelimumab is a selective human IgG2 mAb against CTLA-4. Durvalumab ± tremelimumab in combination with chemotherapy has shown acceptable tolerability and evidence of clinical activity in a Phase 1b study (NCT02537418) in patients with advanced solid tumors, including NSCLC and SCLC. **Method:** CASPIAN (NCT03043872) is a Phase 3, randomized, multicenter, open-label, global study investigating the combination of first-line chemotherapy with durvalumab ± tremelimumab in Stage IV ED-SCLC. Treatment-naïve patients (N=795) will be randomized 1:1:1 to receive durvalumab 1500 mg + tremelimumab 75 mg i.v. q3w + chemotherapy (Arm 1); durvalumab 1500 mg i.v. q3w + chemotherapy (Arm 2); or chemotherapy alone (Arm 3). Durvalumab ± tremelimumab will be concurrently administered with chemotherapy in Arms 1 and 2 and will continue post chemotherapy (one further dose for tremelimumab; until disease progression for durvalumab). Chemotherapy (etoposide with either carboplatin or cisplatin) will be given for up to 4 cycles in Arms 1 and 2 and up to 6 cycles in Arm 3. Co-primary endpoints are OS and PFS using blinded independent central review (RECIST v1.1; Arm 1 vs Arm 3). Secondary endpoints include OS and PFS (Arm 2 vs Arm 3, Arm 1 vs Arm 2); ORR; 18-month OS; proportion of patients alive and progression-free at 6 and 12 months; pharmacokinetics; immunogenicity; HRQoL; safety and tolerability. An independent data monitoring committee will meet at two early stages of enrolment to confirm the safety and tolerability of the proposed combination dosing regimen and will monitor safety every 6 months thereafter. Recruitment is ongoing.



CT, chemotherapy; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; T, tremelimumab; WHO, World Health Organization.

Result: Section not applicable **Conclusion:** Section not applicable

Keywords: SCLC, tremelimumab, durvalumab

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-003 PHASE II TRIAL OF X-396 (ENSARTINIB) FOR CHINESE PATIENTS WITH ALK (+) NON–SMALL-CELL LUNG CANCER WHO PROGRESSED ON CRIZOTINIB

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Background: Crizotinib has been established as the standard first-line treatment for patients with ALK-rearranged non-small-cell lung cancer. However, despite its superiority to chemotherapy, resistance occurs within approximately 12 months. New ALK-inhibitors are needed to overcome the resistance to crizotinib and to increase drug penetration to CNS. X-396 (ensartinib) is a novel, potent ALK tyrosine kinase inhibitor (TKI). Its phase I/II study showed X-396 is well-tolerated with favorable anti-tumor activities in both ALK TKI-naïve and crizotinib-resistant NSCLC patients, as well as patients with CNS metastases. The recommended phase II dose (RP2D) was established at 225 mg, once daily. **Method:** A phase II, multi-center study is evaluating the efficacy and safety of single-agent X-396 in Chinese patients with ALK (+) non–small-cell lung cancer after progression on crizotinib. Eligible patients will have documentation of a positive ALK rearrangement and progression on crizotinib. X-396 225 mg is orally administered until disease progression or intolerable toxicity. The primary endpoint is RECIST 1.1 response rate. Secondary endpoints include PFS, duration of response, and safety. The sample size is calculated using the test for inequality method, assuming that X396 have an ORR of 50% in patients with ALK-positive NSCLC, 15% higher than that from existing second-line therapy. Therefore, up to 144 patients will be enrolled with a significance level and power of 5% and 90%, respectively. Recruitment will be started on September, 2017. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: crizotinib, X-396 (ensartinib), ALK-rearranged non-small-cell lung cancer

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-004 IMPOWER010: A PHASE III STUDY OF ATEZOLIZUMAB VS BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CHEMOTHERAPY IN COMPLETELY RESECTED NSCLC

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Background: Atezolizumab is an anti–PD-L1 mAb that blocks PD-L1 from interacting with its receptors PD-1 and B7.1 and restores anti-cancer immunity. In patients with 2L/3L advanced NSCLC, the OAK trial showed improved mOS in the atezolizumab arm (13.8 mo) vs the docetaxel arm (9.6 mo), with survival benefit observed across all PD-L1 expression levels on tumor cells (TC) or tumor-infiltrating immune cells (IC). In patients with fully resected NSCLC (stages IB [tumors ≥ 4 cm]-IIIA), adjuvant chemotherapy remains the standard of care, but survival benefit is limited. Therefore, more effective therapies are still needed for patients with early-stage NSCLC. IMpower010 (NCT02486718) is a global Phase III, randomized, open-label trial conducted to evaluate the efficacy and safety of atezolizumab vs best supportive care (BSC) following adjuvant cisplatin–based chemotherapy in patients with resected stage IB (tumors ≥ 4 cm)-IIIA NSCLC. **Method:** Eligibility criteria include complete tumor resection 4-12 weeks prior to enrollment for pathological stage IB (tumors ≥ 4 cm)-IIIA NSCLC, adequate recovery from surgery, ability to receive cisplatin-based adjuvant chemotherapy and ECOG PS 0-1. Patients with other malignancies, autoimmune disease, hormonal cancer or radiation therapy within 5 years and prior chemotherapy or immunotherapy will be excluded. Approximately 1127 patients will be enrolled regardless of PD-L1 status. Patients will receive up to four 21-day cycles of cisplatin-based chemotherapy (cisplatin [75 mg/m^2 IV, day 1] + vinorelbine [30 mg/m^2 IV, days 1, 8], docetaxel [75 mg/m^2 IV, day 1] or gemcitabine [1250 mg/m^2 IV, days 1, 8], or pemetrexed [500 mg/m^2 IV, day 1; only non-squamous NSCLC]). Adjuvant radiation therapy is not permitted. Eligible patients will be randomized 1:1 to receive 16 cycles of atezolizumab 1200 mg q3w or BSC post-adjuvant chemotherapy. Stratification factors include sex, histology (squamous vs non-squamous), disease stage (IB vs II vs IIA) and PD-L1 status by IHC (TC2/3 [≥ 5% expressing PD-L1] and any IC vs TC0/1 [< 5%], and IC2/3 vs TC0/1 and IC0/1 [< 5%]). The primary endpoint is disease-free survival, and secondary endpoints include OS and safety. Exploratory biomarkers will be evaluated, including PD-L1 expression and immune- and tumor-related biomarkers before, during and after treatment with atezolizumab and at radiographic disease recurrence or confirmation of new primary NSCLC. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: adjuvant NSCLC, atezolizumab, clinical trials

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-005 GEOMETRY MONO-1: PHASE II, MULTICENTER STUDY OF MET INHIBITOR CAPMATINIB (INC280) IN EGFR WT, MET-DYSREGULATED ADVANCED NSCLC

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M. Hochmair[14], E. Felip[15], N. Reguart[16], M. Thomas[17], T. Overbeck[18], K. Ohashi[19], M. Giovannini[20], R. Yura[21], A. Joshi[21], M. Akimov[20], R. Heist[22]

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Background: Amplification of *MET* leading to oncogenic signaling occurs in 3-5% of newly diagnosed *EGFR* wild type (wt) non-small cell lung cancer (NSCLC) cases with decreasing incidence at higher levels of amplification. Mutations in *MET* leading to exon 14 deletion (*MET*Δ^{ex14}) also occur in 2–4% of adenocarcinoma and 1–2% of other NSCLC subsets. Capmatinib (INC280) is a potent and selective MET inhibitor that has shown strong evidence of antitumor activity in a phase I study in patients with *EGFR* wt advanced NSCLC harboring *MET* amplification and *MET*Δ^{ex14}. **Method:** This phase II, multicenter study (NCT02414139) was designed to confirm the clinical activity of capmatinib in patients with advanced NSCLC by *MET* amplification and *MET*Δ^{ex14} status. Eligible patients (≥18 years of age, Eastern Cooperative Oncology Group Performance Status 0–1) must have *ALK*-negative, *EGFR* wt, stage IIIB/IV NSCLC (any histology). Centrally assessed *MET* amplification (gene copy number [GCN]) and mutation status is used to assign patients to one of the below cohorts: **Pretreated with 1–2 prior systemic lines of therapy for advanced setting (cohorts 1–4):** 1a: *MET* amplification GCN ≥10 (n=69) 1b: *MET* amplification GCN ≥6 and <10 (n=69) 2: *MET* amplification GCN ≥4 and <6 (n=69) 3: *MET* amplification GCN <4 (n=69) 4: *MET*Δ^{ex14} mutation regardless of *MET* GCN (n=69) **Treatment naïve (cohorts 5a and 5b):** 5a: *MET* amplification GCN ≥10 and no *MET*Δ^{ex14} mutation (n=27) 5b: *MET*Δ^{ex14} mutation regardless of *MET* GCN (n=27) Capmatinib 400 mg tablets are orally administered twice daily on a continuous dosing schedule 12 hours apart. Primary and key secondary endpoints are overall response rate (ORR) and duration of response (DOR), respectively (blinded independent review assessment). Other secondary endpoints include investigator-assessed ORR, DOR, time to response, disease control rate, progression-free survival (independent and investigator assessment), safety, and pharmacokinetics. Enrollment is ongoing in 25 countries. Cohorts 1b, 2, and 3 are now closed to enrollment; cohorts 1a and 4 continue to enroll patients who have received 1–2 prior lines of therapy in the advanced setting, and cohorts 5a and 5b are open for enrollment of treatment-naïve patients. Responses have been seen in both *MET*-amplified and *MET*-mutated patients irrespective of the line of therapy. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: advanced NSCLC, MET inhibitor, Capmatinib (INC280)

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P2.04-006 ADAURA: PHIII, DOUBLE-BLIND, RANDOMIZED STUDY OF OSIMERTINIB VS PLACEBO IN EGFR MUTATION-POSITIVE NSCLC POST-TUMOR RESECTION

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Background: EGFR-TKIs are standard first-line therapy in patients with EGFR sensitizing mutation (EGFRm)-positive advanced NSCLC. EGFR T790M resistance mutation is observed in >50% of patients with acquired resistance to EGFR-TKIs. Osimertinib is a third-generation, irreversible, CNS-active EGFR-TKI selective for EGFRm and T790M, recommended in patients with T790M-positive advanced NSCLC who have progressed on first-line EGFR-TKIs. In a recent study (NCT01405079), gefitinib treatment in patients with resected EGFRm-positive NSCLC significantly increased disease-free survival (DFS) vs vinorelbine+cisplatin: median 28.7 vs 18.0 months (hazard ratio 0.60 (95% CI 0.42–0.87), p=0.005), warranting further investigation of EGFR-TKIs in this setting (Wu et al, J Clin Oncol 2017;35:suppl;abs8500). Osimertinib may prolong DFS in adjuvant EGFRm-positive NSCLC. **Method:** Trial Design ADAURA (NCT02511106) is a global, Phase III, double-blind, randomized study, assessing efficacy and safety of osimertinib vs placebo in patients with stage IB–IIIA non-squamous EGFRm-positive NSCLC with complete tumor resection. Approximately 700 patients from 210 sites will be randomized. A planned 60% of patients will be recruited from Asia, 40% from non-Asian countries; 70% stage II–IIIA, 30% stage IB. Patients must be adults ≥18 years (Japan/Taiwan: ≥20) with primary NSCLC staged post-operatively as IB/II/IIIA, and central confirmation of Ex19del or L858R (alone or combined with other EGFR mutations including T790M). Complete surgical resection of the primary NSCLC is mandatory; patients will have baseline CT scans within 28 days prior to treatment confirming radiographic absence of residual disease. Complete surgical recovery is required for randomization; treatment to start at least 4 weeks following surgery. Patients who have received radiation therapy, pre-operative chemotherapy, prior anticancer therapy or neoadjuvant/adjuvant EGFR-TKI treatment are exempt. Standard post-operative adjuvant chemotherapy, consisting of a platinum-based doublet for 4 cycles maximum, is allowed; no more than 10 and 26 weeks may have elapsed between surgery and randomization for patients who have not or have received adjuvant chemotherapy, respectively. Patients will be randomized 1:1 to once-daily osimertinib 80 mg or placebo and stratified by stage (IB/II/IIIA), mutation type (Ex19Del/L858R) and race (Asian/non-Asian). Treatment may continue for 3 years in absence of discontinuation criteria including disease recurrence. Primary objective is to assess the efficacy of osimertinib vs placebo, measured by investigator-assessed DFS. Secondary objectives include assessment of the safety profile of osimertinib vs placebo; DFS rate at 2, 3, 5 years; overall survival (OS); 5-year OS rate; health-related quality of life; pharmacokinetics. Estimated primary completion date (final DFS data collection date): July 2021. **Result:** Section not applicable. **Conclusion:** Section not applicable.

Keywords: osimertinib, NSCLC, EGFR-TKI

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-007 KEYNOTE-604: PHASE 3 RANDOMIZED, DOUBLE-BLIND TRIAL OF PEMBROLIZUMAB/PLACEBO PLUS ETOPOSIDE/PLATINUM FOR EXTENSIVE STAGE-SCLC

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Background: Therapeutic options for small-cell lung cancer (SCLC) remain limited, with etoposide/platinum (EP) as the standard first-line chemotherapy regimen. However, patients with extensive-stage (ES)-SCLC experience high relapse rates within months after initial therapy. Pembrolizumab, a humanized monoclonal antibody against PD-1, has shown antitumor activity as monotherapy in heavily pretreated patients with PD-L1–positive SCLC in the phase 1b KEYNOTE-028 study. KEYNOTE-604 (ClinicalTrials.gov, NCT03066778) evaluates EP plus either pembrolizumab or placebo as first-line therapy for ES-SCLC. **Method:** Section not applicable **Result:** Section not applicable **Conclusion:** In this international, double-blind, phase 3 trial, adults with newly diagnosed ES-SCLC, ECOG PS ≤1, and no previous systemic therapy for SCLC are randomized 1:1 to receive either EP plus a 200-mg fixed dose of pembrolizumab intravenously (IV) once every 3 weeks (Q3W) or EP plus placebo IV Q3W. Randomization is stratified by the chosen platinum therapy (carboplatin vs cisplatin), ECOG PS (0 vs 1), and baseline lactate dehydrogenase concentration (≤ upper limit of normal [ULN] vs > ULN). Study treatment includes a total of 4 cycles of EP and 2 years of pembrolizumab/placebo and continues until documented PD, intolerable toxicity, or withdrawal of consent. Patients with a response after 4 cycles of EP plus placebo or pembrolizumab may receive prophylactic cranial irradiation. Patients who complete 2 years of pembrolizumab treatment or stop pembrolizumab for reasons other than PD/intolerability, but subsequently have documented PD confirmed by blinded independent review, may receive an additional 1 year of pembrolizumab provided that no other systemic therapy has been administered. Patients must meet the eligibility criteria for retreatment; patients in the placebo arm are not eligible for treatment with pembrolizumab at the time of PD. Tumor response is assessed every 6 weeks for 48 weeks, and every 9 weeks thereafter by RECIST version 1.1 by blinded independent central review. AEs occurring during treatment and 30 days thereafter (90 days for serious AEs) are graded per Common Terminology Criteria for Adverse Events, version 4.0. Primary endpoints are PFS and OS. Secondary endpoints are ORR, duration of response, safety, and patient-reported outcomes. Approximately 430 patients will be enrolled.

Keywords: KEYNOTE-604, pembrolizumab, small-cell lung cancer

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P2.04-008 ATLANTIS: PHASE III STUDY OF PM01183 WITH DOXORUBICIN VS. CAV OR TOPOTECAN IN SMALL-CELL LUNG CANCER AFTER PLATINUM THERAPY

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Background: Lurbinectedin (PM01183) is a new compound that blocks active transcription, produces DNA breaks and apoptosis, and affects the inflammatory microenvironment. First signs of synergism with doxorubicin (DOX) and responses, especially in relapsed small cell lung cancer (SCLC) (overall response rate [ORR] ~67%, including about 10% of complete responses [CR]), were reported in a phase I expansion cohort in 21 second-line SCLC patients (ASCO 2015, abstract 7509). Main toxicity was hematological. A lower dose was used to improve safety, and activity was confirmed in an expansion cohort of 27 patients with relapsed SCLC (~37%, with 4% of CR) **Method:** Multinational (20 countries), multicenter (154 sites), open-label, randomized phase III study of PM01183/DOX *vs.* a control arm with investigator choice of either standard cyclophosphamide, DOX and vincristine (CAV) or topotecan (T). A total of 600 patients will be randomized (1:1) and stratified according to ECOG performance status (PS), central nervous system (CNS) involvement, previous treatment with antiPD1/antiPD-L1, chemotherapy-free interval and investigator´s choice of control arm. Patients with clinical benefit after 10 cycles of the combination

could continue with single-agent PM01183 or CAV, until progressive disease or unacceptable toxicity. An interim safety analysis by an independent data monitoring committee (IDMC) is planned when the first 150 patients have been randomized. Most relevant inclusion criteria includes: age ≥18 years and confirmed diagnosis of SCLC (if primary site is unknown, the patient will be eligible if Ki-67 expression >50%), mandatory previous platinum-containing line (additional immunotherapy is allowed), ECOG PS 0-2, and adequate major organ function (including LVEF >50%). Patients are excluded if chemotherapy-free interval is <30 days, pre-treated with PM01183, DOX or T, symptomatic or steroids-requiring CNS involvement, or any medical condition that might preclude safe compliance with study treatment. Primary objective is to determine a difference in progression-free survival (RECIST v.1.1) by independent review committee. Secondary endpoints include overall survival, survival rates at 12/18/24 months, antitumor response (RECIST v.1.1), duration of response, quality of life, safety, subgroup analyses and pharmacokinetics of PM01183/DOX. **Result:** The first patient was included in August 2016. An interim safety analysis, requested by the IDMC, was conducted on the first 50 patients randomized and treated with 2 cycles, and resulted in a recommendation to continue the trial unmodified. **Conclusion:** The ATLANTIS randomized phase III study is currently ongoing. Trial recruitment is expected to be completed at Q1 2018.

Keywords: SCLC, Lurbinectedin, Second Line

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P2.04-009 RANDOMIZED, SINGLE-BLIND PHASE 1 STUDY OF PHARMACOKINETIC EQUIVALENCE OF ABP 215 RELATIVE TO BEVACIZUMAB IN JAPANESE SUBJECTS

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Background: ABP 215 is a proposed biosimilar that is similar to bevacizumab, a VEGF inhibitor, in analytical and functional comparisons. Pharmacokinetic (PK) similarity between ABP 215 and bevacizumab has been demonstrated in a separate phase 1 study. Here we present results from a phase 1 study demonstrating PK similarity between ABP 215 and bevacizumab in healthy adult Japanese men. **Method:** PK similarity was evaluated in a randomized, single-blind, single-dose, parallel-group study in healthy Japanese men comparing ABP 215 with EU-authorized bevacizumab. Primary endpoints were maximum observed serum concentration (C_{max}) and area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}). Secondary endpoints included AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}), safety, tolerability, and immunogenicity. **Result:** Baseline characteristics were similar among the 48 subjects (n=24 in each group). PK similarity was demonstrated for the comparison of ABP 215 with bevacizumab. After 3 mg/kg intravenous infusion, the geometric means (GMs) of C_{max}, AUC_{inf}, and AUC_{last} were 71.2 µg/mL, 25259 µg·h/mL, and 22499.3 µg·h/mL for ABP 215 and 70.16 µg/mL, 25801µg·h/mL, and 22604.6 µg·h/mL for bevacizumab respectively. The GM ratios for C_{max}, AUC_{inf}, and AUC_{last} were 1.015 (90% confidence interval; CI, 0.946–1.088), 0.979 (90% CI, 0.914–1.049), and 0.995 (90% CI, 0.941–1.053) for ABP 215 vs bevacizumab respectively. All CIs fell within the prespecified bioequivalence criteria of 0.80–1.25. The incidence of treatment-emergent adverse events (TEAEs) was comparable between treatment groups. Adverse events (AEs) occurred in 2/24 subjects receiving ABP 215 and 1/24 subjects receiving bevacizumab. There were no deaths, no serious AEs or AEs leading to study discontinuation; no subject was positive for binding antidrug antibodies (ADAs) at any time point during the study. **Conclusion:** ABP 215 was shown to have similar pharmacokinetics compared with bevacizumab in this PK study in Japanese men; CIs were within the standard bioequivalence criteria of 0.80–1.25. Safety was comparable between the two groups; no subjects developed binding ADAs.

Keywords: Biosimilar, bevacizumab, pharmacokinetic equivalence

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-010 AFATINIB IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH STAGE IIIB/IV SQUAMOUS CELL CARCINOMA (SCC) OF THE LUNG

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Background: Afatinib has demonstrated progression-free survival (PFS) and overall survival (OS) improvements in patients with squamous cell carcinoma (SCC) of the lung; pembrolizumab also showed encouraging PFS/OS in lung SCC. Afatinib is a selective and irreversible ErbB family blocker that effectively inhibits signaling from all homo- and heterodimers formed by ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4. Pembrolizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody with high affinity and potent receptor-blocking activity for the programmed cell death 1 (PD-1) receptor. Concurrent inhibition of PD-1 and EGFR pathways represents a rational and promising approach for EGFR-driven tumors such as SCC of the lung, to increase the rate and duration of response, and delay the development of resistance, as single-agent efficacy can be moderate and more treatment options are needed. This trial assesses the efficacy and safety of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) who progressed during or after first-line platinum-based treatment. **Method: Trial design:** Study 1200.283 (NCT03157089. LUX-Lung IO / Keynote 497) is a phase II, open-label, non-randomized single-arm study. Eligible patients have locally advanced or metastatic squamous NSCLC and have progressed during/after first-line platinum-based chemotherapy. Patients must have adequate organ function and ECOG PS 0/1. Prior treatment with immune checkpoint inhibitors or EGFR targeted therapy is prohibited. A safety run-in will be performed using afatinib once daily (starting dose 40 mg) in combination with pembrolizumab, (200 mg fixed dose once every 3 weeks, administered intravenously) to assess the safety profile and confirm the recommended Phase II dose (RP2D). In the main part of the trial, afatinib at the RP2D, in combination with pembrolizumab, may be continued for a maximum of 35 cycles (~2 years). After study completion, further therapy will be decided by the investigator and may include afatinib. Dose reduction of afatinib to 30 mg or 20 mg will be permitted in the case of adverse events. The primary endpoint is investigator assessed objective response (complete response [CR] or partial response [PR] according to RECIST v1.1). Secondary/further endpoints are disease control (CR, PR, or stable disease), duration of objective response, PFS, OS, tumor shrinkage, RP2D, and pharmacokinetics. Exploratory biomarker analysis will also be performed. This study will be conducted in the US, Spain, France, Korea, and Turkey, and will open for enrollment in September 2017; target enrollment is 50-60 patients. **Result:** Not applicable **Conclusion:** Not applicable

Keywords: squamous NSCLC, afatinib, pembrolizumab

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-011 THE USING OF LUNGCARE ELECTROMAGNETIC NAVIGATED BRONCHOSCOPY SYSTEM IN LUNG LESIONS, A NEW PROJECT IN CHINA

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Background: With the application of low dose computed tomography in screening lung cancer for high-risk population, more peripheral pulmonary lesions are found which need to be diagnosed or treated. Traditional methods include transthoracic needle aspiration (TTNA) or transbronchial lung biopsy (TBLB) are not recommended nowadays because of its low diagnostic rate, more complications and high radiation dose for patients. Moreover, they lack real-time navigation system for guiding bronchoscope to the distal lesion where traditional methods hardly reach and highly depends on operators with knowledge of CT scans. Electromagnetic navigated bronchoscopy (ENB) has proven to be a novel technology, including electromagnetic tracking, virtual bronchoscopic navigation and CT reconstruction technologies. Only two commercial ENB systems have been approved by FDA in the United States. And more than 1,000 medical institutions have been equipped with ENB in Europe and the United States. As of the end of June 2016, more than 10 imported ENB systems were installed in China. **Method:** This project has been supported by the ministry of science and technology of the People's Republic of China in 2017(2017YFC0112700). This project will utilize the domestic LungCare ENB system and its improved version to carry out five innovative sub-projects. These projects will cover all the issues of ENB on the early peripheral lung cancers (Stage IA), including the diagnosis, localization and treatment. **Result:** First, the project will utilize the CFDA approved LungCare ENB system to perform a large, prospective, multicenter, randomized study, which aims to enroll up to total 1362 consecutive subjects presenting for evaluation (diagnosis, localization and treatment) of lung lesions utilizing the ENB procedure at up to 3 clinical sites. Second, LungCare ENB system will upgrade their products and develop two new navigation systems including the transthoracic electromagnetic navigation system(TTEN) and the video assisted thoracoscopic surgery electromagnetic navigation system (VATS-EN). Two clinical studies will be performed in 3 clinical sites individually. **Conclusion:** LungCare ENB total solution including ENB, TTEN and VATS-EN, will extend their electromagnetic navigation system of the single use from the bronchus to the thoracic wall, and even through the thoracoscope. The value of the project will form the whole-lung electromagnetic navigation system and focus on the accurate diagnose, localization and treatment of early peripheral lung cancer.

Keywords: Peripheral pulmonary lesions, Electromagnetic navigated bronchoscopy

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-012 FIRST-LINE ENSARTINIB (X396) VERSUS CRIZOTINIB IN ADVANCED ALK-REARRANGED NSCLC (EXALT3): A RANDOMIZED, OPEN-LABEL, PHASE 3 STUDY

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Holding Company, Florida/US,[6]Betta Pharmaceuticals Co, Ltd, Hangzhou/CN,[7]Vanderbilt–Ingram Comprehensive Cancer Center, Nashville/TN/US

Background: Ensartinib (X-396) is a novel, potent ALK TKI with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK. Its phase 1/2 study (NCT01625234) demonstrated that ensartinib is well-tolerated and induces favorable responses in both crizotinib-naïve (ORR 80%) and crizotinib-resistant ALK+ NSCLC patients (ORR 71%), as well as those with CNS metastases. **Method:** In this global, phase 3, open-label, randomized study (eXalt3), 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 Pacific/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 was 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. **Result:** Progress report Phase 3 recruitment began in June, 2016 and currently has 66 active sites in 21 countries. The duration of recruitment will be approximately 24 months. This study is registered with ClinicalTrials.Gov as NCT02767804. **Conclusion:** Section not applicable

Keywords: ensartinib (X-396), first-line, anaplastic lymphoma kinase (ALK)

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-013 ELEVATION:NSCLC-101 – A PHASE 1B STUDY OF PDR001 COMBINED WITH CHEMOTHERAPY IN PD-L1 UNSELECTED, METASTATIC NSCLC PATIENTS

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Background: PDR001 is a high-affinity, humanized antiprogramed cell death-1 (PD-1) antibody that blocks interaction with programmed cell death ligands, PD-L1 and PD-L2. Results from phase 1/2 study have shown that PDR001 has a manageable safety profile and preliminary antitumor activity in advanced solid tumors. ElevatION:NSCLC-101 is the first study to evaluate the safety and preliminary efficacy of PDR001 plus platinum-doublet chemotherapy in patients with PD-L1 unselected, advanced NSCLC. **Method:** ElevatION:NSCLC-101 is an open-label, multicenter, phase 1b study (NCT03064854) of PDR001 plus platinum-doublet chemotherapy in patients (≥18 years) with squamous or nonsquamous, stage IIIB (not a candidate for definitive multimodality therapy) or stage IV or relapsed locally advanced or metastatic NSCLC, lacking EGFR-sensitizing mutation and/or ALK- or ROS1-rearrangements. Other inclusion criteria: ECOG PS 0-1, ≥1 measurable lesion (per RECIST v1.1), relapse for >12 months from the end of neoadjuvant or adjuvant systemic therapy. PD-L1 expression will be assessed but will not be used to determine eligibility. This study comprises 2 parts (dose-confirmation and dose-expansion) and 4 treatment groups (A, B, C, and D). Groups A, B, and C (dose-confirmation and dose-expansion parts) will include treatment-naïve patients. Group D (dose-expansion part) will include second line patients – those who have received only 1 prior systemic therapy consisting of a PD-1 and/or PD-L1 inhibitor ± CTLA-4 inhibitor (last dose of prior immunotherapy, ≥6 weeks prior to start of study treatment). The treatment-naïve patients will receive gemcitabine/cisplatin (group A) or pemetrexed/cisplatin (group B) or paclitaxel/carboplatin (group C) plus PDR001 (initially 300 mg q3w; if intolerable, a provisional dose level (–1) of 300 mg q6w will be explored) for up to 4 cycles followed by maintenance with PDR001 ± pemetrexed (group B). The second-line patients (group D) will be randomized (1:1) to either platinum-doublet chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) alone/combined with PDR001. Primary endpoints: dose-confirmation part – MTD and/or recommended dose for expansion (DLTs during first 6 weeks of therapy; for groups A, B, and C); dose-expansion part – investigator-assessed ORR per RECIST v1.1 (for groups A, B, and C). Secondary endpoints: ORR (for group D); PFS, DCR, DOR, TTR (for groups A, B, C, and D); OS, PK, and safety. The study enrollment is still ongoing. Approximately 6 to 20 treatment-naïve patients will be assigned to each group (A, B, C) and once MTD/RDE is established, ~20 additional patients will be enrolled in each treatment group; ~60 pretreated patients will be enrolled in group D. **Result:** Not-applicable. **Conclusion:** Not-applicable.

Keywords: NSCLC, PDR001, chemotherapy

P2.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.04-014 COMPUTING THE IMPACT OF IMMUNOTHERAPY ON NSCLC LANDSCAPE: THE ADVANCED NON-SMALL CELL LUNG CANCER HOLISTIC REGISTRY (ANCHOR)

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Background: Anti-PD-1 and anti-PD-L1 antibodies including pembrolizumab, nivolumab and atezolizumab have entered clinical practice in the management of metastatic NSCLC as monotherapy and immunotherapy-based combinations. We have established a real-world Advanced Non-Small Cell Lung Cancer Holistic Registry (ANCHoR) to understand how the emergence of immunotherapy impacts choice of treatment, clinical outcomes, and patient reported outcomes (PROs) in the different histo-molecular subtypes of metastatic NSCLC. The objectives of ANCHoR are to determine the treatment choice and treatment sequence by PD-L1 status in the various histo-molecular categories of NSCLC and to understand the impact of such treatment choice on response rates, progression-free survival (PFS), and overall survival (OS). Additionally we will measure the impact the treatment choices have on the PROs by utilizing the validated instruments, EuroQol-5D version 5L (EQ-5D-5L) and MD Anderson Symptom Inventory module specific to lung cancer (MDASI-LC). **Method:** The study will enroll patients with metastatic NSCLC diagnoses who are treated at MD Anderson Cancer Center (MDA) between January 1, 2017 and December 31, 2020. The study period will end on June 30, 2021 to allow a minimum of six months of follow-up. Trained abstractors will collect demographic, diagnostic, clinical, molecular (biomarker and PD-L1), treatment (regimens utilized in sequence and reason for discontinuation), response and survival (including PFS and OS), health care resource utilization and PRO (EQ-5D-5L and MDASI-LC) information that will be integrated in a comprehensive database. Information from the MDA electronic medical record will be extracted and populated in the GEnomic Marker-guided therapy INItiative (GEMINI) database and the PRO database which are linked. EQ-5D-5L followed by MDASI-LC will be completed directly by the patients and these will be automatically populated in the web-based PRO database at treatment initiation, at the time of response assessments and when switching lines of therapy. **Result:** Interim analysis will be conducted every six months to measure the impact of immunotherapy over time. Study results will be presented using descriptive statistics for continuous variables (mean, standard deviation, median, and interquartile range), categorical variables (frequency and proportions), and time-to-event variables (Kaplan-Meier). Regression models will be used for estimating the relationship between dependent variable and one or more predictors. Cox proportional hazards model will be used to estimate hazard ratios for time-to-event outcomes. **Conclusion:** The ANCHoR study is the first comprehensive registry of its kind that will enable the quantification of the changing impact of immunotherapy on the real-world NSCLC treatment landscape.

Keywords: Immunotherapy, NSCLC, registry

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-001 DOES CGA IMPACT QOL AND OVERALL SURVIVAL IN NSCLC PATIENTS TREATED WITH SBRT - RESULTS OF A RANDOMIZED PILOT STUDY

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Background: Overall survival (OS) for medically inoperable patients with localized non-small cell lung cancer (NSCLC) treated with stereotactic body radiotherapy (SBRT) is poorer than for patients undergoing surgery. A possible explanation is contribution of comorbidities to the mortality. Klement et al. demonstrated that comorbidity did not predict the risk of early death for patients with localized NSCLC treated with SBRT. However, it was suggested that a comprehensive geriatric assessment (CGA) could improve OS. We have performed a randomized study to investigate whether CGA added to SBRT impact quality of life (QoL) and OS. **Method:** From January 2015 to June 2016 51 patients diagnosed T1-2N0M0 NSCLC were enrolled. The patients were randomized 1:1 to receive SBRT +/-CGA. EQ-5D QoL health-index and VAS-scores were assessed at start of SBRT, at 5 weeks, and every third months for a year after SBRT. Repeated measures ANOVA compared EQ-5D overall scores and changes from baseline. OS was analyzed by Kaplan-Meier methods and compared with log-rank test. **Result:** 26 vs. 25 patients were randomized in the groups +/-CGA, respectively. 4 patients dropped out. There were no differences in patient characteristics between groups. In both groups QoL decreased from baseline but with no differences between groups. VAS scores decreased significantly in the no-CGA group (Table 1). The 1-year and potential 2-year OS was 92% vs. 73% and 72% vs. 57% for the groups +/-CGA, respectively (p=0.24).

Table 1. Overall EQ-5D health index and VAS scores on CGA and overall changes

	No. of pts +/- CGA	SBRT +CGA	*p-value*[1]	SBRT no-CGA	*p-value*[1]	Diff. between groups (95% CI)	*p-value*
EQ-5D health index score[2]							
Baseline, mean (SD)	22/25	0.77 (0.19)		0.71 (0.19)		0.05 (-0.06-0.16)	0.36
5 weeks, mean (SE)	21/24	0.75 (0.03)	0.46	0.70 (0.03)	0.71	0.05 (-0.06-0.16)	0.39
3 months, mean (SE)	18/16	0.77 (0.04)	0.46	0.74 (0.04)	0.58	0.03 (-0.10-0.15)	0.69
6 months, mean (SE)	22/19	0.69 (0.03)	0.02	0.67 (0.03)	0.02	0.02 (-0.10-0.14)	0.79
9 months, mean (SE)	13/10	0.75 (0.04)	0.20	0.72 (0.04)	0.40	0.03 (-0.13-0.18)	0.75
12 months, mean (SE)	15/15	0.75 (0.04)	0.25	0.67 (0.04)	0.04	0.08 (-0.05-0.22)	0.20
EQ-5D VAS score[3]							
Baseline, mean (SD)	22/25	69 (22)		66 (18)		3 (-10-16)	0.61
5 weeks, mean (SE)	21/24	64 (5)	0.28	60 (4)	0.31	3 (-10-17)	0.62
3 months, mean (SE)	18/16	63 (5)	0.11	58 (5)	0.05	6 (-10-21)	0.47
6 months, mean (SE)	22/19	64 (5)	0.24	59 (5)	0.13	4 (-10-18)	0.54
9 months, mean (SE)	13/10	73 (6)	0.48	54 (6)	0.06	19 (-1-38)	0.05
12 months, mean (SE)	15/15	68 (5)	0.41	49 (5)	**0.002**	19 (3-35)	**0.02**

[1] values are for comparison with baseline scores
[2] Health index score is generated from 5 different dimensions of QoL with 5 different answer possibilities (the score 1.0 equals best possible health state)
[3] VAS score is the patients' subjective opinion on their health state ranging from 0 (worst) to 100 (best)

Conclusion: In patients treated with SBRT for a localized NSCLC, a CGA did improve the subjective opinion (VAS-score) of QoL at 12 months follow up. A CGA did not statistically improve the health index of QoL and OS. However, more patients deceased within the first 12 months after SBRT in the group without a CGA performed. This study suggests that CGA may prevent early death and improve the patients' subjective opinion of QoL after SBRT.

Keywords: comprehensive geriatric assessment, NSCLC, SBRT

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-002 A PILOT STUDY ON THE SAFETY AND THE EFFICACY OF DOSE ESCALATION IN STEREOTACTIC BODY RADIOTHERAPY FOR PERIPHERAL LUNG TUMOR

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Background: Stereotactic body radiation therapy (SBRT) is an important treatment option of solitary lung tumor. A total dose of 48Gy in 4 fractions (fr.) at the isocenter has been most widely used in Japan, however, local recurrences were observed in the long term follow-up study in 10% or more. To improve local control rates after SBRT, the most promising treatment strategy will be dose escalation. Then we started a pilot study to evaluate the safety and efficacy of dose escalation in SBRT for peripheral lung tumor. **Method:** We designed to enroll 35 patients treated with SBRT prospectively. The primary endpoint was the incidence of adverse effects within 1 year after SBRT. Adverse effects were evaluated by the CTCAE ver. 4.0. In this study, the prescription dose was 70 Gy in 4 fr. at the isocenter, covering the planning target volume (PTV) surface with 70%-isodose line. **Result:** A total of 35 patients were enrolled between October 2014 and January 2016. Patient and tumor characteristics are shown in the table. The median follow-up duration was 21.0 months (range, 4.2–31.2 months). Grade 2 radiation pneumonitis and Grade 2 rib fractures were observed in 5 patients (14.3%) and 5 (14.3%), respectively. There was no other Grade 3 or more adverse effect. Local recurrence was observed in one patient, and it was a recurrence of metastatic lung tumor. Out of 32 primary lung cancers, no local recurrence was observed.

Patient and tumor characteristics				
Characteristics			**Number**	**%**
Patients			35	100
Age (y)				
	Median (range)		77 (58-92)	
Gender				
	Male		23	66
	Female		12	34
ECOG performance status				
	0		10	28
	1		22	63
	2		3	9
Disease				
^(	Primary lung cancer		32	91
	Histology			
		Adenocarcinoma	10	28
		Squamous cell carcinoma	3	9
	^(	Clinically diagnosed	19	54
	T-stage			
		T1a	15	43
		T1b	11	31
		T2a	6	17
	Lung metastasis		3	9
Target location				
	Upper/middle		26	74
	Lower		9	26

Conclusion: We confirmed that the treatment method is feasible in the acute and subacute phases. It was also suggested that this method can obtain excellent local control rate.

Keywords: stereotactic body radiotherapy, dose escalation, pilot study

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-003 STAGE BY STAGE COMPARISON OF RADIOTHERAPY VERSUS SURGERY IN NSCLC: THE INFLUENCE OF PROGNOSTIC FACTORS ON SURVIVAL OUTCOME

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Background: Curative intent therapy of stage I-III NSCLC may include surgical resection or definitive radiotherapy. Primary management with surgery or radiotherapy may be influenced by patient and disease characteristics. We sought to perform a stage by stage comparison of patients receiving surgery or radical radiation therapy as their curative treatment, and explore the impact of known prognostic factors on outcome. **Method:** A retrospective review was completed of all patients with stage I-III NSCLC referred to the BC Cancer Agency from 2005-2012. Cases were filtered to identify those receiving curative intent therapy including surgery, radiotherapy, and combined chemo-radiation. Information was collected on known prognostic and predictive factors. The primary outcome measure was overall survival. **Result:** A total of 3873 patients were referred. Of these, 1744 (45%) received curative therapy (713 surgery, 1031 radiotherapy); 592 (34%) presented with stage I disease, 386 (22%) with stage II, and 766 (44%) with stage III. At the time of analysis, 1199 (69%) patients had died. Median overall survival in stage-matched cohorts was significantly shorter in the radiotherapy group compared to the surgery group (stage I 34.9 mo vs 44.8 mo, p=0.003, stage II 27.6 mo vs 42.7 mo, p=0.014, stage III 26.5 mo vs 38.7 mo, p=0.001). However, in a multivariable analysis incorporating age, sex, weight loss, smoking history, and ECOG status, the survival difference between radiotherapy and surgery disappeared for stage I and II disease and persisted for stage III.

Univariate and multivariate analysis of prognostic factors and treatment group on survival				
	Stage I			
	UVA HR	p-value	MVA HR	p-value
Age at diagnosis	1.03	<0.001	1.03	<0.001
Male vs female	1.31	0.01	1.24	0.04
Weight loss 5-10% vs <5% >10% vs <5%	2.01 1.40	<0.001 0.11	1.96 1.15	<0.001 0.51
Smoking status Former vs never Current vs never	1.78 1.65	0.01 0.04	1.58 1.72	0.06 0.03
ECOG >=2 vs 0-1	1.39	0.002	1.18	0.14
Radiotherapy vs surgery	1.36	0.003	1.09	0.44

Univariate and multivariate analysis of prognostic factors and treatment group on survival				
	Stage II			
	UVA HR	p-value	MVA HR	p-value
Age at diagnosis	1.03	<0.001	1.03	<0.001
Male vs female	1.30	0.04	1.12	0.39
Weight loss 5-10% vs <5% >10% vs <5%	0.96 1.44	0.81 0.06	0.87 1.18	0.46 0.39
Smoking status Former vs never Current vs never	2.39 2.73	0.02 0.006	1.85 2.62	0.10 0.01
ECOG >=2 vs 0-1	1.45	0.007	1.31	0.05
Radiotherapy vs surgery	1.37	0.02	1.27	0.07

Univariate and multivariate analysis of prognostic factors and treatment group on survival				
	Stage III			
	UVA HR	p-value	MVA HR	p-value
Age at diagnosis	1.02	<0.001	1.02	0.002
Male vs female	1.14	0.11	1.00	0.99
Weight loss 5-10% vs <5% >10% vs <5%	1.33 1.56	0.02 0.001	1.35 1.28	0.02 0.08
Smoking status Former vs never Current vs never	1.64 1.60	0.003 0.004	1.44 1.32	0.03 0.10
ECOG >=2 vs 0-1	2.06	<0.001	1.98	<0.001
Radiotherapy vs surgery	1.41	0.001	1.36	0.004

Conclusion: In stage I and II NSCLC, the performance of radical radiotherapy and surgery were comparable after controlling for known prognostic factors. Superior survival was observed with surgery in stage III disease however; this may be related to disease characteristics. Surgery and radiotherapy are both viable options for curative intent treatment and selection of the primary modality may relate to underlying patient and disease characteristics.

Keywords: curative, survival, NSCLC

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-004 RADIOTHERAPY PATTERNS OF CARE FOR STAGE I AND II NON-SMALL-CELL LUNG CANCER IN SYDNEY, AUSTRALIA

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Background: Radiotherapy is an alternative to surgery for patients with Stage I and II non-small cell lung cancer (NSCLC) who are medically inoperable or refuse surgery. However, the use of curative radiotherapy in these patients is variable. The aim of this study is to document radiotherapy patterns of care in Stage I and II NSCLC patients at three institutions in Sydney, Australia and evaluate reasons for palliative rather than curative treatment. Stereotactic ablative body radiotherapy (SABR) is a newer treatment technique. However, eligibility for this depends on tumour size and location. A secondary aim is to identify the proportion of patients who would be suitable for SABR treatment. **Method:** Electronic oncology databases at three institutions were queried to retrieve data on patients with Stage I or II NSCLC, who did not undergo surgery and were seen in a radiation oncology clinic between 1/1/2008 to 31/12/2014. Curative radiotherapy was defined as a minimum dose of 50Gy for conventional and 48Gy for SABR. Suitability for SABR was defined as peripheral tumours less than 5cm in size. Factors associated with curative treatment were determined using univariate and multivariate analyses and variables were compared using Chi-square and t-test. **Result:** There were 315 patients, with a median age of 77 years (30-93). Two-hundred-and-five (65%) had Stage I and 110 (35%) Stage II NSCLC. Eastern Cooperative Oncology Group performance status (ECOG PS) at first clinic visit was 0-2 in 252 (80%) patients. Two-hundred-and-six (65%) and 151 (48%) had pulmonary and cardiovascular comorbidities, respectively. Seventy-six (24%) patients received no radiotherapy, 58 (18%) palliative radiotherapy and 178 (56%) curative radiotherapy. Use of curative radiotherapy varied from 43% to 81% between the three institutions and increased from 51% during 2008-2011 to 64% during 2012-2014. The main reasons for receiving palliative or no radiotherapy were chronic obstructive pulmonary disease (COPD) or poor pulmonary function (26%) and comorbidities other than COPD or cardiovascular comorbidities (22%). Excluding patients with N1 disease, 25% who received palliative radiotherapy, 42% of patients who received no treatment and 37% of patients who received conventional radiotherapy were suitable for SABR treatment. ECOG PS (p=0.011), FEV1% (p=0.025) and institution (p=0.001) were significantly associated with use of curative radiotherapy in both univariate and multivariate analyses. **Conclusion:** Use of curative radiotherapy varied among cancer institutions. Patient factors were the predominant reason for palliative treatment. A significant proportion of patients who underwent palliative or no radiotherapy were potential candidates for SABR treatment.

Keywords: Radiotherapy, early stage NSCLC, Stereotactic ablative body radiotherapy

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-005 PROTON BEAM THERAPY FOR EARLY STAGE LUNG CANCER: A MULTI-INSTITUTIONAL RETROSPECTIVE STUDY IN JAPAN

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Background: The purpose of this study to evaluate the clinical outcome of proton beam therapy (PBT) for early stage lung cancer or small lung lesions clinically diagnosed as primary lung cancer in Japan. **Method:** Between April 2004 and December 2013, 669 patients with 682 tumors with histologically or clinically diagnosed Stage I non-small cell lung cancer (NSCLC) according to the 7th edition of UICC were treated with PBT. The medical record and imaging studies were retrospectively reviewed to analyze survivals, local control, and toxicities. **Result:** Four hundred eighty-six (72.6%) of 669 patients were men, with the median age of 76 years (range, 42 – 94 years). Tumors were distributed according to T-stage as follows: T1a (265 tumors, 38.9%), T1b (216 tumors, 31.7%), and T2a (201 tumors, 29.4%). Tumors were distributed according to histology as follows: squamous cell carcinoma (139 tumors, 20.4%), adenocarcinoma (277 tumors, 40.6%), others (32 tumors, 4.7%), and not proven (234 tumors, 34.3%). As for operability, 351 patients were found to be operable, 294 were inoperable, and 24 patients were unknown for operability. The median biological effective dose (BED) of PBT was 109.6 Gy RBE (range, 74.4 – 131.3 Gy RBE). The median follow-up time was 38.2 months (range, 0.6 – 154.5 months) for all patients. The 3-year overall survival (OS), progression-free survival (PFS), and local control were 79.5%, 64.1%, and 89.8%, respectively. Radiation pneumonitis ≥ Grade 3 according to CTCAE v3.0 was observed in 12 (1.8%) patients. The 3-year OS and PFS for 440 patients with histologically confirmed NSCLC were 78.0% (80.7% for IA, 73.0% for IB, p = 0.042) and 66.4% (71.9% for IA, 55.9% for IB, p = 0.0038), respectively. The 3-year OS and PFS for 229 patients with clinically diagnosed NSCLC were 82.4% (86.0% for IA, 60.4% for IB, p = 0.045) and 69.6% (74.0% for IA, 42.6% for IB, p = 0.0052), respectively. The 3-year OS and PFS for 351 operable patients were 86.7% (88.8% for IA, 80.3% for IB, p = 0.096) and 70.6% (76.4% for IA, 52.8% for IB, p = 0.0028), respectively. The 3-year OS and PFS for 294 inoperable patients were 70.5% (74.1% for IA, 62.8% for IB, p = 0.046) and 56.6% (62.6% for IA, 44.6% for IB, p = 0.0062), respectively. **Conclusion:** PBT for early stage lung cancer is an effective treatment option with low incidence of severe radiation pneumonitis.

P2.05: EARLY STAGE NSCLC -
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P2.05-006 CREDENTIALING OF RADIOTHERAPY CENTRES IN AUSTRALASIA FOR A PHASE III CLINICAL TRIAL ON SABR (TROG 09.02 CHISEL)

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Background: A randomised phase III clinical trial comparing Stereotactic Ablative Body Radiotherapy (SABR) with conventional radiotherapy for early stage lung cancer in peripheral location has been conducted in Australia and New Zealand under the auspices of the Trans Tasman Radiation Oncology Group (TROG). As SABR technology at the commencement of the trial was new to most centres in our region and the techniques used are complex and technologically challenging a credentialing program was developed for centres wishing to join the trial. **Method:** The credentialing program used a prospective risk management approach with high risk elements considered to be (i) the ability to create a plan that meets all dosimetric constraints, (ii) the dose calculation in the presence of inhomogeneities and (iii) the management of motion. Participating centres were asked to develop treatment plans for two test cases made available in DICOM format, and inhomogeneity corrections and dose delivery was assessed during a site visit using a phantom with moving inserts (modified Modus Quasar). **Result:** Site visits were conducted in 17 Australian and 3 New Zealand radiotherapy facilities. All centres were able to produce acceptable plans for both test cases, in particular after the protocol was amended to allow delivery of 48Gy in 4 fractions for lesions close to the chest wall in addition to the original trial arm of 54Gy in 3 fractions. The tests conducted during site visit with lung and air inhomogenieties confirmed known shortcomings of the AAA algorithm for dose calculation behind the inhomogeneity. The dose was assessed using an ionisation chamber and radiochromic film in a stationary and moving cylinder (sinusoidal motion, 1cm amplitude, 4s period) in the phantom for a typical treatment delivery including at least one non-coplanar beam. The measurements confirmed in an end-to-end test that all participating centres were able to deliver SABR with the required accuracy. Overall, the site visit took 3 hours of time on the treatment unit and was well received by participating staff. For several facilities it proved to be a useful step in the process of developing a SABR program. **Conclusion:** The credentialing process including a site visit documented that participating centres were able to deliver dose to a phantom as required in the trial protocol. It also gave an opportunity to provide education about the trial and discuss technical issues such as 4D CT, small field dosimetry and patient immobilisation with staff in participating centres.

Keywords: quality assurance, clinical trial, dosimetry

P2.05-007 STEROTACTIC-BODY-RADIOTHERAPY FOR EARLY-LUNG CANCER: IS FDG-PET/TC A PREDICTOR OF OUTCOME?

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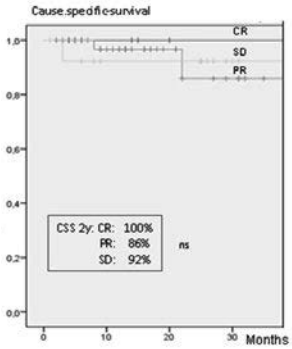
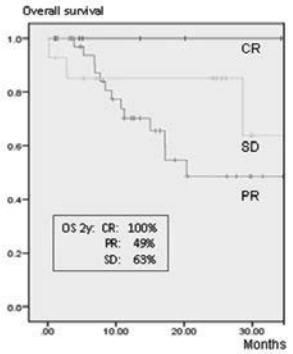
Background: Follow-up recommendations after stereotactic body radiation therapy (SBRT) for early non–small cell lung cancer (NSCLC) patients are not well defined. We analyzed the prognostic value of early response evaluated by FDG-PET/TC scan. **Method:** Between April 2012 and September 2016, 63 primary lung lesions in unfit patients or who refused surgery were treated with SBRT. Three risk-adapted fractionation schemes that ensure DBE>100Gy were considered: 3x18Gy, 5x11Gy and 8x7.5Gy. In all patients two FDG-PET/TC scans were performed: one before the SBRT treatment and another one a month after the completion of the treatment. Changes in FDG-uptake were evaluated. We considered complete response (CR) when the FDG-uptake was normalized, partial response (PR) when there was a decrease and stable disease (SD) when no modification was observed. Local control (LC), cause-specific survival (CSS) and overall survival (OS) were analyzed according to response. **Result:** With a median follow-up of 16 months; LC, CSS, and OS at 2 years were 100%, 91% and 64%, respectively. We correlated the FDG-PET/TC response at one month with LC and OS at 2 years. The FDG-PET/CT response at one month was not related to LC at 2 years, which was above 95% for all patients. For patients who achieved CR at one moth, OS and CSS at 2 years was both 100% while patients with PR was 49% and 86% respectively and for those with SD were 63% and 92% respectively (Figure 1).





Conclusion: Our results suggest that an early complete response on FDG-PET/TC may be a good predictor factor of survival. Based on the grade of early PET-CT response, patients for stricter monitoring could be selected. Longer follow-up to confirm these findings is necessary.

P2.05-008 STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR EARLY STAGE I LUNG CANCER: A REVIEW FROM AN ONCOLOGY CENTER IN HONG KONG

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Background: Traditionally, patients with medically inoperable early stage non-small-cell lung cancer (NSCLC) were treated with conventional radiotherapy of 60 Gray (Gy) over 6 weeks. comparable results as surgery. Primary objective of this review was to evaluate the clinical outcomes of stage I NSCLC patients after SBRT, including 1-year, 3-year and 5-year local control, overall survival and cancer-specific survival rates. Secondary objectives were acute and late toxicities. **Method:** Patients with stage I NSCLC (tumor size ≤5cm), ECOG performance status ≤2, who were not surgical candidates (either inoperable or patient refusal) were treated by SBRT in our hospital since 2012. Tumor motions with respiratory cycles were accounted for by using four-dimensional computerized tomography. A margin of 5mm (1cm superior-inferior) was used to generate the planning target volume. A total dose of 50 or 60 Gy in 5 fractions over 2 weeks was given, depending on the location of tumors. Survival plots were produced by Kaplan-Meier estimate. **Result:** A total of 40 patients were included (male=23, 57.5%; female=17, 42.5%). Median age was 75 (range: 42-85). Half (n=20) of patients had stage Ia disease. Median gross tumor volume and planning target volume were 15.80cm3 (range:2.80-56.80cm3) and 47.6cm3 (range:12.50-117.70cm3) respectively. No concomitant systemic therapies were used. After a median follow-up of 23.6 months (range:3.5-68.6 months), twelve patients died (4 were non-cancer related). Median overall survival (OS) was 35.5 months (range:3.5-68.6 months). The 1-year, 3-year and 5-year OS was 92.4%, 48.2% and 37.2, while the cancer-specific survival was 94.7%, 53% and 40.9% respectively. Nine (22.5%) had local progressions, giving rise to the 1-year and 5-year local control rate of 87.2% and 75.3%. Acute and late toxicities occurred in 35% (n=14) and 17.5% (n=7) of patients but all are grade 1 only. **Conclusion:** SBRT in early stage I NSCLC achieves high local control rate and overall survival comparable to radical surgery. Comparing to conventional radiotherapy, SBRT is better tolerated and reduces the treatment period from 6 to 2 weeks. SBRT should be the preferred treatment for early stage NSCLC when radical surgery is not to be considered.

Keywords: Stereotactic body radiotherapy, early stage lung cancer

P2.05-009 OUTCOME OF STEREOTACTIC BODY RADIOTHERAPY FOR CLINICAL STAGE I NON SMALL CELL LUNG CANCER AND CT FINDINGS: COMPARISON WITH SURGICAL RESECTION

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Background: The standard care for Stage I non small cell lung cancer (NSCLC) is surgical resection, but stereotactic body radiotherapy (SBRT) can be an alternative treatment option, especially for patients with comorbidities. However, it is difficult to compare the outcomes of SBRT with surgical resection because their characteristics are so different, and the risk factors for recurrence after SBRT are not fully understood. In this study, we report pretreatment clinical characteristics and CT findings in patients treated with SBRT, and reviewed patients underwent surgery with similar tumors. **Method:** Between January 2012 and December 2015, patients treated with SBRT for cT1-2N0M0 NSCLC and 218 patients who underwent surgery for cT1b-2N0M0 NSCLC in our institution were analyzed. **Result:** During the study period, 88 patients were treated with SBRT. The 3-year disease free survival (3-year DFS) for all patients was 81.2%. There were 15 cases of recurrences (9 cases of lymph node recurrences, 8 cases of distant metastases and 2 cases of local recurrence. 4 cases were both lymph node and distant metastases). There was no recurrence among the patients with no more than 1cm of consolidation (cT1a or less according to the 8th edition of the Union for International Cancer Control TNM classification) and all recurrent cases were with solid pattern predominant tumors (maximum consolidation diameters were more than 50% of tumor diameters) based on CT findings. Then we evaluated outcomes and clinical characteristics of patients who were treated with SBRT or underwent surgery for cStage I, cT1b or more and solid predominant NSCLC during the same period. 61 patients were treated with SBRT and 218 underwent surgery (190 cases of lobectomy, 21 secmentectomy and 7 wedge resection). Among clinical characteristics, smaller tumor sizes tend to be treated with SBRT (average sizes were 2.25 and 2.57 cm respectively, p=0.055). The mean age was significantly higher in SBRT group (78.5 vs 68.0, p<0.001). Surgical resection was associated with improved DFS (3-year DFS 84.4% vs 73.4%, p=0.004) and lymph node metastasis was found in 34 cases (15.6%) pathologically in patients underwent surgery, suggesting they are incurable with SBRT. **Conclusion:** The main limitations of this study are the small number of cases and different patient characteristics. Taken together, our data suggesting SBRT is acceptable for patients with cT1a or less, cStage I NSCLC, and surgical resection is recommended for patients with more advanced NSCLC.

Keywords: early lung cancer, SBRT, Surgery

P2.05-010 CHANGES BETWEEN PRE- AND POST-OPERATIVE AICS (LUNG) IN NSCLC PATIENTS: PREDICTABILITY OF HIGH-RISK CASES WITH RECURRENCE

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Background: Plasma free amino acid (PFAA) levels are known to change in patients with malignant diseases. We have developed AminoIndex™ Cancer Screening (AICS™) using "AminoIndex Technology", which is a multivariate analysis of PFAA concentrations in various cancer patients and healthy controls. In Japan, AICS™ is now commercially available for simultaneous screening of seven cancer types, including lung cancer. The lung cancer specific AICS [AICS (lung)] are classified as rank A (AICS values: 0.0–4.9), rank B (5.0–7.9), or rank C (8.0–10.0); the closer to rank C, the higher risk of lung cancer. The aim of this study was to evaluate post-operative changes of AICS (lung) in patients who underwent curative surgical resection for lung cancer, as well as the associations of these changes with post-operative cancer recurrence. **Method:** The subjects were lung cancer patients with pre-operative AICS (lung) rank B-C, 44 patients (rank C; 29 cases, B; 15 cases) who underwent surgical curative resection. The pathological stage was 29 stage I, 8 stage II and 7 stage III. AICS (lung) was measured within 1 week prior to surgery

and from 1.2 to 5.5 years after surgery, and the relationship between fluctuation before and after surgery and post-operative recurrence was analyzed. **Result:** Post-operative AICS (lung) ranks and values decreased in 52% (23/44) and 82% (36/44), respectively. For the pre-operative AICS (lung) rank C patients, post-operative AICS (lung) ranks and values decreased in 52% (15/29) and 86% (25/29), respectively. All 12 patients who had recurrence had a pre-operative AICS (lung) rank C. Among the 7 patients had recurred at the time of post-operative AICS (lung) measurement, 6 patients remained AICS (lung) rank C after surgery and 1 patient was rank B after surgery. On the other hand, among 5 patients in which recurrence was observed after post-operative AICS (lung) measurement, 4 patients remained post-operative AICS (lung) rank C and only 1 patient was rank B. **Conclusion:** Most patients had a decrease in the AICS (lung) rank and value after curative surgical resection. However, ten of 15 patients who had both pre- and post-operative AICS (lung) rank C had recurrence after surgery, suggesting the association between pre- and post-operative change in AICS (lung) and recurrence after lung cancer surgery. Pre- and Post-operative AICS (lung) measurement may be able to predict high-risk cases with post-operative cancer recurrent.

Keywords: pre- and post-operative, amino acids, recurrence

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P2.05-011 SEGMENTECTOMY VERSUS WEDGE RESECTION IN PATIENTS WITH CLINICAL STAGE I NON-SMALL CELL LUNG CANCER WHO WERE UNFIT FOR LOBECTOMY

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Background: The purpose of this study is to compare the surgical outcomes after segmentectomy versus wedge resection in patients with clinical stage I non-small cell lung cancer (NSCLC) who were unfit for lobectomy. **Method:** Between April 2007 and December 2015, 99 patients with clinical stage I NSCLC who were considered unfit for lobectomy and underwent sublobar resection were identified. Propensity scores were estimated including variables such as age, sex, smoking history, solid tumor size, SUVmax of the tumor, preoperative pulmonary functions, and Charlson comorbidity index. Surgical outcomes were compared between patients who underwent segmentectomy and those who underwent wedge resection. **Result:** Thirty-nine patients underwent segmentectomy and sixty patients underwent wedge resection. Operation time (median, 169 min vs. 72.5 min, P <0.001) and blood loss (median, 84 g vs. 10 g, P = 0.001) were significantly different between the procedures. Severe postoperative complications (≥Grade IIIa) was more frequently in segmentectomy (15.4%) than in wedge resection (3.3%, P = 0.054). Propensity score-adjusted multivariable analysis showed that operative procedure was an independent predictive factor for severe postoperative complication (segmentectomy, odds ratio = 8.18; P = 0.021). Overall survival (OS) and recurrence-free survival (RFS) were not significantly different between segmentectomy (3 y-OS, 79.1%, 3 y-RFS, 77.7%) and wedge resection (3 y-OS, 86.3%, 3 y-RFS, 68.5%; P = 0.81, P = 0.91, respectively). Propensity score-adjusted multivariable Cox analysis revealed that operative procedure was not an independent factor for OS (segmentectomy, hazard ratio = 1.7, P = 0.24) or RFS (segmentectomy, hazard ratio = 1.1, P = 0.82). In propensity score matching method, similar results were observed. **Conclusion:** Segmentectomy is more toxic, but provides similar prognosis compared with wedge resection. Wedge resection may be an optimal procedure in patients with clinical stage I NSCLC who were considered unfit for lobectomy.

Keywords: sublobar resection, non-small cell lung cancer, wedge resection

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P2.05-012 PROGNOSTIC FACTORS FOR SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER WITH CAVITY FORMATION

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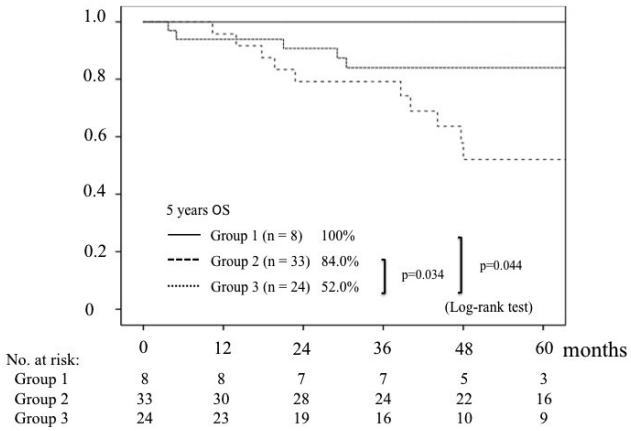
Background: Small pulmonary nodules have been detected frequently by computed tomography (CT). Lung cancers with cavity formation are also easily detected. There are a few reports focused on the cavity wall, although cancer cells exist along the cavity wall, not inside. We evaluated the impact of cavity wall thickness on prognosis and assessed the clinicopathological features in non-small cell lung cancer (NSCLC) with cavity formation. **Method:** Between 2005 and 2011, 1313 patients underwent complete resection for NSCLC. Of these cases, we reviewed 65 patients (5.0%) diagnosed with NSCLC with cavity formation by chest CT. We classified the patients into three groups based on the maximum cavity wall thickness, namely, ≤ 4 mm (Group 1, 8 patients), > 4 mm and ≤ 15 mm (Group 2, 33 patients), and > 15 mm (Group 3, 24 patients). **Result:** The number of patients with pathological whole tumor size > 3 cm was 2 (25%) in Group 1, 17 (52%) in Group 2, and 23 (96%) in Group 3 (p< 0.001). Cases with lymph node metastasis were 0 (0%) in Group 1, 5 (15%) in Group 2, and 10 (42%) in Group 3 (p= 0.016). The 5-year overall survival (OS) rates were 100% in Group 1, 84.0% in Group 2, and 52.0% in Group 3, with significant differences between Group 1 and Group 3 (p= 0.044) and between Group 2 and Group 3 (p= 0.034). In univariate analysis, neither whole tumor size nor lymph node metastasis was a prognostic factor for OS (p= 0.505, p= 0.274). Only cavity wall thickness was a significant prognostic factor by multivariate analysis (p= 0.009).



Conclusion: Maximum cavity wall thickness was an important prognostic factor in NSCLCs with cavity formation, comparable with other established prognostic factors.

Keywords: non-small cell lung cancer, prognostic factor, Cavity wall thickness

P2.05: EARLY STAGE NSCLC -
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P2.05-013 THE RESULT OF PREOPERATIVE LIPIODOL MARKINGS FOR 121 SMALL PULMONARY NODULES IN 115 PATIENTS

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Background: Some pulmonary nodules are so small that we surgeons can't perceive by touch nor visually recognize during operation. For resection of such small nodules we have been undergoing preoperative lipiodol markings for 7 years. The appearance of the marking-spots on computed tomography (CT) is classified into 3 types in a previous research [H Miura, et al: CT findings after lipiodol marking performed before video-assisted thoracoscopic surgery for small pulmonary nodules. Acta Radiologica, 2016, Vol. 57(3) 303-310] . **Method:** CT-guided lipiodol marking for 121 nodules were performed in 115 patients before surgery. Lipiodol was injected using a 23-guage needle near the nodules. During surgery, the location of nodules could be detected using C-arm-shaped fluoroscopic unit as radiopaque spots and we resected them. We classified the CT appearance of the lipiodol marking retrospectively into 3 types; Dense, Punctate and Unclear as the previous research. **Result:** All nodules were successfully resected on the same day as marking performed. The results of pathological examination were 68 lung cancers (56%), 38 metastatic lung tumors (31%) and 15 others (12%). The classification of lipiodol spots resulted as following. 75 spots (62%) were Dense, 45 spots (37%) were Punctate, and 1 spot (0.8%) was Unclear. There was no significant difference in the average operative duration between the group of Dense and Punctate. Patients with smoking history occupied 67% of the Punctate group, on the other hand only 37% of the Dense group had smoking history (P<0.0001). **Conclusion:** Lipiodol marking for small pulmonary nodules are helpful and effective, especially for diagnosis and treatment of early stage lung cancer. Smoking history of patients has something to do with the CT appearance of lipiodol spots. Regardless of how marking shape is, difficulty of surgery doesn't change in the point of operative duration.

Keywords: early stage NSCLC, marking, resection

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P2.05-014 FACTORS ASSOCIATED WITH RECOVERY TIME TO PREDICTED FEV1 IN NON-SMALL-CELL LUNG CANCER PATIENTS AFTER LOBECTOMY

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Background: Long term pulmonary function after lung resection is related with quality of life in patients with lung cancer. Previous studies found that impaired pulmonary function persisted for at least 3months after lung resection followed by gradual restoration, time-dependent improvement. This study aimed to identify

factors associated with delayed recovery to predicted FEV1 calculated with perfusion scan or segment counting method in non-small-cell lung cancer patients after lobectomy. **Method:** Medical records of seventy-four patients with non-small-cell lung cancer who underwent lobectomy and preoperative perfusion scan was retrospectively reviewed. Achieving 100% of predicted FEV1 calculated with perfusion scan was defined as event, and time to event was analyzed with parametric survival model with Weibull distribution handling interval censored data. Another survival model was elucidated with definition of the event as achieving 100% of predicted FEV1 calculated with segment counting method. **Result:** In a multivariable survival model (Perfusion scan), LUL lobectomy had shorter accelerated failure time value compared with RUL lobectomy (p=0.0328), and 'Adjuvant chemotherapy before event' had longer accelerated failure time value (p=0.0202) after adjusting the variable 'CTD indwelling duration after operation more than 10 days'. In another multivariable survival model (segment counting method), LUL lobectomy had shorter accelerated failure time value compared with RUL lobectomy (p<0.001), and 'Adjuvant chemotherapy before event' had longer accelerated failure time value (p=0.034) after adjusting the variable 'CTD indwelling duration after operation more than 10 days' and 'pneumonia within 1 month after operation'. **Conclusion:** LUL lobectomy showed faster recovery to predicted FEV1 than RUL or RML lobectomy. Adjuvant chemotherapy had delayed recovery to predicted FEV1.

Keywords: FEV1, recovery, lobectomy

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-015 WEDGE RESECTION IS ENOUGH FOR CURING GGO PATIENTS WITH MINIMALLY INVASIVE ADENOCARCINOMA (MIA) OF THE LUNG?

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Background: More and more pulmonary ground-glass opacity (GGO) were detected and surgically resected, but the resection extent remains unconcluded, especially for those micro- small lung cancer (≤1cm) (mi-SLC), some are adenocarcinoma in situ (AIS), some minimally invasive adenocarcinoma (MIA), both belonging to early stage lung cancer. Wedge resection may be enough for curing lung MIA. **Method:** Case 1: Woman, aged 59 in Nov 2013, right middle lobe pure GGO 1.0cm, peripheral; sickly weak for years; anti-inflammatory strategy used, GGO size no change. Case 2: man, aged 64 in Oct 2013, right upper lobe mixed GGO 1.0cm, peripheral; with hypertension and chronic bronchitis for years; anti-inflammatory strategy used, the GGO showed a little increased one month later. Both patients were referral to China Medical University Lung Cancer Center for surgical resection, "miMRST", minimally invasive small incision, muscle- and rib-sparing thoracotomy, minimally invasive lung cancer radical surgery, was scheduled. **Result:** About 10cm lateral chest incision, with the latissimus dorsi and serratus anterior muscles protected, no rib cut needed, was enough for most lung cancer resection and mediastinal lymph node dissection, no need for the surgeon's hands entering into the thoracic cavity, not as large-incision standard posterolateral thoracotomy (SPLT) and modified muscle and rib sparing thoracotomy (MRST) usually do. For Case 1, right middle lobe wedge resection was undergone first, frozen pathological diagnosis was atypical adenomatous hyperplasia (AAH), carcinoma should be excluded by following wax slide pathology. For Case 2, right upper lobe wedge resection was performed, frozen diagnosis was AAH, carcinoma should be excluded by following wax slide pathology. Both patients recovered much better and quickly than other patients who underwent SPLT. Postoperative pathology was MIA for both cases. Considering both in a status of sickly and weak health condition, no further tratment was used. Follow-up: both patients are living healthilly, in their 4th year postoperatively, obviously more healthy and stronger than before; no sign of recurrence and metastasis. **Conclusion:** Even though lobectomy and systematic mediastinal lympph node dissection still remains the standard surgical procedure for non-small cell lung cancer, more and more limited (wedege) resection for early stage lung cancer, including SLC and mi-SLC, especially MIA, showed a better outcome. Wedge resection is of first choice for these aged, sickly and weak patients, further, wedge resection might be enough for curing mi-SLC, eapecially those GGO MIA. Prospective observation is needed. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05)

Keywords: micro- small lung cancer, miMRST, MIA

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-016 CLINICAL IMPORTANCE AND APPLICATION OF NEW T DESCRIPTORS IN THE 8TH TNM CLASSIFICATION FOR PATHOLOGICAL T0-1 LUNG ADENOCARCINOMA

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Background: In the new TNM classification (8th), significant revision was made for pathological (p) T descriptors. Tumors, 3 cm or less in size, measuring invasive size, were subclassified into five categories, Tis, T1mi, T1a, T1b and T1c, termed T0-1 tumors here. Purpose of this study was to examine clinical importance of new pT descriptors and apply to indication criteria of limited surgery for pT0-1 lung adenocarcinoma. **Method:** We retrospectively reviewed pathological data of lung adenocarcinomas surgically resected between 2011 and 2016 at our institute, and reclassified them according to the new TNM classification. We found 874 tumors classified as pT0-1. We compared invasion-related factors such as lymph node (LN) metastasis, lymphatic and /or vascular invasion (LVI) and existence of lepidic component among the five T categories. **Result:** There were 154, 196, 195, 255 and 74 cases in the pTis, T1mi, T1a, T1b and T1c category, respectively. LN metastasis was found in 50 of 874 (6%) cases. LN metastasis rates were 0%, 2%, 10% and 27% in T1mi, T1a, T1b and T1c, respectively. In 108 of 874 cases, invasive size was equal to whole tumor size, meaning that they contain less of lepidic component. LN metastasis rates of the 108 cases were 13%, 13% and 27% in T1a, T1b and T1c, respectively, implying that LN metastasis of T1a diseases were much often with less lepidic component. In the 824 cases without LN metastases, LVI was observed in 156 (19%) cases. LVI rates were 1%, 21%, 39 and 46% in T1mi, T1a, T1b and T1c, respectively. In 89 of 824 cases, invasive size was equal to whole tumor size. LVI rates of the 89 cases were 31%, 54% and 54% in T1a, T1b and T1c, respectively, meaning that LVI rates were more frequent in T1a-c diseases with less lepidic component. **Conclusion:** LN metastasis was rare (2%) in T1a diseases, and they may be good candidates for limited surgery such as segmentectomy. However, T1a diseases with less lepidic component, showing 13% of LN metastasis, may be difficult to cure by limited surgery. On the other hand, in T1b and T1c diseases, LN metastasis rates did not significantly differ between cases with and without lepidic component. T1mi diseases, rarely showing LVI, can be managed same as Tis and cured by partial resection. Taken together, it is the most important to predict pathological T descriptors preoperatively accurately by imaging analysis for T0-1 lung adenocarcinoma.

Keywords: Adenocarcinoma, TNM classification, pathological T descriptors

P2.05: EARLY STAGE NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.05-017 PROGNOSTIC IMPACT OF THE CLINICAL T DESCRIPTOR IN THE EIGHTH EDITION OF THE TNM STAGING SYSTEM OF NON-SMALL CELL LUNG CANCER

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Background: The diameter of the solid part of the tumor in a computed tomography (CT) image determines the clinical T descriptor of the new TNM staging system in non-small cell lung cancer (NSCLC). The purpose of this study was to investigate the appropriateness of the clinical T descriptor (cT) in respect to postoperative prognosis. **Method:** This retrospective study included consecutive patients who underwent complete resection in Oita University Hospital between 2006 and 2014 and those who underwent complete resection in Kyushu University hospital between 2003 and 2012. The complete clinical data of 1061 NSCLC patients were available for prognostic analyses. The whole tumor size (TS) in diameter and solid-part size (SPS) in diameter were measured by the thin-section CT image before surgery. The tumors with SPS/TS ratio (STR) = 0, those with 0 < STR < 100, and those with STR = 100 were defined as pure ground glass tumors (GGT), part-solid tumors (PST), and solid tumors (ST), respectively. The survival curves were estimated according to the Kaplan-Meier method and were assessed by the log-rank test. **Result:** The tumors included 809 adenocarcinomas (Ad), 197 squamous cell carcinomas, 31 large cell carcinomas, 18 adeno-squamous cell carcinomas, and 6 other types of tumor. The 5-year survival rate of patients according to the new cT descriptor (version 8) were cTis, 97.6%; cT1mi, 90.7%; cT1a, 87.8%; cT1b, 81.5%; cT1c, 72.8%; cT2a, 69.6%; cT2b, 55.6%; cT3, 55.0%; and cT4, 23.4%. In analyses of Ad patients, the 5-year survival rate of patients according to the whole tumor size were >0 -10 mm, 89.9%; >10 -20 mm, 89.1%; and >20 -30 mm, 84.1%, and that according to the solid part size were 0mm, 97.6%; >0 -10 mm, 91.9%; >10 -20 mm, 84.8%; and >20 -30 mm, 80.8%. The new cT descriptor predicted patient prognosis more effectively than the old cT descriptor of whole tumor size. Postoperative 5-year survivals of the GGT, PST and ST of Ad patients were 97.6%, 89.0%, and 76.3%, respectively (P<.0001). In analyses of the small-size PST (≤ 3 cm), the new cT descriptor did not adequately predict patient prognosis (P=.458). **Conclusion:** The new cT descriptor is a better prognostic indicator than the old cT descriptor in NSCLC. However, patients with small-size PST had a significantly better prognosis than those with ST Ad. Additionally, the new cT descriptor failed to adequately predict the prognoses of the patients with small size PST adenocarcinoma.

Keywords: TNM Staging System, T descriptor, non-small cell lung cancer

P2.05-018 VIDEO-ASSISTED THORACOSCOPIC SURGERY VS THORACOTOMY FOR EARLY-STAGE NON-SMALL CELL LUNG CANCER: SHORT-TERM OUTCOMES OF A RANDOMIZED TRIAL

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Background: Video-assisted thoracoscopic surgery (VATS) has been rapidly gaining popularity worldwide in the treatment of early stage non–small cell lung cancer (NSCLC) because it is potentially less invasive. However, there has not been a large randomized controlled trial (RCT) to prove its superiority over thoracotomy. 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 randomized controlled trial was undertaken at five tertiary 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 mediastinal lymph node dissection was the standard surgery as per protocol. The short-term outcomes including acute phase inflammatory reaction, performance status, postoperative pain, respiratory function and quality of life would be analyzed and reported in this article. Patients continue to be followed up for the primary endpoints (5-year overall and disease-free survival). This study is registered with the ClinicalTrials.gov, number NCT01102517. **Result:** Between January 2008 and March 2014, 508 patients were recruited and 481 were eligible for randomization. 236 patients were randomly assigned to the VATS group, while 245 to the thoracotomy group. Finally, 425 were eligible for analyses (215 and 210, respectively). For acute phase inflammatory reaction assessment, cytokines including IL-2,IL-4,IL-6,IL-10,TNF-α and IFN-γ were tested in different time points within 48 hours postoperatively. No significant difference was found between the 2 groups except IL-6 (P=0.0411). Patients who received VATS procedures had better daily Karnofsky performance status in the first week (P=0.0029). Visual analogue scale (VAS) was applied for pain assessment at the time points of postoperative day 1 to 7 and every 3 months within the first year. Our study showed VATS was superior to open procedures in pain control within the first week after surgery (P=0.0274). However, this benefit diminished within the year. Spirometry was tested at the time points of day 7, 1 and 3 months postoperatively. Both FEV1 and FVC were better preserved in VATS group throughout the time (P=0.0005). Finally, lung cancer symptom scale (LCSS) was used to evaluate the quality of life, and there was no significant difference demonstrated between the 2 groups within the first year after surgery. **Conclusion:** The short-term outcome of our trial has demonstrated that VATS may be superior to thoracotomy in the surgical treatment for NSCLC in terms of short-term performance status, pain control and respiratory function preservation.

Keywords: randomized controlled trial, non-small cell lung cancer, Video-assisted thoracoscopic surgery

P2.05-019 OVERALL SURVIVAL (OS) OF PATHOLOGICAL T1N0 NON-SMALL CELL LUNG CANCER (NSCLC) AFTER RESECTION.

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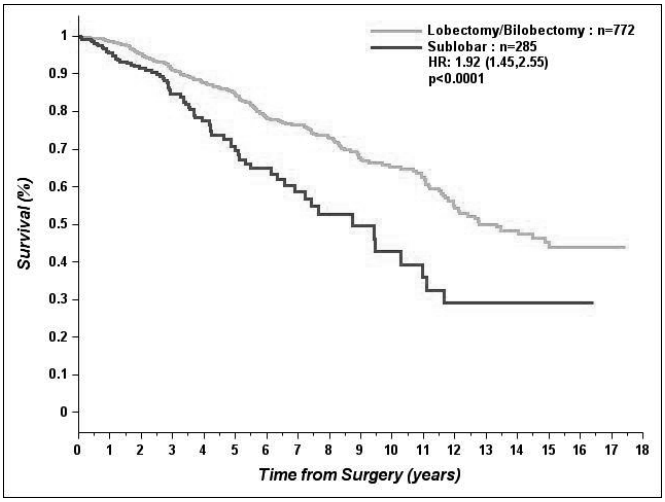
Background: Complete surgical resection is the standard treatment of stage I NSCLC. The aim of the current study was to evaluate overall survival of T1N0 NSCLC after complete resection. **Method:** The *Institut de Cardiologie et Pneumologie de Quebec* Biobank was queried for all patients with pathological T1N0M0 NSCLC who underwent complete (R0) surgical resection between November 1999 and February 2017. Survival was examined using the Kaplan-Meier method with log rank analysis. Significance was set at p≤0.05. **Result:** We identified 1071 eligible patients, 624 (58%) were female with mean age of 64±9y, 763 (71%) were adenocarcinoma and 183 (17%) were squamous cell carcinoma. Regarding surgical modality, 285 (27%) patients underwent sublobar resection, 772 (72%) lobectomy or bilobectomy and 14 (1%) pneumonectomy. The 30-day mortality of the cohort was 0.3% (3 patients). During 17 years of follow-up, a total of 253 (24%) patients died; of these events, 160 (63%) were cancer-related. Median OS of the cohort was 12.8y (CI 11.2 – 14.2). When comparing lobar versus sublobar resection, median OS was 12.8y and 8.7y respectively (HR 1.92; CI 1.45-2.55, p=<0.0001) (Figure 1). Figure 1: Overall survival according to type of resection



Conclusion: In our institutional database study, median OS after complete resection of T1N0 NSCLC was 12.8y. Patient undergoing lobectomy had a survival advantage over patients who had sublobar resection. Until more definitive data confirms our findings, patients with T1N0M0 disease should be treated with lobectomy.

Keywords: Lobectomy, Sublobar resection and NSCLC

P2.05-020 PROGNOSTIC FACTORS IN PATIENTS WITH COMPLETELY RESECTED SUBSOLID NODE-NEGATIVE LUNG ADENOCARCINOMA OF 3CM OR SMALLER

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Background: The operative method in ground glass pulmonary nodules is controversial. The prognostic value of histological subtypes in resected node-negative small-sized lung adenocarcinoma has not been widely investigated. This study aim to investigate the prognostic factors in patients with resected small ground glass nodules with consolidation/tumor (C/T) ratio of 0.5 or less determined by chest computed tomography. **Method:** A total of 377 patients with completely resected node-negative lung adenocarcinoma of 3cm or smaller and C/T ratio of 0.5 or less were included in the study. Prognostic factors for overall survival (OS) or probability of freedom from recurrence (FFR) were investigated. **Result:** The 5-year OS and probability of FFR were 93.7% and 91.5%, respectively. During follow-up, 15 (4.0%) patients developed recurrence. Univariate analysis showed that order age (P = 0.008) and greater tumor size (P = 0.008) had significantly worse OS. Patient underwent sublobar resection had significantly worse OS than those with lobectomy (P = 0.003). Greater tumor size (P = 0.006) and sublobar resection (P = 0.002) were still significant prognostic factors for worse OS in multivariate analysis. Univariate analysis showed that order age (P = 0.007), greater tumor size (P = 0.001), and micropapillary/solid predominant group (P = 0.002) had significantly lower probability of FFR. Operative method (sublobar resection vs. lobectomy) was not a significant prognostic factor for FFR (P = 0.726). Older age (P = 0.016), greater tumor size (P = 0.026), and micropapillary/solid predominant group (P = 0.043) still had significantly lower probability of FFR in multivariate analysis. **Conclusion:** For patients with completely resected node-negative lung adenocarcinoma of 3cm or smaller and C/T ratio of 0.5 or less, greater tumor size was a poor prognostic factor for both OS and probability of FFR. Sublobar resection was a significant prognostic factor for worse OS, but not probability of FFR. The new adenocarcinoma histopatholofgical classification has significant impact on recurrence in these patients.

Keywords: lung adenocarcinoma, ground glass nodule, Prognosis

P2.05-021 OCCULT NODAL METASTASIS FOLLOWING LOBECTOMY FOR CLINICAL STAGE I LUNG ADENOCARCINOMA: IMPLICATIONS FOR SUBLOBAR RESECTION

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Background: We investigated the incidence and location of occult nodal metastasis

(ONM) in patients who had undergone lobectomy and lymph node dissection for clinical stage I lung adenocarcinoma (ADC). We performed a risk regression analysis to identify any associated radiologic and pathologic factors. **Method:** Clinical stage I lung ADC patients (stage II and III were excluded by CT and FDG-PET/CT scans) who underwent lobectomy and systematic lymph node dissection (N=715, 2005-2011) were included in the analysis. ONM were defined as pathologically diagnosed metastatic lymph nodes that are not suspected to be involved by cancer on both CT and PET scans. **Result:** Among 715 patients, 75 (10.5%) ONM were identified: 64 (85%) hilar or peribronchial and 32 (43%) mediastinal. Multivariable risk regression analysis identified tumor diameter, SUVmax, and lymphovascular invasion as risk factors (P<0.01). The incidence of subcarinal lymph node (LN) metastasis was very low among patients whose primary tumors were in the right upper lobe or left upper division (N=1/439, 0.2%). Lower mediastinal LN metastasis was rarely identified only when the primary tumor was located in the right lower or left lower lobe (N=2/210, 1.0%). **Conclusion:** One in ten patients with clinical stage I lung adenocarcinoma showed occult nodal metastases, with the highest incidence in hilar lymph nodes; this observation may be relevant for clinicians when considering sublobar resection for these patients.

Table

Distribution of ONM according to primary tumor location

Primary tumor location (n=715)	ONM(+) (n=75)	UMLN (#2-6)	SCLN (#7)	LMLN (#8, #9)	Hilar or peribronchial (#10-13)
RUL + LUD (n=439)	36 (8%)	12 (3%)	1 (0.2%)**	0 (0%)	30 (6%)*
RML + LLD (n=66)	11 (17%)	2 (3%)	4 (6%)*	0 (0 %)	9 (14%)
RLL +LLL (n=210)	28 (13%)	3 (1%)	12 (6%)**	2 (1 %)*	25 (12%)

RUL: right upper lobe; LUD: left upper division; RML: right middle lobe; LLD: left lingular division; RLL: right lower lobe; LLL: left lower lobe; ONM: occult nodal metastases; UMLN: upper mediastinal lymph nodes; SCLN: subcarinal lymph nodes; LMLN: lower mediastinal lymph nodes
* p<0.05, ** p<0.01

Keywords: stage migration, PET/CT, nodal metastasis, nodal dissection

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-001 CIRCULATING COTININE CONCENTRATIONS, SELF-REPORTED SMOKING, AND LUNG CANCER RISK IN THE LUNG CANCER COHORT CONSORTIUM (LC3)

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Background: Tobacco exposure is the main determinant of lung cancer. Data on tobacco exposure is often collected via self-reported smoking which is prone to misclassification. In the current study we sought to evaluate the extent to which cotinine, an objective measure of recent tobacco exposure, can inform on lung cancer risk. **Method:** We used data from 20 international cohorts and designed a nested case-control study including 5364 incident lung cancer cases and 5364 controls. Cases and controls were individually matched by age, sex, cohort, and smoking status (never, former, current). Cases from never and former smokers were intentionally oversampled. Centralised biochemical analysis was performed to measure circulating cotinine concentrations as an objective indicator of recent tobacco exposure. The association between cotinine and lung cancer risk was evaluated using conditional logistic regression. Discrimination between future lung cancer cases and controls was evaluated using receiver operating characteristic (ROC) curves. **Result:** Higher circulating cotinine concentrations were strongly associated with lung cancer risk among current smokers ($OR_{\text{per doubling in cotinine concentrations}}[_{log2}]$: 1.22, 95% confidence interval [CI]: 1.17-1.28, especially women (OR_{log2}: 1.35, 95% CI: 1.22-1.50). Among former smokers, positive associations between higher cotinine concentrations and lung cancer risk were driven by those participants with cotinine levels consistent with active smoking (OR_{log2}: 1.08, 95% CI: 1.05-1.11). We saw no association between cotinine concentrations and risk in never smokers, with the exception of men from the United States whose cotinine levels may be indicative of active smoking (OR: 1.17, 95% confidence interval [CI]: 1.02-1.34). Having cotinine levels consistent with active smoking (>115 nmol/L) was more common among self-reported former smokers (cases: 14.6%, controls: 9.2%) and less common among self-reported never smokers (cases: 2.7%, controls: 0.8%). A risk prediction analysis in current smokers indicated that circulating cotinine combined with self-reported smoking can provide a small improvement in discrimination between future lung cancer cases and controls in comparison to self-reported smoking alone (improved area under the curve for men: 2%, women: 4%). **Conclusion:** Cotinine as an objective measure of tobacco exposure was consistently associated with lung cancer risk among current smokers, especially women. Former and never smokers with cotinine levels consistent with active smoking also showed increased risk. For lung cancer risk prediction modelling among current smokers, cotinine combined with self-reported smoking performed slightly better than cotinine or self-reported smoking alone.

Keywords: consortium, cotinine, Prospective study

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-002 TOBACCO USE AND PREVALENCE OF HEAD AND NECK CANCERS AMONG MALAYALI TRIBES, YELAGIRI HILLS, TAMIL NADU, INDIA

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Background: India has the second largest tribal population of the world next to the African countries. Despite remarkable world-wide progress in the field of diagnostic, curative and preventive medicine, still there are large populations of people living in isolation in natural and unpolluted surroundings far away from civilisation, maintaining their traditional values, customs, beliefs and myths. Hence the present study was conducted to assess the oral health status, treatment needs among the Malayali tribes in the Yelagiri hills, Tamil nadu. **AIM:** To assess the prevalence of head and neck cancers among the Malayali tribes, Yelagiri Hills, Tamil Nadu, India. To assess the association of tobacco use with head and neck cancers among the Malayali tribes, Yelagiri Hills, Tamil Nadu, India. **Method:** A cross-sectional descriptive study was conducted to assess the tobacco use and head and neck cancer prevalenceamong 660 Malayali tribes in the Yelagiri Hills. Inhabitants of the villages aged 18 to 75 years who were residing for more than 15years were included. Data was collected using a survey proforma which comprised of a questionnaire and WHO Oral Health Surveys – Basic Methods Proforma(1997). The collected data was subjected to statistical analysis. **Result:** .Results showed that among 660 study population, 57.7% had no formal education, 64.5% had indigenous brushing habits. 58% had the habit of tobacco, of which 37% were males and 21% were females. The percentage of oral mucosal lesions observed were as follows: 19.09% leukoplakia, 29% ulceration and 6% malignant tumor. 37% of the study populations had other abnormal conditions like candidiasis and OSMF. Prevalence of oral mucosal lesions in the study population was due to tobacco usage and alcohol consumption and lack of awareness regarding the deleterious effects of the products used. **Conclusion:** The oral health status of Malayali tribes was poor with high prevalence of periodontal disease and dental caries. Oral cancer and cancerous lesions were at a very high percentage. Regular oral examination by dental professionals, dental health education and motivation to maintain oral hygiene should be insisted to improve the oral health status of this community.

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-003 RETROSPECTIVE STUDY OF CEREBRAL THROMBOEMBOLISM OCCURRING BEFORE AND AFTER DETECTION OF LUNG CANCER (TROUSSEAU SYNDROME)

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Background: Armand Trousseau reported the concept of blood coagulation disorders accompanying malignancies in 1865. Currently, Trousseau syndrome is also defined as cerebral infarction due to malignant tumors. Among cerebral infarction patients with cancer, lung cancer (LC) and prostatic cancer are reported to be relatively likely to develop Trousseau syndrome. When it occurs, treatment for cancer is difficult, and prognosis is poor. We conducted a retrospective study of LC patients before and after the onset of cerebral infarction, respectively. **Method:** Among 1,185 cases of patients with LC from 2006 to 2016, we registered 15 cases with complications of cerebral infarction before or after LC detected. Fifteen patients were divided into two groups. One was a group of cerebral infarction before the detection of LC (A group) and the other was a group of infarction complication after LC detection (B group). **Result:** Patient characteristics of A group consisting of 8 cases and B group consisting of 7 cases were as follows, respectively: male/female, 5/3 and 3/4 cases; median age, 67.4 and 72.0 years; small cell lung cancer/squamous cell carcinoma/adenocarcinoma/large cell neuroendocrine carcinoma, 2/1/4/1 and 1/1/4/1 cases; stage I/II/III/IV, 2/1/1/4 and 0/0/2/5 cases; treatment intervention for LC, 8 and 3 cases. Median survival time was respectively 13.7 months for A group and 5.5 months for B group, although there was not significant in Kaplan-Meier survival curve. **Conclusion:** Lung cancer detected after or at the same time of cerebral infarction is considered to have better prognosis since early diagnosis and treatment against LC is possible.

Keywords: Trousseau syndrome, cerebral infarction, lung cancer

P2.06-004 ROLE OF POLYMORPHIC VARIANTS OF BER AND DSBR PATHWAY GENES IN MODULATING LUNG CANCER SUSCEPTIBILITY AND PROGNOSIS OF NORTH INDIAN POPULATION

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Background: DNA repair system uphold individuals' genomic content from consistence impertinence implicated by continuous exposure to DNA damaging agents present in tobacco smoke, ionizing radiations,air pollution etc. BER (Base excision repair) and DSBR (Double strand break repair) are the two important pathways in this respect. However, polymorphic DNA repair genes might modulate the repair capacity and ultimately the survival. **Method:** Genotyping for the SNPs for genes OGG1, MUTYH, XRCC1, XRCC3, XRCC4, XRCC6, XRCC7.was done. Statistical analysis was done using MEDCALC. Logistic regression was used to evaluate the odds ratio. We even did use data mining tools MDR (Multi-dimensionality Reduction) and CART (Classification and regression tree analysis) to analyze the high interacting groups posing high risk. Survival analysis was done using Kaplan meier, and Cox regression analysis. **Result:** Statistical analysis revealed some interesting facts in relation to susceptibility. It was revealed that OGG1 $Ser^{326}Cys$ possessed a potent risk (OR=2.4, p= 0.0003) towards lung cancer whereas mutant genotype (GG) was protective towards lung cancer (OR=0.4, p=0.0185). Further analysis revealed XRCC1 $Gln^{632}Gln$ (OR=2.67, p=<0.001) depicted an overall high risk towards lung cancer. Histological analysis suggested mutant genotype in case of XRCC1 $Pro^{206}Pro$ implied a protective effect for SCLC subtype (OR=0.29, p=0.0017) on the contrary XRCC1 $Gln^{632}Gln$ showed a high risk in SQCC diseased group (OR=4.16, p=<0.0001). A high risk was observed on combining XRCC1 $Gln^{632}Gln$ with XRCC1 $Pro^{206}Pro$ (OR=5.6, p<0.0004) and $Arg^{194}Trp$ (OR=2.10, p=0.03). MDR analysis showed three factor model including XRCC1 206, 632, 280 was the best model (CVC=10, prediction error=0.34). Further Classification and Regression tree (CART) analysis revealed terminal node 1 carrying mutant of *XRCC1 632* and wild type of *XRCC1 280* represented the highest risk group. Further, survival analysis revealed a minor involvement of XRCC1 SNPs in survival. It was observed mutant genotype for XRCC1 $Arg^{399}Gln$ showed an insignificant better survival (MST=9.6). XRCC1 $Gln^{632}Gln$ showed a high hazards rate for SCLC subtype (H.R=0.26, *p=0.05*). An interesting finding of the study was related to chemotherapy regimen where Cisplatin/Carboplatin+ Docetaxel was observed to increase survival for *XRCC1 399* mutant genotype (AA) (H.R=0.26, *p=0.05*). Cisplatin/Carboplatin+ Irinotecan increased survival in both heterozygotes (*GA*) and combined variants (*GA+AA*) (HR=0.22, p=0.014; H.R=0.23, p=0.012). **Conclusion:** To conclude the polymorphic DNA repair genes affect the susceptibility in lung cancer patients of North Indian population. However, the prognosis is not much altered. The analysis of individualized chemotherapy would help us to develop prognostic biomarkers for individualized therapy.

Keywords: dna repair, polymorhisms, lung cancer

P2.06-005 AN EXPLORATION OF ATTITUDES AND BARRIERS TO UPTAKE OF LUNG CANCER SCREENING IN AT RISK ADULTS IN THE UNITED KINGDOM

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Background: Lung cancer screening targets a high risk subgroup of the population, comprising current and ex-smokers. There are data to suggest that smokers view screening in a nihilistic way and perceive early detection to be of limited use and, as such, are less likely to consider screening participation. Other screening programmes have also shown markedly reduced uptake in those from the most deprived groups. Smoking rates and lung cancer incidence are highest in more socially deprived areas and lung cancer survival is worst in this group. An understanding of the key barriers to engagement with lung cancer screening is therefore vital prior to implementation of a national screening programme. **Method:** Focus groups were established in socially deprived communities within the East Midlands, United Kingdom, using community contacts. The Framework approach was used to analyse data into themes and sub-themes. To supplement these focus groups, questionnaires were developed and purposive sampling used to try to obtain a maximum number of views from a cross-section of the deprived communities. Participants were smokers or ex-smokers aged 40 years or older. **Result:** Recruitment to focus groups was very challenging, despite remuneration being offered. In total there were 13 participants and a further 56 people responded to questionnaires. Key barriers to screening participation identified were accessibility, with many participants preferring community-based drop-in sessions, perceived stigma and blame surrounding smoking and fear and nihilism regarding a lung cancer diagnosis. Although many were supportive in principle around the idea of screening, they felt that the way it was presented to them was crucial. Participants emphasised the importance of community engagement and the use of community leaders to talk to those who were eligible for screening in a way that they could understand and thus promote it rather than it coming from a medically qualified individual. **Conclusion:** This work gives an insight into some of the ideas and opinions around lung cancer screening and highlights some barriers that need to be addressed prior to implementation of a national screening programme. A combination of practical and emotional barriers, alongside the role of community engagement and education were identified as important. As lung cancer screening will focus on a high-risk group of smokers and ex-smokers, their perception of smoking stigma and blame will need to be addressed in a non-judgemental way and novel education and invitation material may need to be developed, delivered through community approaches, to promote screening in a positive light.

Keywords: qualitative methods, lung cancer screening

P2.06-006 SCREENING VALUES OF CEA AND CYFRA 21-1 FOR LUNG CANCER IN COMBINATION WITH LOW DOSE CT (LDCT) IN HIGH-RISK POPULATIONS

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Background: Lung cancer screening with low-dose CT (LDCT) decreased lung cancer mortality. However, its major limitation for high false positive rate was concerned. Tumor markers in combination with LDCT may increase its screening value for lung cancer. **Method:** In this prospective LDCT screening study, we enrolled subjects who were former or current heavy smokers (>30 pack-years) aged 50-70 years. The LDCT screening results were classified as negative, indeterminate, or positive (suspicious for primary lung cancer) based on the probability for lung cancer, mainly focused on nodule size and opacity at baseline LDCT and new or nodule growth at the follow-up LDCT. Serum CEA and Cyfra 21-1 were taken only from subjects with indeterminate and positive LDCT result with a cut-off level of 5 ng/ml and 4 ng/ml, respectively. These markers were followed with LDCT at least once a year. Positive tumor marker was defined as an abnormal level of either CEA or Cyfra 21-1. **Result:** Among 634 high risk subjects investigated, there were 70 subjects who had indeterminate LDCT and 22 subjects who had positive LDCT at initial screening cycle. A total of 17 lung cancer cases were diagnosed in 2 years, 9 from initial screening and 8 from follow-up cycles. The likelihood ratio of positive (LHR+) for lung cancer diagnosed in 12 months with positive tumor marker was 6.61 (p=0.003) among subject with indeterminate baseline LDCT, and 1.51 (p=0.670) among those with negative. LHR+ for lung cancer diagnosed after 24-month follow up was 6.31 (p<0.001) and 0.86 (p=0.881) respectively. The LHR+ for lung cancer diagnosed in 12 months among subjects with positive baseline LDCT, with positive and negative tumor marker was 69.44 (p<0.001) and 11.57 (p=0.015), respectively. The corresponding LHR+ for 24-month cancer was 13.61 (p<0.001) and 18.15 (p<0.001), respectively.The crude AuROC of parallel CEA/Cyfra 21-1 & LDCT and of CEA & LDCT for lung cancer screening in combination with LDCT were significantly higher than LDCT alone (0.76 VS 0.68, p=0.033 and 0.75 VS 0.68, p=0.038, respectively). The AuROC was also significantly higher after adjusted for age & smoking status (0.84 VS 0.80, p=0.019, and 0.84 VS 0.80, p=0.029, respectively) **Conclusion:** CEA in combination with LDCT significantly increased values for lung cancer screening in high-risk populations than using LDCT alone particularly in participants in patients with indeterminate baseline LDCT.

Keywords: tumor markers, lung cancer screening, low-dose CT

P2.06-007 DEMOGRAPHIC CHARACTERISTICS OF LUNG CANCER AND ASSOCIATION WITH WOOD SMOKE IN MEXICAN POPULATION

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Background: Retrospective, longitudinal, unicentric and cohort study that analyzes the demographic characteristics of the Mexican population with lung cancer and its association with wood smoke exposure. **Method:** The study had 123 patients pathologically diagnosed with lung cancer between January 2013 to January 2014 at the National Institute of Respiratory Diseases. The primary endpoint was the histological type of lung cancer and the secondary the rate of exposure to wood smoke. Two cohorts were analyzed, the first with patients without exposure to wood smoke and the second with no exposure. **Result:** The sample was formed by 68 men (55.3%) and 55 women (44.7%). They were smokers in 47.2% of the patients, with an average of 12.7 packs/year. The 47.15% had exposure to smoke from wood, with an average of 77.5 hours/year. The 88.6% had non-small-cell lung cancer (69.9% adenocarcinoma, 11.4% squamous and 7.3% other types), and 11.4% small cell lung cancer. The EGFR mutation was positive in 21% of adenocarcinomas. Patients with diagnosis of adenocarcinoma had the highest exposure to wood smoke (p<0.003). The cohort for exposure to wood smoke was significant for the development of lung cancer was 61 hours/year (p <0.001). **Conclusion:** The histological type of lung cancer most prevalent was adenocarcinoma, present in women with high exposure of wood smoke. The cohort of 61 hours/year was determined as a risk factor, the latter is not a

predictor of EGFR mutation.

Keywords: Lung cancer, wood smoke, Mexico

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-008 DIAGNOSIS OF INCIDENTAL DISEASE IN MEDICAID RECIPIENTS DURING LUNG CANCER SCREENING

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Background: The National Lung Screening Trial (NLST) reported reduced all-cause and lung cancer- specific mortality among patients screened for lung cancer with low-dose computed tomography (LDCT). NLST subgroup analyses have shown even greater mortality reductions among socioeconomically disadvantaged racial minorities due to abnormalities other than pulmonary nodules discovered on LDCT. These incidental findings (IFs) often represent clinically significant undiagnosed disease in socioeconomically disadvantaged individuals. In early 2015, the Center for Medicare/Medicaid Services (CMS) added lung cancer screening as a preventive service benefit, which led to the widespread implementation of lung cancer screening programs across the country. Our study aims to quantify the association between insurance type, and the discovery of clinically significant undiagnosed disease on LDCT in high-risk smokers. **Method:** This retrospective cohort study provides a preliminary analysis of electronic health record data from The Ohio State University Lung Cancer Screening Program from September 2016 (when Medicaid coverage for lung cancer screening took effect) to March 2017. Eligible participants met CMS criteria for annual lung cancer screening with LDCT. The outcome of interest was major IFs discovered on LDCT (e.g. coronary artery disease, vascular disease, emphysema) not previously identified in the patient's medical history. Logistic regression analysis was conducted to estimate odds ratios (ORs) to quantify the association between insurance type (Medicaid, Medicare/VA and private) and new incidental diagnosis (yes/no) adjusting for age, gender, race, and smoking history. **Result:** Data from130 patients who had a first-time lung cancer screening were analyzed. Two-thirds of participants were male, 39% were non-white and 57% were current smokers, with mean age of 63 years (SD=5.4). Almost 20% of participants (n=25) received Medicaid, 42% received Medicare/VA (n=54) and 38% had private insurance (n=49). Multivariable logistic regression analysis revealed that the odds of new incidental diagnoses were 8 times higher for patients with Medicaid versus private insurance (OR=8.0; 95%CI=2.6,24.9; p<0.001). The odds for IF were 3.5 times higher when comparing Medicaid versus Medicare/VA (OR=3.5; 95%CI=1.0,11.9; p=0.0430). Covariates age and race were significantly associated with a new IF (OR=2.9; 95%CI=1.03,8.4; p=0.0432 for age and OR=2.5; 95%CI=1.1,5.8; p=0.0328 for race), but gender and smoking history were not statistically significant. **Conclusion:** These results demonstrate increased clinically significant previously unidentified IFs among Medicaid-insured high-risk smokers, and suggest that LDCT lung cancer screening could provide an opportunity for secondary prevention by diagnosing occult disease in socioeconomically disadvantaged individuals. We will continue to monitor these data as more patients are screened and sample size is increased.

Keywords: lung cancer screening, incidental findings, Medicaid

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-009 TRACE ELEMENTS AFFECT LUNG CANCER SUBTYPES

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Background: The cause and mechanism of lung cancer in "never smokers" are still unclear. Additionally, the onset of driver mutations (e.g., *EGFR*, *ALK*, *KRAS*, and *RET*) and the mechanism of their ethnic difference are unclear. Several studies have suggested that some trace elements may affect the onset of lung cancer. However, the effect of trace elements on lung cancer carcinogenesis is poorly understood. The aim of this study was to assess if trace elements may be the cause of carcinogenesis in lung cancer tissues of patients with lung cancer with a non-smoking history, driver mutations, or histology. **Method:** The study included patients with non-small cell lung cancer who had undergone surgical resection. For the measurement of trace elements, surgically resected formalin-fixed paraffin-embedded lung cancer samples were studied using particle induced X-ray emission analysis. In total, 54 elements were investigated in each sample. *EGFR* mutation, *KRAS* mutation, and *ALK* rearrangement were assessed using commercially available CLIA testing. Based on the pathology and driver mutation status, samples were classified into the following groups: lung adenocarcinoma (LADC) with *EGFR* mutation (LADC EGFRm+); LADC with *KRAS* mutation (LADC KRASm+); LADC without *EGFR* mutation, *KRAS* mutation, and *ALK* rearrangement (LADC wt); and lung squamous cell carcinoma (SCC). Tissues from 20 patients with a non-malignant disease (e.g., pneumothorax) were also analyzed for trace elements as controls. **Result:** In total, 80 patients with non-small cell lung cancer were included. The median patient age was 70years. Of the 80 patients, 30 (37.5%) were males and 72 (90%) had stage I/II disease. The levels of 6 trace elements were increased in the LADC wt group. Copper was increased in the LADC EGFRm+ group. Cobalt and zinc were increased in the LADC KRASm+ group. There were no differences in trace element levels between the SCC group and the control group. **Conclusion:** Trace elements may play a role in the pathology and molecular signature of lung cancer.

Keywords: Trace elements, lung cancer subtypes

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-010 ASSOCIATION OF VITAMIN D RECEPTOR BSMI POLYMORPHISM WITH LUNG CANCER RISK: EVIDENCE FROM A META-ANALYSIS

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Background: Several studies have reported an association between the BsmI polymorphism of vitamin D receptor(VDR) and lung ancer risk; however, the results are inconsistent. In this study, a meta-analysis was performed to assess the association between the BsmI polymorphism of VDR and susceptibility to lung cancer. **Method:** Published case-control and cohort-based studies from PubMed ,Embase, Wanfang, and CNKI were retrieved, and data were manually extracted. The odds ratios (ORs) and 95% confidence intervals (CIs) of the included studies were pooled. Begg's and Egger's test were used to evaluate publication bias. **Result:** Nine articles with 2343 cases and 1578 controls were included. The pooled effect size showed an association between the BsmI polymorphism and the risk of lung cancer (dominant model, OR: 0.58, 95% CI: 0.41–0.82; allele model, OR: 0.67, 95% CI: 0.52–0.86). In a subgroup analysis, a significant association between the BsmI polymorphism and low lung cancer susceptibility was detected among Asians (dominant model, OR: 0.47, 95% CI: 0.35–0.62; allele model, OR: 0.54, 95% CI: 0.41–0.71). **Conclusion:** The BsmI polymorphism was found to be significantly associated with a decreased risk of lung cancer, particularly in Asians.

Keywords: lung cancer, meta-analysis, vitamin D receptor

P2.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.06-011 ASSESSING AND ADDRESSING KNOWLEDGE GAPS TO IMPROVE LUNG CANCER SCREENING RATES

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Background: In 2011, the National Lung Screening Trial showed that annual screening with low-dose computed tomography (LDCT) in high-risk patients reduced lung cancer mortality by 20%. The United States Preventative Services Task Force (USPSTF) now recommends lung cancer screening (LCS) for high-risk individuals (Grade B). Evidence from the National Health Interview Survey suggests that only 2-4% of eligible individuals are referred for LDCT, likely in part due to a lack of familiarity among primary care physicians with LCS guidelines. In this analysis, we sought to obtain a baseline acumen of providers' knowledge and awareness about LCS and develop a series of interventions including embedding USPSTF criteria into electronic medical record (EMR) ordering to educate providers and facilitate more effective use of LCS for high-risk patients. **Method:** We surveyed internal medicine residents at the University of Illinois – Chicago (UIC) General Medicine Clinic (GMC) using paper surveys. The survey included six questions on USPSTF LCS guidelines. Next, educational efforts were addressed through a lecture, email reminders, and informational clinic flyers. The EMR order set was updated to include USPSTF criteria directed ordering. The number of appropriately ordered screens through GMC was tracked monthly. A post-intervention survey was distributed to evaluate if providers' knowledge was improved by educational interventions. **Result:** Fifty-three IM residents were surveyed regarding LCS guidelines and appropriateness for LDCT screening. Of the respondents, 87% knew the correct test for screening was LDCT, 66% knew only smokers with ≥30 pack year history were eligible, 45% knew the minimum age criteria (55 years-old), 28% knew the maximum age (80 years-old), 42% knew interval to re-order screening for a negative test (1 year), and 38% knew the maximum time since quitting (15 years). Following the initial interventions, there was an increase in the volume of appropriately ordered LDCT screening tests ordered through GMC clinic (from 6.8 per month [May 2016 to September 2016] to 10.8 per month [October 2016 to April 2017]). Post-intervention knowledge assessment is underway and will be presented. **Conclusion:** Although LCS is recommended by USPSTF, there are gaps in knowledge about eligibility criteria among internal medicine residents. We present data that suggests using educational interventions and changes in EMR to increase awareness and knowledge is associated with an increase in appropriate usage of LDCTs for LCS. Ultimately, we plan to broaden these interventions to additional primary care clinics (eg., Family Medicine, Pulmonary) to improve proper use of LCS at our institution.

Keywords: National Lung Screening Trial, lung cancer screening, low-dose computed tomography

P2.07-001 CLINICOPATHOLOGICAL CHARACTERISTICS OF NSCLC PATIENTS WITH NIVOLUMAB-INDUCED PNEUMONITIS

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Background: Nivolumab, an immune checkpoint inhibitor, exerts anti-tumor effects against various types of malignant tumor, whereas all usual care should be taken to its related adverse events including immune-related adverse events (irAEs). Of these events, nivolumab-induced pneumonitis, which infrequently develops but sometimes results in a fatal outcome, requires an early detection and prompt response. The purpose of this study was to understand the pathogenesis of nivolumab-induced pneumonitis, leading to avoiding its onset and increase in severity. **Method:** We retrospectively compared the clinicopathological characteristics between patients with malignant melanoma (M; n = 2) and those with non-small cell lung cancer (NSCLC) (L; n = 2), all of whom developed nivolumab-induced pneumonitis in Tokyo Medical University Hachioji Medical Center. **Result:** The patients with a median age of 64.5 years (L; 52 years: M, 73 years) were all males, and all NSCLCs consisted of adenocarcinoma histology. The median time from diagnosis to initiation of nivolumab treatment was 34.5 months (L; 33 months: M; 43 months), and that from the initiation of nivolumab treatment to the onset of pneumonitis was 15 days (L; 12.5 days: M; 139.5 days). Image findings showed a non-specific interstitial pneumonia (NSIP) pattern ameliorated by only treatment cessation in one patient with malignant melanoma and organizing pneumonia (OP) patterns that improved with corticosteroids and oxygen inhalation in other three patients. The median survival time from the initiation of nivolumab treatment was 165 days (L; 140.5 days: M; 489 days), and one patient with malignant melanoma who developed the pneumonitis 262 days after nivolumab treatment was successfully retreated with nivolumab. **Conclusion:** Nivolumab had a high incidence of drug-induced pneumonitis, which consisted mostly of OP patterns highly responsive to corticosteroids. Particular attention should be paid to an early onset after the initiation of treatment.

Keywords: non-small cell lung cancer, Nivolumab, pneumonitis

P2.07-002 DRUG-RELATED PNEUMONITIS IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH COMMERCIAL PD-1 INHIBITORS

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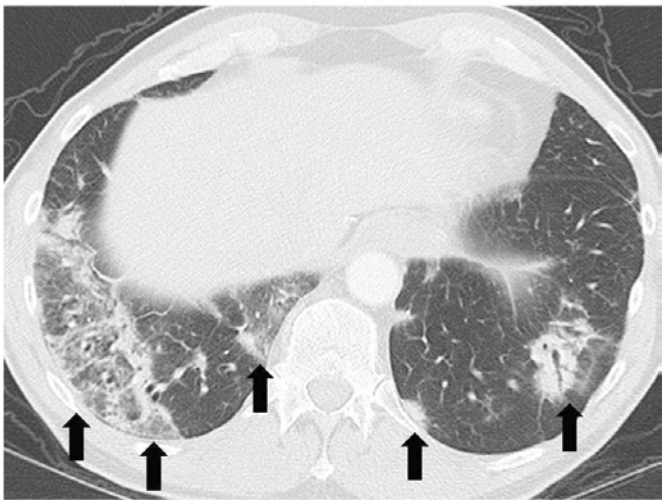
Background: PD-1 inhibitor-related pneumonitis is recognized as a serious immune-related adverse event especially among NSCLC patients. The study investigated the radiographic patterns, clinical course, and risk factors of pneumonitis in advanced NSCLC patients treated with commercial PD-1 inhibitors. **Method:** The study included 210 patients (93 men, 117 women; median age: 65) with advanced NSCLC treated with commercially prescribed single-agent nivolumab or pembrolizumab. Chest CT scans during therapy were reviewed for abnormalities suspicious for pneumonitis by an independent review of two radiologists. Radiographic patterns of pneumonitis were classified using the ATS/ERS classification of interstitial pneumonia. **Result:** Pneumonitis was radiographically detected in 20 patients (20/210; 9.5%). Median time from the initiation of therapy to pneumonitis was 7.8 weeks. The radiographic pattern of pneumonitis was a cryptogenic organizing pneumonia (COP) pattern in 18, a non-specific interstitial pneumonia (NSIP) pattern in one, and a hypersensitivity pneumonitis (HP) pattern in one patient. Fifteen patients (75%) were symptomatic and 5 patients (25%) were asymptomatic with radiographic abnormalities alone. PD-1 inhibitors were held in 17 patients (85%), and corticosteroids were given in 12 patients (60%). Seven patients were hospitalized for treatment of pneumonitis. Three patients were re-treated with PD-1 inhibitors and two developed recurrent pneumonitis. There were no significant differences in clinical characteristics between patients with and without pneumonitis (p>0.34).

PD-1 pneumonitis with a COP pattern in a NSCLC patient treated with nivolumab.



Conclusion: PD-1 inhibitor-related pneumonitis was noted in 9.5% of the advanced NSCLC patients treated with commercially prescribed PD-1 inhibitors. Radiographic pattern of pneumonitis was most commonly a COP pattern. Recurrent pneumonitis was common among those who were re-treated with PD-1 inhibitors. Further studies are necessary to identify risk factors for pneumonitis.

Keywords: PD-1 inhibitors, pneumonitis, Non-small-cell lung cancer

P2.07-003 NIVOLUMAB FOR PATIENTS WITH EGFR MUTATION-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Programmed death-1 (PD-1) inhibitor, nivolumab, is one of the standard second-line treatments for advanced non-small cell lung cancer (NSCLC); however, its efficacy for patients with epidermal growth factor receptor (EGFR) mutation is still debatable. **Method:** We retrospectively reviewed the medical records of 82 patients with advanced NSCLC who were treated with nivolumab at Kyoto University Hospital between December 2015 and December 2016, and identified 24 patients harboring EGFR mutation. In this analysis, 1) treatment effect was compared between patients with and without EGFR mutation, and 2) clinical characteristics affecting the efficacy of nivolumab were examined in patients with EGFR mutation. **Result:** Overall response rate (ORR) was 13% and disease control rate (DCR) was 44% in the entire population. ORR (8% versus 15%, p=0.37) and DCR (25% versus 51%, p=0.024) were lower in patients with EGFR mutation compared with those in patients without EGFR mutation. Median progression-free survival (PFS) was 2.0 months for the entire population (95% confidence interval [CI], 1.73-2.57), and 1.8 and 2.2 months for EGFR mutation-positive and EGFR mutation-negative patients, respectively (hazard ratio [HR]=0.68 (95% CI, 0.4-1.19), p=0.17). In the EGFR mutation-positive population, higher Brinkman index and shorter response duration with precedent EGFR-TKI were correlated with longer PFS with nivolumab. Three patients with EGFR mutation achieved durable disease control lasting more than 1 year, two of whom harbored uncommon EGFR mutation (G719X). **Conclusion:** Nivolumab had limited efficacy in EGFR mutation-positive NSCLC patients; however, some patients derived meaningful clinical benefit from nivolumab. Further studies are warranted to elucidate the clinical characteristics predicting the efficacy of nivolumab in this population.

Keywords: Nivolumab, EGFR, NSCLC

P2.07-004 IMMUNE-RELATED ADVERSE EVENTS (IRAES) OF NIVOLUMAB PREDICTS CLINICAL BENEFIT IN ADVANCED LUNG CANCER PATIENTS

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Background: Immune checkpoint inhibition (ICI) has now become the new standard treatment for non-small-cell lung cancer (NSCLC). However, immune-related adverse events (irAEs) are frequently observed. In melanoma, those patients who had irAEs were shown to be associated with prolonged overall survival. Little is known about

the correlation between the development of irAEs and clinical efficacy in NSCLC patients. **Method:** Patients with advanced NSCLC treated with nivolumab monotherapy at Sendai Kousei Hospital (n=70) between January 2016 to March 2017 were included in our study. Subjects were categorized into either the irAEs-incident group (IrAEs group) or non-irAEs-incident group (Non-irAEs group) and were evaluated with respect to objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall-survival (OS), and treatment continuation rate. They were also further divided into either responder group or non-responder group, and we analyzed predictive factors of treatment responses. **Result:** The median onset of irAEs incidence was 42 days, and categorization of irAEs identified 5 cases of interstitial pneumonia (7%), 5 cases of infusion reactions (7%), 22 cases of skin reactions (31%), 4 cases of neuromuscular disorders (6%), 7 cases of thyroid dysfunction (10%), and 1 case of hepatitis (1%). The following were observed: patient background (IrAEs / Non-irAEs group) number of cases 29/41 cases, median age both 68 years old, male 93% / 83%, treatment response CR/PR/SD/PD (0/17/10/2)/ (1/2/12/26), ORR 59% (17 cases) / 7% (3 cases) [Odds ratio: 0.06, p <.001], DCR 93% (27 cases) /37%(15 cases) [Odds ratio: 0.04, p<.001], Median PFS (months) NR/3.0 [HR (95% CI) 0.15 (0.06–0.39), p =0.001], Median OS (months) NR/10.8 [HR (95% CI) 0.31 (0.10–0.93), p=0.0275], treatment continuation rate 69% (20 cases)/34% (14 cases) [Odds ratio: 0.24, p = 0.014]. The number of subjects in the responder group was 20 and that in the non-responder group is 50. Univariate analysis identified a significantly higher occurrence of irAEs in the responder group than in the non-responder group as well as the number of patients with higher positivity of anti-thyroid-antibody. Upon multivariate analysis, the development of irAEs [Odds ratio: 0.05, p <.001] and the positivity of anti-thyroid antibody [Odds ratio: 0.16, 0.022] were identified as independent predictors of treatment response. **Conclusion:** The development of irAEs during nivolumab monotherapy for NSCLC may be strongly correlated with improved outcomes. The development of irAEs and the positivity of anti-thyroid antibody were independent predictors of treatment efficacy.

Keywords: Nivolumab, immune related Adverse event, immune checkpoint inhibition

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-005 IMPACT OF BASELINE LEPTOMENINGEAL AND BRAIN METASTASES ON IMMUNOTHERAPY OUTCOMES IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Central nervous system (CNS) involvement is frequent in NSCLC patients and associated with poor prognosis. However, its impact on immune checkpoints inhibitors' (ICI) outcomes remains unknown. **Method:** We retrospectively collected the clinical and imaging data of a cohort of 271 patients treated with ICI in our institute from Nov. 2012 to April 2017. We analyzed overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR), and CNS outcomes using brain CT scan and/or MRI. Both body and CNS outcomes were assessed prospectively by investigators. **Result:** With a median follow up of 17 months (95% IC 15-21), 259 patients were evaluated, 48 (19%) had CNS involvement before immunotherapy; 225 were (87%) smokers, 78% had PS ≤1, with median age of 63.1; 166 (64%) had adenocarcinoma; 67 (26%) were *KRAS*mut, 14 (5%) *EGFR*mut and 3 (1%) *ALK* positive. PDL1 was ≥1% by immunohistochemistry in 68 (28%), negative in 28 (11%) and unknown in 163 patients. Median number of prior lines was 1 (0-11). The global ORR was 20%. The median OS was 8 months (95% IC 6-11). No difference was observed in OS between CNS+ vs. CNS- population (p= 0.09). The global ORR was 18% vs. 20%, in CNS+ and CNS- patients, respectively (p=1). To date, CNS–relative data are available for 36 patients: n= 32 brain metastasis, n=7 meningeal carcinomatosis, including 4 cytological positivity, n=2 leptomeningeal and n=1 medullar metastasis. Thirty-one patients (86%) had brain target lesions and 15 were evaluable for CNS outcome (CNS progressive disease (PD) before starting ICI and/or no brain radiation therapy (RT) in the previous 6 months. Median interval between consecutive CNS assessments was 2 months. Twenty-two had CNS PD before immunotherapy: 41% (9/22) received radiation therapy (RT) the month before immunotherapy (4 whole brain RT, 5 stereotactic). No differences were observed according to prior RT, with a median OS of 10 months (95%IC 2-NR) vs. 8 months. (95%IC 5-NR) for prior vs. no prior RT (p=0.79). The median OS for the 7 patients with meningeal carcinomatosis was 2 months (0 to 20). The CNS ORR was 27% (4/15, 3 partial, 1 complete response) and CNS DCR was 60% (9/15). One CNS pseudo progression (7%) and one dissociated brain response (7%) were observed. **Conclusion:** CNS involvement did not seem to be associated with a negative impact on immunotherapy outcomes in advanced NSCLC patients. Final analysis of the entire cohort will be presented.

Keywords: Immunotherapy, brain metastases, non small cell lung cancer

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-006 IRINOTECAN AUGMENTED ANTI-TUMOR ACTIVITY OF ANTI-PD-L1 THROUGH ENHANCING CD8 PROLIFERATION REGARDLESS OF ITS HEMATOTOXICITY

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Background: PD-L1 binds PD-1 and B7.1 on effector T cells to induce anergy and blockade of this interaction unleashes antitumor T-cell activity. Irinotecan, a topoisomerase 1 inhibitor, has been widely used for cancer treatment. Although there are numerous clinical studies evaluating combination of standard chemotherapeutic agents and PD-L1/PD-1 inhibitors, irinotecan has not yet been investigated so that there is little information about its compatibility. In this study, we investigated the efficacy of an anti-PD-L1 antibody in combination with irinotecan using mouse models and analyzed the mode of action. **Method:** Mice were inoculated with the syngeneic breast cancer cell line FM3A and anti-mouse PD-L1 antibody (10 mg/kg, anti-PD-L1) was intraperitoneally (i.p.) administered three times a week, and irinotecan (250 mg/kg) was i.p. administered once on the day of treatment initiation (day 1). The number and activation status of immune cells were analyzed by flow cytometry; the CD8+ cell localization in tumor tissue was assessed by immunohistochemistry. Tumor draining lymph nodes were assessed for tumor-specific immunity by an IFN-gamma release assay. **Result:** Despite a transient decrease of lymphocytes in peripheral blood on day 8, irinotecan augmented antitumor activity of anti-PD-L1 on day 19 (Tumor volume [mean ± SD]: Control = 2226 ± 829 mm^3; anti-PD-L1 = 1265 ± 878 mm^3; irinotecan = 1514 ± 775 mm^3 and Combination = 593 ± 558 mm^3). On day 19, in the combination group tumors, a pathologically confirmed significant increase of CD8+ cells was observed vs each monotherapy group. Tumor cell-stimulated IFN-gamma release by lymph node cells was increased in the combination group and anti-PD-L1 group vs control group. Frequency of Ki67+ CD8+ cells in the combination group significantly increased vs each monotherapy group in both tumors and lymph nodes on day 8. Irinotecan was found to increase MHC I and PD-L1 expression on tumor cells and decrease Treg in both tumors and lymph nodes on day 4. **Conclusion:** The anti-tumor activity of anti-PD-L1 plus irinotecan was significantly higher than each agent alone regardless of initial hematotoxicity. Enhanced proliferation of CD8+ cells in both tumors and lymph nodes was considered to be one of the mechanisms of increased tumor specific CD8+ cells. In addition to direct cytotoxic effects on tumor cells, irinotecan increased MHC I and PD-L1 expression and decreased Tregs, which may contribute to combination effects with anti-PD-L1. The present study may provide a rationale to conduct clinical studies of anti-PD-L1 in combination with chemotherapy, especially irinotecan.

Keywords: PD-L1, PD-1, atezolizumab

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P2.07-007 RETROSPECTIVE ANALYSIS OF ANTITUMOR EFFECTS AND BIOMARKERS OF NIVOLUMAB IN NSCLC PATIENTS WITH EGFR MUTATIONS

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Background: Randomized phase III trials demonstrated that nivolumab was significantly more efficacious than docetaxel in previously treated NSCLC patients; however, subgroup analysis indicated that nivolumab had no superior antitumor effects in patients with *EGFR* mutations. Recent studies have shown that predictive biomarkers, such as PD-L1 expression on tumor cells and infiltration of $CD8^+$ T cells into tumor tissues, were associated with response to nivolumab. The present study was conducted to evaluate the antitumor effects and biomarkers of nivolumab in NSCLC patients with *EGFR* mutations. **Method:** We retrospectively assessed 8 *EGFR*-mutated NSCLC patients treated with nivolumab. **Result:** All patients had adenocarcinoma histology. Six patients had 19 deletion, 1 had L858R and 1 had S768I point mutations. During nivolumab treatment, no patients achieved partial response and stable disease. Seven patients had progressive disease and 1 was not evaluable. The median number of cycles was only 2. The median progression free survival and median overall survival from the beginning of nivolumab was 32 days (95% C.I. 7 to 51) and 370 days (95% C.I. 230 to 480). PD-L1 expression (28-8 pharmDx) was observed in 3/2/1 patients before the start of nivolumab using cutoffs of ≥1%, ≥5% and ≥50% tumor cell staining. Immunohistochemistry revealed that $CD4^+$ and $CD8^+$ tumor infiltrating lymphocytes were observed in all patients before nivolumab. **Conclusion:** The current study indicated that nivolumab was not effective in patients with *EGFR* mutations regardless of predictive biomarkers of nivolumab.

Keywords: Nivolumab, EGFR-Mutation, PD-L1

P2.07-008 DOES PD-L1 EXPRESSION OF THE ARCHIVE SURGICAL SPECIMEN OF PRIMARY TUMOR PREDICT THE SENSITIVITY OF RECURRENCE TO NIVOLUMAB IN PATIENTS WITH NSCLC?

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Background: Nivolumab is an immune checkpoint inhibitor targeting human IgG4 programmed death 1 for advanced or recurrent non-small lung cancer (NSCLC), and programmed death ligand 1 (PD-L1) expression of tumor tissue is expected to be a biomarker of the sensitivity to Nivolumab. More recent biopsy is likely to be more suitable since PD-L1 expression of tumor cells is influenced by time or by anti-tumor therapies such as chemotherapy or radiotherapy, and most clinical studies have referred to the PD-L1 expression using the latest biopsy samples before administration of Nivolumab. Therefore, it remains controversial whether PD-L1 expression of the archive specimen obtained at the time of initial surgery for primary disease is correlated with the sensitivity of recurrent diseases to Nivolumab. **Method:** We retrospectively reviewed 10 NSCLC patients who had undergone radical surgery for primary tumor and received Nivolumab for their recurrent diseases. The median interval between the initial surgery and Nivolumab administration was 28.1 months (2-75), and median number of anti-tumor regimens prior to Nivolumab was 2.2 (1-5). Archive specimens of primary tumors and second biopsy samples of recurrent diseases from the 10 patients were stained to measure PD-L1 expression both with the PD-L1 IHC 28-8 pharmDx Daco (assay 28-8), and with the PD-L1 IHC 22C3 pharmDx Daco (assay 22C3). **Result:** Among the 10 patients, complete response (CR)/partial response (PR)/ stable disease (SD)/ progressive disease (PD) for Nivolumab were 1/2/3/4 patients, respectively. All patients had PD-L1 expressions as tumor proportion score (TPS)≧1%, of which 7 showed TPS≧10% in the assay 28-8. All 3 patients (30%) with CR/PR showed TPS≧10%. The TPS obtained by assays 28-8 and 22C3 were similar in 9 of 10 patients. Two patients underwent biopsies for their recurrent sites, which showed decreased PD-L1 expression compared with primary tumor, resulted in PD for Nivolumab. **Conclusion:** The PD-L1 expressions of surgical archive specimen might be almost associated with the sensitivity to Nivolumab, however, time and antitumor therapies may modulate the PD-L1 expressions and might be able to affect the sensitivity to Nivolumab. Further pre-clinical and clinical studies are warranted to evaluate the availability of surgical archive specimen in the treatment of postoperative recurrence by the immunocheckpoint inhibition.

Keywords: programmed death ligand 1 expression, Nivolumab, lung cancer

P2.07-009 MONITORING NIVOLUMAB BINDING AS A METHOD TO CLARIFY THE RESIDUAL THERAPEUTIC EFFECTS IN PREVIOUSLY TREATED LUNG CANCER PATIENTS

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Background: Although the biological durability of Nivolumab, the PD-1 blocking antibody, was reported to continue longer than 12 weeks, the maximum duration of its efficacy, along with toxicity, after discontinuation and the correlation between residual binding and clinical events in cases of sequential therapeutic regimens remain unclear. **Method:** Peripheral blood, pleural effusion and bronchoalveolar lavage fluid were obtained from non-small cell lung cancer patients previously treated with Nivolumab. To evaluate the efficacy of the treatment, we developed a simple technique to identify Nivolumab binding status — complete binding, partial binding and no binding — in T cells from patient samples using flowcytometry, which can also be used to obtain T cell differentiation markers and transcriptome profiles, particularly in the Nivolumab bound T cell population. Based on this method, we tracked the binding status in T cells primarily from peripheral blood in patients who received a sequential therapeutic regimen after Nivolumab treatment. **Result:** While the decrease in frequency of Nivolumab binding after discontinuation was observed in all cases where long term monitoring was possible, Nivolumab binding in T cells from peripheral blood was detected until more than 20 weeks, though effective binding could have ceased before that time point. We found that the direct effects on Nivolumab binding via sequential treatment were limited. Finally, we observed in clinical cases that our monitoring technique was also helpful in understanding the cause of clinical events and its residual efficacy in patients who previously received Nivolumab. **Conclusion:** Monitoring of Nivolumab binding to T cells after discontinuation can be valuable when planning sequential therapeutic regimens in the following ways: estimating the potential residual efficacy, predicting the risk of immune-related adverse events and the time of relapse due to complete loss of efficacy, and investigating the changes in the immune profile in Nivolumab bound T cells.

Keywords: Nivolumab, residual binding, immune profiling

P2.07-010 IMPACT OF CLINICOPATHOLOGICAL FEATURES ON THE EFFICACY OF PD-1/PD-L1 INHIBITORS IN PATIENTS WITH PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER

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Background: The current study aimed to comprehensively investigate the impact of various clinicopathological features on the efficacy of programmed cell death 1 (PD-1) and ligand (PD-L1) inhibitors in patients with previously treated non-small cell lung cancer (NSCLC). **Method:** Randomized controlled trials that compared PD-1/PD-L1 inhibitors monotherapy with chemotherapy or placebo in patients with previously treated NSCLC were included. **Result:** Five trials were included (n = 3025). For all studies, PD-1/PD-L1 inhibitors significantly prolonged overall survival (OS) [hazard ratio (HR) = 0.70; $P < 0.001$] and progression-free survival (PFS) than chemotherapy (HR = 0.86; $P = 0.020$). Subgroup analysis showed that anti-PD-1/PD-L1 monotherapy could markedly improve OS in elderly (HR = 0.69; $P < 0.001$), female (HR = 0.70; $P < 0.001$), never-smoking (HR = 0.73; $P = 0.001$) and histology of squamous cell carcinoma (HR = 0.67; $P < 0.001$) patients but not PFS. Notably, PD-1/PD-L1 inhibitors can not prolong both the OS (HR = 0.76; $P = 0.390$) and PFS (HR = 0.74; $P = 0.210$) of patients with central nervous system (CNS) metastasis whereas patients without CNS metastasis could benefit from anti-PD-1/PD-L1 monotherapy on OS (HR = 0.71; $P < 0.001$). **Conclusion:** PD-1/PD-L1 inhibitors monotherapy could significantly prolong both OS and PFS in patients with previously treated NSCLC. Elderly, female, never-smoking and histology of squamous cell carcinoma patients could also benefit from PD-1/PD-L1 inhibitors monotherapy on OS. However, whether patients with CNS metastasis could benefit from anti-PD-1/PD-L1 monotherapy remains further validation.

Keywords: clinicopathological feature, non-small cell lung cancer, Immunotherapy

P2.07-011 LONG FOLLOW UP FROM PHASE I STUDY OF NIVOLUMAB AND CHEMOTHERAPY IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: This phase I study investigated the tolerability, safety and pharmacokinetics of nivolumab in combination with chemotherapy in Japanese patients with advanced non-small-cell lung cancer (NSCLC). **Method:** Patients who have stage IIIB without indication for definitive radiotherapy, stage IV,or recurrent NSCLC were eligible. nivolumab (10 mg/kg,day 1) and chemotherapy [arm A: cisplatin (80 mg/m^2, day 1) / gemcitabine (1250 mg/m^2, day 1 and 8), arm B: cisplatin (75 mg/m^2, day 1) / pemetrexed (500 mg/m^2, day 1), arm C: carboplatin (AUC 6, day 1) / paclitaxel (200 mg/m^2, day 1) / bevacizumab (15 mg/kg, day 1), arm D: docetaxel (75 mg/m^2, day 1)] were administered every three weeks. Arm A and B were administrated for four cycles and arm C was for four to six cycles as first-line chemotherapy. After that, nivolumab in arm A, nivolumab / pemetrexed in arm B, and nivolumab / bevacizumab in arm C were continued every three weeks as maintenance therapy until disease progression. Arm D were administrated until disease progression as second-line chemotherapy. **Result:** Six patients each in four arms, total 24 patients were enrolled. Median follow-up time was 20.4 months. Progression free survival [median (range)] were 6.3 (0.7-42.2+) months in arm A, 11.8 (1.4-47.4+) months in arm B, 40.7 (5.3-43.5+) months in arm C, and 3.2 (1.9-10.9) months in arm D. Three-year progression-free survival rates were 20% in arm A, 16,7% in arm B, 62.5% in arm C, and 0% in arm D. **Conclusion:** nivolumab 10 mg/kg showed acceptable toxicity profile and encouraging antitumor activity in combination with chemotherapies in Japanese patients with advanced NSCLC. Especially, arm C showed favorable response rate and long progression free survival in this study.

Keywords: chemotherapy, NSCLC, Immunotherapy

P2.07-012 PATTERNS OF RESPONSE TO NIVOLUMAB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Response Evaluation in Solid Tumors (RECIST) criteria were developed

to assess response to cytotoxic therapy. Response to immune checkpoint inhibitors depends on tumor and host factors including the presence of immune cells (IC) in the tumor environment. Organs differ in IC content. We hypothesized that nivolumab was more active in tumor lesions in IC rich than IC poor organs. **Method:** We retrospectively analysed serial computed tomography (CT) scans of patients treated with nivolumab applying RECIST 1.1 criteria to assess overall response (ORR) and response in different organ sites. CT examinations were performed on a 3rd generation dual-source CT system and read by two experienced radiologists. We classified metastatic sites from NSCLC into three groups: 1) IC rich: lymph nodes, 2) IC intermediate: liver, lungs, 3) IC poor: bone, soft tissue. Standard descriptive statistics were used; time-to-event endpoints were analyzed using Kaplan-Meier methods. **Result:** 52 patients with advanced NSCLC were analyzed. Median age was 66 years, 44% were female, 58% had adenocarcinoma, 92% were former or current smokers. Prior to nivolumab treatment start patients had lesions in the lung (42%), liver (25%), lymph node (56%), soft tissue (13%) and bone (23%). In 62% of the patients the primary tumor was still in situ. ORR and disease-control-rate (DCR) were 20% and 45%, respectively. Median overall survival was 11.9 months, median progression-free survival was 2.3 months and median duration of response (DOR) 10.3 months. Response (RR) to nivolumab differed depending on organ site: RR and DCR according to organ sites were 28% and 90% in lymph nodes, classified as IC rich. RR was 8%, 9% and 16% and DCR was 58%, 55% and 81% in liver, lung metastases and primary tumor, respectively, classified as IC intermediate. In IC poor organs RR was 0% in soft tissue metastases and nine out of 12 patients with bone metastases, which included non-measurable non-target lesions only, had progressive lesions at time of overall tumor progression. **Conclusion:** Immunotherapy has differential effects at different organ sites of metastases. Nivolumab treatment appears to be more active in IC rich organs than at IC intermediate and IC poor sites. Our results suggest that the combination of immune checkpoint inhibitors with local treatment strategies to IC intermediate or poor organs should be explored.

Keywords: NSCLC, Immunotherapy, organ-specific response

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P2.07-013 EFFICACY AND SAFETY OF NIVOLUMAB IN NON-SMALL CELL LUNG CANCER WITH PREEXISTING INTERSTITIAL LUNG DISEASE

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Background: Patients with interstitial lung disease (ILD) have a higher incidence of non-small cell lung cancer (NSCLC) and have few treatment options for NSCLC. While immune checkpoint inhibitors (ICI) are used for NSCLC treatment, the incidence of ICI-related ILD in patients with preexisting ILD is still unknown. Therefore, we retrospectively evaluated the efficacy and safety of nivolumab in patients with NSCLC with preexisting ILD. **Method:** We reviewed patients who were administered nivolumab at National Hospital Organization Kyoto Medical Center, Kyoto University Hospital, and Japan Red Cross Fukui Hospital. All patients were initiated on nivolumab therapy between December 24, 2015 and December 31, 2016 and were reviewed until May 31, 2017 or the date of death. We compared the response rate (RR), disease control rate (DCR), overall survival time (OS), incidence of nivolumab-related ILD, and severity of nivolumab-related ILD between patients with and without preexisting ILD. **Result:** Of 173 NSCLC patients administered nivolumab, 14 (8%) had preexisting ILD. The major radiographic pattern of preexisting ILD was a non-specific interstitial pneumonia pattern (10 patients), followed by the usual interstitial pneumonia pattern (4 patients). The RR and DCR were 21% and 57% versus 12% and 40% in patients with and without preexisting ILD (p = .393 and p = .263), respectively. The median OS from the initiation of nivolumab was not reached (95% confidence interval [CI], 4.1 months to not analyzed [NA]) with preexisting ILD and was 11.7 months (95% CI, 7.5 months to NA) without ILD (hazard ratio, 0.71; 95% CI, 0.29 to 1.77). The incidence of nivolumab-related ILD was significantly higher with preexisting ILD than without ILD (50% vs 15%, p = .004); however, the incidence of grade 3 or 4 nivolumab-related ILD was not significantly different in those with and without preexisting ILD (14% versus 6.3%, p = .251). The median time to the onset of nivolumab-related ILD was 2.3 months (range, 0.5 to 4.0 months) with preexisting ILD versus 2.4 months (range, 0.03 to 12.4 months) without ILD. No ILD-related death occurred. **Conclusion:** Treatment with nivolumab in NSCLC patients with preexisting ILD might offer comparable efficacy to that in those without ILD. Although a higher incidence of nivolumab-related ILD was observed in patients with preexisting ILD, incidence of severe nivolumab-related ILD was not significantly different between those with and without preexisting ILD. Additional studies should be conducted to determine the efficacy and safety of nivolumab in patients with NSCLC with preexisting ILD.

Keywords: immune checkpoint inhibitor, programmed cell death-1, interstitial lung disease

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P2.07-014 IMMUNE CHECKPOINT INHIBITORS FOR BRAIN METASTASES OF NON-SMALL-CELL LUNG CANCER

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Background: Immune checkpoint inhibitors have shown clinical efficacy in non-small-cell lung cancer (NSCLC). However, data for efficacy in brain metastasis is limited because patients with untreated brain metastases were excluded in clinical trials. **Method:** We retrospectively evaluated NSCLC patients with brain metastases who had received immune checkpoint inhibitors at Chiba Cancer Center between January 2016 and May 2017. **Result:** Eighteen patients were eligible for this study. Of these, ten were men, and eight were women; median age was 56 years (range, 32–75 years). Fourteen patients had adenocarcinoma, three had squamous cell carcinoma, and one had a transformation from adenocarcinoma to squamous cell carcinoma. Surgery and whole brain radiation was previously performed in four patients each, while stereotactic radiosurgery was performed in nine patients. Four patients were not treated with local brain therapy. Sixteen patients were treated with nivolumab, while two patients were treated with pembrolizumab. Among 16 patients who had assessable brain metastases, one (6%) had a complete response (CR), ten (63%) had a stable disease (SD), and five (31%) had a progressive disease (PD). Among four patients with locally untreated brain metastases, there was one (25%) each with CR and SD, while two (50%) had PD. Seven (44%) patients had worsening of cerebral edema, including one who was treated with glucocorticoids. Immune checkpoint inhibitors had to be stopped in four patients due to worsening of brain metastases; two of them were treated again with immune checkpoint inhibitors after stereotactic radiosurgery. **Conclusion:** Immune checkpoint inhibitors have the potential to improve brain metastases of NSCLC; however, caution needs to be exercised for worsening of cerebral edema in some cases.

Keywords: immune checkpoint inhibitor, NSCLC, Brain metastasis

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-015 REVIVING CHEMOTHERAPY SENSITIVITY AFTER ANTI-CCR4 MAB (MOGAMULIZUMAB) TREATMENT IN LUNG CANCER PATIENTS

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Background: Patients with advanced lung cancer have poor survival, although they have received multidisciplinary therapy. Therefore, the novel effective therapy is needed. In various malignancies, tumor cells escape the host immune defenses, in which regulatory T cells (Tregs) play an important role. Tregs, maintaining self-tolerance and homeostasis in the immune system, suppress antitumor immune responses in cancer patients. Thus, Tregs are crucial in controlling antitumor immune responses. Several clinical studies show that a number of Tregs at tumor site was correlated with poor prognosis and Tregs suppress the antigen-specific T-cell induction in immunotherapy. Therefore, controlling Treg functions is probably promising immunotherapy. The study of adult T-cell leukemia-lymphoma (ATL) revealed that Tregs strongly express CCR4 molecule of a CC chemokine receptor on their surface. The humanized anti-human-CCR4 monoclonal antibody (mogamulizumab) recognizes CCR4 molecule and shows a robust ADCC activity against CCR4-positive cells such as Tregs. Thus, Tregs depletion by mogamulizumab probably enhances the host immune response against the tumor. We recently finished the clinical trial of mogamulizumab treatment in advanced solid cancer, and the monitoring of Tregs in the peripheral blood mononuclear cells during treatment indicated efficient depletion of those cells, even at the lowest dose of 0.1 mg/kg used. **Method:** In this study, we analyzed the response against chemotherapy before and after mogamulizumab treatment in 6 advanced lung cancer patients who were enrolled in the clinical trial. In 3 of those patients, we analyzed the number of immune cells (CD3 T cells and $CCR4^{+/-}$ $FoxP3^{+}$Tregs) and expression of PD-L1 (SP142) on tumor cells in lung cancer tissues by immunohistochemistry at diagnosis and after mogamulizumab treatment. **Result:** Although the patients finished standard chemotherapy and therefore were to be refractory, 4 of 6 patients showed the partial response (PR) in chemotherapy after mogamulizumab treatment. While 2 of 6 patients showed PR in chemotherapy before mogamulizumab. In 3 of those patients, we observed efficient depletion of $CCR4^{+}FoxP3^{+}$Tregs after mogamulizumab treatment in all patients, while $CCR4^{-}FoxP3^{+}$Tregs were detected in lung cancer tissues. In 2 PR patients in chemotherapy after mogamulizumab treatment, we observed increased number of CD3 and PD-1^{+}cells. In one patient, increased PD-L1 expression on tumor cells was observed. On the other hand, in one SD patient in chemotherapy after mogamulizumab, the number of CD3, PD-1^{+} cells, and expression of PD-L1 on tumor cells were decreased. **Conclusion:** Treg depletion by mogamulizumab may induce inflamed tumor microenvironment in some lung cancer patients, and result in reviving chemotherapy sensitivity.

Keywords: CCR4, Treg

P2.07-016 INMUNOTHERAPY: WHICH IS MORE IMPORTANT, CHOOSING PATIENTS WHO WILL RESPOND OR IDENTIFYING THOSE WHO WILL DIE EARLY?

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Background: Nivolumab has been approved in a second line, of non-small cell lung cancer (NSCLC) after the failure of the first line of platinum-based chemotherapy. The use of immunotherapy is assuming a new challenge in the clinical practice of the oncologist, who has to familiarize himself with a different toxicity profile than chemotherapy.The objective of this study is to describe the clinical characteristics of our patients, focusing on the toxicity profile found and trying to find something that will help us to identify patients who are going to have poor early evolution. **Method:** We have reviewed 49 patients treated with nivolumab, from their use in expanded access, until April 2017.Retrospective information was collected on the clinical, pathological, hematological and treatment characteristics of these patients. Statistical analysis was performed using the SPSS software version 21.0. **Result:** The characteristics of the patients are summarized in Table 1.More than half of the patients presented toxicity, in any of their grades, being approximately 56,5 % grades 1-2, and 8% grade 3. Only one patient was presented grade 4 toxicity. The different toxicities are described in Table 1. Attention is drawn to a large number of patients (23) who receive 4 or fewer cycles, who died quickly, most often in the context of rapid progression, and at other times unable to reevaluate the disease. Regardless of these patients, the time of progression was 7.6 months, and the overall survival was 12.6 months, data that can be superimposed on those seen in EECC.

Table 1 - Baseline Characteristics and Toxicity		
Male no. (%) Female no. (%)	36 (73,5 %) 13 (26,5 %)	
Age -yr (Median, range) Age >75 years (%)	62,8 (44- 77) 8,16%	
ECOG Performance Status score (%)	0-1 (91,1 %) 2 (8,9 %)	
Smoking status - Current or former smokers - Never Smoked	 - 87,8 % - 10,2 %	Cumulative tobacco consumption, ≥ 40 Tobacco packs 46,9 %
Comorbidity: -Yes - No	 - 40,8 % - 59,2 %	
Histology: - Adenocarcinoma - Squamous - NSCLC NOS	 - 32,7% - 53,1% - 12,2 %	
Metastatic localitation % - SNC - Hepatic - Bone	 - 20,4% - 16,3 % - 20,4%	
No. of prior systemic regimens (%): - 1 - 2 - 3 or more	 - 69,4 % - 18,4 % - 12, 2 %	
Best response to most recent prior systemic- % - Complete or parcial respones - Stable disease - Progressive disease - UnKnown	 - 30,6 % - 20,4 % - 16,3 % - 32,7 %	
No. doses Nivolumab (median,range)	9,5 (1- 40)	
Toxicity: - Asthenia - Diarrhea - Pneumonitis - Skin reactions - Hepatitis - Thiroiditis - Neurotoxicity - Nephritis	 - 49 % - 16,3 % - 6,6 % - 2 % - 0 % - 8,2 % - 4,1 % - 6,1 %	
Grade of toxicity: - 1 + 2 - 3 - 4	 - 56,5 % - 8,7 % - 2,2 %	
Tumor response with Nivolumab: - Complete response - Parcial response - Stable disease - Progressive disease - Could not be determined	 - 6,3 % - 12,5 % - 29,2% - 16,7 % - 4,2 %	
Progresion after Nivolumab: - No - Yes	- 43,5 % - 56,5 %	

Conclusion: Immunotherapy in NSCLC has become a basic pillar of treatment, presenting a different toxicity profile to that of chemotherapy, which we are learning to manage.

We thought that it would be important, something that discard those patients who were presumed to have a rapid bad evolution.

Keywords: NSCLC, Nivolumab,toxicity,

P2.07-017 ASSOCIATION BETWEEN THYROID DYSFUNCTION AND PROGRESSION-FREE SURVIVAL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER RECEIVED NIVOLUMAB

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Background: Nivolumab is one of immune-checkpoint inhibitors and has the first agent approved by the U.S. Food and Drug Administration for advanced non-small cell lung cancer (NSCLC). However, the rate of objective responses remains at approximately 20%.Additionally, immune-checkpoint inhibitors often have developed immune-related adverse events. We have previously reported that PD-L1 single nucleotide polymorphisms (SNPs) were possible biomarker for efficacy of nivolumab. We investigated the association between genetic polymorphisms in the PD-1/PD-L1 gene and clinical outcome for nivolumab including response and adverse events. **Method:** A total of 68 consecutive patients with NSCLC were treated with nivolumab from December 2015 to October 2016 at Kyoto University. Of these patients, 59 participated in the present study. The remaining 9 patients were excluded from this study because 3 patients declined informed consent, 2 patients had no follow up blood examination, one patient had a history of double cancer and 4 patients had determined as progression disease within 15days from the first administration of nivolumab. Seven SNPs (PD-L1; rs822339, rs1411262, rs2890658, rs4143815, rs2282055, PD-1; rs2227981, rs2227982) were genotyped using TaqMan genotyping assay. Response was assessed as per the Response Evaluation Criteria in Solid Tumors (version 1.1) by investigators respectively. Adverse events were assessed as per the Common Terminology Criteria for Adverse Events (version 4.0) by an investigator. We defined hyperthyroidism as elevated FT4 or FT3 and hypothyroidism as low FT4.We explored the association of adverse events and the PD-1/PD-L1 SNPs subtypes using the Cochrane-Armitage test and Fisher's exact test as appropriate. Difference of progression free survival (PFS) between each group was assessed using the log-rank test. **Result:** Median PFS in this group was 67days (95% confidence interval, 54 to 107 days). Median PFS was significantly longer in patients with thyroid dysfunction than in those without thyroid dysfunction (152 vs 58 days; P = 0.0349). GG and GT genotype of rs2282055 were related to better PFS (82 vs 65 days; P = 0.0311). There were no significant association between thyroid dysfunction and SNPs. However, absence of thyroid dysfunction in patients with TT genotype of rs22282055 suggests that rs2282055 might be related thyroid dysfunction (P=0.1863 Fisher's exact test). **Conclusion:** In the patients treated with nivolumab, GG and GT genotype of rs2282055 might be a predictive biomarker for response and might contribute the occurrence of thyroid dysfunction.

Keywords: SNPs, thyroid dysfunction, Nivolumab

P2.07-018 CORRELATION OF CLINICAL RESPONSE AND XAGE1 IMMUNITY IN LUNG ADENOCARCINOMA

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Background: Cancer/testis (CT) antigen is a class of antigens that express predominantly in the testes and various tumor types. Some CT antigens have been shown to be highly immunogenic and are considered to be attractive targets for cancer immunotherapy.^(We identified XAGE1 as a dominant CT antigen in lung adenocarcinoma (LAD). In this study, we investigated the correlation of clinical response and XAGE1 immunity in LAD. **Method:** XAGE1 antigen expression and immune checkpoint molecules were determined with tumor tissues by immunohistochemistry. The XAGE1 antibody and T-cell immune responses, as well as immune cell phenotypes, were analyzed with blood samples.^(The overall survival (OS) of the XAGE1 antigen-positive and -negative, and XAGE1antibody-positive and -negative patients were investigated. **Result:** The XAGE1 antigen is expressed in 30 to 40% of LAD. In pStage I-IIIA LAD, expression of the XAGE1 antigen was correlated with shortened OS in both Hokkaido (n=77) and Kawasaki (n=120) cohort, suggesting its relation to malignancy. Based on the expression profiles of XAGE1, and immune checkpoint molecules of PD-L1 and Galectin-9 on tumor cells, we developed a discriminant function capable of efficiently predicting OS in pStage I-IIIA LAD. The XAGE1 antibody response was observed 6% (9/155) in pStage I-IIIA, and 20% (34/167) in cStage IIIB-IV LAD, respectively, suggesting a higher antibody response rate in more advanced stage patients. In the antibody-positive patients, CD4 and CD8 T-cell responses were frequently elicited, and phenotypic and functional analyses of T cells indicated immune activation. Furthermore, we revealed that the OS of antibody-positive patients was prolonged significantly compared with that of antibody-negative patients with either XAGE1 antigen-positive EGFRwt (31.5 vs. 15.6 months, P = 0.05) or EGFRmt (34.7 vs. 11.1 months, P = 0.001) LAD. Multivariate analysis showed that XAGE1 antigen expression was a worse predictor in patients with EGFRmt tumors (HR: 5.23). On the other hand, the presence of the XAGE1 antibody was a strong predictor for prolonged OS in patients with XAGE1 antigen positive tumors (HR: 0.18) and in patients with either EGFRwt or EGFRmt tumors. **Conclusion:** Frequent antibody and T cell responses indicate the strong immunogenicity of the XAGE1 antigen. The findings suggest that production of XAGE1 antibody predicts good prognosis of lung

adenocarcinoma patients as an immune biomarker and sheds light on the role of the protective effect of this naturally occurring immune response supporting the concept of immunotherapy.^(

Keywords: lung adenocarcinoma, XAGE1, Immune response

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P2.07-019 ROLE OF ANTI-ANGIOGENESIS ON THE PROGNOSIS IN ADVANCED NON-SMALL CELL LUNG CANCER WHO ARE TREATED WITH IMMUNOTHERAPY

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Background: Recent development of cancer immunotherapy such as anti-PD-1 inhibitors improved outcome and changed therapeutic landscape in advanced non-small cell lung cancer (NSCLC). However, systemic treatment prior to immunotherapy might influence host T-cell function and therapeutic outcome. Previous anti-angiogenesis treatment may positively or negatively affect outcome of subsequent immunotherapy. **Method:** We conducted a retrospective review of advanced NSCLC patients who were treated with anti-PD-1/PD-L1 inhibitor at University of Kansas Medical Center. Patient characteristics including prior systemic therapy were investigated for association with therapeutic outcome, which included disease control rate (DCR: CR+PR+SD/CR+PR+SD+PD), progression-free survival (PFS), overall survival (OS), and reason for discontinuation of immunotherapy. Kaplan–Meier curves were fitted and the differences were assessed using Log-rank test. In addition, Cox proportional hazard model was used in order to assess the effects of variables on survival of the patients. Association between anti-angiogenesis treatment and other clinical features was assessed using chi-squared or Fisher's exact test. **Result:** Among 141 patients who were treated with anti-PD-1/PD-L1 inhibitor, we analyzed only those who were treated with nivolumab (n=134). Majority of patients had age<70 (76%), stage IV at diagnosis (66%), nonsquamous histology (58%), male sex (58%), performance status 0-1 (77%), EGFR negative or unknown (94%), one prior systemic treatment regimen (81%), and no prior anti-angiogenesis agent (88%). There was significant correlation between prior anti-angiogenesis and stage IV at diagnosis/nonsquamous histology/higher number of systemic treatment lines. With a median follow up of 22.8 weeks, prior use of anti-angiogenesis agent was significantly associated with shorter PFS (Table). There was also a trend of inferior DCR and OS (Table). Multivariate analysis demonstrated that prior anti-angiogenesis agent use had shorter PFS (p=0.0444) and OS (p=0.0741). Frequency of adverse event for reason of discontinuation was not statistically significant.

Table: Influence of prior anti-angiogenesis treatment

Prior anti-angiogenesis	N	DCR%	median PFS (weeks)	median OS (weeks)
Yes	16	30.0	8.29	13.1
No	118	60.7	11.3	27.5
P-value		0.0912	0.0060	0.1697
Statistical method		Fisher's exact	Log-rank	Log-rank

Conclusion: This retrospective analysis suggests prior exposure to anti-angiogenesis agent negatively impact on therapeutic outcome of cancer immunotherapy.

Keywords: Nivolumab, non-small cell lung cancer, Anti-angiogenesis

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P2.07-020 DISTINCT IMMUNE STATUS IN PATIENTS WITH ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA: IMPLICATION FOR IMMUNOTHERAPY OF NSCLC

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Background: Lung cancer is the leading cause of cancer mortality worldwide therefore understanding the role of immune system in antitumor immunity is of a great interest. Here we compared immune cell infiltration and responses in tumors and non-tumoral lung tissue from 43 adenocarcinomas (AC) and 39 squamous cell carcinomas (SCC) of non-small cell lung cancer patients. **Method:** In this study we compared immune cell populations, T cell responses and secreted cytokines in primary tumors and non-tumoral lung tissue as well as in blood of non-small cell lung cancer (NSCLC) patients undergoing neoadjuvant surgery. Moreover, we compared immune suppressive populations such as $CD4^+CD25^+Foxp3^+$ T regulatory cells and myeloid-derived suppressor cells (MDSC). **Result:** Whereas T, B and NK cells infiltration was comparable in AC and SCC, the number of dendritic cells was lower in SCC tumors. $CD8^+$ T cell and NK cell proliferation, IFN-γ-production from T cells and secretion of proinflammatory cytokines after stimulation *in vitro* was lower in SCC compared to AC tumors. A higher number of Tregs was detected in tumors and blood of AC patients, whereas a higher number of MDSC was found in SCC patients. The suppressive function of Tregs was comparable between AC and SCC patients, but MDSC in SCC patients displayed a higher suppressive function as shown by inhibition of CD3z expression and IL-2 and IFN-γ production in T cells, Lox-1 plasma concentrations compared to AC patients and age-matched controls. **Conclusion:** Our results suggest that immune system of SCC patients might be subjected to higher immunosuppression than AC patients. Our observations also give rationale to target specifically MDSC in SCC patients and Tregs in AC patients for designing combinatorial immunotherapeutic approaches.

Keywords: Non-small cell lung cancer, tumor infiltrate, immune suppression, immunotherapy

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P2.07-021 A CHECKPOINT MOLECULE B7-H3 AS A NOVEL IMMUNE THERAPY TARGET FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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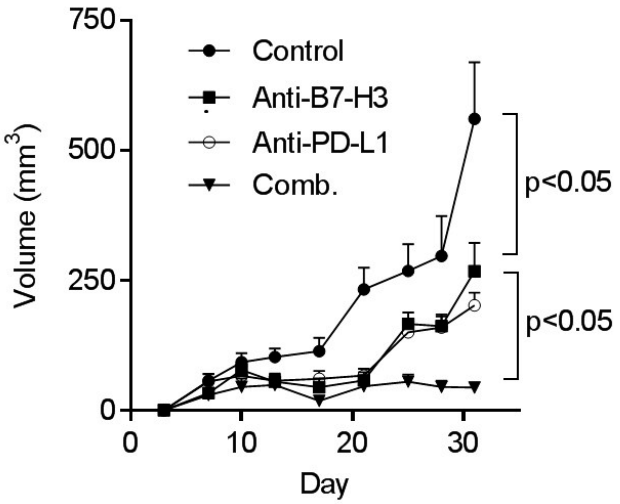
Background: Anti-PD-1 immune therapy improved survival in NSCLC, whereas some patients were not responding to this treatment, indicating the requirement of alternative strategies for these patients. B7-H3, an immune checkpoint molecule, has known to be expressed in some cancer cells including NSCLC. In this study, we examined the therapeutic potential of targeting B7-H3 using a mouse model, also elucidated the expression levels of B7-H3 on NSCLC tumor cells. **Method:** Pan02 murine cancer cells were inoculated in syngeneic mice, and anti-tumor efficacy of anti-B7-H3, anti-PD-L1 antibodies were evaluated. T-cell expression of IFN gamma was evaluated in the spleen and tumor infiltrating lymphocytes using flow-cytometer. B7-H3 expression on tumor cells in patients with NSCLC (n=69) was evaluated by immunohistochemistry. **Result:** In the mouse model study, the treatment with anti-B7-H3 antibody significantly prevented the tumor-growth as compared to isotype antibody. The numbers of CD4+ and CD8+ T-cells infiltrated in the tumor significantly increased following treatment with anti-B7-H3 antibody. Importantly, depletion of CD8+ T-cells cancelled the anti-tumor effect of anti-B7-H3 antibody treatment, indicating that the blockade of B7-H3 potentiates anti-tumor CD8+ T-cell responses. In fact, CD8+ T-cell expressions of IFN gamma in response to tumor cells were improved when mice were treated with anti-B7-H3 antibody. Furthermore, combination with anti-B7-H3 and anti-PD-L1 antibody treatment showed synergic effect in inhibiting tumor-growth. The expressions of B7-H3 were evident on NSCLC tumors, which consists 62% of NSCLC patients. **Conclusion:** Anti-B7-H3 antibody exhibited CD8+ T-cell-mediated anti-tumor effects in the mouse model study. B7-H3 was aberrantly expressed in NSCLC tumor cells. Anti-B7-H3 antibody or its combination with anti-PD-1 antibody is suggested to be effective for patients with NSCLC.



Keywords: PD-1, PD-L1, B7-H3

P2.07-022 INFLAMMATORY CYTOKINE INDUCTION AFTER ANTI-PD-1 AB ADMINISTRATION RELATES TO THE EFFICACY AND SAFETY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: PD-1/PD-L1 interaction affects various immune cells, including macrophage and dendritic cells, which play crucial roles in anti-cancer immunity. Early alteration of inflammatory cytokines, such as IL-6, TNF-α, or CRP, which is a surrogate marker for IL-6, following anti-PD-1 antibody administration may represent activation of those cells and be related to the efficacy and safety of anti-PD-1 antibody treatment; however, these remain unexplored thus far. **Method:** Serum IL-6 and TNF-α were measured with CLEIA/ELISA method in 10 non-small cell lung cancer patients having evaluable serums before and after anti-PD-1 antibody (nivolumab or pembrolizumab) administration. For CRP, medical records were reviewed and serum CRP was measured in 34 non-small cell lung cancer patients before and after anti-PD-1 antibody administration. The relationship of IL-6, TNF-α, and CRP alterations within 7 days with the response rate and frequency of severe adverse events (≥ Grade 3) (SAEs) was analyzed. **Result:** In 10 patients analyzed for IL-6/TNF-α, age was 68 (45 – 74) (median [range]) years, PS 0/1: 7/3, Sqc/Non-Sqc: 4/6, and the days before/after anti-PD-1 antibody administration were 0 (0 – 7)/ 3.5 (2 – 7). IL-6/TNF-α was 20.3 (2.6 – 49.9) pg/mL /1.6 (0.7 – 6.3) pg/mL at pre-treatment, and 22.9 (3.6 – 96.1)/3.3 (0.7 – 9.6) at post-treatment, respectively. Partial or complete responses were seen at 4/7 (57%) and 0/3 (0%) in IL-6 elevated and non-elevated cases, respectively (p=0.048), while 2/6 (33%) and 2/4 (50%) of TNF-α elevated and non-elevated cases showed response (p=0.589). SAEs were significantly frequent in TNF-α elevated cases (3/6 [50%] *vs.* 0/4 [0%] in non-elevated cases, p=0.048). In 34 patients analyzed for CRP, age was 67 (45 – 89); PS 0/1/2/3: 18/12/2/2; Sqc/Non-Sqc: 14/20; the days before/after anti-PD-1 antibody administration: 1 (0 – 7)/ 3 (2 – 7). CRP was significantly increased after anti-PD-1 antibody administration (1.8 [0.1 – 17.8] mg/dL at pre- and 2.4 [0.0 – 27.8] at post-treatment; p=0.001), and in 31 efficacy-evaluable cases, more responses were recognized in CRP-elevated cases (10/22 [45%]) compared to non-elevated cases (1/9 [11%]), although not statistically significant (p=0.054). SAEs were seen in 5/25 (20%) of CRP-elevated cases *vs.* 4/9 (44%) of CRP-non-elevated cases (p=0.17). **Conclusion:** Anti-PD-1 antibody affected inflammatory cytokine production and significantly increased CRP within a week in patients with non-small cell lung cancer. The early induction of inflammatory cytokines after PD-1 antibody administration may have a key role on the induction of anti-cancer immunity and adverse effects.

Keywords: CRP, anti-PD-1 antibody, inflammatory cytokine

P2.07-023 SAFETY OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH PREEXISTING AUTOIMMUNE DISEASE

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Background: Immune checkpoint inhibitors (ICIs), by inhibiting immunosuppressive molecules overexpressed in the tumoral environment like CTLA-4 or PD1, increase the anti-tumor immune response and have been approved for an increasing number of cancers. However, they are responsible for immune related adverse effects (IRAEs), and patients with preexisting autoimmune diseases (PAD) have been excluded from clinical trials evaluating those molecules. The aim of this study was to evaluate their safety in routine practice in patients with PAD and the anti-tumoral response in this population. **Method:** Three national expert networks, focusing respectively on skin cancers, thoracic cancers, and inflammatory diseases, participated in the study. All patients who received an ICI despite a PAD were retrospectively included in this nationwide retrospective study. **Result:** 31 patients were included in the study (19 men (61%), median age of 66). Most frequent PADs were rheumatoid arthritis (n=9; 29%), psoriasis (n=6; 19%), lupus (n=4; 13%), ulcerative colitis (n=3; 10%), and spondyloarthritis (n=3; 10%). Eleven patients were receiving an immunosuppressive therapy when the ICI was initiated, and 10 had an active disease at that time. Neoplasm types were melanoma (n=16; 52%), non-small-cell lung carcinoma (n=12; 39%), and urologic neoplasms (n=3; 9%), with a median disease duration of 19 months. The majority of the patients (30/31) received an anti-PD1 drug, for a median duration of 4 months. PAD flares were frequent (n=18; 58%) but mostly mild: CTCAE grade 1-2 (n=12; 67%), grade 3-4 (n=3; 17%). 14 patients (78%) received corticosteroids or NSAIDs, and 3 (17%) methotrexate or acitretine for the treatment of these flares. IRAEs not associated with PAD appeared in 10 patients (32%): arthralgia (n=5), colitis (n=2), thyroiditis (n=2), vitiligo (n=2) with mild severity. None of the patients received TNF blockers, neither for a flare nor for an IRAE. 5 patients discontinued the immunotherapy because of an adverse effect. Regarding the cancer response rate, 4 patients over 11 who were taking an immunosuppressive treatment were responders (36%), versus 12 over the 20 other patients (60%). **Conclusion** PAD flares are frequent during ICI therapy and other IRAEs are also possible, usually easily managed with corticosteroids only. Anti-tumor response could be reduced when an immunosuppressor is ongoing at the beginning of the ICI, within the limit of the number of patients already so far. Overall, the tolerance of ICIs in patients with PAD seems acceptable, but a multidisciplinary follow-up with the PAD referral physician is appropriate to manage frequent PAD flares and/or IRAEs.

Keywords: Autoimmunity, Immunotherapy, Cancer

P2.07-024 REAL-WORLD DATA OF NIVOLUMAB FOR PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER PATIENTS IN JAPAN: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Background: Real-world data in non-small cell lung cancer (NSCLC) patients treated with nivolumab are currently lacking. This study aimed to obtain a detailed understanding of the characteristics and outcomes of these patients. **Method:** We retrospectively analyzed data for stage IIIB-IV (7th edition) NSCLC patients treated with nivolumab between January 2016 and January 2017. **Result:** A total of 394 patients were included in the study. Most patients had a PS of 0 or 1 (76%) and non-squamous histology (80%). Epidermal growth factor receptor (EGFR) gene mutations were detected in 16% of all patients. Two hundred and seventy-two patients (69%) had received ≥ 2 prior systemic therapies. Response rate was 20.8%, and median progression-free survival (PFS) was 2.2 months. Estimated PFS and overall survival (OS) at 1-year were 17 % and 55 %, respectively. Multivariate analysis using Cox proportional hazards models identified poor performance status (PS 2-4) and *EGFR* mutation as independent predictors of PFS (hazard ratio [HR] 2.17; 95% confidence interval [CI], 1.68 to 2.80, P<0.001; HR 1.44; 95% CI, 1.02 to 2.02, P=0.04, respectively). In 255 patients without these negative predictive factors for PFS, response rate was 27.3%. In these patients, estimated PFS and OS at 1 year were 23% and 64%. Severe immune related adverse events (≥Grade 3) were identified in 11.2% of all patients, and 8.3% of the patients developed pneumonitis (any grade). Overall incidence of pseudoprogression was approximately 2%. **Conclusion:** Nivolumab has demonstrated a favorable efficacy and safety profile in real-world patients. Poor PS and EGFR mutation positivity were independent negative predictive factors for PFS. Importantly, pseudoprogression was rare in real-world patients.

Keywords: Nivolumab, non-small cell lung cancer, Real-world

P2.07-025 INCREASED ANTITUMOR RESPONSE TO CHEMOTHERAPY ADMINISTERED AFTER PD-1/PD-L1 INHIBITORS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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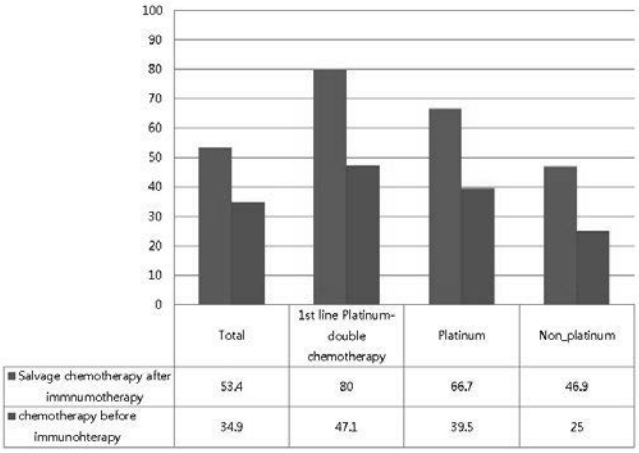
Background: The role of anti-PD-1/PD-L1 inhibitor monotheapy has been demonstrated for advanced non-small cell lung cancer (NSCLC). However, its benefits in terms of response and progression-free survival are limited to small proportion of patients. The successful treatment of advanced NSCLC requires a combination of various treatment modalities. Therefore, this study evaluated whether subsequent chemotherapy administered after immunotherapy (PD-1/PD-L1 inhibitors) (SCAI) would have enhanced antitumor response in patients with NSCLC. **Method:** This study included patients with available response data for their SCAI. We compared the objective response rates of SCIA with those of the last chemotherapy administered before immunotherapy (LCBI). **Result:** In total, 73 patients met the inclusion criteria and were included into the analyses. Among them, 10 patients received PD-1/PD-L1 inhibitors as first-line therapy, and therefore 63 had available response data for LCBI. The ORR of SCAI and LCBI were 53.4% and 34.9%, respectively (P = 0.03). Out of 73 SCAI, 24 were platinum-doublet chemotherapy and 49 were non-platinum monotherapy, and among 63 LCBI, 43 and 20 were platinum-doublet and non-platinum monotherapy, respectively. The ORR for platinum-doublet of SCAI and LCBI were 66.7% (16/24) and 39.5% (17/43), respectively (p = 0.03). The ORR for non-platinum of SCAI and LCBI were 46.9% (23/49) and 25.0% (5/20), respectively

(p = 0.09). 4



Conclusion: The ORR for SCAI was significantly higher than that of LCBI. This data indicate anti-PD-1/PD-L1 inhibitors could make tumors more vulnerable to subsequent chemotherapy.

Keywords: salvage chemotherapy, objective response rate, Immunotherapy

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P2.07-026 NIVOLUMAB IN NON-SMALL CELL LUNG CANCER (NSCLC): FACING THE REALITY

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Background: Nivolumab, a human IgG4 programmed death (PD)-1 immune checkpoint inhibitor antibody, is approved in Israel and other parts of the world, for the treatment of patients with advanced non-small cell lung cancer (NSCLC) and disease progression during or after platinum-based chemotherapy, without a need to determine the level of PD-L1 expression in the tumor. In this series, we retrospectively analyzed the results of treating patients with NSCLC by nivolumab. This series represents real life results, out of a clinical trial, with broad inclusion criteria. **Method:** A retrospective analysis was carried out in a thoracic oncology service in a tertiary medical center (Tel-Aviv Medical Center), on patients with NSCLC, any subtype. All the patients were treated by nivolumab as part of a generous compassionate program supported by BMS. **Result:** The patients were allocated to one single arm of nivolumab 3mg/kg administered intravenously once every 2 weeks. Response assessment was performed in 63/77 patients who got at least four cycles of nivolumab. There was a complete response in 1 patient, partial response in 11, stable disease in 25, progressive disease (PD) in 25. The observed response rate of nivolumab as a service treatment in unselected patients with unknown PD-L1 status adenocarcinoma of the lung was 19 %. The disease control rate was 58.7%. Median progression free survival (PFS) from the first dose of nivolumab to treatment interruption is 4 months. Survival data were analyzed after 22 months. The overall survival was 34.9%, while PFS was 19.3%. All failures of nivolumab occurred within the first 12 months of administration. Median overall survival (OS) from the first dose of nivolumab till death or last follow up when alive, is 8 months. **Conclusion:** Anti PD1 agents are active and well tolerated in patients with NSCLC. This is based on selected population in clinical trials and on non-selected cohorts reflecting daily service in thoracic oncology units.

Keywords: Daily Practice, Nivolumab, NSCLC

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P2.07-027 EFFICACY AND SAFETY OF NIVOLUMAB THERAPY FOR ADVANCED NSCLC IN THE EXPANDED ACCESS NAMED PATIENT PROGRAM IN TAIWAN

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Background: Nivolumab is current standard of care for patients with pretreated advanced non-small cell lung cancer (NSCLC). The patients' and physicians' experience of using nivolumab in real-world clinical practice in Taiwan is unknown. We aimed to evaluate the efficacy and safety of nivolumab therapy in Taiwan. **Method:** We retrospectively reviewed the medical records of the patients with age > 20 years who were diagnosed to have advanced NSCLC and received nivolumab therapy through the Expanded Access Named Patient Program in 2016. Nivolumab 3 mg/kg was administered intravenously every 2 weeks. **Result:** A total of 94 patients were included in this analysis. The median age was 60 years (range, 31-76), and 63.8% of these patients were non-smoker. Most of the patients (75.5%) had adenocarcinoma histology, and 34.0% of the patients harbored an *EGFR* mutation. The median cycle number of nivolumab therapy was 9 (range, 1-28). The median treatment duration was 4.6 months (95% CI, 3.0-6.6). Nivolumab monotherapy is still ongoing in 16 patients (17.0%) on the date of data cutoff. The objective response rate was 13.8%. The median overall survival was 12.0 months (95% CI, 9.2 to not reached). In univariate analysis, sex, age, smoking history, *EGFR* mutation, squamous histology, and previous extracranial irradiation therapy were not predictors of prolonged survival. Only ECOG performance status (PS) < 2 before starting nivolumab therapy was a predictor of prolonged survival (HR: 0.32; 95% CI, 0.17-0.59). The most common treatment related adverse events (AEs) included fatigue (34.0%), nausea (17.0%), rash (12.8%), asthenia (8.5%), and pyrexia (5.3%). Grade ≧ 3 AEs developed in 7.4% of the patients. All grades interstitial lung disease developed in 4.3% of the patients. One patient died of grade 5 diarrhea after one dose of nivolumab therapy. **Conclusion:** The efficacy and safety data in Taiwan were in line with previous clinical trial reports. Patients with PS < 2 may have better survival outcome after receiving nivolumab therapy.

Keywords: Expanded Access Program, non-small cell lung cancer, Nivolumab

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P2.07-028 EFFICACY AND SAFETY OF NIVOLUMAB IN NON-SMALL CELL LUNG CANCER PATIENTS WHO RELAPSE AFTER THORACIC RADIOTHERAPY

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Background: In patients undergoing thoracic radiotherapy (TRT), anti-programmed cell death-1 (PD-1) antibodies including nivolumab and pembrolizumab may enhance cytotoxic effects. However, the risk of pneumonitis may be increased and this issue is truly worthy of consideration. **Method:** We retrospectively evaluated a total of 42 patients with non-small cell lung cancer who relapsed after TRT with or without concurrent chemotherapy and have undergone nivolumab at two institutions between December 2012 and May 2017. **Result:** The median age of all patients was 67.5 years (range 39–76 years), and 5 patients (12%) were female. Five patients (12%) had postoperative recurrent disease, 7 patients (17%) had stage IV disease and the remaining 30 patients (71%) had stage III disease. Thirty patients (71%) received thoracic radiotherapy concurrent with cytotoxic chemotherapy. Eleven patients received nivolumab within 6 months after completion of TRT (Group A) and 31 patients received nivolumab more than 6 months after completion of TRT (Group B). For the patients in this study, response rate (RR) was 19% and median progression-free survival was 3.2 months. Group A had significantly shorter PFS than Group B (Group A; 1.4 months vs Group B; 5.5 months, p=0.018, log-rank test). Nine patients (21%) experienced possible treatment-related pneumonitis, two patients were in Group A and 7 patients were in Group B. All three patients who experienced grade 5 pneumonitis were in Group B; received nivolumab after 9 months, 11 months and 46 months after completion of TRT, respectively. **Conclusion:** Patients who were resistant to TRT had significantly shorter PFS. Regarding pulmonary toxicity, the risk of pneumonitis may be higher in the patients who received nivolumab after TRT and more attention should be paid to the patients who received it more than 6 months of completing TRT.

Keywords: Nivolumab, non-small cell lung cancer, thoracic radiotherapy

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P2.07-029 CHECKMATE 169: SAFETY/EFFICACY OF NIVOLUMAB IN CANADIAN PRETREATED ADVANCED NSCLC (INCLUDING ELDERLY AND PS 2) PATIENTS

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Background: Nivolumab demonstrated efficacy and safety in patients with previously treated advanced/metastatic NSCLC in the two phase 3 trials CheckMate 017 and 057 (median OS, 9.2–12.2 months; 1-year OS rate, 42–51%; 2-year OS rate, 23–29%; any-grade treatment-related AEs [TRAEs], 68%; grade 3–4 TRAEs, 10%). As patients with ECOG PS 2 were excluded from these phase 3 trials, there is limited evidence for nivolumab efficacy in this patient subgroup. CheckMate 169 (NCT02475382) is an expanded access program (EAP) of nivolumab in patients with advanced NSCLC and disease progression after ≥1 prior systemic therapy; efficacy/safety results from the Canadian cohort are presented here. **Method:** Eligible patients were aged ≥18 years with relapsed stage IIIb/IV NSCLC and an ECOG PS of 0–2 who had received ≥1 prior platinum-containing therapy. Patients with carcinomatous meningitis or untreated brain metastases were excluded. Nivolumab (3 mg/kg IV Q2W) was administered until disease progression or unacceptable toxicity for a maximum of 2 years. In addition to providing nivolumab to patients, the primary objective was to assess safety and OS. Outcomes in specific patient subgroups, including elderly patients (aged ≥70 years) and those with poor performance status (PS 2), were assessed in post hoc analyses. **Result:** Of 161 patients treated in Canada, 53% were male, 94% were current/former smokers, 32% had squamous NSCLC, and 43% had received ≥2 prior therapies. 30% were aged ≥70 years and 19% had an ECOG PS of 2. At the time of analysis, 76% of patients had discontinued treatment. Nivolumab was well tolerated. In the overall population, TRAEs of any grade were reported in 69% of patients, with grade 3 or 4 events in 14%; no TR deaths occurred. 9% of patients discontinued due to TRAEs. The safety profile of nivolumab in patient subgroups (age ≥70 years and PS 2) was similar to the overall population. The median OS (95% CI) in the overall population was 9.1 months (7.5, 14.4), with a 1-year OS rate of 44%. The median OS was 8.0 months (5.3, 12.9) for elderly patients and 5.9 months (3.6, 7.9) for those with PS 2. The presentation will include patient case studies from the subgroups. **Conclusion:** In this EAP of nivolumab in Canadian patients with previously treated NSCLC, safety and OS were consistent with observations from prior controlled trials. Safety in elderly patients and those with PS 2 was consistent with the overall population.

Keywords: subgroups, Nivolumab, Expanded Access Program

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P2.07-030 REAL LIFE SECOND-LINE NIVOLUMAB IN ADVANCED NON-SMALL-CELL-LUNG CANCER: A FRENCH OBSERVATIONAL MULTICENTER STUDY OF 259 PATIENTS

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Background: Survival data with nivolumab are based on selected populations and might not reflect outcomes in clinical practice. Overall Survival (OS) and Progression Free Survival (PFS) with anti-PD1 therapy in a large population of unselected patients with advanced Non-Small-Cell-Lung Cancer (NSCLC) are not well documented. We aimed to assess survival data with nivolumab in a large cohort of unselected patients and association of OS with clinical and biological factors. **Method:** Clinical and survival data were collected in a cohort of NSCLC patients treated with nivolumab who experienced confirmed progressive disease (PD) after ≥ 1 line of chemotherapy (CT). Patients received nivolumab at a dose of 3 mg/kg every 2 weeks until PD or unacceptable toxicity. Nivolumab benefit was analyzed according to PFS and OS. The overall response rate (ORR) was analyzed by RECIST 1.1. Age, response to prior CT, eosinophil counts (Ec), prior radiotherapy (RT), lymphocyte counts (Lc), neutrophil counts (Nc), LDH rate were assessed. Kaplan-Meier and Cox regression were performed. **Result:** 257 patients treated with nivolumab were enrolled from 9 centers between Sept. 2015 and Oct. 2016. Median age was 62 years [29-85]; 186 patients were males (72%), 93% PS≤1 at the time of the diagnostic; 220 (86%) smokers; 219 (85%) stage IV ; 130 patients (51%) received prior RT. 163 patients (63%) had adenocarcinoma, 70 (27%) squamous cells carcinoma ; 54 (21%) were KRASmut, 11 (4%) EGFRmut, 3 (1%) ALKpositive. PD-L1 expression was unknown (test not required in current practice for nivolumab). The median of prior lines was 1 [1-6]. Median PFS with nivolumab was 3 months [1,9-4]. Median OS was 15 months [1-; NR]. The ORR was 23% (58 patients), the disease control rate was 42% (109 patients). The median duration of response was 6 months [1- ;16]. Age (> or < 70) (p=0.202), response to prior CT (p=0.05) and Ec ≥ 0.5 G/l (p=0.606) were not significantly associated with improved OS. Prior RT was significantly associated with poor OS (p=0.004). Lc < 1 G/l (p=0.019), Nc ≥ 7 G/l (p=0.018), LDH ≥ 500 U/l (p=0.008), were significantly associated with poor OS.**Conclusion:** 1) Efficacy of nivolumab in real life is the same as reported in published studies with a median OS of 15 months in clinical practice. 2) In our study neutrophil, lymphocyte and LDH rates predict a poor OS.

Keywords: Nivolumab, clinical daily practice, NSCLC

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-031 RELATIONSHIP BETWEEN CLINICAL FACTORS AND THE EXPRESSION OF PROGRAMMED DEATH LIGAND 1 IN LUNG CANCER

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Background: Immune checkpoint inhibitors have progressed a new treatment option in non-small cell lung cancer. The tumor proportion score (TPS) of programmed death ligand 1 (PD-L1) is a predictive biomarker for determining the efficacy of treatment by immune checkpoint inhibitors. However, the relationship between clinical factors and the TPS is not well understood. **Method:** We retrospectively investigated patients whose samples were submitted for TPS evaluation from January 2017 to May 2017 and compared a TPS of 0% with a TPS of over 1% to identify the correlation between clinical factors and the TPS. **Result:** A total of 86 patients had samples evaluated for the TPS within study period. PD-L1 IHC testing was performed using a PD-L1 IHC 22C3 pharmDx kit for all samples. Two samples were determined to be unsuitable. Age, sex, tissue type, smoking history, performance status, stage, and gene mutation status were investigated as clinical factors. The diagnostic procedure, biopsied organ, tissue, or stored samples were investigated for their association with the TPS. The chi-square test was performed for the univariate analysis of all these factors. There was a significant difference in a TPS of 0% and a TPS of more than 1% in patients with ADC (P = 0.0339, odds ratio: 0.352, 95% CI: 0.0427–0.959) and an EGFR mutation (P = 0.0417, odds ratio: 0.427, 95% CI: 0.250–0.729). In addition, female sex tended to be associated with a TPS of 0% (P = 0.0526, odds ratio: 0.575, 95% CI: 0.335–0.986). However, SCC (P = 0.0113, odds ratio: 0.288, 95% CI: 0.0745–0.802), TBLB (p = 0.0278, odds ratio: 0.288, 95% CI: 0.0873–0.0951), and EBUS-TBNA (P = 0.0161, odds ratio and 95% CI: not applicable) were identified as factors associated with a TPS of over 1% in the same statistical analysis. Lymph node biopsy tended to be associated with a TPS of over 1% (P = 0.0643, odds ratio: 0.263, 95% CI: 0.0543–1.28). **Conclusion:** Adenocarcinoma and EGFR mutations are associated with a TPS of 0%, and squamous cell carcinoma is associated with a TPS of over 1%.

Keywords: PD-L1, lung cancer, Immune therapy

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P2.07-032 OUTCOMES OF NIVOLUMAB IN METASTATIC NSCLC PATIENTS VIA THE ACCESS PROGRAM ACROSS MULTIPLE TERTIARY ONCOLOGY CENTRES.

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Background: Immune checkpoint inhibitors are the standard of care for non-small cell lung cancer (NSCLC) patients following first line therapy. There is limited information available on the outcomes of patients receiving these therapies for NSCLC outside of a clinical trial. **Method:** We retrospectively collected data from patients who received Nivolumab for advanced NSCLC on the Bristol-Myers Squibb (BMS) Access Program across four tertiary oncology institutions in Brisbane, Australia, to analyse their outcomes in a real-world setting, and compare these outcomes to those in Phase III randomised clinical trials. **Result:** 85 patients were enrolled to this Ethics Committee approved audit - 32 females (37.6%); 53 males (62.4%); 54, PS 0-1 (63.5%); 30, PS 2-3 (35.3%); median age 67 yrs (range 42-84). 84 patients were evaluable for progression. 20% (17/84) of patients had a radiological partial response (PR) during the course of their treatment, and an additional 22.4% (19/84) patients had stable disease (SD) as their best response. In PS 0-1, 24% (13/54) had a PR, compared with only 10% (3/30) in PS 2-3 patients. The overall median progression-free survival (PFS) was 1.8 months, being 2.7 months in PS 0-1 versus 1.2 months in PS 2-3 patients. Median overall survival (OS) was 5.9 months; 6.5 months in PS 0-1 versus 2.3 months in PS 2-3 patients. Median OS for adenocarcinoma was 6.2 months, versus 4.7 months for squamous cell carcinoma. At 12 months after initiation of nivolumab 34% of patients were alive; 44% PS 0-1 versus 16% PS 2-3 patients. Grade 3 or 4 treatment related adverse events were observed in 10% of patients. Analysis of the prognostic relevance of routine haematological and biochemical parameters is ongoing. **Conclusion:** Nivolumab has clinically significant long term benefits in the treatment of relapsed NSCLC with 12 month survival rates in keeping with clinical trials in PS 0-1 patients. The development of predictive biomarkers remains central to identifying those patients, particularly with poor performance, most likely to benefit from immune checkpoint inhibitors.

Keywords: NSCLC, Immunotherapy, Nivolumab

P2.07-033 ANTI-PD1-INDUCED ROTATOR CUFF INJURY: A CASE SERIES

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Background: Immunotherapy is now part of the standard of care for the treatment of metastatic non-small cell lung cancer (NSCLC). Immune checkpoint blockers, including anti-PD1 and anti-PDL1 therapies are generally well tolerated, but pose a risk of immune-related toxicities. With 40-50% of patients surviving at 12 months post second-line nivolumab treatment, survivorship concerns such as quality of life need to start being considered in these patients. Immune-related musculoskeletal symptoms are often overlooked, but can result in significant morbidity for a patient. **Method:** We present a case series of four patients who developed significant anti-PD1-induced rotator cuff injury during treatment for either metastatic NSCLC or metastatic mesothelioma. **Result:** Three patients were given nivolumab for advanced NSCLC, and one patient was given pembrolizumab for metastatic epithelioid mesothelioma. The severity of rotator cuff injuries ranged from tendonitis and bursitis, to a full thickness rotator cuff tear. One patient had bilateral rotator cuff injuries. The symptoms began 6-12 weeks after commencing immune checkpoint anti-PD1 therapy and resulted in significant morbidity for the patients in terms of daily activities. All injuries were managed conservatively with a combination of steroid injections, anti-inflammatories and physiotherapy. Pembrolizumab was ceased in the mesothelioma patient after 6 cycles, and the musculoskeletal symptoms rapidly resolved. Two of the NSCLC patients ceased nivolumab due to progressive disease, at 5 months and 9 months respectively. The third NSCLC patient continues on nivolumab, with stable disease at 17 months. In the NSCLC patients who had continued on nivolumab despite musculoskeletal symptoms, the rotator cuff injuries settled over time with conservative management. **Conclusion:** Immune-related musculoskeletal symptoms are inadequately reported in clinical trials, but can result in significant morbidity for patients, and therefore may impact on their compliance with immune checkpoint blockade therapy. Increased vigilance and prompt management of this condition within the context of multi-disciplinary care may assist with symptom-control.

Keywords: Rotator Cuff, Immunotherapy, NSCLC

P2.07-034 HEALTH STATUS IN PATIENTS WITH SMALL-CELL LUNG CANCER TREATED WITH NIVOLUMAB ALONE OR COMBINED WITH IPILIMUMAB: CHECKMATE 032

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Background: CheckMate 032 (NCT01928394) is an open-label, phase 1/2 trial evaluating the efficacy and safety of nivolumab monotherapy and nivolumab plus ipilimumab in patients with advanced or metastatic solid tumors. In this study, nivolumab ± ipilimumab showed durable responses, encouraging survival, and manageable safety in patients with small-cell lung cancer (SCLC) that progressed after ≥1 previous platinum-containing regimens. An exploratory objective is to describe changes in patient-reported health status using the EuroQoL-5 Dimensions (EQ-5D) instrument. **Method:** The EQ-5D visual analog scale (VAS; scale: 0–100 [worst–best health]; minimally important difference [MID]=7) was assessed in the treatment period at baseline (week 1 prior to study drug administration) and then every 2 weeks in the nivolumab (3 mg/kg) arm and at baseline and then every 3 weeks in the nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) arm through week 13, and in both arms at subsequent tumor assessments (every 6 weeks until week 24 and every 12 weeks thereafter). After treatment discontinuation, the EQ-5D was assessed at follow-up visits 1 and 2, and at survival visits. EQ-5D VAS mean and mean within-patient change from baseline were estimated at each assessment. Time to first deterioration (TTD) in health status was also evaluated. **Result:** In the nivolumab (n=245) and nivolumab plus ipilimumab (n=156) arms, EQ-5D VAS completion rates were 90% and 85%, respectively, at baseline and remained ≥60% at the last assessment (≥5 patients/arm; weeks 97 and 121, respectively). Baseline mean EQ-5D VAS scores for the nivolumab and nivolumab plus ipilimumab arms were 67.1 and 65.2, respectively, scores similar to a lung cancer population norm (68). With monotherapy, EQ-5D VAS mean within-patient changes from baseline suggested health status stability while on treatment (estimated changes <MID). With the combination, stability was suggested through week 37 (n = 24 at this timepoint); 4/6 subsequent assessments (through week 109) suggested improvements from baseline (estimated changes ≥MID). Mean EQ-5D VAS scores increased over time, approximating the general population norm (80.05) in the nivolumab and nivolumab plus ipilimumab arms from weeks 37 and 49, respectively, onward. Additional data, including TTD, will be presented. **Conclusion:** Preliminary EQ-5D VAS results from CheckMate 032 showed that on-treatment health status in patients with recurrent SCLC remained stable with nivolumab and improved (ie, increases in scores exceeded the MID) with nivolumab plus ipilimumab. For patients remaining on treatment for ≥6 months, mean EQ-VAS scores in both arms trended towards the population norm.

Keywords: EuroQoL-5 visual analog scale, Nivolumab, small-cell lung cancer

P2.07-035 CORRELATION BETWEEN IMMUNE-RELATED ADVERSE EVENTS AND EFFICACY IN NON-SMALL CELL LUNG CANCER TREATED WITH NIVOLUMAB

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Background: Nivolumab has been established as a novel standard of care in patients with pre-treated non-small-cell lung cancer (NSCLC). Patients treated with nivolumab sometimes experience its unique adverse events, called immune-related Adverse Events (irAEs). Given the mechanisms of action of immune-checkpoint inhibitors (ICIs), occurrence of irAEs may potentially reflect antitumor response. Here, we report the clinical correlation between irAE and efficacy in NSCLC patients treated with nivolumab. **Method:** Between Dec 2015 and Feb 2017, 38 advanced NSCLC patients were treated with nivolumab at our institution. All patients were enrolled in our single-institutional observational cohort study (UMIN000024414). We divided the patients into two groups: irAEs group and no-irAEs group and evaluated the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Efficacy was assessed by RECIST version 1.1, and toxicity was graded based on CTCAE version 4.0. **Result:** Of thirty-eight, median age was 68.5 (range, 49 to 86), 74% was male, 68% was non-squamous cell carcinoma, and 82% was performance status of 0-1. Among overall population, ORR was 23.7%, and median PFS was 91 days. Eleven patients (29%) experienced irAEs and median time to onset irAEs was 53 days (range, 14 to 213 days). There was no significant correlation observed between PD-L1 expression on tumor and occurrence of irAEs. Most common irAE was pneumonitis (n = 5) and others were hypothyroidism (n = 4), hyperthyroidism, hypopituitarism, hepatitis, rash and elevated thyroid stimulating hormone (one, each). Patients with irAEs had significantly higher efficacy compared with those without (ORR: 63.6% versus 7.4%, $p < 0.01$ (Fisher's exact test), mPFS: not reached (NR) versus 49 days, $p < 0.01$ (log-rank test). Landmark analysis in patients who achieved progression free ≥ 12 weeks showed a similar trend ($p = 0.07$). Next, we performed additional analyses on correlation with specific irAEs. Patients with pneumonitis and those without demonstrated similar outcome ($p = 0.95$ (log-rank test)). With regard to endocrine irAEs, the similar result was also observed ($p = 0.95$ (log-rank test)). **Conclusion:** In our study, there was a correlation between irAEs and efficacy in NSCLC patients treated with nivolumab. Occurrence of specific irAE was not necessarily associated the efficacy.

Keywords: Non-small-cell lung cancer(NSCLC), Nivolumab, immune-related Adverse Events(irAEs)

P2.07-036 APPROPRIATE USE OF IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NSCLC: EFFECTIVENESS OF UNIQUE CASE-BASED EDUCATION ON CLINICAL DECISION-MAKING

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Background: The past several years have witnessed unparalleled changes in treatment for patients with advanced NSCLC. Although these changes present significant hope, it remains unclear if oncologists have been able to stay current on the breadth of practice changes, and effectively incorporate evidence-base into practice. The objective of this study was to evaluate oncologists' competence regarding the use of immune checkpoint inhibitors (ICI) in the management of advanced NSCLC and the impact of education on narrowing gaps in clinical practices. **Method:** An online education environment that employed video vignettes to simulate practice, presented 3 CME-certified case activities, each illustrating a clinical challenge. Questions regarding point-of-care decisions were posed as a means of testing the oncologist's ability to make treatment decisions and to communicate effectively with patients who have NSCLC. These case activities included patients with non-squamous and squamous NSCLC and who exhibited adverse events. For each activity, an assessment instrument using case-based, multiple-choice questions was administered to compare each oncologist'a responses to questions posed before and after the education was presented. Confidentiality of respondents was maintained, responses were de-identified, and aggregated prior to analyses. McNemar's χ^2 test compared learners› responses from pre- to post-assessment. The activities were launched between October 21, 2016, and December 6, 2016, and data were collected through April 26, 2017. **Result:** 2,399 oncologists participated in at least one of the 3 activities. Responses of 325 participants who answered all questions during the study period were included. Upon completion of the activities, an improvement was observed in oncologists' ability to: Identify the correct evidence-based regimen

including when to use ICIs for a patient that has progressed on first line therapy (76% vs 98%, $P<0.001$) Counsel patients on the expected effectiveness of ICI in patients (69% vs 89%, $P<0.001$) Select the most appropriate monitoring strategy to detect immune-related adverse events in patients receiving an ICI (52% vs 78%, $P<0.001$) Order appropriate tests to identify the etiology of symptoms that appear during treatment (60% vs 92%, $P<0.001$) Properly manage immune-related adverse events due to treatment with ICI (67% at baseline to 88% post education, $P=0.001$) In addition, comfort with prescribing ICIs also increased. **Conclusion:** Use of online, case-based CME utilizing video vignettes to simulate practice improved competence among participating oncologists, demonstrating that online CME can be an effective tool to improve clinical decision-making in the rapidly changing environment of advanced NSCLC disease management.

Keywords: NSCLC, Immunotherapy, Education

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-037 DEVELOPING A PREDICTIVE CLINICAL OUTCOME MODEL FOR ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

Receiving Nivolumab

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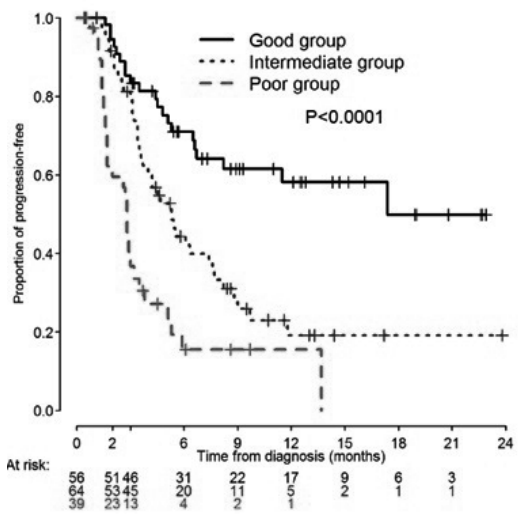
Background: Despite significant improvement of clinical outcomes of the patients with advanced non-small cell lung cancer (NSCLC) receiving immune checkpoint inhibitors, our knowledge of optimal predictive and prognostic biomarkers are still evolving **Method:** We retrospectively evaluated 159 advanced NSCLC patients who received nivolumab after platinum-based chemotherapy. We correlated several variables with progression free survival (PFS) to develop the iSEND model (Sex, ECOG [Performance status], NLR [Neutrophil-to-Lymphocyte Ratio] & DNLR [Delta NLR = NLR after treatment - pretreatment NLR]). We categorized the patients into good, intermediate, and poor iSEND groups and evaluated clinical outcomes of each group. Performance of iSEND model was evaluated at 3, 6, 9, and 12 months by receiver operating characteristic (ROC) curves. We performed bootstrap internal validation to evaluate the predictive performance of the iSEND model by using the split-sample validation technique. We used logistic regression to correlate different iSEND groups and clinical benefit. **Result:** The median follow-up was 11.5 months (95% C.I.: 9.4-13.1). There were 50 deaths and 43 other progressions without death. The 3-, 6-, 9-, and 12-months PFS rates were 78.4%, 63.7%, 55.3%, and 52.2% in the good group, 79.4%, 44.3%, 25.9% and 19.2% in the intermediate group, and 65%, 25.9%, 22.8%, and 17.8% in the poor group, respectively. (Figure 1) Time-dependent area under curves (AUC) of the iSEND model for PFS at 3-, 6-, 9-, and 12-months were 0.718, 0.74, 0.746, and 0.774. The poor iSEND group had significant correlation with progressive disease compared to the good group at 12+/-2 weeks. Figure 1. Kaplan-Meier curves for Progression Free Survival of different iSEND model groups



Conclusion: The iSEND model is an algorithmic model that can categorize clinical outcomes of advanced NSCLC patients receiving nivolumab into good, intermediate, or poor groups and may be useful as a predictive model.

Keywords: biomarker, Advanced Non-Small Cell Lung Cancer, Nivolumab

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-038 THYROID DYSFUNCTION ARISING DURING KEYNOTE-001 ASSOCIATED WITH IMPROVED EFFICACY OF PEMBROLIZUMAB IN NSCLC PATIENTS AT UCLA

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Background: PD-1/PD-L1 blockade has rapidly been adopted for treatment of NSCLC. However, much remains to be learned about the implications of the side-effect profile of PD-1/PD-L1 blockade. We previously showed that the 38 patients who experienced a treatment related AE (trAE) on the KEYNOTE-001 trial at UCLA had superior clinical outcomes compared to the 59 that did not. Treatment related hypothyroidism was the most predictive trAE for response to therapy [objective response rate (ORR): 83.3% (5/6 patients with response)]. The highly predictive nature of treatment related hypothyroidism led us to further evaluate the implications of thyroid dysfunction in our patient cohort by analyzing the association between therapeutic efficacy and thyroid specific laboratory values obtained on trial. **Method:** We performed a retrospective analysis of the 97 NSCLC patients treated on KEYNOTE-001 at UCLA with either 2 mg/kg Q3W or 10 mg/kg Q2/3W of pembrolizumab (data cut-off 12/2016). Patients had Thyroid Stimulating Hormone (TSH), free Thyroxine 4 (fT4), and Triiodothyronine (T3) assessed at baseline (prior to therapy), cycle 2, and every other cycle thereafter. In some instances, labs were obtained at safety follow-up and unscheduled visits. Tumor response was evaluated using investigator assessed immune related response criteria (irRC), with imaging q9wks. **Result:** 97.9% (95/97) of the patients treated at UCLA on KEYNOTE-001 had a baseline set of thyroid indices, while 74.7% (68/97) had $\geq$3 sets of values. Patients with an abnormal TSH during study participation had a higher ORR, 35.5% (11/31), than those that did not, 14.1% (9/64) (p=0.0296), with an acquired TSH abnormality (first observed after C1D1) more predictive of response than a baseline abnormality [acquired TSH abnormality: ORR 42.9% (9/21) vs baseline abnormality: ORR 20% (2/10)]. An abnormal fT4 or abnormal T3 on trial were also both independently associated with improved response to therapy [fT4 abnormality+: ORR: 50% (5/10) vs fT4 abnormality-: 17.7% (15/85) (p=0.0317) and T3 abnormality+: ORR 47.4% (9/19) vs T3 abnormality-: ORR 14.5% (11/76) (p=0.0037)]. As with TSH, acquired fT4 and T3 abnormalities were associated with higher ORR than baseline abnormalities. **Conclusion:** Thyroid dysfunction, assessed by abnormalities in TSH, fT4, or T3, was associated with improved efficacy of pembrolizumab on the KEYNOTE-001 trial at UCLA and an acquired thyroid abnormality, defined as first occurrence after C1D1, was more predictive of improved efficacy than a baseline abnormality. Future work is ongoing to evaluate this association in a larger patient population and molecular mechanisms that may be underlying this observation.

Keywords: NSCLC, anti-PD-1 therapy, Thyroid

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-039 NIVOLUMAB EXPERIENCE IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) IN TOLEDO, SPAIN

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Background: Nivolumab is a fully human IgG4 programmed death-1 (PD-1), an immune checkpoint inhibitor antibody and it has demonstrated durable responses and tolerability in heavily pretreated patients with advanced NSCLC. This is an observational study to describe our experience with Nivolumab in previously treated patients with advanced NSCLC . **Method:** The aim of the study was to report the efficacy and safety profile of Nivolumab in pretreated patients with advanced NSCLC of our everyday clinical practice. The exploratory assessments include the progression-free survival (PFS) and overall survival (OS) and the rates of treatment related adverse events (AEs). Elegibility criteria included, histologically or citologically confirmed NSCLC clinical stage IIIB vs IV, evaluable disease, at least one prior therapy from January of 2016 to current date. **Result:** From January of 2016 to May of 2017 , a total of 46 patients were enrolled in the study from our Hospital. The patients demographics were: median age 64 years (47-77), 6 (14%) female and 38 (86%) male. El 61% (n=27) non squamous-cell and 39% (n=17) squamous-cell carcinoma. The stage was IV in 71%(n=53) and III in 29% (n=13) .All the stage III patients have been treated with concurrent chemoradiotherapy. 41 patients (93%) have received platinum-based therapy previously to Nivolumab : 22 (50%) combined with Premetrexed and 19 (43%) with other drugs. 72% (n=20) have been treated with 2 or more prior therapy lines. Among 48 patients evaluated the best response to Nivolumab was: 4% (n=2) complete response, 36%(n=34)partial response and 25%(n=11) disease stabilization At the time of database lock, the median of PFS with Nivolumab was 2.3 IC 95% (1.2-2.7) and OS was not reached. 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. **Conclusion:** Early data from this study suggest that Nivolumab is effective and well tolerated in patients with pretreated advanced NSCLC but in our

serie the toxicity was relevant with some patients

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P2.07-040 PRE-TREATMENT TUMOR VOLUME IN NON-SMALL CELL LUNG CANCER (NSCLC) AS A PREDICTOR OF RESPONSE TO PD-1 INHIBITORS

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Background: PD-1 inhibitors are new anti-cancer treatments that aimed to re-instate the natural anti-cancer immune-mediated cytotoxicity. Although this new class of therapy offers hope for many advanced stage cancer patients (pts), little is known on the characteristics of pts who are likely to respond. We hypothesized that response rate (RR) and overall survival (OS) would be inversely associated with pre-treatment tumor volume (PTV), independent of other variables such as age, lymph node (LN) metastasis and liver metastasis. **Method:** Data from NSCLC pts who received at least one dose of PD-1 inhibitors before August 31, 2016 were captured from our institution's pharmacy database. The primary objective was to determine the correlation of PTV to best response, evaluated using RECIST v1.1 criteria. PTV was measured using the Philips Intellispace Multi-Modality Tumor Tracking (MMTT) application. Secondary objectives were estimation of progression free survival (PFS) and overall survival (OS). **Result:** Data on 113 NSCLC pts with at least one site of measurable disease were captured. They received at least one dose of PD-1 inhibitors prior to data cut-off. Median age was 64 (IQR: 57-70). 64 (56.6%) were male. 69 (61.1%) were treated on a clinical trial. There were 75 (66.4%) adenocarcinoma, 32 (28.3%) squamous cell carcinoma (SCC) and 6 (5.3%) poorly differentiated NSCLC. Median PTV was 60.2 cm^3 (IQR: 15.1-115.8). 89 (78.8%) pts had LN metastasis and 25 (22.1%) had liver metastasis at baseline prior to treatment. 2 (1.8%) had complete response, 25 (22.1%) had partial response, 42 (37.2%) had stable disease and 34 (30.1%) had progression of disease documented as their best response. The association between PTV and best response, considered as an ordered 4-category variable was not strong (Kendall's tau-b=0.11, p=0.14). PTV, age and LN metastasis were not associated with OS with hazard ratio and p value of hazard ratio (HR) 1.1 [95%CI 0.9-1.46] p=0.26, HR 1 [95%CI 0.96-1.01] p=0.29 and HR 0.8 [95% CI 0.39-1.52] p=0.45, respectively. However, having liver metastasis prior to treatment was associated with significantly shorter survival with HR 2.6 [95%CI 1.35-4.81] p=0.004. **Conclusion:** Contrary to our hypothesis, pre-treatment tumor volume in NSCLC did not prove to be a predictor of response to PD1 inhibitors but having liver metastasis prior to treatment was associated with significantly shorter survival.

Keywords: Checkpoint inhibitors, liver metastases, tumor burden

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-041 IMMUNO-RELATED CUTANEOUS ADVERSE EVENTS (IRCUTAES) IN PATIENTS (P) WITH ADVANCED NSCLC: A SINGLE-INSTITUTION PROSPECTIVE STUDY

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Background: Despite the impressive benefits of the immune checkpoint blockade in NSCLC, its use can be hampered by the occurrence of serious adverse events. IRcutAEs are underestimated and poorly described according to data from the clinical trials. **Method:** Before starting immunotherapy, all NSCLC p were prospectively referred to the Dermatology Department. Periodic monitoring visits were also scheduled for each p, in order to describe the IRcutAEs and their treatments. The study included data from all consecutive NSCLC p treated with immunotherapy in our institution. **Result:** Since May 2016, 50 p were recruited for the present study. According to clinical characteristics; 18 p had squamous histology, 43 p received treatment as second line or further, and 36 p were treated with nivolumab. During the follow-up period, 15 p (30%) developed IRcutAEs. Lichenoid reactions were the most common AE (9 p, 60%), but some specific conditions were also observed, such as a cutaneous lupus (1 p, 6.6%) or an eruptive pseudoangiomatosis (1 p, 6.6%). **Conclusion:** IRcutAEs are common during antiPD1-PDL1 therapy. By offering a dermatological follow-up, the diagnosis and management of this type of toxicity can be provided to NSCLC p initiating immunotherapy.

Keywords: Immunotherapy, toxicity, Cutaneous Adverse Events

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-042 FEASIBILITY STUDY OF NIVOLUMAB AND DOCETAXEL IN PREVIOUSLY TREATED PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Nivolumab (NIV) is a standard second-line treatment for previously treated patients with advanced non-small cell lung cancer (NSCLC). Although there is a possibility that a higher effect can be expected by combination NIV and cytotoxic agents, verification in a clinical trial is required. Because there was only one report of phase Ib trial (N=6) of NIV + docetaxel (DTX) combination (Kanda et al, Ann Oncol 2016), we planned a feasibility study to examine the safety of this combination prior to large scale clinical trials. **Method:** Eligibility criteria included a history of platinum-based chemotherapy, PS 0-1, and adequate organ functions. Patients received NIV 3 mg/kg (days 1, 15) and DTX 60mg/m^2 (day 1) every 4 weeks for a maximum of 2 courses. The primary endpoint was safety of 1st course and evaluated dose-limiting toxicities (DLT). This study used a 3 + 3 design and was considered to be feasible if DLT occurred in one-thirds or less of the patients. The secondary endpoints were the adverse events and the response rate. DLT was defined in accordance with the phase Ib study of Kanda et al . **Result:** Between Aug 2016 and Sep 2016, three patients were enrolled into this trial in 2 centers in Japan. First case was 57 years old female / adenocarcinoma, 2nd case was 44 years old male / squamous cell carcinoma, 3rd case was 58 years old male / adenocarcinoma. Grade 3 or more adverse events occurred only in one case of Grade 4 neutropenia, and no DLTs were observed in any cases. All patients completed 2 courses and objective tumor responses were PD, SD, PR, respectively. Two of three patients still survive more than 10 months from start of this therapy. **Conclusion:** NIV+ DTX combination therapy was acceptable for safety and further evaluation is warranted. Because the use of combination NIV plus cytotoxic agents is not approved in Japan, we are planning to conduct a phase II / III trial (CONDUCT study) comparing NIV + DTX with NIV alone in previously treated patients with advanced NSCLC in the Thoracic Oncology Research Group (TORG), using an Advanced Medical Healthcare in Japan.

Keywords: nivolumab+docetaxel, non-small cell lung cancer

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-043 EFFICACY AND SAFETY OF ANTI-PD-1 ANTIBODY AS THE FIRST LINE TREATMENT IN ELDERLY PATIENT WITH ADVANCED LUNG SQUAMOUS CELL CARCINOMA: A CASE REPORT

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Background: To evaluate the efficacy and safety of PD-1 antibody in first-line treatment of advanced lung squamous cell carcinoma **Method:** To analyze the short-term efficacy and related adverse effects of PD-1 antibody in one elderly patient with advanced squamous cell carcinoma of the lung. **Result:** An eighty-year-old male was hospitalized due to "cough with blood-stained sputum for two months", who was physically healthy in the past years and had a long-term history of smoking. Two months ago, he began to cough with blood-stained sputum occasionally. He had no chest pain, dyspnea, fever and night sweat. He went to local hospital for diagnosis and chest CT showed right upper lobe mass and atelectasis. The up-mentioned symptoms got worse one month ago and percutaneous aspiration lung biopsy was performed in local hospital. The pathological study showed squamous cell carcinoma of lung and the result of EGFR mutation testing was wild type. After transferring to our hospital, bronchoscopy revealed lumen in upper right was completely obstructed by neoplasm and trachea and right middle bronchus presented with compressive stricture. Biopsy was performed and immunohistochemistry study confirmed the diagnosis of lung squamous cell carcinoma. PD-L1 immunohistochemistry staining found high expression of PD-L1 in nucleus. No abnormal result was found in baseline assessment of routine blood count, biochemistry analysis of blood, thyroid and adrenal cortex function. PD-1 antibody 200mg, d1, Q3w was used according to the instructions. In routine assessment before the second cycle of treatment, he was found hyperthyroidism and adrenal insufficiency, but the patient had not any related symptoms. Thus, the adverse effects were designated as grade 1, unnecessary for intervention. The serum tumor marker related to squamous cell carcinoma was significantly reduced, so he continued to receive the treatment according to previous schedule. During the assessment before the third cycle of treatment, the routine blood test and all serum tumor markers were found normal. Chest CT showed partial remission of the neoplasm according to RECIST criteria. There was no further deterioration in thyroid and adrenal cortex function, etc. **Conclusion:** Significant objective response to PD-1 antibody could be expected in first-line treatment of advanced squamous cell carcinoma of lung with high PD-L1 expression. but early-onset abnormal function of multi-organ may occur simultaneously which warrants intensive focus and follow-up.

Keywords: advanced NSCLC, first-line, PD-1 antibody

P2.07-044 THYROID DISFUNCTION IN ADVANCED NSCLC PATIENTS TREATED WITH NIVOLUMAB OUT OF CLINICAL TRIAL: A REAL-WORLD DATA ANALYSIS

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Background: Immune-related adverse events occur in a subset of patients (pts) treated with immune checkpoint inhibitors blocking PD1/PD-L1 interaction. It has been reported that NSCLC pts treated with pembrolizumab who developed thyroid dysfunction (TD) had better clinical outcome. In this retrospective study, we examined the prognostic value of TD in advanced NSCLC pts treated with nivolumab. **Method:** Ninety-seven pts with advanced NSCLC treated with nivolumab in second and latter lines out of clinical trial at the Institut Català d'Oncologia (Barcelona, Spain) between November 2015 and March 2017 were included in this analysis. Thyroid tests were assessed at baseline and at the clinician's discretion during treatment. TD was defined as abnormal levels of TSH value during nivolumab treatment. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. **Result:** Of 97 pts, most patients received nivolumab in second line (73%). The median age was 63 years (38-82), most were men (76%), former or active smokers (87%), with adenocarcinoma (59%) or squamous cell carcinoma (31%), and had good performance status (88% ECOG PS 0-1). With a median follow-up of 8 months, 42 (43%) patients had died and 60 (62%) presented progressive disease. Sixteen pts (16.5%) developed TD that was G1 (9, 56%) or G2 (7, 44%). Two pts who developed G2 hyperthyroidism required steroid treatment and 5 pts who developed G2 hypothyroidism received substitutive hormone therapy. Median time until TD was 41 days (95% CI 37-45) and pts with TD received more cycles of nivolumab compared with euthyroid pts (11.5 versus 4, respectively). Pts with TD were more likely to achieve a tumor response compared to euthyroid pts (44% versus 14%, p=0.13). Median PFS and OS were significantly longer in pts who developed thyroid dysfunction compared with euthyroid pts. Median PFS was 3.7 months in euthyroid pts vs NR in pts with TD (p=0.001; *odds ratio*, 0.14; 95% CI 0.04-0.48) and median OS was 8.1 months vs NR, respectively (p=0.005; *odds ratio*, 0.15; 95% CI 0.03-0.69). **Conclusion:** This real-world data analysis showed that treatment-related TD predicts favorable clinical outcome from nivolumab in advanced NSCLC pts. A comprehensive analysis of thyroid stimulating hormone (TSH) kinetics will be presented at the meeting.

Keywords: immune checkpoint inhibitor, immune-related adverse events, Thyroid disfunction

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P2.07-045 A RETROSPECTIVE ANALYSIS OF NIVOLUMAB-RELATED PNEUMONITIS IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Nivolumab is a human IgG4 monoclonal antibody that targets programmed cell death-1 (PD-1). In advanced non-small-cell lung cancer patients, nivolumab has been well tolerated. However, some patients develop nivolumab-related pneumonitis. **Method:** We retrospectively analyzed the clinical features and prognosis of nivolumab-related pneumonitis in non-small cell lung cancer patients in the institutions of the Nagasaki Thoracic Oncology Group. **Result:** From January 1, 2016 to May 31, 2017, 101 non-small cell lung cancer patients were treated with nivolumab monotherapy and 8 patients (7.9%) developed nivolumab-related pneumonitis. 7 were male, and 1 was female, with a median age of 70 years. The histological subtype was squamous cell carcinoma in 3 patients, non-squamous cell carcinoma in 5 patients. 6 patients were stage III or IV. 2 patients were postoperative recurrence. Radiographic pattern was cryptogenic organizing pneumonia (COP) in 6 patients and acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) in 2 patients. The median time from nivolumab treatment initiation to development of pneumonitis was 8.5 weeks (range, 1-16). 2 patients of AIP/ARDS pattern developed pneumonitis within 2 weeks. Bronchoalveolar lavage conducted in 4 patients and bronchoalveolar lavage fluid revealed elevation of lymphocyte in all patients. All patients received corticosteroids. 6 patients of COP pattern had clinical and radiographic improvement. 2 patients of AIP/ARDS pattern worsened clinically and died during the course of pneumonitis treatment. One of patient experienced recurrent pneumonitis in the course of corticosteroid taper. **Conclusion:** We retrospectively analyzed the clinical features and prognosis of nivolumab-related pneumonitis in non-small cell lung cancer patients. Nivolumab-related pneumonitis showed variable onset and radiographic patterns. COP pattern was most common. Most patients were successfully treated with corticosteroids, but AIP/ARDS pattern was risk of poor prognosis.

Keywords: lung cancer, Nivolumab, pneumonitis

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY -
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P2.07-046 NIVOLUMAB EXERTS REMARKABLE ANTITUMOR ACTIVITY IN NSCLC AFTER AN IMMUNE-MODULATING BIOCHEMOTHERAPY REGIMEN

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Background: Dose-dense cisplatin and daily oral etoposide +/- bevacizumab, mAb to the vascular endothelial-growth factor is a safe and active treatment for un-resectable NSCLC patients. It elicited remarkable Immunological effects, including rise in central-memory-T-cells and activated-dendritic cells and decline in regulatory-T-cells, potentially additive to anti-PD-1/PDL-1 immune-checkpoint inhibition. We therefore, performed a retrospective analysis aimed to evaluate both overall survival (OS) and progression free survival (PFS) in patients receiving treatment with Nivolumab, a mAb to PD-1, after they had received different first line chemotherapy regimens. **Method:** Statistical analysis (Log-rank test) was performed on forty-nine consecutive NSCLC pts engaged to receive Nivolumab (3mg/kg every 15 days) between October 2015 and December 2016. All of them had received frontline platinum-based doublets for advanced disease and 15 of them had received the mPEBev regimen. **Result:** A prolonged PFS was found in patients who received frontline mPEBev compared to the other treatments (mPEBev vs. standard doublets: 14.30 vs. 7.9 months; p=0.038). In this group, we also detected a trend to longer survival (mPEBev vs. standard doublets: 15.6 vs. 11.34 months; p=0.107 with a 12-month-OS-rate of 79% and 32.6%, respectively). We finally recorded that baseline neutrophil and LDH values were correlated with both PFS (neutrophil counts < vs. ≥ median value: 6.28 vs. 14.4 months; P=0.095. LDH < vs. ≥ median value: 14.25 vs. 8.53 months; p= 0.036) and OS (neutrophil counts < vs. ≥ median value: 9.6 vs. 16.8 months; p= 0.101, with a 12-month OS-rate of 42% vs 63%, respectively; LDH < vs. ≥ median value: 16.66 vs. 11.51 months; p=0.039). **Conclusion:** Frontline chemotherapy may affect the efficacy of Nivolumab treatment; the mPEBev regimen, in particular, may induces immunological patterns able to improve the effectiveness of PD-1/PDL-1 blockade. Perspective studies and immunological correlations are presently ongoing.

Keywords: immunotherapy; biochemotherapy; Nivolumab

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P2.07-047 POOR PERFORMANCE STATUS AND BRAF MUTATION PREDICT GRADE 3-5 IMMUNE-RELATED ADVERSE EVENTS IN PTS WITH ADVANCED NSCLC

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Background: Anti-PD1/PDL1 immunotherapy has been regarding as standard second line therapy in patients with advanced NSCLC, also as the 1st line setting in subpopulation with PDL1 expression of more than 50%. Anti-PD1/PDL1 drugs such as nivolumab, pembrolizumab and atezolizumab showed a durable response in those benefit population, while immune-related adverse events(irAEs) were also frequently happened. This study aimed to describe the high-risk factors for irAEs in patients with advanced NSCLC after the treatment of anti-PD1/PDL1 monoclonal antibody. **Method:** We retrospectively reviewed 72 patients with advanced non small cell lung cancers treated with PD-1/PD-L1 inhibitors (nivolumab =27, pembrolizumab =44, atezolizumab =1) in Shanghai Pulmonary Hospital from Jun 2015 to May 2017. All adverse events were assessed and classified by grades according to NCI CTCAE (version 4.0). **Result:** AEs occurred in 34 patients (47.22%). Grade 1 or 2 events included increased amylase (5), increased lipase (5), transaminitis (4), rash/ pruritus (4), xerostomia (3), nausea (3), fatigue(3), anemia (3), decreased WBC (2), hypokalemia (2) and fever, arthralgia, sense of neck stiffness, cardiac arrhythmia, decreased PLT and hypocalcemia in 1 patient each.Twelve (16.67%) patients experienced grades 3-5 events including 6 cases with ILD(grade 5=1), 3 with pleural effusions/pericardial effusions, 2 with hypothyroidism, and 1 with grade 3 fatigue. Subgroup analysis showed that patients with BRAF mutations(2 with adenocarcinomas,1 with squamous carcinomas and 1 with NSCLC) experienced significantly higher rate of serious AEs (2 ILD and 2 pleural effusions) after receiving pembrolizumab (100%vs 11.76%,p<0.001), while it was similar according to the other driver genes mutation status (EGFR, KRAS, HER2, ALK). Patients with poor ECOG PS experienced a marginally statistically significant higher grade 3-5 AEs (p=0.063), while it was similar according to different subgroup of age (p=0.538), gender (p=0.189), histological type (p = 0.999), smoking status (0.122), lines of previous therapy (p=0.172), baseline serum LDH level(p=0.290) and CD8+ of peripheral blood (p=0.814). In addition, prior thoracic radiation has a numerical higher prone to develop ILD (23.07%vs 5.08%, p = 0.116). **Conclusion:** Poor performance status and BRAF mutation might predict irAEs in patients with advanced NSCLC receiving PD-1/PD-L1 inhibitors, further large cohort study is warranted to investigate the high-risk factors for irAEs in patients with advanced NSCLC.

Keywords: BRAF, poor performance status, immune-related adverse events

P2.07-048 IMMUNOTHERAPY VS. TARGETED THERAPY - WHO WINS? A CASE SERIES

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Background: Data are mounting regarding rare mutations such as MET (exon 14 skipping mutation and MET amplification), ROS1 translocation and rare EGFR mutations and response to targeted therapy, simultaneously data are increasing concerning treatment of Non-Small Cell Lung Carcinoma (NSCLC) patients with immune check point inhibitors. As yet, the role of immunotherapy in patients with rare genomic alterations has not been determined. We describe a case series of patients who can benefit from both therapies and summarizes their response for each treatment. **Method:** We present a retrospective case series of four patients with NSCLC and genomic alterations, diagnosed and treated from November 2015 to June 2017 in a single tertiary center with targeted therapy and immunotherapy. Hybrid capture-based next generation sequencing was performed. **Result:** Two males and two females (mean age 58) were included. Three of them were diagnosed with Adenocarcinoma and the remaining one was diagnosed with squamous cell carcinoma. Each patient was diagnosed with a specific gene alteration (C-met exon 14 skipping mutation, EGFR Q861L, MET amplification and ROS1 translocation). Patients underwent targeted therapy as well as immunotherapy. Two patients had PD-L1 staining >50%. One patient demonstrated an early and durable complete response with immune check point inhibitors, one patient had progressed on immunotherapy quickly but respond well to targeted therapy, two patients responded as expected to targeted therapy and got immune check point inhibitors as a second line and still being treated with good response. **Conclusion:** The role of immunotherapy for patients with uncommon EGFR mutations, ROS1 and C-MET who express PD-L1 is still unclear. Further studies in this unique population are needed.

Keywords: Immunotherapy, Targeted therapy, Driver Mutations

P2.07-049 EARLY CLINICAL PREDICTORS OF PROGRESSIVE DISEASE OR NON-RESPONSE TO PD-1/PD-L1 INHIBITORS IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Treatment with PD-1/PD-L1 inhibitors are now the standard of care for patients with advanced non-small cell lung cancer. PD-L1 expression, in addition to interferon score and tumour mutational burden, are predictive biomarkers, however early clinical predictive biomarkers are lacking. **Method:** Patients with NSCLC who received treatment with PD-1/PD-L1 inhibitors between 1 Jan 2014 – 31 Dec 2016 were retrospectively identified from electronic health records. Data was collected on patient, treatment and tumour characteristics. Discrete variables were compared using Fisher's exact test. Odds ratios (OR) were calculated with 95% confidence intervals (CI) for significant associations, using contingency tables. **Result:** We identified 91 patients, with a mean age of 65 years, of whom 52% were male. The majority were ex-smokers (69.2%), followed by never smokers (23.1%). Non-squamous histology was seen in 59.3% of patients and 86.8% of the patients had ECOG performance status 0-1. The lactate dehydrogenase (LDH) at baseline, cycle 2, and the change-in LDH≥10% at cycle 2 and 6 weeks, did NOT predict for disease control rate (DCR) at the first tumour response evaluation (TRE). A LDH ≥ upper limit of normal at 6 weeks DID predict disease progression at the first TRE (*P*-value=0.04), with an OR of 3.58 (95% CI 1.11 – 11.52). The neutrophil-lymphocyte ratio (NLR) at baseline and 6 weeks, and the change-in NLR>10% at cycle 2 and 6 weeks did NOT predict for DCR at the first TRE. A NLR ≥5 at cycle 2 DID predict for disease progression at the first TRE (*P*-value=0.008), with an OR of 3.92 (95% CI 1.48 – 10.39). Receiver operator curve analysis of the early LDH/NLR score (1 point each for 6 week LDH ≥ upper limit of normal and cycle 2 NLR ≥5) predicted for disease progression at the first TRE (C-index 0.77, *P*-value <0.0001). **Conclusion:** The LDH greater than upper limit of normal at cycle 2 and NLR ≥5 at 6 weeks predicts for disease progression at the first TRE. These routine early predictive biomarkers could be used to identify non-responders when treating with PD-1/PD-L1 inhibitors prior to a CT scan. This data needs validation in a larger cohort.

Keywords: non-small cell lung cancer (NSCLC), Lactate dehydrogenase (LDH), Neutrophil-Lymphocyte ratio (NLR)

P2.07-050 IMPACT OF STEROID USE FOR IMMUNE RELATED ADVERSE EVENTS ON OUTCOMES IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH CHECKPOINT INHIBITORS

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Background: Checkpoint inhibitors targeting PD-1 and PD-L1 have emerged as the standard of care for patients with NSCLC. While generally well tolerated, immune related adverse events (irAEs) are a known complication and when serious, may require use of systemic corticosteroids. The impact of steroid use on checkpoint inhibitor efficacy remains unclear. Previous data suggest comparable response rates among patients who require steroids and those who do not. Here, we seek to confirm those findings and explore the impact of systemic steroids for irAEs on time to treatment failure (TTF) in patients with NSCLC. **Method:** Retrospective analysis was performed on all patients with advanced NSCLC at five institutions who received a checkpoint inhibitor (anti-PD-1 or anti-PD-L1 antibody) between January 1, 2011 and April 1, 2017. TTF was defined as the time from initiating therapy to start of a new therapy, last day of follow up or death. Development of any irAE and use of systemic corticosteroids was noted and median TTF and RR were compared between subgroups. **Result:** We identified 141 eligible patients with NSCLC treated with checkpoint inhibitors. Nineteen patients were excluded from the final analysis due to lack of any follow up or receipt of investigational agents or combinations. For the 122 evaluable patients, median TTF and RR were 169 days and 18%. A total of 30 (25%) patients developed any irAEs with median TTF and RR of 497 days and 32%. A total of 11 (9%) patients received systemic corticosteroids for irAEs. Among the patients who received steroids for irAEs, the median TTF and RR were 502 days and 27%. Our observation failed to demonstrate a statistically significant difference in median TTF among patients who received steroids and those who did not (p=0.4155). **Conclusion:** These retrospective data do not demonstrate a difference in response or treatment failure among patients who received steroids for irAEs and support the use of steroids when necessary.

Keywords: Check point inhibitors, Toxicites, Time to treatment failure

P2.07-051 IMMUNE CHECKPOINT ASSOCIATED CARDIOTOXICITY: AN UPDATE

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Background: Immune checkpoint inhibitors have revolutionized the field of oncology. nivolumab, pembrolizumab, ipilimumab, and atezoluzimab have been approved by the United States Food and Drug Administration for various malignancies. Because these antibodies rely on activating the host immune system, unique autoimmune side effects have been discovered, including reactions against the cardiovascular system. We would like to summarize our institutional experience with immune checkpoint inhibitor associated cardiotoxicity and review the current literature on this subject. **Method:** Retrospective review of the patient medical record and review of PubMed indexed literature on immune checkpoint inhibitor associated; cardiotoxicity, cardiomyopathy, autoimmune myocarditis, heart failure. **Result:** To date we have experienced two cases of immune checkpoint inhibitor associated cardiotoxicity in our patients treated at Markey Cancer Center, Lexington Kentucky. Both these patients were treated for metastatic non-small cell lung cancer who had previously progressed on frontline chemotherapy. Both patients received nivolumab. One of the patient developed congestive heart failure within couple of days after first dose of nivolumab. Extensive cardiac workup for ischemia was negative. On returning of cardiac functions to baseline he was re-challenged with second dose of nivolumab. Patient again developed decomensated CHF with ejection fraction of 30-40%. Subsequent therapy was aborted. Patient continues to have stable disease off therapy for the past 8 months. Our second patient developed moderate to severe pericardial effusion after fifth dose of nivolumab. Pericardial fluid cytology was negative for malignancy and CT scans showed stable visceral metastatic disease. He is currently off therapy and will get a prolonged 8 week steroid taper. Our literature review revealed only nineteen documented cases of immune checkpoint mediated cardiotoxicity. Seventeen of the 19 patients had metastatic melanoma; the remaining two had non-small cell lung cancer (one adenocarcinoma and one squamous cell). Six of the 19 patients developed cardiotoxicity within five weeks of treatment initiation. One of the patients developed biopsy confirmed immune mediated cardiotoxicity 31 weeks after initiation of treatment. Seven patients were treated with ipilimumab alone, four with nivolumab, one with pembrolizumab and the remaining seven patients received a combination of PD1/PDL-1 and CTLA-4 antibody either sequentially or concurrently. Six out of 19 patients died from toxicity of the respective drugs. **Conclusion:** Immune checkpoint associated cardiotoxicity is rare but well defined in literature. Patients can present with decompensated heart failure, arrhythmia or pericardial effusions. Early recognition, prolonged steroid taper and optimization of cardiac function with diuretics, ACE inhibitors and beta blockade are critical steps for

the successful management.

Keywords: Cardiotoxicity, immune checkpoint inhibitor

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P2.07-052 DETECTION OF KRAS MUTATION IN BLOOD PREDICTS FAVORABLE RESPONSE TO IMMUNOTHERAPY IN NSCLC

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Background: Immunotherapy has brought new therapeutic options to non-small cell lung cancer. PD-L1 has been established as the primary clinical biomarker for PD-1/PD-L1 targeting antibodies, with higher expression correlation with superior therapy responses. Tumor mutational burden and other biomarkers have been similarly implicated in prediction of immunotherapy responses. These markers are obtained from tumor tissue based on immuno-histochemistry or next generation sequencing. Availability of tissue has remained a significant clinical challenge. Mutations in KRAS have been reported to correlate with improved survival. We interrogated our data base to investigate whether KRAS detected in blood could serve as a surrogate marker for immunotherapy selection. **Method:** We screened a total of 239 cases of non-small cell lung cancer with positive tissue evaluation. 89/239 cases tested positive for presence of a KRAS mutation. 56 KRAS mutant cases of NSCLC, matched tissue (NGS and PD-L1) and blood (NGS) analyses were available. 17 cases had PD-L1 expression of greater than 50% on IHC. 39 cases had PD-L1 expression of less than 50%, defined as low expression. 34 patients had received single agent, PD-1 targeting immunotherapy (nivolumab or pembrolizumab). We reviewed these cases with low PD-L1 expression treated with immunotherapy in a retrospective analysis for clinical outcomes. **Result:** In the cohort with low PD-L1 low/KRAS mutant status, a response rate (PR+CR) of 53% (n=18) was observed, including 13% (n=5) complete responses. The average progression-free survival in this subset was 11.1 month. KRAS status correlated expectedly with prior or current smoking history (97%), and elevated tumor mutational load (16 mutations per megabase). **Conclusion:** Selection of appropriate candidates for immunotherapy has remained a clinical challenge. In our analysis, liquid biopsy was obtained without complication and correlated strongly between blood and tissue. Compared to historical controls, KRAS mutant status appears to have a higher response rate and prolonged progression-free survival independent of PD-L1 status. In addition to previously established PD-L1 and TML markers, our data supports a role of KRAS as a surrogate marker for immunotherapy response that should be investigated in prospective clinical trials.

Keywords: immunogram, Immunotherapy, KRAS

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P2.07-053 A CASE OF SMALL CELL LUNG CANCER COMPLICATED DURING NIVOLUMAB ADMINISTRATION AS SECOND LINE TREATMENT FOR SQUAMOUS CELL LUNG CANCER

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Background: We experience secondary cancer merging after anticancer medications. Also, as a mechanism of resistance of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors to patients with non-small cell lung cancer (NSCLC) harboring activating mutations of EGFR, conversion to small cell lung cancer is well known. However, little is known about the occurrence of secondary cancer during the use of immune checkpoint inhibitors. **Method:** We report a 71 years old man who was diagnosed small cell lung cancer during nivolumab administration as second line treatment for advanced squamous cell lung cancer. **Result:** He suffered from diffuse large B-cell Lymphoma (DLBCL) at the age of 65 years old. He received eight cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone combined with rituximab), and he remitted DLBCL. During his follow up by a hematologist, he pointed out a new nodule in left upper lung and small nodules in right lung with CT scan. He was diagnosed with squamous cell lung cancer by bronchoscopic biopsy. He received four cycles of carboplatin and nanoparticle albumin-bound paclitaxel combination chemotherapy as first line treatment, and he obtained partial response (PR). After 12 months of this treatment, the primary tumor re-increased and relapsed, he received nivolumab as a second line treatment. Although he obtained stable disease by nivolumab, another new lung nodule appeared in right lower lobe gradually. After 12 cycles of nivolumab, he was diagnosed with small cell lung cancer by endobronchial ultrasound transbronchial biopsy with guide-sheath. He received four cycles of combination chemotherapy with carboplatin and etoposide, and he obtained PR. We plan to resume nivolumab as the next line treatment. **Conclusion:** We reported a case of small cell lung cancer complicated during immune checkpoint inhibitor (nivolumab) administration as second line treatment for squamous cell lung cancer. In this case, monotherapy with nivolumab failed to suppress the emergence of small cell lung cancer.

Keywords: Nivolumab, small cell lung cancer, Squamous cell lung cancer

P2.07: IMMUNOLOGY AND IMMUNOTHERAPY - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.07-054 COST-EFFECTIVENESS OF PEMBROLIZUMAB AS FIRST-LINE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy is changing the therapeutic perspective and expectations for solid tumors and constitutes a major therapeutic advance for advanced non-small cell lung cancer (NSCLC). We assessed the cost-effectiveness of pembrolizumab (anti-PD-1 antibody) as compared to platinum-doublet chemotherapy as first-line therapy for advanced NSCLC. **Method:** We developed a Bayesian Markov model of disease states with a 5-year horizon. We retrieved survival, progression, and safety data comparing pembrolizumab to contemporaneous platinum-doublet chemotherapy as first-line therapy for PD-L1 expression equal to or greater than 50%, EGFR non-mutated, ALK non-translocated lung carcinoma patients. Published estimated US and UK costs were applied to inform the incremental cost-effectiveness ratio (ICER). We estimated costs in USD and summarized effectiveness as discounted quality-adjusted life-years (QALYs). **Result:** Patients treated with pembrolizumab accumulated 0.65 QALYs (95% credible interval [95% CrI] 0.5-0.91) as compared to 0.19 QALYs (95% CrI 0.16-0.22) to 0.32 QALYs (95% CrI 0.27-0.37) for those treated with platinum-doublet chemotherapy. From a current US cost perspective, ICERs varied from $173,000 (95% CrI $163,000-$183,000) to $201,000 (95% CrI $182,000-232,000) for one end-of-life (EoL) adjusted QALY, while from a British National Health System (NHS) perspective, ICERs varied from $154,000 (95% CrI $144,000-$166,000) to $193,000 (95% CrI $165,000-$248,000) per EoL adjusted QALY gained. **Conclusion:** At current price, pembrolizumab is not cost effective considering the usual NICE threshold in the UK. In the US, these numbers would be considered cost-effective according to the WHO definition.

Keywords: pharmacoeconomics, Immunotherapy, chemotherapy

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P2.07-055 INDIRECT COMPARISON BETWEEN IMMUNE-CHECKPOINT INHIBITORS FOR 2ND LINE NON-SMALL CELL LUNG CANCER – A NETWORK META-ANALYSIS

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Background: Treatment with immune checkpoint inhibitors (ICIs) improves overall survival with lower toxicity when compared to classic chemotherapy in the management of advanced non-small cell lung cancer (NSCLC). While emerging, the role of PD-L1 expression as a biomarker remains controversial. In addition, all clinical trials that included previously treated patients compared ICIs with docetaxel and there is a lack of data comparing each agent against each other. This network meta-analysis aims to (i) compare overall survival (OS) with nivolumab, pembrolizumab, and atezolizumab against docetaxel in previously treated advanced non-small cell lung cancer (NSCLC) patients and (ii) to perform indirect comparisons between ICIs in the PD-L1 unselected population and by PD-L1 expression levels. **Method:** We searched Pubmed for randomized controlled trials comparing the ICIs nivolumab, pembrolizumab and atezolizumab in the treatment of patients with previously treated advanced NSCLC. Two independent reviewers screened each study. We performed network meta-analyses of survival outcomes in the PD-L1 unselected population and by PD-L1 expression levels <1%, ≥1%, ≥5%, ≥10%, and ≥50%. Head-to-head indirect comparisons of nivolumab, pembrolizumab and atezolizumab were constructed and treatment rankings provided in terms of SUCRA and probability that a treatment is best. We also assessed the potential survival benefits of selecting patients by PD-L1 expression level as compared to a PD-L1 unselected population. **Result:** Five trials with 3,024 total patients were included in the meta-analysis. ICIs improved OS in previously treated advanced NSCLC patients across PD-L1 expression levels compared to docetaxel with HRs of 0.70 (95% CrI 0.61-0.81), 0.79 (0.65-0.97), 0.67 (0.57-0.77), 0.55 (0.44-0.69), 0.43 (0.30-0.63), and 0.49 (0.37-0.63) for PD-L1 expression levels as follows: unselected, <1%, ≥1%, ≥5%, ≥10%, and ≥50%. However, for individual ICIs nivolumab and atezolizumab in PD-L1<1%, there was only weak evidence of benefit with HR of 0.77 (0.57-1.04) and 0.81 (0.62-1.08) respectively compared to docetaxel. Nivolumab, pembrolizumab and atezolizumab showed little survival differences between each other (nivolumab vs pembrolizumab HR 0.94 (0.63-1.39), nivolumab vs atezolizumab 0.91 (0.62-1.35), and pembrolizumab vs atezolizumab 0.97 (0.68-1.41) in PD-L1 ≥1%). When interpreting these data, it is important to note that while nivolumab and pembrolizumab trials used tumor cells for PD-L1 cutoffs, atezolizumab used both tumor and/or immune cell cut-offs and PD-L1≥50% in atezolizumab trials comprised patients with tumor cell PD-L1≥50% or immune cell PD-L1≥10%. **Conclusion:** ICIs improve survival across PD-L1 expression levels compared to docetaxel. None of the available ICIs, nivolumab, pembrolizumab and atezolizumab, seem to be better than the others.

Keywords: Immunotherapy, metanalysis, Evidence-Based Medicine

P2.07-056 SAKK 16/14 – PERIOPERATIVE ANTI-PD-L1 ANTIBODY DURVALUMAB IN PATIENTS WITH STAGE IIIA(N2) NON-SMALL CELL LUNG CANCER (NSCLC)

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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 radiotherapy as third treatment modality to chemotherapy and surgery. Our results consistently showed a 5-year overall survival (OS) of 37%. However, it seems very difficult to further improve the OS by conventional therapies. **Method:** This is a single-arm phase II clinical trial designed to evaluate the addition of perioperative immunotherapy with the anti-PD-L1 antibody durvalumab to the previously established standard of care for stage IIIA(N2) patients, which is based on the trials SAKK 16/96 and SAKK 16/00. 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. Patients with R1/R2 resection and patients with extracapsular spread of mediastinal lymph node metastases may undergo standard radiotherapy prior to adjuvant treatment with durvalumab. 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. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Lung cancer, neoadjuvant, immune checkpoint inhibition

P2.07-057 ANTI-PD-1/PD-L1 ANTIBODIES COMBINE WITH CHEMOTHERAPY OR CTLA4 ANTIBODIES FOR FIRST-LINE TREATMENT OF ADVANCED LUNG CANCER

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Background: Checkpoint inhibitors showed satisfactory efficacy in treating lung cancer. We conducted this meta-analysis to explore the therapeutic efficacy and safety of anti-PD-1/PD-L1 antibodies combine with chemotherapy or CTLA4 antibodies as first-line treatment on advanced lung cancer. **Method:** A quantitative meta-analysis was performed through a systematic search in PubMed, Web of Science, the conference abstracts and so on. The pooled ORR, 6-month progression-free survival rate (PFSR6m), and 1-year overall survival rate (OSR1y) were calculated and compared. 9 trials were included in this meta-analysis. **Result:** Our analyses demonstrated the pooled ORR and DCR of anti-PD-1/PD-L1 antibodies combine with chemotherapy for non-small-cell lung cancer were 48.0% (40.2–56.0 %) and 84.8 % (78.1– 89.7%), respectively. The pooled OR and DCR of anti-PD-1/PD-L1 antibodies combine with chemotherapy for small-cell lung cancer were 42.9% (18.5–71.2 %) and 73.6 % (32.8–94.1%), respectively. The pooled PFSR6m of anti-PD-1/PD-L1 antibodies combine with chemotherapy for NSCLC and SCLC were 62.9% (46.3–79.6%) and 27.6 % (18.9–36.2 %), respectively. The OSR1y of anti-PD-1/PD-L1 antibodies combine with chemotherapy for NSCLC and SCLC were 70.1 % (57.4%-82.8 %) and 32.0 % (25.2–38.9 %). In addition, the pooled ORR and DCR for anti-PD-1/PD-L1 antibodies plus CTL4 antibodies treatment group was 29.6% (11.4%-657.8%) and 48.7% (16.8%-81.7%), respectively. **Conclusion:** Anti-PD-1/PD-L1 antibody plus chemotherapy can serve as a promising treatment option for lung cancer. While patients treated anti-PD-1/PD-L1 antibodies plus CTLA4 antibodies may benefit less compare with anti-PD-1/PD-L1 antibodies combine with chemotherapy. Encouraging activity with tolerable adverse effect was observed.

Keywords: lung cancer, Checkpoint inhibitors, chemotherapy

P2.07-058 FIRST-IN-HUMAN STUDY OF JNJ-64041757, A LIVE ATTENUATED LISTERIA MONOCYTOGENES IMMUNOTHERAPY, FOR NON-SMALL CELL LUNG CANCER

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Background: JNJ-64041757 (JNJ-757) is a live attenuated, double-deleted (LADD) *Listeria monocytogenes* (*Lm*)-based immunotherapy engineered to induce adaptive immune responses against the tumor-associated antigen mesothelin. The goals of Part 1 of this first-in-human (FIH) study were to establish the recommended phase 2 dose (RP2D), characterize the safety profile, and evaluate the immunological activity of JNJ-757 in patients with adenocarcinoma of the lung. **Method:** This is an ongoing FIH trial in patients with advanced adenocarcinoma non-small cell lung cancer (Stage IIIb or IV) who have progressed after standard therapy (ClinicalTrials.gov: NCT02592967). Patients were treated at 1 of 2 dose levels (10^8 CFU or 10^9 CFU), infused over 1 hour every 3 weeks until disease progression or unacceptable toxicity. Dose limiting toxicities (DLTs) were evaluated during the first cycle. Disease response was assessed every 3 cycles according to RECIST 1.1. Post-infusion blood, urine, fecal, and saliva samples were evaluated for the presence of JNJ-757. Immunological activity of JNJ-757 was assessed by evaluation of peripheral cytokines and immune cells as well as ELISPOT analysis to defined antigens. **Result:** Nine subjects were enrolled; 6 at 10^8 CFU and 3 at 10^9 CFU. There were no DLTs in either dosing cohort, and 10^9 CFU was identified as the RP2D. Most adverse events (AEs) were of grade 1/2 severity, with fatigue, headache, nausea, and vomiting as the most reported events. One drug-related AE of grade ≥3 severity (hypokalemia, grade 3) was reported in the 10^8 CFU cohort. Best response was stable disease. Four patients had received at least 7 cycles (range, 1 to 14 cycles). JNJ-757 was quickly cleared after infusion, with 7/9 patients showing negative blood cultures at 2 hours; all were negative after 24 hours. Correlative studies demonstrated activation of both innate and adaptive immune responses. Natural killer cell and T cell activation were observed 24 hours after infusion, coinciding with elevated cytokine production (i.e., IFN-γ, TNF-α). Specific T cell responses against *Listeria* listeriolysin O and mesothelin antigens were documented in a subset of patients, consistent with the mechanism of LADD to prime new immune responses. **Conclusion:** The RP2D of JNJ-757 is 10^9 CFU, with a safety profile consistent with other LADD *Lm*-based agents such as CRS-207. Both innate and mesothelin-specific adaptive immune responses were demonstrated in multiple patients. Recruitment in the trial continues to further characterize the safety profile and immune response, and a phase 1b/2 trial with JNJ-757 and nivolumab is planned.

Keywords: Immunotherapy, mesothelin, Listeria monocytogenes

P2.07-059 PHASE I TRIAL OF GENE MEDIATED CYTOTOXIC IMMUNOTHERAPY (GMCI) FOR MALIGNANT PLEURAL EFFUSION (MPE) AND MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Background: GMCI is a tumor-specific immune-stimulator through local delivery of *aglatimagene besadenovec*, an adenovirus-based vector expressing the HSV-1 thymidine kinase gene (AdV-tk) followed by anti-herpetic prodrug. We conducted a phase I dose escalation trial of intrapleural administration of *aglatimagene besadenovec* followed by standard chemotherapy in patients with MPE. **Method:** The primary end-point of this dose escalation trial was safety. Eligibility included patients with MPE or MPM with a clinical indication for placement of pleural catheter, age ≥18 yrs, ECOG PS 0-1, FEV1> 40% predicted and adequate end organ function. Intra-pleural (IP) AdV-tk was administered at doses of 1x 10^{12} viral particles (vp) (Cohort 1); 1x10^{13} vp (Cohort 2); and 1x10^{13} vp plus celecoxib (Cohort 3). Three patients were treated per cohort with 10 patients in the expansion phase. Valacyclovir (2 gm PO TID x 14 days) started the day after AdV-tk followed by chemotherapy. Secondary end-points included response rate, progression free survival, overall survival and immune response. **Result:** From 2013 to 2015, 19 patients were enrolled and completed therapy: median age 69.5 years (range 41-89), 14 malignant mesothelioma (MM) (9 epithelioid, 3 sarcomatoid, 2 biphasic), 4 non-small cell lung cancer (NSCLC) and 1 breast cancer. Eight patients received IP AdV-tk upon diagnosis, 7 prior to 2nd line and 4 prior to 3rd line chemotherapy. Safety results have previously been reported. Response according to RECIST was evaluable for 17 pts. Best response was PR in 4 patients (3 with MM, and one pt with NSCLC), 9 SD and 4 PD. As of 05/2017, three patients are alive and in active follow up (one with NSCLC, and 2 with MM), range of follow up 21-32 months. Of the 4 patients with NSCLC, 3 had prolonged disease

stabilization (median overall survival 25.7 months post-GMCI), and one patient is still alive 3.6 years from initial diagnosis (29 month post-GMCI). **Conclusion:** We previously reported that GMCI can be safely administered at high-doses IP in combination with chemotherapy. With median follow up of 31 months, we report that the majority of the patients experienced clinical benefit and sustained disease stabilization was seen in patients with NSCLC. Three patients are still alive and in active follow up. Phase II studies are warranted to further determine efficacy based on these preliminary encouraging observations; NCT01997190.

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P2.07-060 RESPONSE ASSESSMENT AND SUBGROUPS ANALYSIS ACCORDING TO THE LUNG IMMUNE PROGNOSTIC INDEX (LIPI) FOR IMMUNOTHERAPY IN ADVANCED NSCLC PATIENTS

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Background: LIPI is a score that combine dNLR (neutrophils/(leucocytes-neutrophils) and lactate dehydrogenase (LDH) and correlate with prognosis of NSCLC patients treated with immune checkpoint inhibitors (ICI). We report the predictive role of LIPI on response and in various subgroups of patients. **Method:** Baseline dNLR and LDH were retrospectively collected in 431 patients treated with ICI from Nov. 2012 to Jan. 2017, from 8 European centers. LIPI delineates 3 groups: good (dNLR<3+LDH<upper limit of normal (ULN), intermediate (dNLR>3 or LDH>ULN), poor (dNLR>3+LDH>ULN). Response rate (RR) and disease control rate (DCR) were assessed according to the investigator's criteria. The subgroup analysis was performed according to the age, histology, performance status (PS) and PD-L1 status by immunohistochemistry (positivity if ≥ 1% on tumor cells). **Result:** With a median follow-up of 12.8 months (m.) [95%CI 11.9-14], 431 patients were included. Baseline characteristics are summarized in table 1. The median overall survival (OS) and progression-free survival (PFS) were 10.5m. [95%CI 9.5-13] and 3.9m. [3-4.4], respectively. The median OS was 4.8m. *vs.* 10 m. *vs.* 16.5m., and median PFS was 2m. *vs.* 3.1m. *vs.* 5m. for the poor, intermediate and good LIPI groups, respectively (both p<0.0001). LIPI was correlated with response rate (p<0.0001). In multivariate analysis, the intermediate and poor group were associated with progressive disease, with an OR of 2.20 [CI95% 1.26-3.84] p=0.005) and an OR of 3.04 [CI95% 1.46-6.36] p=0.003), respectively. LIPI was correlated with OS, regardless the age (<70 years (p<0.0001) *vs.* older (p=0.0006) and the histology non-squamous (p<0.0001) *vs.* squamous (p=0.02). In PS 0-1 and in smoker population, LIPI correlated with OS (both p<0.0001), but not in PS ≥2 (12%) and non-smokers (8%). LIPI was correlated with OS for positivity (p=0.01) and unknown PD-L1 (p=0.0001), but not negativity. *(See table next page.)*

	LIPI 0 Good (*N*=162, 37%)	**LIPI 1 Intermediate (*N*=206, 48%)**	**LIPI 2 Poor (N= 63, 15%)**	**All population cohort** N = 431 (%)
Sex				
Male	102 (63)	131 (64)	42 (67)	275 (64)
Age at diagnosis				
Median (years, range)	62 (36;86)	63 (29;86)	62 (39;84)	62 (29;86)
Smoking status				
Non-smoker	13 (8)	18 (9)	5 (8)	36 (8)
Former	80 (49)	115 (56)	46 (73)	241 (56)
Current	67 (42)	69 (33)	11 (17)	147 (34)
Unknown	2	4	1	7
Histology				
Non-squamous	111 (69)	132 (64)	41 (65)	284 (66)
Squamous	51 (31)	74 (36)	22 (35)	147 (34)
Molecular alteration				
EGFR mutation	3 (2)	13 (6)	3 (5)	19 (4)
ALK rearrangement	2 (1)	2 (1)	1 (2)	5 (1)
KRAS mutation	34 (21)	31 (15)	8 (13)	73 (17)
PDL1 status				

Negative	16 (36)	14 (25)	1 (5)	31 (25)
Positive	28 (64)	43 (75)	20 (95)	91 (75)
Unknown	118	149	42	337
Performance Status				
0	51 (32)	45 (22)	10 (16)	106 (25)
1	96 (60)	132 (64)	42 (67)	270 (63)
≥ 2	12 (8)	28 (14)	11 (17)	51 (12)
Stage at diagnosis				
IIIb	18 (11)	33 (16)	14 (22)	65 (15)
IV	101 (62)	135 (66)	38 (60)	274 (64)
Metastases sites				
Median (Range)	2 (0;6)	2 (0;7)	2 (1;7)	2 (0-7)
Bone	43 (27)	58 (28)	20 (32)	121 (28)
Liver	28 (17)	39 (19)	16 (25)	83 (19)
Brain	22 (14)	19 (9)	9 (14)	50 (12)
Immunotherapy				
PD1 inhibitor	133 (82)	167 (81)	48 (76)	348 (81)
PDL1 inhibitor	19 (12)	34 (17)	12 (19)	65 (15)
PDL1 inhibitor- CTLA4 inhibitor	10 (6)	5 (2)	3 (5)	18 (4)
Immunotherapy line				
Median (Range)	2 (1;11)	2 (1;12)	2 (1;8)	2 (1-12)
Response rate				
Complete response (CR)	6 (4)	3 (1)	0 (0)	8 (2)
Partial response (PR)	42 (26)	53 (26)	18 (28)	113 (26)
Stable disease (SD)	66 (41)	59 (29)	8 (13)	133 (31)
Progression	40 (25)	81 (39)	33 (52)	154 (36)
NA	8	10	4	25
Dissociated response	14 (9)	15 (7)	2 (3)	31 (7)

Conclusion: Baseline LIPI predicts response to ICI, and was correlated with OS regardless of age and histology.

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P2.07-061 NIVOLUMAB FOR PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA IN PATIENTS WITH PROGRESSION TO ONE OR MORE LINES OF CHEMOTHERAPY IN MEXICAN POPULATION

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Background: Nivolumab is a PD-1 inhibitor that has been approved as a treatment in adenocarcinoma and squamous cell lung cancer. This study examines the experience with nivolumab as a compassionate use in Mexican patients. **Method:** Descriptive, observational, retrospective and unicentric study that analyzed 38 patients diagnosed with stage III and IV lung cancer who progressed to one or more line of chemotherapy and received nivolumab from April 2016 to March 2017 at the National Institute of Respiratory Diseases. The primary endpoint was overall survival and secondary progression-free survival and response rate measured based on RECIST 1.1. **Result:** The sample was formed by 12 men (35.3%) and 22 women (64.7%), that had an initial ECOG of I in 23.5%, II in 58.5% and III in 17.6% and clinical stages was III 2.9% and IV 97.1%. They were smokers in 52.8% of the patients, with an average of 9.1 packs/year and 47.1% had exposure to smoke from wood, with an average of 62.1 hours/year. The 88.2% had adenocarcinoma, 5.9% squamous, from which 54.4% received nivolumab in second line and 45.6% in third line or more. The median progression-free survival was 8.1 months. The average overall survival, has not been able to achieve since 12 moths of treatment, the 51.4% of patients still alive. The response to the treatment by RECIST 1.1 was 38.2% for partial response (13 patients), stable disease in 41.2% (14 patients) and complete response 20.6% (7 patients). **Conclusion:** The use of nivolumab in patients with non-small cell lung carcinoma in advanced clinical stages (III and IV) progressing to a first line or more of chemotherapy demonstrated a better progression-free survival and overall survival in Mexican patients.

Keywords: Nivolumab, lung cancer, Mexico

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P2.07-062 PIVOT-02: PHASE 1/2 STUDY OF NKTR-214 AND NIVOLUMAB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMOR MALIGNANCIES

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Background: Abundance and functional quality of tumor infiltrating lymphocytes are positively linked with tumor response and improved survival with checkpoint inhibitors. NKTR-214 is a CD122-biased agonist that targets the IL2 pathway and is designed to provide sustained signaling through the heterodimeric IL2 receptor pathway (IL2Rβγ) to preferentially activate and expand NK and effector CD8+ T cells over CD4+ T regulatory cells within the tumor microenvironment. NKTR-214 is administered on an outpatient basis as a 15-minute IV infusion and has been administered to 28 patients with advanced solid tumors. Single-agent NKTR-214 demonstrates a substantial increase in both CD8+ T and NK cells within the tumor microenvironment in those patients with prior immune checkpoint therapy (Bernatchez et al, SITC poster 2016). Given the favorable safety profile and strong biomarker data, a trial combining NKTR-214 and nivolumab was initiated. **Method:** PIVOT-02 is a phase 1/2 open-label trial in patients with locally advanced or metastatic melanoma (MM), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial carcinoma, or triple-negative breast cancer (TNBC). Approximately 250 patients will be enrolled across 5 tumor types and 8 indications, with 26-38 patients per indication. Patients who are immunotherapy naïve will be studied for all 5 tumor types. MM, RCC, or NSCLC patients who are relapse/refractory on one prior anti-PD-1/PD-L1 containing regimen will be studied separately. The

primary objectives are to evaluate safety and tolerability, determine the recommended phase 2 dose (RP2D), and assess tumor response by RECIST 1.1. The dose-escalation portion of the trial has enrolled 23 patients (MM= 8, RCC= 11, NSCLC=4), in 5 different cohorts including NKTR-214 at 0.003 (q2w), 0.006 (q2w or q3w), or 0.009 (q3w) mg/kg in combination with a flat dose of nivolumab at 240 (q2w) or 360 (q3w) mg. Extensive blood and tumor tissue samples are being collected in both escalation and expansion phase to measure immune activation using immunophenotyping including flow cytometry, immunohistochemistry (IHC), T-cell clonality and gene expression analyses. Based on safety/tolerability, PK/PD and early biomarker data, the recommended phase 2 dose of NKTR-214 is 0.006 mg/kg q3w with nivolumab 360 mg q3w. The expansion phase of the study is now open for accrual. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Nivolumab, NKTR-214, PIVOT-02

P2.08: LOCALLY ADVANCED NSCLC -
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P2.08-001 HAND GRIP STRENGTH IS AN INDEPENDENT PROGNOSTIC FACTOR FORMORTALITY IN PATIENTS WITH NSCLC UNDERGOING RADIOTHERAPY

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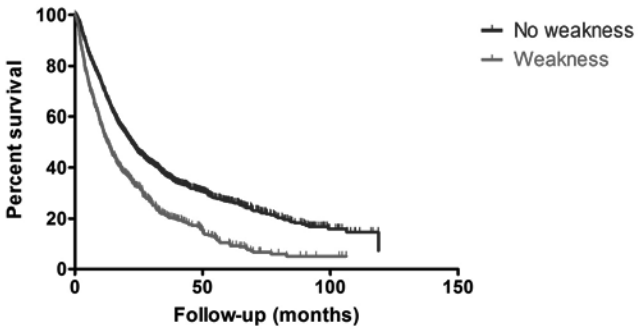
Background: Loss of muscle mass and function is common in patients with non-small cell lung cancer. Handgrip strength is a simple screening measure of general limb muscle function which is clearly associated with mortality in the general population and in some chronic disease populations. It is largely unclear to what extent handgrip strength provides prognostic information in patients with non-small cell lung cancer. **Method:** Handgrip strength was bilaterally assessed with a Jamar handheld dynamometer before initiation of radiotherapy. Normative values for handgrip strength have been proposed based on centile scores in over 224,000 healthy adults, adjusted for age, sex, height and measurement side. Patients were defined as weak if handgrip strength at one side (left or right) was below the tenth centile of the general population. Cox proportional hazard models were used to assess the relationship between handgrip weakness and mortality. Follow-up time was calculated from the day of assessment. Results are reported unadjusted and adjusted for disease stage (I to IV), World Health Organization Performance Score (WHO PS), gender and age. **Result:** We included 1497 patients for analysis (age 68±10; 63% male; stage I:17%; II:9%; III:60%; IV:14%). During follow-up 1109 patients (74%) deceased (time to death 18 ±17 months); mean follow-up in survivors was 46±25 months. Baseline weakness was present in 29% of patients. Unadjusted analysis shows an association between handgrip weakness and mortality (HR 1.64 (1.45-1.86; p<0.001; see figure 1). After covariate adjustment, handgrip weakness remained significantly related to mortality (HR 1.46 (1.27-1.68; p<0.001). Figure 1.



Conclusion: Our findings suggest that handgrip strength provides prognostic information in addition to well-established prognostic markers including disease stage, functional performance score and age in NSCLC patients who undergo radiotherapy. The detection of handgrip weakness is easy and quick and therefore might have a role in routine pre-treatment screening in this patient group.

Keywords: NSCLC, survival, Prognostic factors

P2.08: LOCALLY ADVANCED NSCLC -
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P2.08-002 A NOMOGRAM FOR PREDICTING UNDERLYING BENEFICIARIES FOR RESECTABLE IIIA/N2 NSCLC PATIENTS

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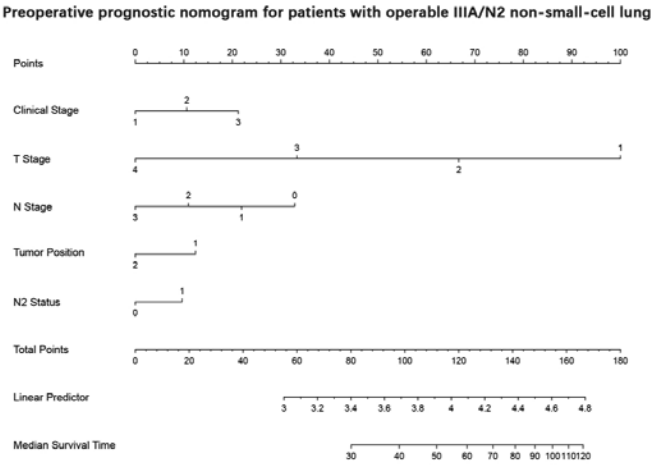
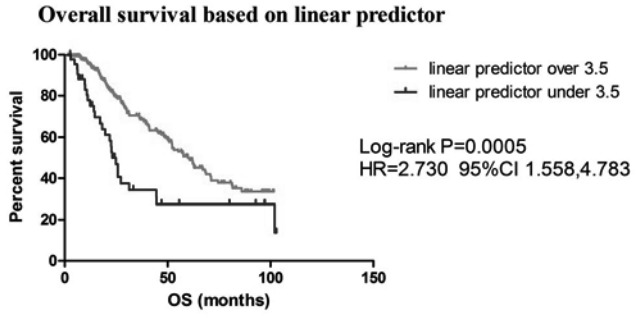
Background: Stage IIIA/N2 non-small-cell lung cancer (NSCLC) is a heterogeneous condition with multidisciplinary approaches involved. For operable IIIA/N2 NSCLC, surgery combined with chemotherapy is considered as an optimal management. Yet no solid evidences to conduct appropriate treatment modality for operable IIIA/N2 NSCLC and patients through curative treatment still surfer unsatisfactory prognosis. **Method:** 329 pathologically confirmed IIIA/N2 NSCLC patients through curative treatment were enrolled. Multivariate analysis was performed to select highly correlated clinical characters for nomogram. C-index and further survival analysis were given to validate the efficacy of the model. **Result:** Multivariate analysis indicate independent factors for overall survival including clinical stage, T stage, N stage, N2 status and tumor position which were then integrated into the model. The calibration curves showed moderate concordance between nomogram prediction and actual observation. Linear predictor of 3.5 was set to be the cutoff of the model through X-tile plot, and patients with linear predictor over 3.5 revealed significant longer median survival than those under 3.5 (59.90 vs. 24.90, log-rank P=0.0005).





Conclusion: We established a nomogram that may well distinguish the potential subgroup of patients benefit from curative treatment modalities. Further perspective study should rigorously clarify the issue of which multimodality treatment to be chosen for IIIA/N2 NSCLC patients.

Keywords: Non-small-cell lung cancer, Stage IIIA, Nomogram

P2.08: LOCALLY ADVANCED NSCLC -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.08-003 AN AUDIT OF CONCURRENT CHEMORADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER AT THE LEEDS CANCER CENTRE (LCC)

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Background: Concurrent chemoradiotherapy is the standard non surgical management of locally advanced NSCLC. Radiation pneumonitis is a well recognized complication of lung radiotherapy. This retrospective study examines the clinical outcomes and treatment toxicities of patients treated with chemoradiotherapy(CRT) for NSCLC in 2014 at the LCC in UK. **Method:** Data was retrospectively collected from patients with locally advanced NSCLC treated with concurrent CRT from 1/1/14-31/12/14 at LCC. Patients received 3-D conformal radiotherapy to a dose of 60-66Gy/30-33# over 6-6.5 weeks. Individual patient's clinical data was reviewed on Patient Pathway Manager for tumour and patient demographics. Radiotherapy dosimetric data were studied with V20, mean lung dose(MLD) and PTV volume. Treatment associated haematological toxicities and radiation pneumonitis were analysed. Overall and progression free survival were calculated. In addition, correlations between clinical/dosimetry parameter and clinical diagnosis of radiation pneumonitis were analysed. **Result:** 58 patients were included in the study. Median follow up was 18.6 months. 66% of patients received weekly carboplatin/paclitaxel and the rest received 3 weekly cisplatin or carboplatin with etoposide. 78% of patients completed both chemotherapy and radiotherapy. For all radiotherapy plans, median V20 was 20.9Gy (range 3.4-29.8Gy), median MLD was 12.8Gy (range 2.3-16.5Gy) and median PTV was 395cc (range 73-819cc). 34% of patients developed grade 3-4

neutropenia, 64% grade 3-4 lymphopenia and 5% grade 3-4 thrombocytopenia. Neutropenic sepsis occurred in 10% of patients with one grade 5 toxicity. Radiation pneumonitis was diagnosed in 17% of patients, all below grade 3. Median time to pneumonitis was 133 days post radiotherapy. Radiation pneumonitis correlated strongly with V20(r = 0.93). Correlations with MLD and PTV were less. There were no correlations with neutropenia, lymphopenia or thrombocytopenia during treatment. 2/3 of the recurrences were distant metastases. 90 day mortality was 5%(three patients died from oesophageal perforation, colitis and pneumonia). The median progression free survival was 20.1 months. The median overall survival was not reached. **Conclusion:** At the LCC, chemoradiotherapy has been a safe and effective treatment for locally advanced lung cancer. Consistent with existing evidence, V20 remains the most powerful predictor of radiation pneumonitis following lung radiotherapy.

Keywords: Chemoradiotherapy, locally advanced lung cancer, Radiation pneumonitis

P2.08: LOCALLY ADVANCED NSCLC -
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P2.08-004 PATHOLOGIC COMPLETE RESPONSE AS AN INDEPENDED PROGNOSTIC FACTOR IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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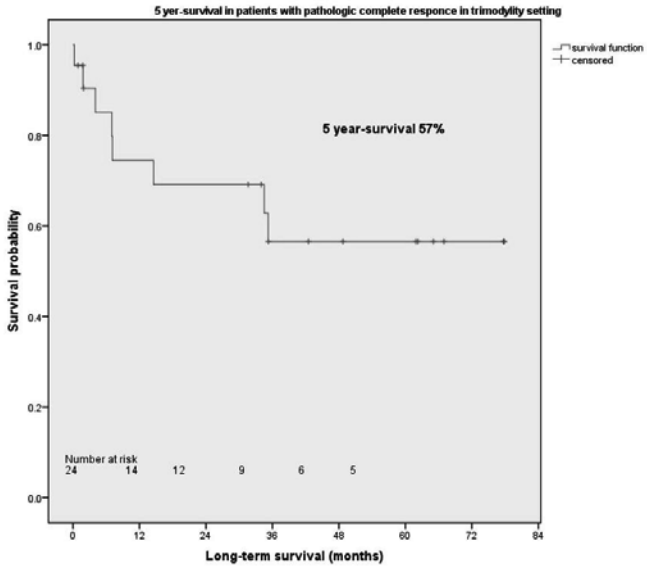
Background: Pathological complete response (pCR) after trimodality therapy in locally advanced non-small cell lung cancer (NSCLC) is associated with favorable long-term survival (LTS). The implication of pCR into daily practice is poorly defined. The aim of the study was to identify the correlation of pCR and different prognostic factors influencing long-term survival (LTS), tumor recurrence pattern and progressive-free interval (PFI). **Method:** A cohort of patients with locally advanced stage III NSCLC treated with induction chemoradiation (CRT) and subsequent surgery at a single center was retrospective reviewed. The subgroup of patients with pCR after the initial CRT, combined with application of 45Gy radiation dose, was extracted for further analysis. The statistical analysis stratified by descriptive statistics, Kaplan-Meier survival curves and estimated 3- and 5-years survival time combined with long-rank tests and Cox multivariate-analysis. **Result:** Between March 2008 and December 2016, a total of 24 patients with proven pCR were included in the retrospective analysis. The median age was 58.8 years [range, 46.4-76]. Fourteen patients (63.6%) were younger than 65. The median radiation dose applied was 50.4 Gy (range 45-56 Gy). The mean interval between the induction therapy and operation was 7.4±3.3 weeks and complete (R0) resection was achieved in 22 (91.6%) patients. The prognostic influence of gender, age, initial tumor stage and grade, histological subtype on pCR was analyzed using log-rank test and multivariate Cox regression model. The estimated 3- and 5-year survival rates for LTS were 64% and 57%, respectively. The estimated 3- and 5-year rates for PFI were 53% and 48%, respectively.



Conclusion: Favorable LTS is associated with pCR after CRT and followed by curative surgical resection. During the analysis pCR was identified as an independent prognostic factor. The distant tumor control remains the main limiting factor for LTS.

P2.08: LOCALLY ADVANCED NSCLC -
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P2.08-005 SALVAGE LUNG SURGERY FOLLOWING DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The incidence of local failure and residual tumor after definitive chemoradiation therapy (dCRT) for locally advanced non-small-cell lung cancer is even as high as 30%, irrespective of applied radiation dose (>59 Gy). So-called salvage surgery has been suggested a feasible treatment option after failure of definitive chemoradiation for locally advanced non-small cell lung cancer. Experience with salvage lung surgery is limited and long-term survival is rarely reported. The aim of this retrospective study was to assess postoperative survival and perioperative morbidity/mortality in order to identify prognostic factors and to define patient selection criteria. **Method:** Records of 13 consecutive patients with locally advanced non-small cell lung cancer, who underwent salvage lung surgery for local recurrence and persistent tumor after definitve chemoradiation therapy at a single institution between March 2011 and November 2016, were reviewed. Descriptive statistics were applied for patient characteristics, surgical and oncological outcome. Survival rates were calculated using Kaplan-Meier method and compared with long-rank test. **Result:** All patients initially received curative-intent definitive chemoradiation with median radiation doses of 66 Gy (range 59.4-72) and concurrent platin-based chemotherapy. Clinical tumor stage before definitive chemoradiation was IIIA in 9, IIIB in 3, IV in 1 patients. The indication for salvage surgery were in 6- a local recurrence and in 7 patients a persistent primary tumor. Median interval between definitive chemoradiation and salvage surgery was 6.7 months. Perioperative morbidity and 30-days-mortality was 38% and 7.7%, respectively. The median postoperative survival and estimated 5-year survival rate were 29.7 months and 46%, respectively. **Conclusion:** Salvage lung surgery for local failure in patients with locally advanced non-small cell lung surgery following definitive chemoradiation therapy is feasible, prolongs long-term survival and allows local tumor control. Selection criteria remain undefined and patients should be considered surgical candidates during multidisciplinary team conference.

P2.08: LOCALLY ADVANCED NSCLC -
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P2.08-006 IMMUNOLOGICAL BIOMARKERS CHARACTERIZATION IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH CONCURRENT CHEMO-RADIOTHERAPY

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Background: The immune microenvironment of locally advanced non-small cell lung cancer (NSCLC) has not been systematically studied. Our aim was to determine the prognostic value of immunological biomarkers expression in a cohort of patients (pts) in this clinical setting. **Method:** We retrospectively reviewed 46 bronchial biopsies from locally advanced NSCLC. Pts were treated between 2010 and 2014 with concurrent chemo-radiotherapy (cCRT) at the Catalan Institute of Oncology. The following immunological markers were assessed by immunohistochemistry: PD-L1, ≥5% membrane expression on tumor cells was considered positive (+); HLA-Class I expression was classified into 0,1+,2+ according to membrane intensity; CD8+ tumor infiltrating lymphocytes (CD8 TILs) classified into low ≤5% or high >5% intratumoral infiltration. Chi-square test for assessing correlation and survival analysis by Kaplan-Meier method were used. **Result:** From 46 pts: Median age was 65 (43-81); gender: male 94%, female 6%; ECOG≤1 96%; smoking status: current 67%, former 30%, never 3%; histology: squamous cell carcinoma (SCC) 63%, adenocarcinoma (ADC) 24%, NSCLC (NOS+large cell) 13%; cN0-1 30%, cN2 57%, cN3 13%. Platinum doublet CT: Cisplatin 57%, Carboplatin 43%. PD-L1 was positive in 38% of cases and was positively correlated with HLA-I expression (p= 0.015) and CD8-TILs (p= 0.008). No correlations between PD-L1/CD8 TILs status and G3-4 radio-induced toxicities (pneumonitis, esophagitis) were found. At a median follow-up of 48 months (m), 53% of pts had relapsed. According to immune phenotype, median overall survival (mOS) was 20m (PD-L1 +, CD8 high; n=10) vs 17 m (PDL1 negative, CD8 low; n=19) vs not reached (PD-L1 negative, CD8 high; n=5) (p=0.23). Considering CD8 TILs, mOS in high CD8 (n=15) was 35m vs 18 m in low CD8 (n=26) (p=0.22). **Conclusion:** PD-L1, HLA-I and TILs CD8 expression was positively correlated. The potential role of TILs CD8+ as a prognostic biomarker in this cohort of pts that comprised mostly SCC histology, is promising. These results should be investigated in a larger cohort.

Keywords: Immunophenotype, Stage III NSCLC, TILs CD8

P2.08-007 FIVE-YEAR RESULTS OF CONCURRENT CHEMOTHERAPY AND ISOTOXIC RADIOTHERAPY DOSE-ESCALATION WITH IMRT IN STAGE III NSCLC (NCT01166204)

D. De Ruysscher[1], B. Reymen[2], G. Bootsma[3], A. Dingemans[4], W. Geraedts[3], C. Pitz[5], W. Van Elmpt[2], M. Oellers[1], A. Van Baardwijk[1], R. Wanders[1], J. Van Loon[1]

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Background: Previous studies by our group showed that that increasing the radiotherapy (RT) dose in an overall treatment time (OTT) of less than 6 weeks on basis of the isotoxic principle is feasible and could potentially increase the overall survival (OS) with non-concurrent chemo-RT without increasing the toxicity. No data were yet available for IMRT treated patients. **Method:** From 04-05 2009 until 26-04-2012, 185 patients with stage III NSCLC, treated with concurrent chemo-RT were included in this single center phase II trial. OS update was done on June 7, 2017. The primary endpoint of this study was OS, with in-field nodal failures (INF) and toxicity as secondary endpoints. Patients received 1 cycle of cisplatin-etoposide followed by two cycles of the same chemotherapy with concurrent radiotherapy (IMRT, 45 Gy BID followed by 2 Gy QD to the maximal organ at risk constraint). **Result:** Patient characteristics: Gender: Male: 61.1 %, Female: 38.9 %. Age 63.9 ± 8.9 years (44-86). Smoking: Never 2.9 %, current 36.8 %, former 60.3 %. WHO performance status: 0 (36.2 %) 1 (56.8 %), 2 11 (5.9 %), 3: 1 pt , 4:1 pt. Histology: Squamous 55 (29.7 %), Adenocarcinoma 49 (26.9 %), Large cell 26 (14.1 %), NSCLC-NOS 55 (29.7 %). GTV (T+N) 120.4 ± 132 ml (16.8-708.5), Total Tumor Dose 66.0 ± 12.8 Gy (36.0-73.0). Number of fractions: 39.7 ± 3.4 (24-44). OTT 38.2 ± 26.8 days (16-93) MLD 17.3 ± 3.0 Gy (4.9-21,2). Mean Esophageal Dose 29.0 ± 9.3 Gy (6.3-54.1). OS: stage IIIA (n=42), median 16.7 Mo (8.7-24.7), 5-year 16.7 %; stage IIIB (n=143) 20.3 (16.2-24.4), 5-year 27.3 % (P=0.10). INF: 3/185 (1.6 %). Loco-regional failures: 59/185 patients (31.8 %) Toxicity: Dyspnea *Grade Baseline Maximal score* 0 102 (55.1 %) 71 (38.4 %) 1 68 (36.8 %) 103 (55.7 %) 2 15 (8.1 %) 5 (2.7 %) 3 0 6 (3.2 %) 88% of patients experienced any grade of dysphagia: 22% experienced grade 1 dysphagia, 44% grade 2, while 22% experienced grade 3 dysphagia. **Conclusion:** Isotoxic accelerated radiotherapy delivered with IMRT and concurrently with chemotherapy leads to low INF and toxicity is comparable to the best series using standard fractionation schedules. Long term OS remains low and therefore other strategies are needed.

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

P2.09-001 EFFECTS OF TUMOR BURDEN REDUCTION ON SURVIVAL IN EPITHELIOID PLEURAL MESOTHELIOMA

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Background: Surrogate endpoints are commonly utilized in oncology clinical trials and have been adopted by regulatory agencies for the approval of many agents. To date, the effects of tumor size reduction on survival have not been determined for the only Food and Drug Administration (FDA)-approved regimen fo malignant pleural mesothelioma (MPM), but its widespread use mandates its validation. MPM is a challenging disease to assess and standard Response Evaluation Criteria for Solid Tumors (RECIST) were not optimized to measure pleural disease. Modified pleural RECIST (mRECIST) have been adopted by mesothelioma experts for the measurement of responses in MPM and mRECIST are the most commonly used response criteria in clinical trials for MPM. Although the gold standards for oncology outcomes are overall survival and quality of life, cross-over to subsequent therapies and competing risks influence survival outcomes. We sought to evaluate the relationship of response with survival in the clinical trial of the only FDA approved regimen for MPM. **Method:** We reviewed the clinical trial that randomized patients with MPM to receive cisplatin or cisplatin and pemetrexed. Patients with epithelioid MPM were categorized by whether or not they responded to cisplatin or the combination of cisplatin and pemetrexed accoring to the original study determination. Responders had ≥30% reduction in the thickness of the pleural rind measured at up to 3 points on 3 separate slices of the CT scan. Median progression-free (PFS) and overall survivals (OS) were determined and the hazard ratios for responders and non-responders were determined and compared by the logrank test. **Result:** We identified that patients with epithelioid MPM who responded to front-line therapy had a significantly longer overall survival (HR 0.341, 95% CI 0.239-0.486; median 20.6 months, 95% CI: 15.3-not reached) than those who did not respond (median 9.4 months, 95% CI: 8.1-11.0; p<0.001). Similarly patients who responded to front-line therapy had a significantly longer progression-free survival (HR 0.496, 95% CI: 0.385-0.639; median 7.8 months, 95% CI: 6.5-8.5) than those who did not respond (median 3.7 months, 95% CI: 2.9-4.3; p<0.001). **Conclusion:** Our findings demonstrate that a reduction in tumor burden was strongly associated with OS and PFS in epithelioid MPM treated with cisplatin or cisplatin and pemetrexed.

Keywords: mesothelioma, response, survival

P2.09-002 PREVALENCE AND SURVIVAL OF MALIGNANT PLEURAL MESOTHELIOMA PATIENTS TREATED IN A SINGLE BRAZILIAN CANCER CENTER

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Background: Malignant pleural mesothelioma (MPM) is an unusual neoplasm, originated from the mesothelial surface of the pleural cavity. The disease is associated with occupational exposure to asbestos. Although it has low incidence, it carries an elevated morbimortality, determined by its aggressiveness and aggravated by the lack of efficient therapeutic strategies. Most patients are diagnosed at advanced stages and median overall survival (OS) remains around 9-17 months. In Brazil, some studies have suggested the number of new cases will increase till 2030, nevertheless there is no official epidemiologic data available. **Method:** Clinicopathological data from patients diagnosed with MPM and treated at A.C.Camargo Cancer Center between January/2000 and December/2014 were retrospectively collected from medical records. Demographics and clinicopathological variables were described using descriptive statistics. OS was calculated from the date of diagnosis to death. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression or death. Kaplan–Meier method was used to calculate survival curves. The impact of relevant variables on survival was evaluated by the log-rank test. **Result:** We identified 29 patients between 2000 and 2014. Median follow-up was 108 months. Median age at diagnosis was 68 years (43-85y). 72.4% was men and most were Caucasian (51.7%). Tobacco consumption reported (58.6%), history of asbestos exposure (44.8%) and positive family history of cancer (34.5%). The presenting symptom was dyspnea (44.8%); followed by chest pain (24.1%). Epithelioid subtype was reported (69%) and most patients were diagnosed in stage III (34,5%) and IV (24.1%). 79% of patients were submitted to surgery: pleural decortication (36,4%), pleurodesis (31,8%), and pleuro-pneumonectomy+mediastinal lymphadenectomy (31,8%). Chemotherapy was administered to 72.4% and radiotherapy to 24.1%. Median PFS was 8 months (95%CI 5.4-10.5) and the only factor associated with improved PFS was disease resectability (resectable vs. unresectable: 10mo vs. 7mo; p=0.041). Median OS was 12 months (95%CI 5.6-18.3). Variables associated with improved OS were lack of distant metastasis at diagnosis (M0 vs. M1-MX: 15mo vs. 6mo; p=0.008) and being able to receive further lines of chemotherapy (yes vs. no: 18mo vs. 6mo; p=0.016). **Conclusion:** Since there is no national official data in Brazil, collection of local data is extremely relevant to help unraveling the epidemiological scenario in our country. Our data reinforce the low prevalence of the disease, though it could also reflect issues regarding patient referral to specialized centers. As expected, we observed an association with occupational exposure to asbestos and a poor PFS and OS.

Keywords: Brazil, Mesothelioma, epidemiology

P2.09-003 DISSECTING THE IMMUNE ENVIRONMENT IN MALIGNANT PLEURAL MESOTHELIOMA: RESULTS FROM A PROSPECTIVE ASSESSMENT

C. Riganti[1], M. Pradotto[2], L. Righi[2], C. Marchiò[3], E. Capelletto[2], C. Buttigliero[2], L. Costardi[4], J. Kopecka[1], P. Bironzo[2], E. Ruffini[4], S. Novello[2], G. Scagliotti[2]

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Background: Malignant pleural mesothelioma (MPM) cells grow in the context of immune cells, either infiltrating the tumor or present in the associated pleural effusion. Specific immune cell subsets and immune-checkpoints on T-lymphocytes infiltrating the tumor have been proposed as possible prognostic factors (Uiije, DOI:10.1080/2162402X.2015.1009285; Awad, DOI:10.1158/2326-6066.CIR-16-0171) and therapeutic targets (Marcq, DOI:10.1080/2162402X.2016.1261241; Khanna, DOI: 10.1016/j.jtho.2016.07.033). The immune cells infiltrating MPM are however dynamically exchanged with those present in the pleural fluid (Lievense, DOI: 10.1016/j.lungcan.2016.04.015). The heterogeneity of tumor bulk, ranging from terminally differentiated cells to tumor-initiating cells (TIC), makes the interactions between tumor and immune cells even more jeopardized. Our study is the first that analyzes at the same time the immune-phenotype of MPM cells, immune cells infiltrating the tumor and present in the matched pleural fluid, to obtain a comprehensive signature of MPM immune-environment and precise indications for personalized immunotherapy-based interventions. **Method:** From June 2015 to June 2017, we collected 120 pleural fluids and biopsies from patients that undergone diagnostic thoracoscopy: 34 samples were diagnosed as MPM (25 epithelioid, 5 sarcomatoid, 4 biphasic MPM), 56 samples were reactive non neoplastic pleuritis, 30 samples were pleural localization of lung adenocarcinoma or other tumors. Cells of pleural fluids were analyzed by cell sorting and flow cytometry. Biopsies were cut and digested, and cell populations were analyzed as well. We isolated, expanded and analyzed the TIC-component from 5 epithelioid and 5 sarcomatoid MPM. **Result:** MPM significantly differed from non neoplastic pleuritis for the increased number of

CD3+CD8+T-lymphocytes in pleural essudate coupled with the reduction of this population within the tumor (p<0.001). M2/M1-macrophages ratio was also higher (p<0.02). The increased number of T-regulatory cells and granulocytic/monocytic myeloid-derived suppressor cells in both pleural fluid and tumor significantly (p<0.005) differentiated MPM from non neoplastic pleuritis and other malignancies. Either CD3+CD8+or CD3+CD4+T-lymphocytes present in pleural fluid and infiltrating the tumor had higher expression of PD-1, LAG-3, TIM-3 immune-checkpoints (p< 0.02), coupled with increased expression of PD-1L, LAG-3, TIM-3 and GAL-9 on matched MPM (p<0.05) compared to non neoplastic pleuritis. Interestingly, immune-checkpoints were down-regulated in TIC, suggesting that immune-checkpoint inhibitors may be poorly effective against this MPM component. **Conclusion:** Our study identified an immune-signature that discriminates MPM from pleuritis secondary to other tumors or non malignant diseases. Such immune-signature will help to refine prognostic factors and define a precision immunotherapy for MPM.

Keywords: granulocytic/monocytic myeloid-derived suppressor cells, T-regulatory cells, Mesothelioma immune-infiltrate

P2.09: MESOTHELIOMA -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.09-004 PD-L1 PROTEIN EXPRESSION IS NEGATIVE PROGNOSTIC FACTOR IN MALIGNANT PLEURAL MESOTHELIOMA IN CENTRAL EUROPE

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Background: Early data on immune-checkpoint blockade with PD-1 inhibitors show promising response rates and survival benefit mainly in PD-L1 positive malignant pleural mesothelioma (MPM) patients. Reported rate of PD-L1 positivity of MPM is between 20-40%. However, the role of PD-L1 protein expression positivity in prediction of a response to PD-1/PD-L1 inhibitors remains controversial. We assessed the prognostic value of PD-L1 expression in patients with MPM in central Europe. **Method:** We evaluated protein expression of PD-L1 in formalin-fixed paraffin-embedded surgical specimens of 176 MPM patients from Austria, Croatia, Hungary and Slovenia. PD-L1 antibody clone E1L3N (Cell Signaling) was used. Cut-off point of >10% of PD-L1-positive tumor cells at any staining intensity was correlated with clinicopathologic characteristics (age, gender, IMIG clinical stage, histology (epithelioid vs non-epithelioid) and survival). **Result:** There were altogether 49 females and 127 males, median age 63 years. PD-L1 protein expression of >10% was observed in higher proportion in a patient with higher IMIG stage (III+IV vs. I+II), as well as in patients with non-epithelioid histology, later being also statistically significant (p=0.0026). Median survival of patients with high PD-L1 expression (>10%) in tumor cells was significantly shorter in comparison with patients demonstrating lower PD-L1 expression (26 vs. 67 weeks respectively, p<0.001). PD-L1 expression (>10%) proved to be an independent prognostic factor in a multivariate cox regression analysis (hazard ratio [HR] 2.902; 95% confidence interval [CI] 1.425 to 5.937; p = 0.003). **Conclusion:** High expression of PD-L1 on tumor cells (>10%) is negative independent prognostic factor in malignant pleural mesothelioma regardless of histology.

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P2.09-005 THE C-REACTIVE PROTEIN/ALBUMIN RATIO IS A NOVEL SIGNIFICANT PROGNOSTIC FACTOR IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a devastating neoplasm. However, some patients show a good response to chemotherapy or multidisciplinary therapy. It is therefore important to investigate the factors that can be used to select patients who will benefit from such treatment. The C-reactive protein/albumin ratio (CAR) has been used to predict the prognosis in other diseases. The aim of this study was to elucidate the prognostic utility of the CAR in MPM patients. **Method:** The data of 83 patients, who were treated with surgery, chemotherapy, or multidisciplinary therapy at National Kyushu Cancer Center between 1995 and 2015, were analyzed in the present study. The CAR was calculated as C-reactive protein value divided by albumin value using the results of blood examination just prior to starting the treatments. A cut-off value of CAR was set to 0.58 according to the receiver operating characteristics (ROC) curve for 1-year-survival. **Result:** Thirty of the 83 (36.1%) patients were classified into the high CAR group. Twenty-seven (32.5%) and 56 (67.5%) patients underwent surgery and only chemotherapy, respectively. The ROC curve showed that the CAR had good diagnostic ability with 78.9% sensitivity and 68.0% specificity (AUC=0.761). A high CAR group was significantly correlated with advanced clinical stage (III/IV) (p=0.002) and chemotherapy alone (p=0.005). The high CAR group had significantly poorer overall survival (OS) (p<0.001) and disease or progression free survival (DFS/PFS) (p<0.001). The clinical stage and the CAR were independent predictive factors for the OS (I/II and III/IV, p=0.008; ≤0.58 and >0.58, p=0.034, respectively). The clinical stage and the CAR were also independent predictive factors for the DFS/PFS (I/II and III/IV, p=0.031; ≤0.58 and >0.58, p=0.019, respectively). In the subgroup analysis of the patients who underwent only chemotherapy, the high CAR group showed significantly poorer OS and DFS/PFS compared with the low CAR group (p=0.002 and p<0.001, respectively). However, the difference in OS and DFS/PFS of the patients who underwent surgery was not apparent between the high and low CAR groups (p=0.061 and p=0.187, respectively). **Conclusion:** The CAR was an independent predictor of a poor prognosis in the MPM patients. The high CAR group showed a significantly poorer prognosis in patients with MPM treated by only chemotherapy. This score provides useful information for selecting patients who will benefit from treatment, especially chemotherapy. These findings should be validated in further prospective studies.

Keywords: malignant pleural mesothelioma, Prognosis, C-reactive protein/albumin ratio

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P2.09-006 FISH ANALYSIS OF P16 AND BAP1 IMMUNOHISTOCHEMISTRY FOR THE DIAGNOSIS OF MESOTHELIOMA

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Background: Distinction between mesothelioma and reactive mesothelial proliferation is difficult because of cytological and morphological overlap between these conditions. It is also difficult to differentiate sarcomatoid mesothelioma from fibrous pleuritis on biopsy. However, separation of reactive mesothelial proliferation from epithelioid mesothelioma and that of fibrous pleuritis from sarcomatoid mesothelioma is important because of therapeutic option and prognosis of the patients. There are some reports claiming that ancillary techniques such as fluorescence in situ hybridization (FISH) analysis of *p16* and immunohistochemistry of BAP1 improve the diagnostic accuracy of mesothelioma. However, reported sensitivity of *p16* FISH and BAP1 loss is different depending on the subtype of mesothelioma and on studies from various authors. The aim of this study was to elucidate the frequency of *p16* deletion and BAP1 loss in mesotheliomas by multiple institutions in Japan. **Method:** We collected 262 malignant pleural mesotheliomas, 29 malignant peritoneal mesotheliomas, 23 cases with reactive mesothelial proliferation, and 37 cases with fibrous pleuritis from Tokyo Women's Medical University, Chiba Rosai Hospital, Fukuoka University, Hyogo Medical University, Kagawa University, and Kanagawa Cancer Center. FISH analysis was performed with *p16* probe. Immunostaining was performed with anti-BAP1 antibody. **Result:** We analyzed 262 pleural mesotheliomas (170 epithelioid, 38 biphasic, and 54 sarcomatoid) with *p16* FISH, and 92 pleural mesotheliomas (58 epithelioid, 20 biphasic and 14 sarcomatoid) with BAP1 immunohistochemistry. Homozygous deletion (HD) of *p16* was observed in 74% of epithelioid, 92% of biphasic, and 100% of sarcomatoid mesotheliomas. BAP1 loss was observed in 64% of epithelioid mesotheliomas and 55% of biphasic mesotheliomas, but not in sarcomatoid mesotheliomas. Concordance of HD of *p16* and BAP1 loss between epithelioid and sarcomatoid components of 19 biphasic mesotheliomas was 100%. We analyzed 29 peritoneal mesotheliomas (25 epithelioid, 2 biphasic, and 2 sarcomatoid) with *p16* FISH and 9 peritoneal epithelioid mesotheliomas with BAP1 loss. HD of *p16* was observed in 52% of epithelioid mesotheliomas, 50% of biphasic mesotheliomas, and 50% of sarcomatoid mesotheliomas. BAP1 loss was observed in 56% of epithelioid mesotheliomas. No case with reactive mesothelial proliferation or fibrous pleuritis harbored HD of *p16* and showed BAP1 loss. **Conclusion:** Separation of epithelioid or biphasic mesothelioma from reactive mesothelial proliferation may be possible with *p16* FISH and/or BAP1 immunohistochemistry. Because all of the pleural sarcomatoid mesotheliomas but no cases with fibrous pleuritis harbor HD of *p16*, *p16* FISH helps the separation of sarcomatoid mesothelioma from fibrous pleuritis, but BAP1 does not.

Keywords: BAP1, p16, Mesothelioma

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P2.09-007 PLEURAL BIOPSY IN PATIENTS SUSPECTED OF MALIGNANT PLEURAL MESOTHELIOMA CONSECUTIVE 377 CASES

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Background: Video-assisted thoracic surgery (VATS) pleural biopsy is a most reliable diagnostic procedure for malignant pleural mesothelioma (MPM), however, its surgical outcomes are still unknown. The purpose of this study was to analyze the surgical outcome of VATS pleural biopsy in patients suspected of MPM. **Method:** A total of 377 patients received VATS pleural biopsy with suspected of MPM from March 2004 to December 2016 were included in the study. We evaluated their surgical outcome based on diagnostic accuracy, mortality, morbidity. **Result:** Of 377 patients, VATS pleural biopsy led to diagnosis as MPM in 250, carcinomatous pleurisy in 22 and chronic pleuritis in 105. However, of these 105 chronic pleuritis patients, 10 patients were received re-biopsy to establish the definitive diagnosis. Re-biopsy revealed 9 patients finally diagnosed as MPM, and 1 patient as carcinomatous pleurisy. The diagnostic accuracy of initial VATS pleural biopsy for MPM was 96.5% (250/259). The causes of miss-diagnosis were sampling error in all 9 cases, and the causes of sampling error as follows: no visible tumor in 4, complicated empyema in 2, severe adhesion in 2, and desmoplastic MPM in 1. The median postoperative stay was 5 days (1-114).Postoperative complication. Median age was 68 years (range, 40-85 years), with a 5- day (range 1-114 days) median length of stay. Postoperative complication occurred in 25 patients (5.7%), and 1 patient (0.26%) died due to postoperative empyema. Complications of this study included the following: injury of lung parenchyma in 7, wound infection in 4, re-expanding pulmonary edema in 3, empyema, gastrointestinal perforation and delirium in 2, fetal arrhythmia, cholecystitis hemothorax, liver dysfunction, acute respiratory failure in 1. **Conclusion:** VATS pleural biopsy could lead to definitive diagnosis in most case of MPM, but we should consider their limitation of diagnostic ability and the risk of VATS biopsy.

Keywords: Mesothelioma, diagnosis, Pleural biopsy

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P2.09-008 USEFULNESS OF IMMUNOHISTOCHEMISTRY IN THE DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MESOTHELIOMA AND LUNG SQUAMOUS CELL CARCINOMA

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Background: The differential diagnosis between epithelioid mesothelioma (EM) showing a solid histological pattern (solid EM) and poorly differentiated squamous cell carcinoma (SCC) can be challenging with conventional light microscopy (haematoxylin and eosin-stained specimen) alone. The role of immunohistochemistry in distinguishing pleural EM from lung adenocarcinoma (LAC) has received much attention. Currently, many immunohistochemical markers are available for distinguishing pleural EM from LAC. . However, there are only a few reports on the immunohistochemical differential diagnosis of EM and lung SCC. Ordonez et al. have reported the immunohistochemical analyses of 30 EMs showing a solid pattern and 30 pulmonary non-keratinizing SCCs, and have recommended the combination of two positive (Wilms' tumour gene product; WT1 and calretinin/mesothelin) and two negative (p63 and Epithelial-related antigen; MOC31) markers for differentiating EM from lung SCC. The aims of this study were to clarify the usefulness of immunohistochemistry in the differential diagnosis of solid EM and poorly differentiated SCC, and to confirm the validity of a specific type of antibody panel. Additio nally, we aimed to clarify the pitfalls of immunohistochemical analyses. **Method:** Formalin-fixed paraffin-embedded specimens from 36 cases of solid EM and 38 cases of poorly differentiated SCC were immunohistochemically examined for calretinin, podoplanin (D2-40), WT1, cytokeratin (CK) 5/6, p40, p63, carcinoembryonic antigen (CEA), MOC31, claudin-4, thyroid transcription factor-1 (TTF-1), and napsin A. **Result:** WT1 showed the highest diagnostic accuracy (85.1%) as a mesothelial marker, and CEA, p40 and claudin-4 showed higher diagnostic accurac ies (95.9%, 94.6%, and 93.2%, respectively) as carcinoma markers. Calretinin (diagnostic accuracy: 75.7%), D2-40 (diagnostic accuracy: 67.6%), CK5/6 (diagnostic accuracy: 63.5%), TTF-1 (diagnostic accuracy: 55.4%) and napsin A (diagnostic accuracy: 52.7%) could not differentiate between solid EM and poorly differentiated SCC. Among these markers, the combination of calretinin and WT1 showed the highest diagnostic accuracy (86.5%) as a positive marker, and the combination of p40 and CEA showed the highest diagnostic accuracy (97.3%) as a negative marker. The combin ation of CEA and claudin-4 also showed relatively high diagnostic accuracy (94.6%) as a negative marker. **Conclusion:** We recommend the combination of WT1 and calretinin as a positive maker, and the combination of CEA and claudin-4 as a negative marker, for diff erential diagnoses of solid EM and poorly differentiated SCC.

Keywords: Mesothelioma, Squamous cell carcinoma, Immunohistochemistry

P2.10: NURSING/PALLIATIVE CARE/ETHICS -
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P2.10-001 FACTORS ASSOCIATED WITH QUALITY OF LIFE AMONG PATIENTS WITH LUNG CANCER

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Background: Lung cancer is the third incidence and first mortality of cancer disease in Taiwan. The survival time of lung cancer patients was extended. The overall 2 year survival rate from 29% to 49.8% at National Cheng Kung University Hospital (NCKUH). Factors associated with quality of life have become the issues of focus and need to be elucidated as the improvements of medical science prolong the survival of patients with lung cancer. The purpose of this study was to describe the long-term trend on the quality of life of patients with lung cancer, and to understand the related factors. **Method:** This was a retrospective study with secondary data analysis and chart review. The study samples were lung cancer patients who were diagnosed from 2005 to 2012 at NCKUH and joined WHOQOL interview research program. We assessed personal characteristic, health status, lung cancer disease status and treatment. The authors analyzed secondary databases included the NCKUH cancer registration database and the NCKUH Cancer QoL Study database. The analyzing protocol was also approved by the institutional ethics committee. Using SAS 9.3 software, the regression models and mixed-models were constructed to explore related factors and the time trend of QoL. **Result:** Total 1887 questionnaires were included in research. The proportion of female subject was 47.7%.

Image 1. Mixed Model Parameter Estimates Each Domains of QoL

Domains	Physical Health				Psychological				Social Relationship				Environment			
Variables	Estimate	S.E.	P	F	Estimate	S.E.	P	F	Estimate	S.E.	P	F	Estimate	S.E.	P	F
Gender (Female/Male)	**-0.94**	0.40	*	5.6	**-0.74**	0.31	*	5.7	**-0.34**	0.16	*	4.8				
Employment (No/Yes)	**-1.73**	0.51	**	12	**-1.36**	0.36	***	15	**-0.39**	0.19	*	4.2	**-0.93**	0.45	*	4.3
Educational (< / ≥ high school)	-0.81	0.43		3.6												
Diagnosis ECOG	-0.63	0.35		3.2									-0.82	0.33	*	6.3
Diagnosis Age (y/o)	**-0.06**	0.02	*	7.5					**-0.03**	0.01	**	14.8	0.009	0.018		0.2
Economic (< /50000)													**-0.88**	0.40	*	4.8
Married (No/Yes)									**-1.41**	0.18	***	61.5	-0.76	0.44		3
COPD (No/Yes)	1.94	1.28		2.3												
HTN (No/Yes)					-0.40	0.33		1.6	-0.25	0.16		2.3	-0.16	0.09		3.5
CKD (No/Yes)									1.45	0.59	*	6				
Brain metastasis (No/Yes)	**2.33**	0.51	***	21	**1.24**	0.40	**	9.7								
Tumor size (cm)													-0.16	0.09		3.5
Radiotherapy (No/Yes)	**1.11**	0.55	*	4	0.77	0.44		3.1					0.83	0.55		2.3
Time (Month)	0.014	0.008		3.2	0.01	0.006		3.1	0.001	0.003		0.1	**0.02**	0.006	**	11

*p<0.05 **p<0.01 ***p<0.001

Conclusion: The physical, psychological, environment domains and global QoL among lung cancer patients was improved over time, which showed the promising quality of treatment and care in NCKUH. The factors associated with QoL among patients with lung cancer include gender, age, married status, employment status, income, and with chronic kidney disease or brain metastasis. More resources are to be explored for patients who are single or have lower income, and special attention should be paid to patients who are unemployed, female, elder, or to under radiotherapy that would improve their QoL.

Keywords: Lung cancer, Quality of life, Factors

P2.10: NURSING/PALLIATIVE CARE/ETHICS -
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P2.10-002 A STUDY ON THE RELATION BETWEEN GENDER AND QUALITY OF LIFE FOR LUNG CANCER PATIENTS

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Background: Two papers showed that female lung cancer patients have poorer QoL. But others papers didn't have consistence conclusion. In author's NCKUH-10207013 study, the result showed that male patients improved more than female over time in the domains of physical, psychological and social quality of life. The purpose of this study was to understand the demographic status and characteristic of QOL in different gender. And to understand the related factors of the QOL in different gender. **Method:** The study design was to analyze secondary databases. The study samples were lung cancer patients who were diagnosed at National Cheng Kung University Hospital and joined WHOQOL interview in DOH100-TD-C-111-003 study. The databases included the cancer registration database, the diagnosis and treatment database for lung cancer, and the NCKUH quality of life database. Using SPSS and SAS 9.3 software, regression madel and mixed-models were constructed to explore the difference and related factors of quality of life between gender. **Result:** 409 females and 446 males lung cancer patients were included this study. Female lung cancer patients were diagnosed with younger age, higher proportion of non-working status and single status. Female had lower score in psychological domain of QoL at 6th months after diagnosis. But female had better score than male in physical domain of QoL at 9th months after diagnosis. For the QoL details items of each domains, there were significant negative differences of female in pain, energy, active ability, sleep, daily activity, thinking, bodily image, self-esteem, negative feeling.

	Gender (Female/Male)			
QoL Domains	Estimate	S.E.	P	F
Physical_health				
Q3_Pain	-0.23	0.06	**0.0001**	15.04
Q4_Medical Dependence	0.052	0.069	0.45	0.56
Q10_Energy	-0.11	0.054	0.049	3.9
Q15_Active Ability	-0.15	0.063	0.018	5.66
Q16_Sleep	-0.21	0.058	**0.0003**	12.94
Q17_Daily Activity	-0.11	0.048	0.021	5.34
Q18_Working capacity	-0.035	0.054	0.52	0.42
Psychological				
Q5_Positive Feelings	0.03	0.059	0.61	0.26
Q6_Spirituality	-0.04	0.059	0.48	0.48
Q7_Thinking	-0.11	0.051	0.039	4.29
Q11_Bodily image	-0.22	0.046	**<0.0001**	22.79
Q19_Self-Esteem	-0.15	0.05	0.0036	8.52
Q26_Negative Feelings	-0.35	0.06	**<0.0001**	34.1

Conclusion: The larger significant differences between gender were pain and sleep of the physical domain, and bodily image and negative feelings of the psychological domain. The results of this study could understand the differences of QoL between gender. More resources and care plans should to be explored for different gender to improve their QoL and prevention QoL decrease.

Keywords: Lung cancer, Quality of life, Gender

P2.10: NURSING/PALLIATIVE CARE/ETHICS -
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P2.10-003 THE DETERIORATION AND PROGNOSTIC VALUE OF FUNCTIONAL CAPACITY IN PATIENTS WITH LUNG CANCER: A SYSTEMATIC REVIEW

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Background: Performance status (PS) scoring systems are of immense prognostic and clinical importance, however, the subjective evaluation of a patient's global physical functioning is limited in sensitive prognostic stratification and existing literature present contradictory inter-rater reliability of PS assessments. The subjective assessment indicates the level of physical functioning, but does not provide a targeted treatment aim. Better treatment aims could be provided, if the level of decline in physical functioning was objectively collected and evaluated. To our knowledge, the significance of functional capacity in patients with lung cancer has never been evaluated prior to this review. Thus, the aim of this study was to identify and evaluate the evidence objectively examining 1) the decline in functional capacity in patients with lung cancer during cancer treatment, and 2) the prognostic value of functional capacity for patients with lung cancer. **Method:** The systematic review was reported according to PRISMA guidelines. A search in three databases: PubMed, EMBASE and Web of Science, generated 171 articles. Quantitative study designs, including case-series and case-controls, assessing functional capacity in patients with lung cancer were included. Self-reported functional capacity was excluded. No restrictions on publication date were imposed. Only articles published in English were considered for inclusion. **Result:** Eight studies on a total of 908 patients with lung cancer met the inclusion criteria. The majority of the studies were prospective cross-sectional studies (n=7), remaining was a case-control (n=1). Patients with lung cancer had already declined in functional capacity at baseline compared to healthy adults, and deteriorated further during initial cancer treatment. Functional capacity as a predictive measure was not associated with radiation induced lung injury. A 6-minute walking distance (6MWD) >400 m was associated with a 56 % reduction in the risk of death, and every 50 m improvement in 6MWD was associated with a 13 % risk reduction. **Conclusion:** The results of this review demonstrate that functional capacity (6MWD) declines following non-surgical NSCLC treatment as well as low functional capacity being associated with higher risk of mortality. By implementing an objective measure for functional capacity at the time of diagnosis, it could be possible to generate targeted treatment aims throughout the medical treatment and rehabilitation process. In addition, an objective measure for functional capacity could provide a better prognostic stratification.

Keywords: performance status, functional capacity, Prognosis

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P2.10-004 EFFICACY AND SAFETY OF VISCUM ALBUM (HELIXOR M) TO TREAT MALIGNANT PLEURAL EFFUSION IN PATIENTS WITH ADVANCED LUNG CANCER

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Background: Lung cancer, the most common metastatic tumor to the pleura, accounts for approximately 40% of all malignant pleural effusion (MPE). Regarding symptomatic MPE, local therapies including pleurodesis and treatment of primary malignancy are required to alleviate dyspnea and/or pleuritic pain. Helixor-M made from European mistletoe (Viscum album) has been used as adjuvant anticancer treatment by boosting immune system. We have used Helixor-M as sclerosing agent for pleurodesis to control MPE. The aim of this study is to evaluate efficacy and safety of Helixor-M to control MPE. **Method:** Between 2009 and 2015, we consecutively enrolled 52 patients with lung cancer who were treated with Helixor-M for MPE and analyzed retrospectively. For pleurodesis, we instilled 100mg of Helixor-M via pleural catheter at Day 1. After 3-hour of frequent repositioning we drained residual pleural fluid. If prior procedures were not effective, we repeated this procedure up to 5 times every second day with increasing dose by 100mg. Our primary study outcome was reappearance of pleural effusion 1-month after pleurodesis. **Result:** The median age was 63 years and 77% were male. Among 52 patients, 69% were adenocarcinoma, followed by squamous cell (13%), not otherwise specified (10%), and small cell lung cancer (8%). About 85% of MPE were cytogenetically malignant. Among 52 patients, 39 (75%) were evaluable for recurrence of MPE. The 1-month recurrence rate was 49% (19/39). Among 19 patients who experienced recurrent MPE, 6 required recurrent pleural drainage. One fourth of patients experienced significant pain after pleurodesis. Only 15% of patients experienced fever. **Conclusion:** Our results suggest that a pleurodesis with Helixor-M was effective and tolerable procedure to control MPE in advanced lung cancer patients.

Keywords: malignant pleural effusion, pleurodesis, helixor M

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P2.10-005 OVERALL SURVIVAL OF LUNG CANCER PATIENTS WITH BRAIN METASTASES IN A DEVELOPING COUNTRY

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Background: Brain metastases (BM) are common in due course of lung cancer (LC). The clinical presentation of BM can be very distressing for family/caregivers and urges for immediate treatment. Despite the early diagnosis and multimodality treatment of BM, prognosis remains poor. Considering the fact that treatment options in developing countries are limited (WBRT, surgery and SBRT) individual approach and specific prognostic assessment is highly important for further disease management. Aim of this study was to gather information and make approximation of overall survival (OS) of LC patients with BM. **Method:** This observational trial was conducted at the Institute for Pulmonary Diseases of Vojvodina, Serbia in the period from March 2010 to April 2015 taking into account all newly diagnosed LC patients. All data were harvested from the hospital based data capture system. The survival estimations were calculated regardless of the therapeutic interventions applied. Median OS was determined via Kaplan-Meier curves for all subgroups of LC patients with BM. **Result:** BM were diagnosed in 336 (5.1%) out of 6.624 LC patients in this 5 year period. Out of them, 182 patients were eligible for evaluation in this trial, the rest were excluded due to missing data. Majority of patients were male 68.1% (124), older than 60 years 50.0% (91), smokers 73.6% (134) with ECOG PS 1 76.4% (139). Most frequent LC type was adenocarcinoma 59.3% (108) followed by small-cell, squamous cell, and other types; 19.2% (35), 13.2% (24) and 8.2% respectively (13). One BM was present in 63.0% (63), 2-3 BM in 52.0% (52) and more than 3 in 34.6% (63) of patients. Extra cranial metastases (ECM) were present in 60.4% (110) of patients Median OS of all patients with BM regardless the histology was 8.5 (95%CI: 7.8-12.2) months. Median OS of patients with NSCLC, SCLC and other tumour types was 8.5 months (95%CI: 6.0-10.9), 10.0 months (95%CI: 7.8-12.2), and 5.5 months (95%CI: 0.1-11.0) respectively. Lowest median survival period was observed in patients with ECOG PS >3; 3.60 (95%CI: 0.2-7.0) months. **Conclusion:** The survival results of this trial show consistency with historical survival times. These results may suggest that survival outcomes for LC patients with BM are independent of applied therapy. Approximate survival prognosis taking into consideration individual (age and ECOG) and objective (tumour type, number of BM and presence of ECM) patient characteristics is highly important for further disease management in order to decrease patients burden and increase cooperation with family/caregivers.

Keywords: palliative medicine, brain metastases, lung cancer

P2.10: NURSING/PALLIATIVE CARE/ETHICS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.10-006 PROGNOSTIC FACTORS OF MORTALITY AND RECURRENCE OF MALIGNANT PLEURAL EFFUSION IN HIGH-RISK TUMORS ACCORDING TO THE LENT SCORE STUDY

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Background: The aim of this study was to identify predictors of overall survival (OS) and recurrence after palliative pleural procedures in patients with malignant pleural effusion (MPE) and high-risk tumors according to the LENT Score Study. **Method:** Data was collected from our database between January 2013 and December of 2015 of

patients high-risk tumors according to the LENT Score and MPE. All patients were followed-up at least 30 days after the pleural procedure. We studied radiological aspects, biochemical and hematimetric parameters beyond clinical features. To analyze OS, patients were divided into two groups. Group I included OS greater than 30 days and Group II included OS shorter than 30 days. Prognostic factors for pleural recurrence and OS were identified by univariate analysis, using Fisher's exact and Student's T-Test. Subsequently, the significant variables were entered into a multivariate logistic regression analysis ($p < 0.05$). **Result:** A total of 134 patients were included in the analysis. Median follow-up time for surviving patients was 56 (range 2 to 623) days. High-risk primary tumors included lung 66,4%, gastrointestinal 24,6%, sarcoma 3,7%, urological 3,7% and others 1,5%. There were 44 patients in Group I who had OS shorter than 30 days. Recurrence occurred in 22 patients of the entire cohort. Factors affecting OS in univariate analysis were: procedure, ECOG, albumin, leukocytes, neutrophil to lymphocyte *ratio* (NRL) e hemoglobin in peripheral blood. Factors affecting recurrence were: procedures, quimiotherapy line (QL), albumin and platelets. At the multivariate analysis in Group I, the type of procedure (therapeutic pleural aspiration – TPA) ($p = 0.011$), ECOG 3 e 4 ($p = 0.004$), NLR > 5 ($p = 0.037$) and leukocytes > 8000 ($p = 0.042$) were identified as independents predictors of OS. About recurrence, only QL further than first line ($p = 0.042$) was identified as independent predictor. **Conclusion:** Patients with MPE who underwent TPA, ECOG 3 and 4, with leukocytes > 8000, NLR > 5 were significantly associated with shorter OS, and QL greater than first line was associated with recurrence. The identification of those prognostic factors may assist the choice of the optimal palliative technique for high-tumors risk patients according LENT score study.

Keywords: recurrence, palliative care, pleural effusion

P2.10: NURSING/PALLIATIVE CARE/ETHICS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.10-007 QUALITY OF LIFE ACROSS VARIOUS TREATMENT LINES IN METASTATIC LUNG CANCER PATIENTS

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Background: Lung cancer is second most common cancer in Indian men and is a leading cause of cancer deaths in India. Most lung cancer patients in India are diagnosed at an advanced or metastatic stage and predominantly receive palliative treatment. In patients with metastatic lung cancer quality of life (QOL) improvement is the main treatment goal since survival can be prolonged only marginally despite the use of several new therapeutic modalities. **Method:** We divided metastatic lung cancer patients into four groups depending on the treatment they received: Group A - palliative chemotherapy, Group B – palliative radiotherapy, Group C – both palliative chemotherapy and radiotherapy and Group D – only symptomatic therapy and best supportive care. All patients completed quality of life questionnaire for lung cancer (EORTC QLQ C30 version 3.0 and LC13) translated in the native language before treatment and on follow up after receiving the planned treatment. Apart from QOL questionnaires few other variables were also studied including age, gender, histology, smoking status, stage, performance status and financial status. **Result:** 92 patients were prospectively included in the study with 23 patients in each group. All aspects of functioning were most preserved in patients who received palliative chemotherapy (physical, emotional, social, cognitive, role and global QOL) and were most disturbed in patients who received only symptomatic therapy. Chemotherapy reduced symptoms like dyspnea, insomnia, loss of appetite, dysphagia, and haemoptysis, but also increased nausea, vomiting, fatigue and alopecia. Radiotherapy reduced pain, coughing, dyspnea, dysphagia and hemoptysis but worsened physical and social functioning. **Conclusion:** Any modality of treatment is superior to the use of only symptomatic treatment in improving QOL in metastatic lung cancer patients and therefore some form of treatment should be offered if possible. Patients on chemotherapy have better QOL than those on radiotherapy or combined chemotherapy and radiotherapy.

Keywords: palliative treatment, quality of life, metastatic lung cancer

P2.11: PATIENT ADVOCACY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.11-001 EVALUATION OF A CULTURAL NOTEBOOK OF SELF-EXPRESSION AND FOLLOW-UP AMONG PATIENTS WITH LUNG CANCER IN FRENCH POLYNESIA

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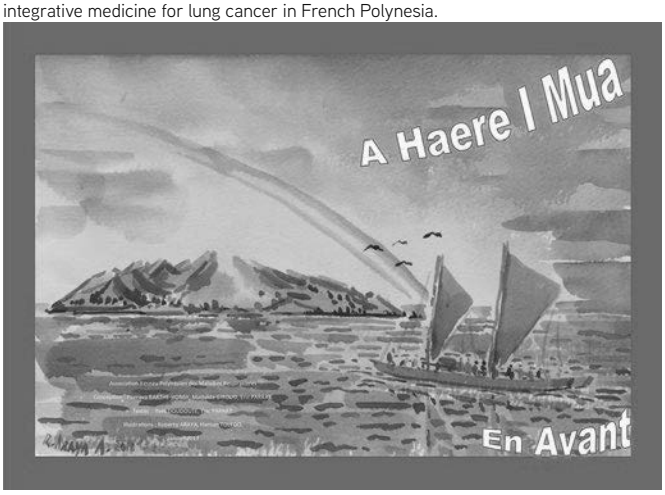
Background: The management of lung cancer (LC) in French Polynesia may pose problem, especially intercultural communication between patients (PT) and health professionals (HP). **Method:** Attractiveness, use and utility of a PT's self-expression and follow-up cultural notebook "A Haere I Mua", was evaluated among 171 HP (self-administrated questionnaires) and among 35 PT suffering from incurable LC (interview). Comparisons were made between PT and HP (Fisher's test). **Result:** The notebook pleased PT and HP (77.4%, 81.3% respectively), especially its images (90.3%, 81.3%), texts (80.6%, 69.6%) and expression areas (87.1%, 63.7%) (p>0.05 for all). PT's health representations were focused on hope and future (the canoe and "A Haere I Mua"), HP's ones on care and present (storm and difficult times).The subgroup of the Polynesian PT better made the connection with the disease (p = 0.02) and have a better perception of expression areas (p = 0.004) than the HP. While 80.6% of PT consulted the notebook, only 38.7 % used it. The Polynesian PT were more likely than the HP to have found the notebook useful (13/15 items p≤ 0.05), expect for the items "say or write things that I do not dare to say" (p=0.32) and "be better understood" (p=0.11). **Conclusion:** The notebook "A Haere I Mua" is an intercultural communication tool adapted to the Polynesian PT. It could be used in the announcement program and supportive cares, but requires training of the HP and a greater awareness of the PT. It may also contribute to the emergence of a project of integrative medicine for lung cancer in French Polynesia.



Keywords: Communication, lung cancer, Culture

P2.11: PATIENT ADVOCACY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.11-002 TO LIVE AND WORK WITH LUNG CANCER: COPING STRATEGIES OF A STAGE 4 PATIENT

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Background: Due to significant advances in the treatment of the lung cancer, it has become possible now to live and work with the disease. However, keeping a good balance between work and treatment is still a challenge for many patients. The paper describes the coping strategies and positive effects of work on the condition and treatment outcomes for a stage 4 NSCLC patient. **Method:** Case study of a 56-year old Japanese male patient diagnosed with pulmonary adenocarcinoma NSCLC (stage 4) metastases in July 2010, and living and working with cancer for 7 years. **Result:** The patient's treatment started with PTX CBDCA and Bev in July 2010. As EGFR was positive, Gefitinib was used for second and fourth line. Palliative care and cancer rehabilitation were also undertaken. The sixth line treatment was a clinical trial (1st Phase) of AZD9291 from Mar. 2014 to Jan. 2016. After a one-year interval, Osimertinib became again effective from Jan. 2017, especially for brain metastases. After diagnoses of cancer, the patient's lifework became to create a society where people with cancer can live and work, even those with advanced stage cancer. He started the new project on "Working with Cancer" in his company and contributed to the publication of books and websites introducing various patient case studies. He has also helped to establish the Japan Lung Cancer Alliance in Nov. 2015. These activities provided fulfillment and motivation in the patient's life and improved treatment outcomes. **Conclusion:** The experience of this patient indicated the link between the work and the longer survival. First, the patient identify his mission and remain conscious of it. We gain a sense of usefulness, of connection with society, and meaning in life through work. Second, the patient tried to manage his mindset and maintain his own QOLs. The life of the patient has had its ups and downs, but he never give up on the treatment. He kept the mindset not being too influenced or passive in the care, but more proactive and decisive. Third, the case shows the importance of cooperation from his co-workers and the patient effort to communicate with them. The patient's record about his treatment and condition helped his co-workers to adapt the situation. Fourth, the patient sought advice not only from the chief physician, but also from other specialized doctors, seeking second opinions, looking for clinical trial information. The patient tried to evaluate all the information and make his own decision.

Keywords: patient's literacy, working with cancer, coping strategies

P2.12-001 EARLY EXPERIENCE WITH RADIAL ENDOBRONCHIAL ULTRASOUND WITH GUIDE SHEATH FOR DIAGNOSIS OF PERIPHERAL PULMONARY LESION

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Background: Diagnostic yield for routine unguided bronchoscopy for peripheral pulmonary lesion (PPL) is less than 20%. Hence, CT guided transthoracic needle aspiration (TTNA) is currently the preferred method with a high diagnostic yield of 90%, however running risk of pneumothorax of around 25%. Radial endobronchial ultrasound with guide sheath (R-EBUS-GS) for diagnosis of PPL is a novel technique with diagnostic yield of 70.6% with good safety profile. However, this advanced technique is not readily available in developing nations and were further limited by the availability of other supporting modalities such as thin section computed tomography (CT) scan, fluoroscopy, thin bronchoscope, availability of rapid onsite evaluation (ROSE) and a established cytology services. To the best of our knowledge, this is the first series of R-EBUS from Malaysia. **Method:** Retrospective review of our early experience with R-EBUS-GS in diagnosing PPL at Respiratory Medicine Unit, Sarawak General Hospital over six months duration from October 2016 to May 2017. **Result:** 65 patients with 68 targets were enrolled. 48 (71%) male and 20 (29%) female patients with mean age of 60.5±13.2 years old. Up to 54 (79%) cases will undergone CT guided TTNA if without R-EBUS-GS. All procedures were performed as day case under conscious sedation with mean procedure time of 37 minutes. Mean PPL size was 3.87±1.2 cm and 53.1% located in the upper lobes. We were able to localize the lesion in 58 (85.3%) cases, failed to identify in 4 (5.8%) and 3 (4.4%) had endobronchial lesion. Overall diagnostic yield for PPL that could be localized was 63.8%. Diagnostic yield for patient who suspected malignancy was 57.5%. Higher diagnostic yield is associated if lesion was orientated within the radial probe rather than adjacent to it (85.2% vs. 20%, $p<0.005$). Fluoroscopic guidance, CT bronchus sign and lesion size did not contribute significantly to diagnostic yield. Overall complication rate was 3% with only 1 (1.5%) patient developed pneumothorax, which was self-limiting. **Conclusion:** Radial EBUS-GS is an effective tool to guide biopsy during peripheral bronchoscopy with low complication rate. Despite various resource constraints and challenges, our early experience with R-EBUS-GS shown promising result and our center anticipates further experiences with this technique in the future.

Keywords: radial ebus, bronchoscopy, lung cancer

P2.12-002 RADIAL PROBE ENDOBRONCHIAL ULTRASOUND (R-EBUS) GUIDED TRANSBRONCHIAL CRYOBIOPSY IN THE DIAGNOSIS OF PERIPHERAL LUNG MASS

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Background: Radial probe endobronchial ultrasound (R-EBUS) is a novel technique in localizing peripheral lung mass with overall diagnostic yield of 70%. Conventional biopsy techniques using forcep or fine needle aspirates guided by R-EBUS occasionally resulted in small sample which may not be suitable for immunohistochemical or molecular studies. R-EBUS guided transbronchial cryobiopsies in peripheral lung mass is a feasible technique to obtain larger tissue samples without affecting safety. We described our initial experience with three consecutive patients who underwent R-EBUS guided transbronchial cryobiopsy in our unit in May 2017. **Method:** Therapeutic flexible bronchoscope with a 2.8mm working channel, 2.0mm 20 Hz ultrasound probe (*UM-S20-20R, Olympus Medical*) within a 2.2mm flexible guide sheath and 1.9mm flexible cryoprobe (*1150mm ERBE, Medizintechnik, Germany*) was used in all cases. **Result:** The mean age was 60±11.6 years (range 47-68 years). Two cases were performed under conscious sedation and one under total intravenous anaesthesia. Mean procedural time was 48.3±15.9 minutes. All lesions were located in right upper lobe. Two patients had non-diagnostic computed tomography (CT) guided biopsy prior. Mean lesion size was 2.6±0.4cm with mean distance to the pleural of 1.2cm. All lesions were able to be identified via R-EBUS with two lesions orientated within the radial probe while one adjacent to it. Cryobiopsy was obtained by freezing the tip of cryoprobe for 5 seconds. Three attempts were performed in Case 1 and 3, two in Case 2. First two cases were guided with fluoroscopy. All patients had minimal intra-procedure post biopsy bleeding which was easily managed. Mean specimen size was 10.6mm. All biopsies yielded adenocarcinoma of lung with immunohistochemistry positive for CK7 and TTF-1. **Conclusion:** Our initial experience shows that R-EBUS guided transbronchial cryobiopsy is safe and can potentially increase the diagnostic yield of peripheral lung mass. Our center anticipate further experience with this technique in the future.

Keywords: radial EBUS, cryobiopsy, peripheral lung mass

P2.12-003 THE HISTORY OF EBUS TBNA

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Background: Once there were mediastinoscopy and now there is EBUS TBNA. It started in 1997. the development of a real time Ultrasound guide TBNA system were proposed in 1997 and in Dec 2002 the first EBUS TBNA paper were published Then 1 in 2003, 2 in 2004 and 3 in 2005 describing the use of EBUS TBNA for staging of the mediastinum. All ready in 2006 the first paper describing the effectiveness in combining EUS FNA and EBUS TBNA using 2 different types of scopes. This combination was not widely used until Felix Herth and his group demonstrated the usefulness of the EBUS TBNA scope in the esophagus. In 2007 the first paper on the use of EBUS TBNA in sarcoidosis was published, the first review and the use of cytology and EGF. 2008 was the year when the issue of diagnosing lymphoma was raised and the diagnosing metastases in the mediastinum from other organs and mediastinal tumors was shown feasible. 2009 was the year of the first metaanalysis and the first randomized study. The first complication was mentioned. The chemosensitivity and cell receptors were discussed. In 2010 the number of papers exploded. Restaging, TB, the number of stations punctured, one scope in esophagus and trachea, cost benefit, learning curves, sedation, elastography were the main topics. Mediastinoscopy was still the golden standard 2011 another randomized study. More papers on hematological diseases and more receptors were demonstrated in cytology and a biopsy forceps were introduced and more complications were described 2012 the 19 G needle and cell block and ROSE were introduced. The first paper using the EBUS TBNA in treatment was described. And it was the year of the ASTER trial 2013 is the year of molecular biology and EBUS TBNA. The literature from this year was characterized by the establishment of EBUS TBNA's role in the staging and diagnostic process of cancer in the lung and mediastinum 2014 is the year of the acceptance of EBUS TBNA with the new ESTS guidelines 2015-16 is characterized of different metaanalysis and many reviews on a wide spectrum of topics using the EBUS TBNA in diferent areas of pulmonology **Method:** A review of the literatur **Result:** Section not applicable **Conclusion:** EBUS TBNA have in a very short time revolutionized the diagnostic of chest diseases and the staging og lung cancer. There is still room for improvement of the system and the role of EBUS TBNA is stil developing

Keywords: History, development, EBUS TBNA

P2.12-004 LUNG CANCER DETECTION RATE OF CONVENTIONAL BRONCHOSCOPIC TECHNIQUES: A TERTIARY HOSPITAL EXPERIENCE JUNE 2011- DECEMBER 2016

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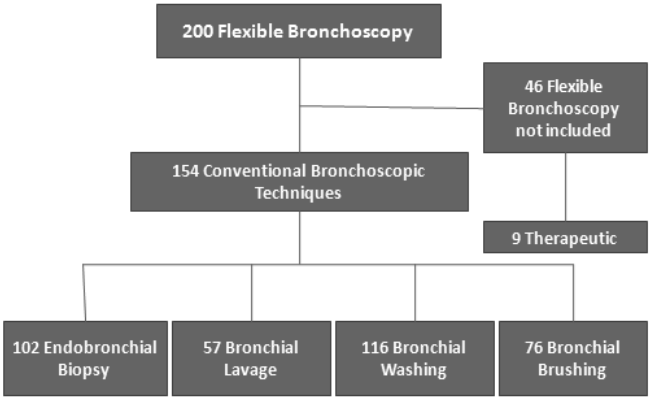
Background: Flexible Bronchoscopy was developed in 1976 by Shigeto Ikeda and has become the mainstay investigation in the evaluation of patients suspected of lung cancer. It is an indispensable tool for diagnosis and therapeutics. It is convenient to perform, safe and well tolerated. The British Thoracic Society guidelines recommended biopsies, brushings and washings for sampling. However, reported diagnostic yield from bronchoscopies in patients with lung cancer varies greatly. Due to the lack of data regarding the lung cancer detection rate of conventional bronchoscopic techniques available in our institution, our study is mainly intended to present the experience gathered in 200 cases in the use of bronchoscopy. **Method:** We retrospectively reviewed all patient data that underwent conventional bronchoscopic techniques at Perpetual Succour Hospital, Cebu City, Philippines between June 2011 and December 2016. Inclusion criteria includes 1. all bronschopies performed with conventional bronschopic techniques; 2. final histopathologic diagnosis of malignant lung disease obtained during bronchoscopy.



Result: A total of 200 patients have undergone bronchoscopy,154 patients undergone conventional bronchoscopic techniques. Majority were males, the main indication was diagnostic and done via conscious sedation. Endobronchial biopsy had the highest rate of positive yield for malignant lung disease with 34%. The most common histopathological result is Squamous Cell CA for both endobronchial biopsy and brushing while Adenocarcinoma and Small Cell for bronchial lavage and washing. The presence of endobronchial lesion was associated with malignant lung disease. **Conclusion:** It can be concluded that majority of our patients are males whose main indication was diagnostic. Endobronchial biopsy was the technique with the highest rate of positive yield for malignant lung disease. Endobronchial visibility is a predictor of a positive rate for malignancy.

Keywords: Conventional Bronchoscopic Techniques, Flexible Bronchoscopy, lung cancer

P2.12: PULMONOLOGY/ENDOSCOPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.12-005 COMPARISON OF NEEDLE GAUGE USED TO OBTAIN SPECIMENS DURING EBUS-TBNA IN PATIENTS WITH LUNG CANCER

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Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive modality for sampling of mediastinal and hilar lesions. Two dedicated aspiration needles are used for EBUS-TBNA. The relative utility of 21- versus 22-gauge needles remains controversial. The aim of this study was to evaluate the two needles in terms of the adequacy of histological specimens and cellularity of cytological specimens in patients with lung cancer. **Method:** Sixty-eight patients with metastatic hilar/mediastinal lymphadenopathy with lung cancer or tumors adjacent to the central airway (115 lesions in all) underwent EBUS-TBNA using 21- or 22-gauge needles between September 2014 and April 2016. Samples were assessed by an experienced pathologist blinded to the needle gauge used; rapid on-site cytological evaluation was not performed. The adequacies (in terms of histopathology and cellularity) of aspirates were evaluated. **Result:** We found no significant difference between the two groups in terms of sex, age, the characteristics of primary malignancy, lesion size, location of the evaluated lesions, or number of needle passes. For samples obtained using 21- and 22-gauge needles, the histological adequacies were 82.5% and 79.4% (p=0.81), and the cytological adequacies 77.1% and 55.2% (p=0.018), respectively. No significant complication was associated with either procedure. **Conclusion:** The 21-gauge needle afforded better specimen cytology but the needles did not differ in terms of adequacy of the histological specimens in patients with lung cancer.

Keywords: needle gauge, histology and cytology, Endobronchial ultrasound transbronchial needle aspiration

P2.12: PULMONOLOGY/ENDOSCOPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.12-006 EVALUATION OF NEW 25G NEEDLE IN EBUS-TBNA COMPARING CONVENTIONAL 22G NEEDLE IN DIAGNOSIS FOR NODAL METASTASIS OF LUNG CANCER

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Background: Dedicated 22G needle is usually used for EBUS-TBNA, which is a main diagnostic tool for nodal staging in lung cancer. Recently new 25G needle is developed and expected less invasive nodal biopsy. Although, diagnostic yield and complication of the EBUS-TBNA using 25G needle are still unclear. **Method:** From September 2016 to May 2017, 39 hilar or mediastinal lymph nodes in 25 patients were consecutively biopsied using both 22G (Olympus, Tokyo, Japan) and 25G (Boston Scientific, MA) needles for diagnosis or staging of lung cancer. Concordance rates of rapid on-site cytologic evaluation and cytological and pathological diagnosis between the EBUS-TBNAs using the two types of needles were evaluated. And also, bleeding score of cytological specimen (0-3: higher is more contaminated) and calculated area of histological core (the number of high-power field microscopically in paraffin-embedded slides) were compared for evaluating sample qualities. The results obtained from EBUS-TBNA using 22G needle were regarded as control to evaluate the diagnostic ability of that using 25G needle in this analysis. **Result:** No complication was recorded during the study period. Thirty three Mediastinal nodes (#2(n=2), #3(n=1), #4R(n=16), #4L(n=2), #7(n=12)) and 6 hilar nodes (#10(n=1), #11(n=3), #12(n=2)) were biopsied and concordance rate between 22G and 25G was 87% (34/39) in the rapid on-site cytologic evaluation, 95% (37/39) in the cytological diagnosis and 85% (35/39) in the histological diagnosis. Final decision whether metastatic or not according to the combined cytologic and histologic diagnosis in the EBUS-TBNA using 22G needle was 19 metastases and 20 benign nodes, and the concordance rate with the two types of needles was 92% (36/39). In the 3 nodes with discrepancy, 2 nodes were diagnosed as lung cancer metastasis by the 25G needle sampling. Both bleeding score and calculated area of histological core showed no significant difference (p=0.3 and 0.7) between 22G and 25G, with respective values of 1.8±0.9 vs. 2.0 ±0.7, and 20±2.2 vs. 21±2.2. **Conclusion:** EBUS-TBNA using 25G needle is feasible and as useful as that using conventional 22G.

Keywords: EBUS-TBNA, diagnosis, 25G

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-001 HERBAL COMPOUND AS A POTENTIAL LEAD TARGETS LUNG CANCER STEM CELLS

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Background: Cancer stem cells (CSCs) have been proposed to be responsible for tumor initiating, drug resistance, metastasis, and recurrence. Many novel therapeutic strategies have been designed to target and eliminate CSCs. According to our previous study, we have established a model of CSCs and cancer associated fibroblasts (CAFs) co-culture system for anti-CSCs drug screening. Here, we report one of the potential hits screened via this platform and the anti-CSCs activity was further investigated both *in vitro* and *in vivo*. **Method:** Human lung CSCs and CAFs were primary cultured from patient with lung adenocarcinoma according to our previous study. Image–based high content screening system was used to analyze different parameters after drug treatment. Tumorogenicity and self-renew ability are examined by sphere forming ability. Aldehyde dehydrogenase (ALDH) activity was used to analyze stem cell population by flow cytometry. The expression level of stemness-related genes, Nanog, Oct3/4 and Sox2 were validated by real-time reverse transcriptase Q-PCR. The efficacy of the lead on tumor growth was examined by the xenograft model. Lung cancer stemness markers of the xenograft tumor tissues were also evaluated by immunohistochemistry. **Result:** Using the CSC/CAF co-culture model with the image–based high content screening system to screen over one thousands of compounds, we have identified aloe-emodin (AE), an anthraquinone isolated from traditional herbs (e.g., Aloe vera), shows higher potency on lung CSCs (under 1 μM dosage) and relative selection for targeting on the cancer cell lines with the IC_{50} less twenty μM; compared to normal human bronchial epithelium cells and human normal fibroblast represented by IC_{50} (26.77 μM v.s. 39.13 μM). The level of stemness markers, Nanog, Sox2 and Oct3/4 were significantly down-regulated after AE treatment compared to cisplatin treatment. AE could suppress tumor initiating abilities and self-renew capacities by inhibiting the tumorous sphere forming in CL152 $ALDH^+$ cells. Besides, AE could inhibit ALDH population in CL152 cells (40% reduced). Also, the AE can inhibit the cisplatin-induced ALDH population as well. Furthermore, we found that the combination treatment of AE and cisplatin could inhibit tumor growth as comparing to cisplatin treatment in subcutaneous xenograft models in NOD/SCID mice, whereas, AE can significantly inhibit the level of Nanog in mice tumor tissues. **Conclusion:** According to these results, AE is a potential lead targeting on lung CSCs. To discover the pharmacological mechanism of AE on CSCs will be helpful to develop new strategy for lung cancer therapy.

Keywords: Drug screening, Cancer stem cells, Tumor microenvironment

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-002 THE LUNGSCREEN WA PROJECT: FEASIBILITY OF LDCT SCREENING WITH THE $PLCO_{M2012}$ RISK MODEL AND PANCAN NODULE RISK CALCULATOR

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Background: Low-dose CT (LDCT) screening for lung cancer is currently recommended in the USA but not in Australia, as there remain important knowledge gaps. We aimed to evaluate the feasibility of lung cancer screening in the Australian healthcare setting using the $PLCO_{m2012}$ model to identify high-risk participants and the PanCan nodule malignancy risk-calculator to guide management of detected pulmonary nodules. **Method:** Current/former smokers, aged 55-74 years, were recruited from the community. Eligibility for LDCT-screening was defined as $PLCO_{m2012}$ ≥1.51% over 6 years. Participants underwent interview, spirometry and LDCT. Detected nodules were managed with a risk-based algorithm using the PanCan nodule calculator (highest-risk nodule score used if multiple nodules present). If risk-score <1.5%: repeat LDCT at 24 months; 1.5-6%: LDCT at 12 and 24 months; 6-10%: LDCT at 3, 12 and 24 months; >10%: consider immediate investigation. If no nodules detected, no further LDCT arranged. We report results after 24-month follow-up. **Result:** We received 104 enquiries – 54 were eligible and 49 underwent screening LDCT. Results are summarised in Table 1. In participants with pulmonary nodules (n=26), the PanCan risk-score was <1.5% in 12 (46.2%), 1.5-6% in 5 (19.2%), 6-10% in 6 (23.1%) and >10% in 2 (7.7%). Of note, 65% of nodule-positive participants did not require further investigation within the first year of screening. Lung cancers were identified in 2 (4.1%) participants – 1 underwent surgical resection of a Stage 1b adenocarcinoma, the other had an enlarging nodule treated with stereotactic

radiotherapy (no biopsy due to surrounding emphysema). A further participant is due surgery for a 53mm³ slow-growing nodule with growth between 12 and 24 month scans. Table 1. Characteristics and LDCT findings of screened-individuals.

	All, n=49	Nodule positive, n=26	Nodule negative, n=23
Mean Age (SD)	66.0 (±5.3)	65.5 (±5.3)	66.5 (±5.4)
Median Age (IQR)	66 (62-71)	64 (62-70.5)	66 (64.5-70.5)
Gender (Ratio of males:females)	25 M, 24 F 1.04	14 M, 12 F 1.17	11 M, 12 F 0.92
Current smoker (%)	23 (46.9%)	12 (46.2%)	11 (47.8%)
Mean number of pack years (SD)	51.1 (±15.6)	47.2 (±12.0)	55.7 (±18.3)
Median $PLCO_{m2012}$ (IQR)	3.48% (2.43-5.65)	3.34% (2.64-5.07)	3.60% (2.41-7.96)
Number of nodule-positive scans - >4mm (%) - ≤4mm (%) - Av. no. of nodules/person (SD)	26 (53.1%) 14 (28.6%) 12 (24.5%) -	- 14 (53.8%) 12 (46.2%) 2.08 (±1.44)	N/A
Spirometric evidence of COPD (any) Mild Moderate Severe Very Severe	23 (46.9%) 10 10 3 0	12 (46.2%) 4 7 1 0	11 (42.3%) 6 3 2 0
CT evidence of emphysema (%)	32 (65.4%)	16 (61.5%)	16 (69.6%)
CT evidence of pleural plaque (%)	3 (6.1%)	1 (3.8%)	2 (8.7%)
CT evidence of coronary artery calcification (any grade)	38 (77.6%)	20 (76.9%)	18 (78.3%)
CT evidence of interstitial lung disease	2 (40.8%)	2 (7.7%)	0 (0%)

Conclusion: A targeted, algorithmic approach to lung cancer screening is feasible and identifies early-stage lung cancers. Use of the PanCan nodule risk calculator simplifies downstream investigation after baseline LDCT.

Keywords: Screening, CT, lung cancer

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-004 ROLE OF LOW-DOSE CHEST COMPUTERIZED TOMOGRAPHY IN LUNG CANCER SCREENING AMONG NEVER-SMOKERS

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Background: The incidence of lung cancer among never-smokers has been increasing rapidly. The US National Lung Screening Trial study showed that screening using low-dose chest computerized tomography (LDCT) effectively reduced lung cancer mortality among heavy-smokers. However, its effectiveness in never-smokers has not been studied. Therefore, this study investigated the role of LDCT in lung cancer screening among never-smokers. **Method:** In this single-center, retrospective, cohort study, we identified 4,054 (13.5%) non-smokers (age range: 40-75 years) among 30,080 patients who underwent LDCT for lung cancer screening at Seoul National University Bundang Hospital Health Promotion Center, between May 2003 and June 2016. We analyzed patients with abnormal LDCT findings and cancer rates. Abnormal LDCT findings, such as nodules, were classified according to the Lung-RADS criteria and the final pathologic outcomes were further analyzed. If multiple nodules were found, we selected one dominant nodule. **Result:** Among the 4,054 never-smokers, 2,519 (62.1%) were women. Among the 846 patients (20.8%) with lung nodules, 636, 112, 56, 34, and 8 had nodules categorized as 2, 3, 4A, 4B, and 4X, respectively, according to the Lung-RADS criteria. Among these, 315 (37.2%), 95 (11.2%), and 436 (51.5%) nodules were solid, part-solid, and non-solid, respectively. Moreover, 448 (52.5%) patients underwent further diagnostic work-up, including follow-up CT or diagnostic procedures. Finally, 38 (0.9%) patients were pathologically diagnosed as lung cancer. Among these patients, 34 (89.5%) were in stage I, and 33 (86.8%) had adenocarcinoma. No cancer-related death occurred, and the diagnostic work-up did not cause significant morbidity. **Conclusion:** In the never-smoker population, LDCT screening helped detect a significant number of lung cancers. Most of these lung cancers were detected at a very early stage.

Keywords: never-smokers, lung cancer screening, low dose chest CT

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-005 EARLY RESULTS OF LUNG CANCER SCREENING IN AN AFRICAN AMERICAN POPULATION

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Background: African Americans have been underrepresented in trials showing survival benefit to lung cancer screening. We implemented a multidisciplinary lung cancer screening program in an African American population. We hypothesize that lung cancer screening in an African American population will lead to safe detection and treatment of lung cancer. **Method:** In an urban, academic medical center, we prospectively gathered information on African American patients referred to a multidisciplinary lung cancer screening program from October 2015 to December 2017 with a 6 month follow up. We studied, age, gender, smoking history and level of education. We measured lung cancer screening results using Lung-RADs categorizations, diagnosis of cancer, treatment modality and complications. **Result:** Of 160 African Americans undergoing lung cancer screening, the average age was 64.2 (SD 5.75), 95 (59.3%) were women, 111 (69.3%) were current smokers, average pack years was 47.2 (SD 17.1) and level of education was less than high school in 52 (32.5%), high school in 53 (33.1%), advanced education in 45 (28.1%) and 10 (6.2%) declined to report. LDCT results were 1 (0.6%) with Lung-RADs 0; 69 (43.1%) with Lung-RADs 1; 73 (45.6%) Lung-RADs 2; 7 (4.3%) Lung-RADs 3; 10 (6.3%). Of the 6 people undergoing invasive procedure for biopsy (3 CT guided needle biopsy, 1 transbronchial needle biopsy, 2 surgical resection) 4 were diagnosed with stage I non-small cell lung cancer. Three of these underwent surgical resection for treatment, and one underwent radiation treatment.

Lung Cancer Screening in an African American Population

	Number	Percent	
Total	160	100%	
Average Age	64.2		
Average Pack Years	47.2		
Active Smokers	111	69.4%	
Former Smokers	49	30.6%	
Gender			
Women	95	59.4%	
Men	65	40.6%	
Education			
Less Than High School	52	32.5%	
High School	53	33.1%	
Advanced Education	45	28.1%	
Declined to Answer	19	6.3%	
Lung-RADs Category			
Lung-RADs 0	1	0.6%	
Lung-RADs 1	69	43.1%	
Lung-RADs 2	73	45.6%	
Lung-RADs 3	7	4.4%	1 diagnosed with stage I lung cancer with CT guided biopsy

Lung Cancer Screening in an African American Population			
	Number	**Percent**	
Lung-RADs 4	10	6.3%	3 diagnosed with stage I lung cancer, 1 with CT guided biopsy, 2 with surgical biopsy
Total Receiving Biopsy	6	3.8%	
CT Guided	3	1.9%	2 diagnosed with stage I lung cancer
Transbronchial	1	0.6%	
Surgical Resection	2	1.3%	2 diagnosed with stage I lung cancer
Lung Cancer Diagnosis	4	2.5%	
Stage I	4	2.5%	
Stage II	0	0%	
Stage III	0	0%	
Stage IV	0	0%	
Adenocarcinoma	4	2.5%	
Squamous Cell	0	0%	
Treatment			
Surgical Resection	2	1.3%	
Radiation	1	0.6%	
Complications	0	0%	

Conclusion: Implementation of a multidisciplinary lung cancer screening program enrolling African Americans at high risk of lung cancer led to detection and treatment of lung cancer in 2.5%. Only 10.7% had positive screens (lung-RADs 3 or 4), 3.8% had an invasive biopsy and no one had complications from diagnostic procedures or treatment. Further study is necessary to understand long-term survival benefit of lung cancer screening.

Keywords: lung cancer screening, implementation, African American

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-006 ENHANCED SHARED DECISION MAKING IN LUNG CANCER SCREENING: ADDRESSING QUESTIONS OF WILLINGNESS AND ABILITY TO UNDERGO LUNG CANCER TREATMENT

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Background: Lung Cancer Screening with low dose CT (LDCT) can reduce lung cancer death, but only if those found to have lung cancer proceed with lung cancer treatment. When implemented into diverse populations, lung cancer screening may prove less effective if patients are unwilling or unable to undergo lung cancer treatment. We employed an enhanced shared decision making (SDM) model to address willingness and ability to undergo lung cancer treatment before low dose CT (LDCT) scanning. We hypothesized that enhanced SDM was feasible and did not discourage patients or providers from proceeding with lung cancer screening. **Method:** We performed a prospective study of patients referred for lung cancer screening between October of 2015 and May of 2017. We measured race, gender, adherence to the consent process and questions regarding willingness and ability to undergo lung cancer treatment. Subsequent uptake of LDCT, outcomes of cancer diagnosis and failure to follow up were also studied. **Result:** Of 363 enrolled study participants, 59% were African American, 12% were Caucasian, 12% were Hispanic and 2% were Asian. The gender distribution was 186 male (51.2%) and 177 female (48.8%). All 363 patients had a documented SDM visit addressing the risks and benefits of lung cancer screening and consented to discuss lung cancer treatment if lung cancer is diagnosed. When asked if they were willing to undergo lung cancer treatment, 15 (4.1%) people responded "no", 4 (1.1%) people responded "unknown" and 8 (2.2%) did not have a documented answer. When asked if they were able to undergo lung cancer treatment 10 (2.8%) people responded "no", 2 (0.5%) people responded "unknown" and 8 (2.2%) people did not have a documented answer. Overall, 6 (1.7%) people were diagnosed and treated for lung cancer. Only 1 person declined screening despite being willing and able to undergo lung cancer treatment. One (0.2%) person failed to follow up on a suspicious nodule found on lung cancer screening despite reporting being willing and able to undergo lung cancer treatment. **Conclusion:** Though SDM is essential to lung cancer screening, there are few guidelines on how to conduct this process. This study demonstrated that an enhanced SDM experience, including questions about willingness and ability to undergo lung cancer treatment, is a feasible practice that did not deter patients or providers from proceeding with lung cancer screening. Our enhanced SDM experience gave clinicians and patients a framework to emphasize the importance of appropriate follow up of positive screens.

Keywords: lung cancer screening, implementation, shared decision making

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-007 RELATIONSHIP OF NODULE COUNT AND LUNG CANCER PROBABILITY IN NEW NODULES DETECTED AFTER BASELINE IN CT LUNG CANCER SCREENING

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Background: In low-dose computed tomography (LDCT) lung cancer screening new nodules are frequently found after baseline. Currently, there is no evidence concerning the relationship between a participant's number of nodules and the lung cancer probability of new nodules. **Method:** This study is part of the ongoing Dutch-Belgian Randomized Lung Cancer Screening (NELSON) Trial. Participants with solid and sub-solid nodules detected after baseline and registered as new by the NELSON radiologists were included. Three nodule counts were calculated: The participant's total number of new nodules present at new nodule detection, the participant's overall number of nodules detected before new nodule detection, and the participants overall number of calcified nodules detected until new nodule detection. The discriminative performance of the nodule counts for prediction of lung cancer was assessed through the area under the receiver operating characteristic curve (AUC). On participant level, a multivariable logistic regression analysis with eventual lung cancer diagnosis in a detected new nodule as outcome was performed, including the nodule count and participant's largest new nodule size (categorized as $<50mm^3$, $50-<500mm^3$, $\geq 500mm^3$). On nodule level, the equivalent analysis was performed, including the nodule count and nodule size while adjusting for clustering of data within participants using Huber-White robust estimators. **Result:** A total of 706 participants with 964 new nodules (median 1, range 1-12) were included. Eventually, 9% (65/706) of the participants had lung cancer in one of the new nodules. The lung cancer probability was 10% (56/552) for participants with 1 new nodule, 7% (7/100) with 2 new nodules, and 4% (2/54) with ≥3 new nodules (P=0.21). On nodule level, the number of new nodules provided moderate discrimination for lung cancer (AUC: 0.67, P<0.001) and remained a significant predictor after adjusting for nodule size (odds ratio [OR] 0.42, 95% confidence interval [CI] 0.26-0.68, per additional new nodule present). On participant level, the number of new nodules provided poor discrimination for eventual lung cancer diagnosis in a detected new nodule (AUC: 0.55, P=0.22), but was significantly associated with lung cancer when corrected for largest new nodule size (OR 0.61, 95%CI 0.39-0.98 per additional new nodule present). The participant's overall number of nodules before new nodule detection and the number of calcified nodules were not associated with lung cancer. **Conclusion:** While an increased number of detected new nodules signifies a reduced lung cancer probability of each individual new nodule, the impact on the participant's overall lung cancer probability in the new nodules is limited.

Keywords: nodule count, Multinodularity, new nodules after baseline screening

P2.13-008 LUNG CANCER SCREENING IMPROVES MORTALITY: EXAMINING SCREENING PATTERNS IN AN URBAN UNDERSERVED COMMUNITY

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Background: The landmark Lung Cancer Screening (LCS) Trial demonstrated a significant reduction in mortality. However, European LCS trials have not confirmed such benefit. We examined the impact of LCS-led diagnosis on the mortality of newly diagnosed lung cancer patients at an urban medical center. **Method:** Medical records of patients diagnosed with primary lung cancer for the period 2013-2015 (n=638) were reviewed to identify those who had an established primary care provider (PCP), were LCS-eligible/ non LCS-diagnosed, and LCS-eligible/LCS-diagnosed as per the United States Preventative Services Task Force (USPSTF) guidelines. Baseline characteristics between LCS-eligible/non-diagnosed patients and LCS-eligible/ diagnosed patients were analyzed using chi-squared and Wilcoxon-Mann-Whitney tests. Kaplan-Meier curves were generated, and predictors of overall survival were evaluated using Cox proportional hazards modeling. **Result:** 134 primary lung cancer patients had an established PCP and were LCS-eligible; 19/134 (14%) were LCS-diagnosed. LCS-eligible/LCS-diagnosed patients were of younger age (p=0.03), English-speaking (p=0.03), of higher socioeconomic status (p=0.02), active smokers (p<0.01), and had earlier disease stages (p=0.02) than LCS-eligible/non-diagnosed patients. All-cause mortality was significantly lower in LCS-eligible/diagnosed patients compared to LCS-eligible/non-diagnosed patients (p=0.03). Disease stage was found to be the main factor associated with higher mortality by multivariate regression analysis (HR: 6.13, stage 4 vs. stage 1-2, p<0.01). **Conclusion:** To our knowledge, this is the first report of lung cancer mortality differences in LCS eligible patients as a function of them undergoing or not LCS in a single-center setting since the inception of the USPSTF guidelines. Patients with an LCS-led diagnosis had a reduced mortality, probably as a result of having an earlier disease stage, which echoes the findings of large prospective LCS trials. LCS-led diagnosis rates remain low among lung cancer patients. Fully implementing the USPSTF guidelines constitutes a great unrealized opportunity to decrease lung cancer mortality.

Keywords: Lung cancer screening, mortality, health disparity

P2.13-009 RESULTS OF LOW-DOSE CT LUNG CANCER SCREENING AT A NON-UNIVERSITY TERTIARY HOSPITAL SYSTEM IN OREGON, USA

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Background: Since the National Lung Screening Trial (NLST), doubt has been expressed as to whether the results could be replicated in a community setting. We aim to document our experience over 3.5 years and over 3000 CT scans. **Method:** The Providence Cancer Center in Portland Oregon initiated a lung cancer screening program in 2013 that included 7 hospitals (2 non-university tertiary medical centers and 5 community hospitals). Lung cancer screening candidates were referred by primary care providers from Noverember 2013 through May 2017. Candidates were screened using NLST criteria. Initially, shared decision making was provided by the team, but in 2015 transitioned to the PCP. Dedicated radiologists at the tertiary centers read all CTs and assigned Lung-RADS assessment categories. All Lung-RADS category 4 scans were reviewed by a multidisciplinary team of thoracic surgery, pulmonary, radiology and oncology to generate management recommendations. The navigator recorded all imaging, procedures, pathology, staging and complications. This individual ensured follow-up scans were completed. **Result:** 2983 patients were referred. 353 were not eligible and 529 declined participation. 1950 underwent initial CT screening. 178 were presented at the multidisciplinary conference. Additional imaging included 1160 follow CT scans and 75 PET scans. Invasive diagnostic procedures included bronchoscopy (27) and CT-guided biopsy (19). Thoracic surgical procedures included pneumonectomy (1); lobectomy (21); segmentectomy or wedge resection (10). 55 cancers were diagnosed. 40 non-small cell lung cancers were found including 26 stage I; 5 stage II; 4 stage III and 5 stage IV. 6 small cell lung cancers were diagnosed including limited stage (3) and extensive stage (3). Lung cancer rate was 2.4%. 9 extra-thoracic malignancies were diagnosed including thyroid, renal cell (4), breast, colon, liver and prostate. The intervention rate was 5.6% with 46 major procedures (surgery) and 64 minor procedures (bronchoscopy, CT-guided biopsy, EUS, EGD). Adverse event rate was low and included pneumothorax (8) with 4 requiring chest tube, intra-operative bleeding requiring thoracotomy (1) and post-operative bleeding requiring repeat thoracoscopy (1). There was one death in a post-operative lobectomy patient. **Conclusion:** Low-dose CT screening for lung cancer can be done with low intervention and complication rates in a non-university setting using a systematic, multidisciplinary approach. This large group of screened patients demonstrates a stage shift toward early stage lung cancers with complication rates approximating those of the NLST. Our data contradict the argument that lung cancer screening cannot be done successfully and safely in the community.

Keywords: community hospital, lung cancer screening

P2.13-010 FIVE-YEAR-LONG FOLLOW-UP OF THE LOW-DOSE COMPUTED TOMOGRAPHY SCREENING PROGRAMME IN GDANSK, POLAND

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Background: According to the World Health Organisation's report published in 2010, neoplasms, cardiovascular diseases (CVD), diabetes and chronic obstructive pulmonary disease (COPD) are responsible for over 75% of all deaths in the world and they have the same modifiable risk factors - smoking, bad dietary habits, lack of activity and alcohol abuse. Lung cancer screening participants that represent a high risk population of developing a lung cancer constitute the group that exactly matches these criteria, being simultaneously exposed for CVD, diabetes and COPD. **Method:** Between 2009 and 2011, 8649 individuals participated in the Gdańsk Lung Cancer Screening Programme (Poland), where 107 neoplasms (1,24%) were detected. Eligibility criteria included age 50 to 79 and significant, accumulated exposure to smoking (>20 pack-years). Every participant underwent a low-dose computed tomography (LDCT) followed by a standard evaluation protocol and blood sampling for the molecular studies. In order to find the incidence of lung cancer, CVD, diabetes and COPD in the lung cancer screening cohort during a 5-year-long follow-up, the records of all screenees were checked and collected from the Polish National Health Service - the only healthcare provider in the country. **Result:** Out of 8649 patients, after the programme's termination, 459 (5,3%) new cases of lung cancer were detected in a 5-year-long follow-up. Two thousand seven hundred sixty five (31,9%) patients developed one of the cardiovascular diseases - in 2418 (28%) cases a coronary artery disease and in 309 (3,6%) a stroke were registered, while 38 (0,4%) had an episode of the acute coronary syndrome. One thousand and seven hundred forty (20,1%) patients developed COPD. There were 2104 (24,3%) patients registered with diabetes - 460 (5,3%) had an insulin-dependent and 1644 (19%) non-insulin-dependent type. **Conclusion:** Accumulated lung cancer detection rate in the Polish lung cancer screening programme after a 5-year-long follow-up was 6,5%. Lung cancer screening programme offers a great potential for joint screening of lung cancer, CVD, diabetes and COPD, which enhances a social significance of such an effort.

Keywords: lung cancer, follow-up, low-dose computed tomography screening

P2.13-011 OPTIMAL SELECTION CRITERIA FOR LDCT LUNG CANCER SCREENING

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Background: Lung cancer screening programs with low dose computed tomography (LDCT) could be economically viable if they targeted high-risk people. The optimal selection criteria have not been defined in prospective clinical trials. The goal of this prospective study is to test the hypothesis that lung cancer screening based on a highly predictive risk model: The Prostate, Lung, Colon, Ovarian ($PLCO_{m2012}$) is superior to applying National Lung Screening Trial (NLST)-like criteria. **Method:** Participants were enrolled through three screening studies, two in Canada (Vancouver and Alberta) and one in London, UK. Eligibility included a PLCOm2012 6-year lung cancer risk ≥1.5% or NLST-like criteria (≥30 pack-years smoking history and quit ≤15 years with some variation in age limits – 55 to 80 years in BC, 55 to 74 in Alberta and 60 to 75 in UCL). The proportion of participants who have been found to have lung cancer or high risk lung nodules, requiring repeat imaging studies or biopsy prior to the next scheduled annual screening were compared between the two selection methods. **Result:** The demographics of participants are shown in Table 1. To date, 1,533 received a LDCT, of these, 341 met the PLCOm2012 criteria alone, 169 met NLST-like criteria and 1023 met both criteria. Twenty-seven participants have been found to have lung cancers. All 27 met the PLCOm2012 selection criteria alone while 62% met NLST- like criteria. No lung cancer was found in participants who met NLST-like criteria alone. There are 129 participants with suspicious lung nodules under close surveillance or scheduled for biopsy. Among these, 97% met the PLCOm2012 criteria and 74% met NLST-like criteria.

Table 1. Clinical and Demographic Features of Study Cohorts				
Study Site	British Columbia	Alberta	London	Total
No. Contacted	802	1661	1990	4453
No. Eligible	364	741	812	1917
No. Screened	241	688	604	1533
Age (yrs)	65+/- 6.3	63.5 +/- 4.2	66+/-4.2	64.8+/- 5.7
Sex (female/ Male)	91F:150M	342F:346M	273F:331M	706M;827M
Current: Former Smoker	103CS:138Ex	341CS:347Ex	443CS:161Ex	887CS:646Ex
Pack Years (Mean +/-SD)	47.3+/-22	42.4+/-15.8	47.7+/-22.3	45.3+/-19.8
Median Follow-up(months)	7.5	9.7	9.7	
No. of lung Cancers	3	7	17	27
Participants with suspicios nodules	21	41	67	129

Conclusion: Our preliminary results show that fewer people are eligible for screening using NLST-like criteria compare to a highly predictive risk model such as PLCOm2012. Thirty-seven percent more participants with lung cancer are identified by PLCOm2012.

Keywords: lung cancer screening, Optimal Selection, PLCOm2012

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P2.13-012 RECRUITMENT FOR LUNG CANCER SCREENING

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Background: The efficiency of a lung cancer screening program with low dose computed tomography (LDCT) is influenced by the screening uptake. The most efficient method to improve participation rate of individuals in the general population who are eligible for screening has not been determined. We evaluated different methods of recruitment on the participation rate. **Method:** The BC lung screening trial is part of the International Lung Screen Trial (ILST) in Canada, Australia, the UK and Hong Kong. ILST aims at defining the optimal selection criteria for LDCT by comparing the relative sensitivity of the US Preventative Services Task Force criteria versus the PLCOm2012 prediction model with 6-year lung cancer risk>=1.5%. Individuals with a chest CT within 2 years are excluded from the screening study. Different methods [social media, radio, newspaper, QuitNow smoking cessation program, BC Lung Association and referrals by general practitioners (GP)] to recruit eligible individuals are compared. **Result:** Of the 802 participants referred or self-referred to the study, 364 (41% female, 59% males, 53% ex-smokers and 47% current smokers) were eligible. The largest draw was radio which reached 64% of respondents, however only 29% of these were eligible. General practitioners (GP) reached only 24% but of these 70 % were eligible. 13% had a CT scan within 2 years, and but only 40% would have been eligible via risk criteria (Table 1). Table1.

Means of Recruitment	Total Numbers Invited	Number of eligible participants	Number of ineligible participants				
			CT scan in last 2 yrs	Outside age	Previous lung cancer	Other	Did not meet risk score
Facebook	8	7	-	-	-	-	1
GP	196	138	9	13	1	5	30
Radio	510	147	92	76	13	3	179
Newspaper	3	1	-	-	-	-	2
Friends & family	15	13	-	-	-	-	2
Quit now Eblast	37	30	-	-	-	-	7
Online advertisment	22	20	2	-	-	-	1
Poster and other	4	2	-	-	-	-	1
Hospital Email	6	6	-	-	-	-	-
Study website	1		-	-	-	-	1
Total	802	364	103	89	14	8	224

Conclusion: The largest number of eligible participants were referred by their GPs. Media (radio) reached a larger number of participants but many were ineligible. A combined approach of media publicity and GP referrals may be the best way to reach the target the population. Ad hoc screening is likely occurring in the absence of a publicly funded screening program inappropriately exposing participants outside of the criteria.

Keywords: recruitment, lung cancer screening

P2.13: RADIOLOGY/STAGING/SCREENING - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-013 DETERMINATION OF THE DETECTION LEAD TIME FOR AUTOANTIBODY BIOMARKERS IN EARLY STAGE LUNG CANCER USING THE UKCTOCS COHORT

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Background: Tumor associated (TA) autoantibodies are present during early stage lung cancer and have been detected up to five years before diagnosis. However the detection lead time provided by their measurement has never been accurately determined due to a lack of suitable patient samples. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) recruited 202,638 postmenopausal women. Annual blood samples were collected for over 10 years during which time a number of lung cancer cases were diagnosed. The primary aim of this study was to determine the detection lead time of tumor associated autoantibody assays for a subset of the UKCTOCS cohort. **Method:** A set of 142 primary lung cancer cases (NSCLC 83%, SCLC 12%) with 7 serial samples over a pre-diagnosis period of 10 years were randomly split into Training (n=100) and Validation (n=42) cohorts and matched to healthy controls by age-at-diagnosis, age-at-first sample and smoking history. TA autoantibody profiles were produced for each patient by measuring autoantibody levels against a panel of tumour associated antigens (p53, SOX2, CAGE, NY-ESO-1, GBU4-5, MAGE A4, HuD, CK8, CK20, LMYC, SSX1, p53-95, p16 and p62) using ELISA. The profiles for each patient were compared to those for the preceding time point using a multivariate distance measure to determine if a statistically significant positive change had occurred. Comparison against a population based cut-off for the earliest time point sample for each patient was used to determine initial positivity. An optimised algorithm was developed on the Training cohort and then applied to the Validation cohort. **Result:** There were 49 positive patients in the training cohort: 11 at the earliest time point and 38 during serial sampling. For the Validation cohort there were 14: 3 at the earliest and 11 during serial sampling. The median detection lead time for the Training cohort was 4.0 years (0.3 to 9.4 range) and for the Validation cohort 4.3 years (0.1 to 9.0 range) before clinical diagnosis. The median was 4.1 years (0.1 to 9.4 range) for the entire cohort. **Conclusion:** This is the first time statistically sound estimates of detection lead time have been reported for tumor assoicated autoantibody tests run on such a large cohort of pre-diagnostic serial samples. These cancer biomarkers can be detected on average 4 years before diagnosis. Monitoring autoantibody profiles could be hugely beneficial by enabling earlier detection and stratification of screening populations for cancer. This could lower mortality rates and reduce healthcare costs.

Keywords: Screening, Early Detection, serum biomarkers

P2.13: RADIOLOGY/STAGING/SCREENING - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-014 COMPUTED TOMOGRAPHY-BASED RADIOMIC CLASSIFIER DISTINGUISHES MALIGNANT FROM BENIGN PULMONARY NODULES IN THE NATIONAL LUNG SCREENING TRIAL

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Background: In the National Lung Screening Trial (NLST), indeterminate pulmonary nodules were detected in 40% of high-risk individuals screened by low dose high-resolution computed tomography (HRCT). However 96% of these nodules were benign indicating that overdiagnosis represents a major challenge for the clinical implantation of CT based lung cancer screening. While current clinical-radiological risk prediction models are very valuable, optimization of the clinical management of larger (≥ 7 mm) screen-detected nodules to avoid unnecessary diagnostic interventions including futile thoracotomies better strategies are needed. Herein we demonstrate the potential value of a novel radiomics based approach for the classification of screen-detected indeterminate nodules. **Method:** Independent quantitative variables assessing various radiologic nodule features such as sphericity, flatness, elongation, spiculation, lobulation and curvature, using 726 nodules (all ≥ 7 mm) were developed from the NLST dataset (benign, n=318 and malignant, n=408). Multivariate analysis was performed using least absolute shrinkage and selection operator (LASSO) method for variable selection and regularization in order to enhance the prediction accuracy and interpretability of the multivariate model. To increase the stability of the modeling, LASSO was run 1,000 times and the variables that were selected in at least 50% of the runs were included into the final multivariate model. The bootstrapping method was then applied for the internal validation and the optimism-corrected AUC was reported for the final model. **Result:** Eight radiologic features were selected by LASSO multivariate modeling out of 57 quantitative radiological variables considered for inclusion. These 8 features include variables capturing vertical location (centroid_Z), volume estimate (Min Enclosing Brick), flatness, texture analysis (SILA_Tex), surface complexity (Max_SI and Avg_SI), and estimates of surface curvature (Avg_PosMeanCurv and Min_MeanCurv), all with P<0.01. The optimism-corrected AUC is 0.939. **Conclusion:** Our novel radiomic HRCT-based approach to non-invasive screen-detected nodule characterization appears extremely promising. Independent external validation is needed.

Keywords: indeterminate pulmonary nodules, Overdiagnosis, lung cancer screening

P2.13-015 THE PRIMARY CARE PROVIDER ROLE IN THE US SCREENING CONTEXT: CURRENT PRACTICES AND STRATEGIES FOR PHYSICIAN ENGAGEMENT

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Background: As lung cancer screening has become more mainstream in the US, increasing attention has been paid to appropriate referral and follow up to minimize harms. This has been particularly focused on community-based programs as concerns have been voiced about the dearth of RCT evidence to support screening implementation in that setting. In addition, with the release of the US Preventive Services Task Force (USPSTF) and Centers for Medicare/Medicaid Services (CMS) recommendations for screening, more of the decision-making has been shifted to the primary care community. Primary care providers (PCPs) are expected to increase awareness of screening with their high-risk patients, perform counseling and shared decision-making (SDM), and manage screening outcomes more than ever before. **Method:** In a sample of mostly hospital-based lung cancer screening programs, program managers completed an application update as required for their continued participation in a national network. The applications were completed between March-June 2017 and covered areas of requirement for the designation, including: eligibility criteria, screening protocols, smoking cessation resources, multidisciplinary team make-up, SDM, and results reporting. 222 health systems responded, which represents 473 individual health care facilities out of 549 facilities that received the application (an 86% response rate). **Result:** Regarding counseling and SDM – required by CMS prior to generation of a written order - 82% of respondents reported that patients accessed SDM via the PCP. However, the majority of these respondents also indicated that the patient accessed SDM via a member of the screening team in addition to the PCP. Academic programs were less likely to see screening patients who received SDM through the referring provider and screening team (59%) compared to community/non-academic programs where 75% of patients received SDM through a referring provider and the screening team. We also examined the make-up of multidisciplinary clinical teams. 36% of respondents reported primary care as a team member. This was more common with community/non-academic programs when compared to academic programs. **Conclusion:** Data collected from screening program self-reporting indicates interesting trends in how primary care is incorporated into the lung cancer screening process prior to the referral through shared decision-making and during the review of screening results through the multidisciplinary care team. With patient awareness of lung cancer screening still reported to be low and PCP awareness and buy-in for lung cancer screening still considered to be inconsistent, supporting the integration of primary care into the workflow may help increase uptake of screening in a high risk population.

Keywords: screening, PCP, multidisciplinary

P2.13-016 SELF-REPORTED PROGRAM BARRIERS TO INCREASING LUNG CANCER SCREENING RATES IN THE US AND IMPLICATIONS FOR THE SCREENING COMMUNITY

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Background: Despite approval and coverage for lung cancer screening in the US for a high-risk population, recent research indicates that screening rates are still far lower than anticipated. Jemal and Fedewa (2016) looked at rates during 2011-2015 and found only a 3.9% screening rate in the eligible population. While some of that low rate may be due to lack of insurance coverage in both private and Medicare populations during the bulk of the study time period, screening programs continue to report challenges that may be barriers to increasing screening rates even though it is covered by most insurance plans and Medicare. **Method:** In a network of mostly hospital-based lung cancer screening programs in the US, 152 programs representing both academic and community programs completed a survey on practices and statistics, achieving a 61% response rate. The survey was completed using SurveyMonkey between March-June 2017 and asked a range of questions based on the 2016 program experience, including program statistics, current smoking cessation referrals, participation in research and programmatic barriers. The reported data here represent screening program managers' perceptions of continued challenges to screening as captured through two specific questions: "What barriers continued to cause problems for you in 2016?" and because insurance/billing issues constitute a broader category, "What was the nature of the insurance/billing issues you faced in 2016?" **Result:** The majority of respondents indicated that insurance/billing issues, lack of patient awareness, internal workflow challenges, and lack of support from referring providers were barriers that continued to cause problems in 2016. Only 30% of respondents indicated that lack of patient interest in screening was a barrier and 41% indicated that staffing/time limitations was a barrier. Other barriers identified by respondents included lack of provider awareness and challenges (often technical) with complying with the Medicare requirement for submission of registry data. Because insurance/billing issues continue to be significant, respondents provided more detail about the nature of these issues, including claims denials, coverage co-pays or deductibles, coding errors, and receiving prior authorizations. **Conclusion:** Despite widespread insurance coverage in the eligible screening population in the US, screening programs are still facing barriers to increasing screening service usage. It is clear that communities and professionals supportive of screening need to focus attention in increased patient and provider education around lung cancer screening. However, insurance and billing issues remain a major challenge, even though coverage is theoretically in place.

Keywords: screening, barriers, insurance

P2.13-017 FOUR YEARS OF DATA IN AN ESTABLISHED LOW DOSE CT (LDCT) SCREENING PROGRAM

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Background: Lung screening with LDCT has demonstrated a significant improvement in lung cancer specific overall survival including the National Lung Screening Trial (NLST) comparison of LDCT vs chest x-ray. LDCT is recommended by the USPSTF and covered by Medicare, prompting the development of lung screening programs. In January, 2012, Lahey began a program for lung screening by low dose CT scan. **Method:** All individuals enrolled in the Lahey screening program fulfilled the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Lung Cancer Screening v1.2012 (NCCN Guidelines®) high risk criteria for lung cancer and had a physician order for CT lung screening. Patients qualifying by NCCN Group 2 criteria were included in our free program from 2012-2015. **Result:** More than 11,000 LDCT lung screening scans have been performed in the Rescue Lung Rescue Life program on about 4500 patients. As of June, 2017 the program has diagnosed 135 cancers, of which approximately 70% are early stage non-small cell lung cancers. The rate of positive scans in year 1 of patient enrollment is about 15% and decreases substantially in following years. About 84% of patients continued in the program with recommended follow up scans. A very small number of patients undergo an invasive intervention without ultimately having a cancer diagnosis. We will present updated numbers. **Conclusion:** The reported numbers from screening trials have impacted the discussion about lung cancer screening program development and expectations. Our single institution data set of more than 11,000 scans shows a lower rate of positive screening tests with a higher positive predictive value than that reported in NLST, in part due to evolution of the recommended nodule size categorization. The high rate of patient retention in the program suggests follow up scans and regular screening are feasible. Our data showing limited intervention in patients with benign nodules, and about 70% of patients diagnosed with early stage disease, further demonstrates the importance of lung screening and limited risk associated with lung screening in an established program. The largest lung screening study performed to date, NLST, evaluated low dose CT chest vs chest x-ray yearly for 3 years. We provide data from an established lung screening program over more than 4 years.

Keywords: lung cancer, low dose CT, Lung Screening

P2.13-018 CLINICAL OUTCOMES STAGE I/0 ADENOCARCINOMA LUNG DIAGNOSED BY LOW DOSE CT (LDCT) SCREENING VS INCIDENTALLY DISCOVERED

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Background: Although LDCT lung screening has demonstrated improvement in overall survival, some have worried that indolent BAC-like adenocarcinomas (ADCA) may be over-detected/treated. We previously reported comprehensive and detailed pathologic comparison of stage I/0 lung ADCAs detected by LDCT screening vs incidentally discovered ADCAs stratified by NCCN risk criteria, demonstrating the presence of high grade invasive disease and high risk features in the LDCT group similar to incidentally discovered cancers. We now report clinical outcomes from a single institution LDCT program with associated pathology details. **Method:** Comprehensive histologic subtyping was performed on 54 consecutive stage I/0 LDCT screen detected ADCAs in patients meeting NCCN group 1/2 high risk (HR) criteria and compared to 77 incidentally detected stage I/0 ADCAs meeting HR criteria. We evaluated clinical outcomes in relation to details from pathologic evaluation. **Result:** We provide clinical data including disease free interval and recurrence in patients treated with curative intent for stage I adenocarcinoma detected by lung cancer screening vs incidentally discovered in HR patients with associated detailed pathologic evaluation. Screen detected and incidentally detected ADCAs show an equally low-rate of indolent, non-invasive/minimally invasive ADCAs. A collection of lepidic predominant (BAC-like) ADCAs associated with aggressive non-predominant cribriform and/or solid patterns and high proportion of lymphatic invasion were more frequently observed in the screen-detected group. Subgroup analysis of screen detected NCCN group 1 vs. 2 shows group 2 tumors exhibit histologic features which are at least as aggressive as group 1 tumors. Updated numbers with a larger cohort than previously reported and associated clinical data will be presented. **Conclusion:** We have demonstrated that many BAC-like tumors in LDCT screen detected patients

bear histologic features of aggressive ADCAs, including among those still in a lepidic predominant phase. We provide the clinical data associated with updated numbers of the first detailed pathologic comparison of LDCT screen and incidentally detected ADCA of NCCN HR tumors.

Keywords: low dose CT, lung cancer, Lung Screening

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-019 ATTRITION RATE IN COMMUNITY-BASED LUNG CANCER SCREENING: ONE AND DONE

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Background: Community-wide lung cancer screening has the potential to significantly impact lung cancer mortality. Thus, much emphasis has been placed on program development and recruitment of high-risk individuals. Lung cancer screening is a continuum, and shared decision-making focuses on the need for participants to remain engaged. Currently, little is known about screening follow-through in the community setting outside of clinical trials. Thus, we aimed to quantify the rate of attrition in our Lung Cancer Screening Program (LCSP) and identify contributing factors. **Method:** We reviewed all individuals enrolled in our LCSP, which is led by an independently practicing nurse practitioner within a multidisciplinary team, from 2012-2016. We identified all individuals who were closed out of the program, the closure date, and reason for closure. Of these, attrition was defined as declined further screening or lost to follow-up. A formal process for documentation of attrition included failure to respond to a written communication, a minimum of three contact attempts, and a clinical note forwarded to the referring provider. **Result:** Of the 520 individuals enrolled in the LCSP, 23% (122) were officially closed out. Thirteen percent (67/520) were closed out for clinical, geographic, or other identifiable reasons. Attrition from the program was identified to be 11% (55/520). Of the individuals that dropped out, 69% (38/55) were smoking upon enrollment compared to 52% (205/398) of retained individuals (*p=0.014*). In addition, 78% (43/55) had only one CT scan prior to attrition (Figure).

	Attrition (N=55)	Still in program (N=398)	P-value
Median months to attrition	14 (IQR: 13-17))	NA	NA
Percentage with one scan before attrition	78.2%	NA	NA
Percentage smoking on first visit	69.1%	51.5%	**0.014**
Mean readiness to quit score (for smokers)	2.0 ± 1.0	2.2 ± 1.0	0.174
Percentage with nodule(s) (1st scan)	67.3%	71.6%	0.506
Largest nodule size (mm)	8.4 ± 13.0	6.3 ± 5.8	0.341
Median distance travelled (miles)	9.2 (IQR: 5.1-14.2)	9.0 (IQR: 5.8-16.3)	0.909

Conclusion: We identified an 11% attrition rate in our community-based LCSP. Individuals who failed to follow-up with the LCSP were more likely to be current smokers. The majority of individuals who failed to follow-up did not return after the initial CT scan. Future work needs to focus on promoting the continuum of screening and support the highest risk communities to minimize attrition.

Keywords: lung cancer screening, Attrition

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-020 LUNG-RADS USED IN LUNG CANCER SCREENING: DOES GRANULOMATOUS DISEASE INTEREFERES WITH THE RESULTS? INITIAL FINDINGS AT A BRAZILIAN CANCER CENTER

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Background: Lung cancer is the leading cause of cancer death in the world. Screening has proved effective in reducing mortality in one major trial. In countries where granulomatous disease is prevalent, CT-screening false positive results may increase, even when Lung-RADS is used in the screening-CT analysis. Purpose: To analyze the outcomes of low-dose computed tomography (LDCT) lung cancer screening using Lung CT Screening Reporting and Data System (Lung-RADS) at a Brazilian cancer center. **Method:** Medical records of 552 patients initially selected to baseline LDCT- lung-cancer-screening program between May/2016 and April/2017 were analyzed. Only 287 patients complied NLST[1] inclusion criteria and were included in the study. These had a mean age of 61.8 years and a history of smoking of a mean of 45.3 pack-year. Mean Dose Length Product (DLP) of LDCT was 21.3 mGy/cm^2 with a mean effective dose of 0.30 mSv. LDCT findings were classified according to Lung-RADS[2] assessment categories. **Result:** Most patients (n=207; 72.1%) had a negative screening CT (Lung-RADS categories 1 or 2), 55 (19.2%) had probably benign findings (Lung-RADS category 3) and 25 (8.7%) had suspicious findings (Lung-RADS categories 4A [5.6%], 4B [2.1%] and 4X [1.0%]). The most common finding was a solid nodule (64.1%), followed by non-solid nodule (8.7%) and then by part solid nodule (2.8%). One patient classified as Lung-RADS category 3S had an incidental diagnosis of chest wall lymphoma, confirmed after biopsy. Patients in Lung-RADS category 4A (n=9) had a CT follow-up and most of them (n=7) showed stable findings and in two patient the nodules increased in size on follow-up CT. Histologic results confirmed lung cancer in 2 cases (prevalence of 0.7% of all screened patients). **Conclusion:** Lung cancer prevalence in our sample was compatible with the literature. However, we had a higher prevalence of Lung-RADS categories 3 and 4A than expected[3]. This may be associated with the higher incidence of granulomatous disease, especially tuberculosis, in the Brazilian population. 1.National Lung Screening Trial Research Team, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 Aug 4;365(5):395-409. doi: 10.1056/NEJMoa1102873. 2.American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS) 3.Pinsky PF, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. Ann Intern Med 2015 Apr 7;162(7):485-491 doi: 10.7326/M14-2086.

Keywords: computer tomography, lung cancer, Screening

P2.13: RADIOLOGY/STAGING/SCREENING -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.13-021 COMMUNITY NETWORK LUNG CANCER SCREENING EXPERIENCE UNDERREPRESENTS MEDICALLY UNDERSERVED AND GEOGRAPHICALLY REMOTE INDIVIDUALS

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Background: The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality. However, it's study centers may not have represented remote populations with low socioeconomic status and/or health care access. Previous reports on other cancers have demonstrated higher rates of screening in urban populations, with lower adoption in underserved and geographically remote communities. We aimed to quantify the proportion of screened individuals from medically underserved and geographically remote areas represented in our multi-state hospital network lung cancer screening programs (LCSPs). **Method:** We performed a multi-institution review using data from individuals enrolled in Pacific Northwest LCSPs, which form part of a multi-state hospital network. Individuals from programs spanning Washington State, Oregon, Montana, and Alaska from 2012-2016 were included. Definitions include: medically underserved area [MUA; healthcare resources deficient region], medically underserved population [MUP; area with economic/cultural/linguistic barriers to primary care services], health professional shortage area [HPSA; primary care physician shortage]. **Result:** We identified a total of 2,379 screening participants. Of these, 22% (529) resided in a medically underserved area and 5% (108) were from a medically underserved population. Only 9% (216) resided in a HPSA, compared to the combined state data reporting a rate of 20% HPSA residents. Individuals lived a median of 6 miles from the screening site. Data stratified by state is shown in the figure, and demonstrates a high capture rate of individuals residing in MUAs in Montana.

	Total n=2,379	Washington n=429	Oregon n=1,494	Montana n=237	Alaska n=219
State population size, number*	-	7,288,000	4,093,465	1,042,520	741,894
Percent approximate at-risk population (number)					
Over age 65 currently smoking*	-	1.3 (75,504)	1.4 (56,326)	1.4 (14,710)	1.0 (7,418)
Individuals residing in HPSA#	20 (2,650,187)	18 (1,291,662)	24 (961,240)	25 (261,129)	18 (136,156)
Percent of screening participants from underserved community (number)					
Individuals residing in a *MUA*	22 (529)	27 (114)	7 (112)	91 (215)	31 (70)
Individuals residing in a *MUP*	5 (108)	3 (13)	5 (81)	0 (0)	0 (0)
Individuals residing in a *HPSA*	9 (216)	12 (51)	5 (71)	26 (62)	0 (0)
Median distance from screening site, miles (interquartile range)	6	9 (6-16)	6 (3-10)	4 (3-16)	5 (4-8)

*United States Census Bureau
#Washington, Oregon, Montana, and Alaska Departments of Public Health– data not available for MUA and MUP

Conclusion: All sites showed poor penetration into communities identified as MUPs and HPSAs. All sites also had poor penetration into MUAs; except for Montana, likely due to its overwhelming rural nature. However, the vast majority of screening participants lived in close proximity to screening centers. Therefore, novel approaches such as telemedicine and mobile screening clinics may be needed to reach underserved populations for LCS.

Keywords: Screening, Underserved, Rural

P2.13-022 LUNG NODULE SURVEY: ONE PATHOLOGY, PERSPECTIVES FROM THORACIC SURGEON, PULMONOLOGIST AND RADIOLOGY POINT OF VIEW

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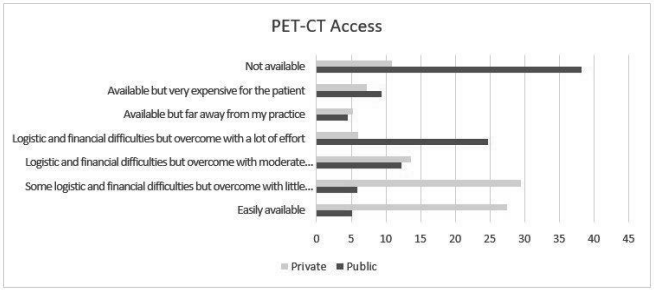
Background: Screening program for lung cancer are leading for more incidental lung nodules diagnosis.This study aimed to address the lung nodule management from different specialty perspective working in different settings. This is the first survey uniting national societies in Brazil and in Latin America. **Method:** A web-based survey was developed by thoracic surgeons, pulmonologists and radiologists to evaluate lung nodule perception and management. This survey was sent to their respective national societies members and answers collected between August and December 2016. That included multiple choice questions regarding age, specialty, lung nodule management, accessibility to exams and interventional procedures characterizing public (SUS) and supplementary(SHS) working settings. **Result:** A total of 461 questionnaires were answered. More than half of participants live in cities with over one million population. Specialties were reasonable equilibrated with 43.5% radiologists, 33.5% thoracic surgeons, 20.3% pulmonologist and 2.6% others. Most of the respondents work in both public and private sector (72.7%). SHS has a similar reality compared to well developed nations regarding exams accessibility and interventions. SUS setting has a significant difference according to the participants. CT is only easily available in 31.9% of cases, PET-CT is easily available in 24.4%(graphic1), bronchoscopy is unavailable and almost unavailable for 33.1%, IR biopsy is unavailable in 38.2% and video-assisted thoracic surgery (VATS) biopsy is easily available in 42.8%. When there is a probability of malignancy of 50% or higher, 46.5% of participants would be comfortable recommending surgical biopsy. When the probability higher than 10%, only 36.9% would be comfortable following up radiologically.



Conclusion: Brazil has a very different setting for SUS and SHS patients regarding exams availability and management options. That might explain why participants have a higher tendency to choose interventional diagnosis and explains why current guidelines may not be applicable to developing countries reality.

Keywords: lung nodule, Screening, lung cancer

P2.13-023 LUNG CANCER RISK AND ELIGIBILITY FOR LUNG CANCER SCREENING IN PATIENTS UNDERGOING COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY

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Background: Computed Tomography Coronary Angiography (CTCA) is frequently performed for non-invasive coronary artery assessment. Extracardiac findings are frequent, with indeterminate pulmonary nodules the commonest incidental finding. Given the established efficacy of lung cancer screening with low dose CT (LDCT), CTCA has been suggested to be an opportunity for "opportunistic" lung cancer screening. This rationale has been used to justify full field of view imaging, despite limited field of view significantly reducing prevalence of nodules detected and therefore reduce downstream healthcare costs. Distribution of lung cancer risk of patients undergoing Cardiac CT has not previously been reported. We performed a cross-sectional survey to determine the proportion of patients undergoing CTCA who would be eligible for lung cancer screening, and to determine the lung cancer risk profile of eligible patients. **Method:** Patients attending two tertiary hospitals in Melbourne, Australia, for clinically indicated out-patient CT coronary angiography were screened for inclusion in the study. Patients eligible for Lung Cancer screening according to the US Preventive Services Task Force (USPSTF) recommendations were invited to complete a questionnaire including smoking history and demographic details, to determine 6-year lung cancer risk, according to the $PLCO_{m2012}$ risk prediction model. A threshold PLCOm2012 risk at least 1.5% was used to identify a sub-group in whom LDCT screening is most likely to be cost-effective and reduce lung cancer mortality. **Result:** In a four month period, 216 patients (60% male) were screened prior to CTCA across both sites. Only 57 patients (26%) were potentially eligible for lung cancer screening according to USPSTF guidelines: 126 (58.3%) were never-smokers, with a further 33 patients (15.3%) outside the reccomended 55-80 years age range. Of 57 eligible patients, 48 (84%) consented to the questionnaire. Thirty-four were male (71%), with mean age 65.6+/-6.0 years. Median (IQR) PLCOm2012 risk was 1.30% (0.45–2.19%). Only 22 patients (45.8% of patients completing the questionnaire, estimated 12% of total cohort)had a $PLCO_{m2012}$ risk score >1.5%, and just 18 of 48 (37.5% of patients completing the questionnaire) had a PLCOm2012 risk > 2.0% **Conclusion:** A majority of patients undergoing CTCA were never-smokers. Only 26% would be eligible for screening according to USPSTF criteria. Therefore routine use of Cardiac CT for "opportunistic" lung cancer screening is likely to result in net harm and is not appropriate A small proportion of patients undergoing CTCA have high risk for lung cancer and may benefit from full thoracic imaging at the time of CTCA

Keywords: Screening, lung cancer risk, cardiac CT

P2.13-025 SELECTING THE RISK CUT OFF FOR THE LLP MODEL

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Background: The application of risk prediction models for the selection of individuals for lung cancer (LC) screening requires risk thresholds to distinguish between individuals eligible and ineligible for screening. However, little is known about the performance of risk prediction models across different risk thresholds. The UKLS trial utilised the Liverpool Lung Project risk model (LLP_{v2}) with a risk threshold of 5% for 5-year LC incidence as the selection criteria in the trial. The UKLS yielded a 1.7% LC detection rate at baseline, which was higher than the NLST or NELSON trials. This study evaluates the performance of different risk thresholds for the selection of individuals for lung cancer screening utilising the LLP_{v2} model. **Method:** The performance of the LLP_{v2} risk model to predict 5-year LC incidence was evaluated in ever-smokers from the PLCO. The sensitivity (the proportion of LC in the total population that occur within those selected for screening), specificity (the proportion of individuals excluded from screening which do not develop LC), and proportion of individuals eligible for screening was assessed across a wide range of risk thresholds. In addition, the trade-off between the sensitivity and the proportion of individuals eligible for screening was assessed. **Result:** Applying low risk thresholds yielded high sensitivities, at the cost of low specificities and higher ratios of persons eligible per LC included within the eligible population. For example, a LLP_{v2} risk threshold of 1.0% would yield a sensitivity of 91.5% at the cost of a specificity of 37.2% and a ratio of 39 eligible individuals per LC. In contrast, a LLP_{v2} risk threshold of 5.0% would only yield a sensitivity of 36.5%, but had a specificity of 88.8% and a ratio of 18 eligible individuals per LC. A LLP_{v2} risk threshold of 2.03% yielded a similar sensitivity, but higher specificity and a more favourable ratio of eligible individuals per LC compared to the NLST criteria. LLP_{v2} risk thresholds between 2.0-3.0% may provide an advantageous balance between sensitivity and the ratio of eligible individuals per LC. **Conclusion:** The level of the risk threshold applied to select individuals for screening has an inverse relationship between the efficacy and efficiency of LC screening. Implementing LC screening programs which use risk prediction models to determine screening eligibility require further assessment of the trade-off between these aspects with regards to the long-term benefits, harms and cost-effectiveness to ascertain the optimal risk threshold.

Keywords: lung cancer screening, Risk prediction, Risk modelling

P2.13-026 DETERMINING THE EFFECT OF SCREENING ON LUNG CANCER MORTALITY

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Background: The current lung cancer screening recommendation of the United States Preventive Services Task Force (USPSTF) is to perform annual low-dose computed tomography (CT) scans for high risk current smokers (at least 30 pack-years), or quitters in the past 15 years, age 55-80 years. Our study aims to assess if early detection of lung cancer by screening decreases the lung cancer mortality burden and, if so, how drastically for those considered at highest lung cancer risk. **Method:** Lung cancer screening prevalence was calculated from the 2010 to 2015 National Health Interview Surveys (NHIS). Probability of screening was derived from logistic regression models using race, age, gender, smoking and health insurance status as predictors. Beta values for these covariates were then used to estimate the probability of screening in the 1999-2004 National Health and

Nutrition Examination (NHANES) cohort, for which lung cancer mortality information was available through linkage with the National Death Index. Using the predictor values generated in the NHIS dataset, probability of screening was estimated for the at risk NHANES participants, to make inferences about the effects of screening on lung cancer mortality. **Result:** Of the 60829 NHIS study participants, 2296 met the definition for being at high for lung cancer. The overall screening prevalence for this at-risk population was 10.4%; 7.7% had chest radiography while 5.7% had CT scans. Screening occurred more frequently in former smokers (p=0.0474), people who had health insurance coverage (p= 0.0017), and those older than 68 years (p = 0.0439). In the NHANES cohort, out of 31126 participants, 668 met the USPSTF recommendation for screening and 25 of them died of lung cancer. Lung cancer mortality was significantly higher in the high-risk group than in the low-risk group (HR_{adj} 8.59, 95% CI: 5.12-14.41). Based on the screening predictors obtained from NHIS data, 347 (51.95%) of the 688 high risk individuals would undergo a screening; 16 of them (4.6%) have died of lung cancer. If screening had occurred, overall lung cancer mortality would have potentially been reduced by 64%, provided that individuals had screening-detected early stage operable tumors. **Conclusion:** Increasing CT screening among those at high-risk for lung cancer should significantly reduce deaths from lung cancer in this population. Screening needs to be combined with continued smoking cessation efforts.

Keywords: CT scan, Screening, NHIS

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-001 MID-TREATMENT PERFUSION PET/CT IS MORE EFFECTIVE THAN VENTILATION PET/CT IN FUNCTIONALLY-ADAPTED RADIOTHERAPY FOR NSCLC

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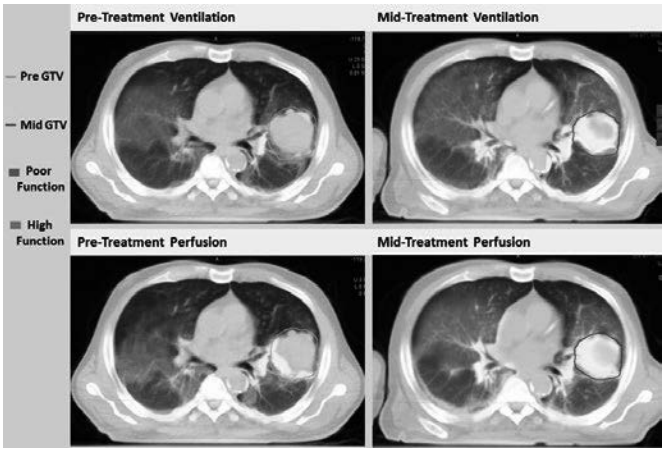
Background: To assess the utility of four-dimensional (4D) ventilation/perfusion (V/Q) PET/CT lung imaging to facilitate mid-radiotherapy treatment adaption with volumetric modulated arc radiotherapy (VMAT). **Method:** In a prospective clinical trial, patients with non-small cell lung cancer (NSCLC) underwent ^{68}Ga-4D-V/Q PET/CT scanning before and during a six-week (60Gy) course of definitive chemoradiation. Functional lung volumes were delineated on both datasets as 'highly perfused' (HPLung) and 'highly ventilated' (HVLung), using a 70th centile SUV threshold. Three VMAT plans were created on the mid-treatment datatsets: optimised to anatomical lung, HPLung, and HVLung volumes, respectively. Functional dose volumetrics were assessed using the parameters of mean lung dose (MLD), and lung volume receiving 5, 20 or 30Gy, (V5, V20, and V30). Plan quality was assessed for consistency with respect to conformity indices, and doses to critical structures. **Result:** The study cohort consisted of 10 patients resulting in a total of 30 VMAT plans. PTV volumes reduced by a mean of 5.5% between scans. HVLung volume increased between scans by a median value of 39.2%. Subsequent volumetric and spatial changes were reflected in varying DICE similarity coefficients, or DSC (ranging from 0.336-0.923). HPLung decreased by a median value of 4.5% with spatial discrepancy represented by DSC of 0.568-0.805. Increase in ventilated function was most prevalent adjacent to the target, limiting the benefit of adaptive planning (**Fig 1**). Plan quality was consistent with the median PTV D95 ranging from 60.6-61.3Gy, and mean conformity index ranging from 1.23-1.25. Functional MLD of HPLung decreased by a mean of 7.3%, p=0.02. Plans optimised to HPLung resulted in a reduction of perfused lung V5 by a mean of 13.2%, $p<0.01$, with HVlung plans yielding a decrease in ventilated lung V5 of 9.6%, $p=0.02$. **Fig 1**



Conclusion: To achieve reduced irradiation of functional lung, radiotherapy adaptation is more effectively facilitated by perfusion rather than ventilation imaging.

Keywords: functional lung, Positron emission tomography, Radiotherapy

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-002 IMPACT OF PRE-EXISTING CARDIAC DISEASE AND HEART DOSES ON SURVIVAL IN NSCLC TREATED WITH POST-OPERATIVE THORACIC RADIOTHERAPY

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Background: Recent randomized and observational studies suggested that pre-existing cardiac disease and higher radiation heart doses were associated with more cardiac events and worse overall survival (OS) in locally-advanced non-small cell lung cancer (NSCLC) treated with definitive chemoradiation. Post-operative thoracic radiotherapy (PORT) delivered via non-modern radiation techniques had also been shown to increase cardiac mortality. Hence we performed this study to determine the impact of pre-existing ischaemic heart disease and radiation heart dose on OS in NSCLC patients treated with PORT using contemporary radiation techniques. **Method:** Study eligibility criteria included stage I to III NSCLC treated with PORT at two institutions from 2007 to 2014. Clinical data and dosimetric parameters affecting overall survival were collected from the institutional electronic medical records as well as the national death and acute myocardial infarction registries. Univariate cox regression was performed using Stata version 13. **Result:** Twenty eligible patients were identified. Median follow-up duration was 30.4 months (2.3-81.9). Median age was 59 years. Median prescription dose was 57 Gy. Median mean heart dose was 12Gy. 10% had pre-existing ischaemic heart disease. 75% underwent lobectomy. 60% had pathological stage III disease. 40% had left-sided disease. 70% received chemotherapy. The 1- and 2-year OS were 75% and 60% respectively. Univariate analysis showed that pre-existing ischaemic heart disease was significantly associated with worse OS (hazard ratio 7.13, 95% confidence interval 1.17-43.47, P value < 0.03). Mean heart dose and the other cardiac dosimetric parameters (volume of heart receiving ≥ 5, 25, 30, 40, 50Gy, and dose to ≥ 30% of heart volume) were not associated with OS. **Conclusion:** Pre-existing ischaemic heart disease was a significant predictor for worse OS in NSCLC patients treated with modern PORT. We plan to expand the cohort to confirm these findings. Patients should be screened for ischaemic heart disease and cardiac function optimised prior to PORT and on follow-up.

Keywords: non-small cell lung cancer, Ischaemic heart disease, Radiotherapy

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-003 CLINICAL OUTCOMES OF SBRT IN INOPERABLE ELDERLY PATIENTS WITH NSCLC: EXPERIENCE FROM A DEVELOPING COUNTRY

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Background: Stereotactic body radiation therapy (SBRT) has emerged as a treatment option for patients with early-stage lung cancer, especially in the medically inoperable population. As most reported data are from developed countries, the purpose of this study was to report clinical outcomes and toxicity for SBRT in these patients from a single academic institution from Brazil. **Method:** Between January 2007 and September 2015, 102 consecutives lung lesions at Hospital Sírio–Libanês, São Paulo, were treated with SBRT, of which 59 primary non-small cell lung cancer (NSCLC) (biopsy-proven) lesions from 54 inoperable patients were reviewed from a specific registry (43 lesions were excluded: metastatic or with no biopsy). For patient immobilization, semi-rigid (vaclok based) system was used. The CTV was delineated based on CT data from 3 phases superimposed on 3-dimensional radiation treatment planning systems to obtain an internal target volume (ITV). A median dose of 54Gy (45-60Gy) was prescribed in 3 – 5 fractions per lesion and image guidance was mandatory. Treatment outcomes for in-field local control (LC) per lesions, progression free survival (PFS) and overall survival (OS) were assessed with Kaplan-Meier estimates. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0 **Result:** Of the 54 patients analyzed, the majority were elderly (average age 75.7 years; SD ±8.8 years). More than 90% were PET/CT staged with Stage IA 40 (68%) and adenocarcinoma 46 (78,0%) representing the most common stage and histology, respectively. Median follow-up was 21,3 months (4 -55 months) for LC, 22.3 months (4 -55,8 months) for PFS, and 18.7 months (4.2 - 56,4 months) for OS. The 2-year rates of LC, PFS and OS were 89.1%, 79%, and 80.3%. Median LC, PFS, OS was 48.5 months, not reached, 41,8 months, respectively. Histology, size and stage of the primary were not a significant predictor for LC (P = 0.58; P = 0.26; P= 0.64, respectively), PFS (P = 0.81; P = 0.86; P = 0.64, respectively), or OS (P=0.21; P = 0.62; P = 0.94, respectively). Grade 3+ toxicities were observed in 2 patients (3.7%), of which 1 was grade 3 pneumonitis and one was grade 4 skin toxicity. **Conclusion:** Our data also show that SBRT is effective and feasible in a predominantly elderly and medically inoperable patient population in Brazil.

Keywords: Lung; Non Small Cell Lung Cancer; SBRT; Radiotherapy

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-004 COMPARABLE LOCAL CONTROLS AFTER TWICE-DAILY AND ONCE-DAILY CHEST RADIOTHERAPY IN EXTENSIVE STAGE SMALL CELL LUNG CANCER

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Background: The optimal radiation schedule for small cell lung cancer (SCLC) has not yet fully established. This study was designed to compare the clinical outcomes between twice- and once-daily radiotherapy in the treatment of SCLC. **Method:** One hundred and twenty-four consecutive patients diagnosed with extensive stage SCLC and treated with chemoradiotherapy were retrospectively reviewed. Either twice-daily hyper-fractionated irradiation (45 Gy/30 fractions/BID), or alternative schedules, including hypo-fractionated (45 Gy/15 fractions/QD) or conventionally fractionated (50 Gy/25 fractions/QD or 60 Gy/30 fractions/QD) radiation was delivered, with etoposide and platinum prescribed concurrently or sequentially. Local controls and overall survivals were calculated and compared between twice- and once-daily schedules based on Kaplan-Meier method. Toxicities were record according to Common Terminology Criteria Adverse Events. **Result:** There were 67 and 57 patients received twice- and once-daily chest radiotherapy, respectively. With a median follow-up of 27 and 24 months, the local control rates were reported 64.2% and 63.2%. The 2-year estimated local progression-free survival rates were similar (61.6% *vs* 61.0%, p=0.90). Progressive disease identified three months after radiotherapy was correlated to increased local failure (p=0.026). There was no difference between the incidences of grade 3-4 toxicities between twice- and once-daily schedules (23.9% vs 12.3%, p=0.16). **Conclusion:** Either twice- (45 Gy/30 fractions/BID) or once-daily (45 Gy/15 fractions/QD, 50 Gy/25 fractions/QD, 60 Gy/30 fractions/QD) radiation schedule could be considered in the treatment of SCLC, resulting in comparable local control and toxicities.

Keywords: local control, small cell lung cancer, schedule

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-005 DETERMINATION OF OPTIMAL CUT OFF SUV THRESHOLD FOR AUTO-CONTOURING OF GTV USING PETCT FOR EARLY STAGE NSCLC

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Background: ^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG-PET-CT) has the potential to increase the precision in contouring of gross tumour volume (GTV). However, detection of tumour edge in the halo around the tumour has been a problem. A surgical histopathological examination is the current gold standard for tumour size estimation in NSCLC. The aim of this study was to determine an optimal cut-off of standardized uptake value (SUV) on FDG-PET-CT images that correlates best with tumour size on surgical histopathology examination. **Method:** From January 2013- July 2014, 25 consecutive patients with diagnosed early NSCLC (pT1-pT3,N0M0) who underwent surgical resection (either a lobectomy or pneumonectomy) were accrued. GTVs were delineated on a preoperative FDG-PET-CT scan (acquired within 8 weeks before surgery) by automatic delineation using % threshold SUV at 20%, 30%, 40%, 50% of maximal uptake and threshold as absolute SUV 2, 2.5, 3, 3.5 and 4. The maximum tumour size was recorded from the surgical histopathology reports. First order linear regression was used to obtain values of optimal cut off SUV for each patient at which maximum size of GTV on FDG-PET-CT matched with maximum tumor size on histopathology. Different SUV thresholds of GTV delineation were compared with histopathology with respect to the estimation of maximum tumour size using Bland-Altman plots. The above methodology was carried out in 25 patients in test set. 12 additional patients were used to validate the results of the test set. **Result:** On analysis of 25 patients in the test set using first order linear approximation, the mean optimal cut-off values for GTV delineation on FDG-PET-CT images were 35.6 % ± 18.6 for % threshold SUV and a 4.35 ± 1.7 for absolute SUV. On analysis of 12 more patients in the validation set, the mean optimal cut-off values for GTV delineation on FDG-PET-CT images were 36.9 ± 16.9 % threshold SUV and a 4.1 ± 1.6 absolute SUV. After combined analysis of all 37 patients, the mean optimal cut-off values for GTV delineation on FDG-PET-CT images were 36 ± 17.9 % threshold SUV and a 4.27 ± 1.7 absolute SUV. On comparing various methods of delineation by Bland-Altman plots, auto-contouring with percentage threshold of 40% and absolute SUV 4 were in greater agreement with the histopathological tumour size. **Conclusion:** Auto-contouring of GTV in NSCLC with the help of optimal cut-off SUV in FDG-PET-CT will improve precision in delineation, reduce inter-observer variability and importantly will save time.

Keywords: NSCLC, SUV, auto-contouring

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-006 A PILOT, RANDOMIZED TRIAL OF DAILY LISINOPRIL VS PLACEBO TO PREVENT RADIATION-INDUCED PULMONARY DISTRESS (ALLIANCE MC1221)

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Background: We report the results of a randomized, placebo-controlled pilot study for measuring the effect of lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, on pulmonary distress in patients receiving thoracic radiotherapy (TRT) with or without chemotherapy. We aimed to evaluate the practicality for developing a larger-scale, randomized phase III study in the future. **Method:** Twenty-three (23) eligible patients receiving TRT (≥45 Gy) for predominantly non-small cell lung cancers were enrolled; an ECOG performance of 2 or better was required. The patients were randomized to receive either 20 mg of lisinopril or placebo once daily during and up to 3 months post-RT. The trial stopped early due to lower accrual than anticipated. The baseline and weekly during RT patient-reported outcome (PRO) results for Symptom Experience Questionnaire (SEQ), Lung Cancer Symptom Scale (LCSS), the EORTC for Lung Cancer Questionnaire (EORTC-QLQ-LC13), and Function Assessment of Cancer Treatment were analyzed. Adverse events (AE) were measured according to CTCAE v4.0. Our primary endpoint was safety and AE profile of lisinopril, followed by PRO comparisons; multiple comparisons for secondary analyses were not adjusted. **Result:** There were 11 and 12 eligible patients on the placebo and lisinopril arms, respectively. Mean age was 63.5 years; 13 (62%) were male. Eighteen (86%) were either former or current smokers. All baseline characteristics were balanced. All baseline PRO results were balanced except for more shortness of breath by SEQ/LCSS which were slightly worse in the placebo arm. The placebo patients reported more dyspnea on climbing stairs at baseline on EORTC-QLQ-LC13. The incidences of grade 2 hypotension were 2 vs. 4 patients for placebo and lisinopril, respectively (P=0.26). One (1) patient taking lisinopril had grade 2 acute kidney injury (P=0.20). One (1) patient developed grade 4 dyspnea on placebo arm. No patients experienced grade 5 toxicities. Patients taking lisinopril did not have more cough or allergic reaction. Acute respiratory distress as measured by worst dyspnea score was poorer in placebo vs. lisinopril patients (42.0 vs. 77.5 respectively, P=0.006). The rest of the PRO indices were with no clinically meaningful differences between arms. **Conclusion:** Although this novel trial was underpowered which was not intended, the results provided a strong signal for safety and perhaps even efficacy, by PRO, in concurrently administering lisinopril, an ACE inhibitor, for advanced lung cancer patients who require RT-based therapies. Using lisinopril for mitigating or preventing radiation-induced pulmonary distress or pneumonitis will require future trial testing. Support: UG1CA189823.

Keywords: Lisinopril, Pulmonary Distress, Randomized Clinical Trial

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-007 HISTOLOGICAL DIFFERENCE IN OUTCOMES OF DEFINITIVE CHEMORADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER

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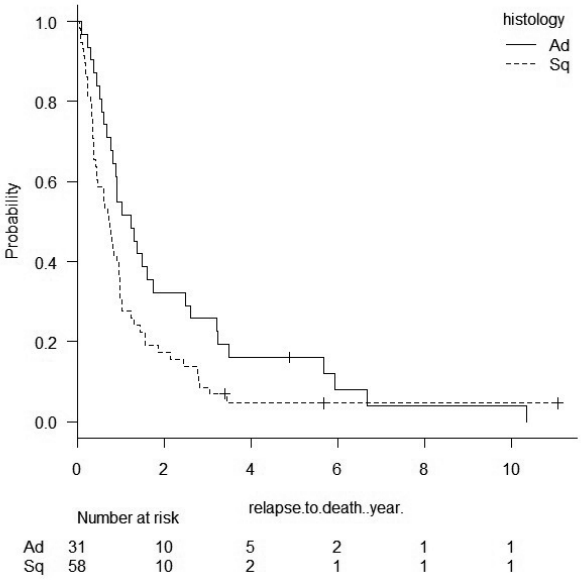
Background: Chemoradiotherapy is the standard treatment for locally advanced non-small cell lung cancer. Histological difference has not been taken into account in the chemoradiotherapy unlike in chemotherapy for metastatic disease. The purpose of this study is to evaluate the results and relapse pattern difference between squamous cell carcinoma (Sq) and adenocarcinoma (Ad) histology. **Method:** We retrospectively analyzed the outcomes and relapse pattern in patients who received definitive chemoradiotherapy for locally advanced non-small cell lung cancer in our institute between 2003 and 2012. **Result:** There were 74 Sq patients and 36 Ad patients. Sq patients had more advanced T Stage, and less female ratio. Other factors were well balanced. Median follow-up time in all patients and surviving patients were 21.3 and 79.6 month, respectively. Median survival time was not significantly different between Sq and Ad patients (P=0.61; 20.8 and 26.7 month, respectively). Relapse pattern was different between the two histologies (P=0.0149). Locoregional, distant, and simultaneous relapse of locoregional and distant sites were observed in 32 (55.2 %), 23 (39.8 %) and 3 (5.2 %) for Sq patients; and 7(22.6 %), 20(64.5 %) and 4(12.9 %) for Ad patients, respectively. The time from relapse to death in Sq patients were

shorter than Ad patients (median, 8.9 months and 14.9 months; P=0.046). Numbers of patients surviving without any relapse for 5 years or more were 9 (12.2 %) in Sq and 1 (2.8 %) in Ad.



Conclusion: More than 10% of Sq patients could achieve relapse-free survival longer than 5 years. However, in relapsed patients, prognosis was poorer in Sq patients compared to Ad patients. Dominant pattern of relapse was locoregional in the Sq patients. More aggressive local treatment such as combination with surgery or dose escalation of radiotherapy may improve survival in Sq patients.

Keywords: chemoradiation for non-small cell lung cancer, histological difference

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-008 PARTIAL AND FULL ARC VMAT IN LUNG CANCER SBRT WITH DIFFERENT DEFINITIONS OF INTERNAL TARGET VOLUME BASED ON 4D CT

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Background: Three dimensional conformal radiation therapy (3DCRT) with 10-15 static fields is the most common technique used to create the desired conformal dose distribution for SBRT. The main drawback of 3DCRT planning is the lengthy treatment time relating to patient setup and radiation delivery resulted from many fields needed to create an acceptable treatment plan. The capability of VMAT to increase the sparing of organs at risk (OARs) without compromising conformal dose distributions in a shorter treatment time compared to IMRT and 3DCRT has been demonstrated for both conventional fractional radiotherapy and SBRT in the treatment of lung cancer. The purpose of this study is to investigate the feasibility of partial arc volumetric modulated arc therapy (VMAT) in lung cancer stereotactic body radiotherapy (SBRT), as well as the volumetric and dosimetric effects of different internal target volume (ITV) definitions with 4D CT. **Method:** Fourteen patients with primary and metastatic lung cancer underwent SBRT were enrolled in this study. Full and partial VMAT plans were generated with four different ITVs: ITVall, ITV_{MIP}, ITV_{AIP} and $ITV_{2phases}$, representing ITVs generated from all 10 respiratory phases, maximum intensity projection (MIP), average intensity projection (AIP), and 2 extreme respiratory phases. Volumetric and dosimetric differences, as well as MU and delivery time were investigated. **Result:** Full arc VMAT irradiated less dose 2 cm away from the PTV compared with partial arc VMAT (P=0.002), other than this, there was no significant difference on target coverage between partial and full arc VMAT plans. However, partial arc VMAT irradiated less MLD and V5 compared with full arc VMAT. Partial arc VMAT also achieved better protection on spinal cord, heart and esophagus compared with full arc VMAT. The average MU and delivery time of full arc VMAT plans were 240 and 1.6 min more than those of partial arc VMAT. No other significant difference was observed between these two planning schemes. There were no significant differences on target coverage and organ at risks (OARs) sparing among four ITVs. The average percent volume differences of ITV_{MIP}, ITV_{AIP} and $ITV_{2phases}$ to ITV_{all} were 8.6%, 13.4%, and 25.2%, respectively. **Conclusion:** Partial arc VMAT was feasible and more efficient for lung SBRT. Although ITV_{MIP}, ITV_{AIP} and $ITV_{2phases}$ were smaller than ITVall, no significant dosimetric differences resulted due to a relative small target volume of lung SBRT.

Keywords: volumetric modulated arc therapy, internal target volume, stereotactic body radiotherapy

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-009 ASSESSING THE VALUE OF RADIOTHERAPY FOR LUNG CANCER IN THE INTENSIVE CARE UNIT – A POPULATION-BASED ANALYSIS

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Background: As the use of radiotherapy (RT) in lung cancer patients in the ICU is poorly described; we evaluated characteristics, outcomes, RT utilization and costs in a population-based cohort of ICU lung cancer patients in Ontario, Canada. **Method:** Eligible patients between April 1, 2007 and March 31, 2014 were identified through provincial administrative healthcare databases. Given that a patient could receive multiple RT deliveries, each ICU stay was analyzed separately as an episode of care. Significant differences in patient, treatment, institution and tumor characteristics between RT and non-RT groups were compared with t-tests and chi-square tests, as appropriate. Pre-ICU disposition was by ER admission, same institution admission or different institution transfer. The Kaplan-Meier method was used to estimate overall survival (OS), measured from index ICU admission to death, censoring at the end of the observation period. Differences in OS between the RT and non-RT groups were compared using the log-rank test. Univariable and multivariable Cox proportional hazard modeling were performed to assess the effect of RT on OS. Daily costs were calculated in 2015 Canadian dollars (converted using consumer price indices) for RT patients only, based on acute hospitalizations, ER visits, cancer clinic visits, same-day surgeries, and physician billings. For all analyses, a p-value threshold of <0.05 was used to define statistical significance. **Result:** In 13,739 unique lung cancer ICU patients, RT was delivered in 133 episodes to 1.0% (n=131) of patients. The RT group tended to be younger (median age 65 vs. 68, p<0.001), on some form of ventilation (79.8% vs. 38.2%, p<0.001) and with longer ventilation durations ((median [IQR]) 6 [1-11] vs. 0 [0-2] days, p<0.001). RT patients were more likely to present from the ER (28.2% vs. 21.9%, p=0.002) or via transfer (35.3% vs. 9.7%, p<0.001). While ICU discharge was common in both RT (56.4%) and non-RT (71.4%) cohorts, 1-year OS was poor with both groups, but most notably in the RT group (11.3% vs. 42.4%). RT was associated with inferior 1-year OS on unadjusted modeling (HR=1.99, 95% CI:1.65-2.38, p<0.001), with ventilation status and pre-ICU disposition adjusting this finding towards the null on multivariable modeling (HR=1.17, 95% CI:0.97-1.40, p=0.095). The median daily cost of medical care in RT patients was $2771 (IQR $1757-$3753), with acute hospitalization accounting for more than half (median $1723) of calculated costs. **Conclusion:** The use of RT needs to be considered judiciously for lung cancer patients in the ICU, given the poor prognosis and increased costs incurred.

Keywords: ICU, Radiotherapy, palliative care

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-010 THE TIME-WEIGHTED MID-VENTILATION TECHNIQUE: REDUCING PLANNING TARGET VOLUMES FOR PATIENTS UNDERGOING LUNG STEREOTACTIC BODY RADIOTHERAPY.

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Background: Stereotactic Body Radio Therapy (SBRT) is a curative treatment option for patients diagnosed with primary lung cancer, who are deemed unsuitable for surgical resection. Currently, the most commonly used contouring method utilises 4D-CT delineated Internal Target Volumes (ITVs). This takes into account the tumour positions throughout all phases of the respiratory cycle but can result in unnecessarily large Planning Target Volumes (PTVs). The time-weighted mid-ventilation (TWMV) method is an alternative contouring method in which the gross tumour volume (GTV) is contoured on a single 3D-CT structure from the 4D dataset at the phase closest to its time-weighted average position. We hypothesise that the TWMV method will result in significantly smaller PTV and treated lung volumes when compared with the ITV method **Method:** 5 consecutive lung SBRT patients who participated in a Phase 2 Clinical Trial were contoured with the ITV method using Velocity Advanced Imaging software (v.3.2.0). The PTVs and irradiated lung volumes were recorded. The GTVs were then re-contoured both manually on each phase of the 4D-CT and automatically using deformable image registration (DIR). The time-weighted average tumour position was determined and PTV volumes generated from the phase closest to this position using patient-specific margins described by Wolthaus et al. Finally, PTVs and treated lung volumes were recorded and compared with those from the ITV plans. **Result:** There was close agreement in both manual and automatic contouring methodologies for the time-weighted average position, with a three-dimensional vector error between the GTV centroids of 1.6mm ± 0.8 mm (1 SD). The manual contouring methods resulted in the same phase from the 4DCT being used for the mid-ventilation approach for all 5 patients. Using the mid-ventilation approach, the PTV volumes decreased by an average of 24.5% (range 19.8% - 33.7%), corresponding to an average decrease in irradiated healthy lung of 17.1cc ± 6.5cc. The decrease in PTV volume was greater for patients with a larger cranio-caudal tumour motion, with a linear relationship found between the two (R^2 = 0.995). **Conclusion:** For patients undergoing lung SBRT, contouring using the TWMV method resulted in a

significant decrease in both PTVs and irradiated lung volumes compared with the ITV method. DIR for implementation of the mid-ventilation technique was feasible and reproducible. Application of this technique may improve the therapeutic ratio, and enable dose escalation for treatment of patients with unfavourable lung function to reduce lung toxicities.

Keywords: SBRT, time weighted mid-ventilation, Radiotherapy planning

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-011 RECOMBINANT HUMAN ENDOSTATIN (ENDOSTAR) COMBINED WITH CONCURRENT INTENSITY MODULATED RADIATION THERAPY FOR ELDERLY LOCAL ADVANCED NSCLC

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Background: Recombinant human endostatin (Endostar) is an angiogentic medicine with mild toxicity and strong efficacy in systematic treatment of NSCLC. Recently, several studies proved that Endostar combined with radiotherapy could enhance NSCLC treatment efficiency according to mechanism of microenvironment normalization. However, this combination therapy has not tested in elderly population up to now. In this trial, we observed the efficacy and safety of Endostar combined with concurrent intensity modulated radiation therapy (IMRT) for inoperable elderly local advanced NSCLC. **Method:** This trial was perspective, open-labeled study. A total of 40 inoperable elderly local advanced NSCLC were randomly assigned into two arms. Twenty patients received IMRT alone in control arm, the dosage of primary tumor and mediastinal lymph node metastasis was DT 60 66 G/30 33/6- 7w. Intravenous infusion of Endostar concurrently inducted with IMRT in experimental arm. Endostar is administrated in 15mg once daily for two weeks followed by one week interval, repeated twice. The efficacy was evaluated according to RECIST 1.1 criteria and recorded ORR, DCR, mDFS and mOS. Safety and efficacy evaluation were performed based on NCI CTC v4.0 criteria. **Result:** In the experimental arm, 15 cases were PR and 5 cases were SD. Although a superiority of patient number showed comparing to the control group, there is no statistical difference between two arms either ORR (75.0% vs. 80.0%, p=0.326) or DCR (100% vs. 90.0%, p = 0.031). The mDFS (9.4M vs. 6.8M, p=0.286) and mOS (17.5M vs. 14.1M, p=0.052) in the two groups were not significantly different. One year survival rate were 79.4% vs 61.1%, and 2 year survival rate was 9.0% vs 0% in experimental arm and control arm, respectively. In the experimental arm, risk of disease progression decreased by 35% by using Endostar plus IMRT, HR = 0.649 (95% CI, 0.288 to 1.464), meanwhile the risk of death decreased by 66%, HR = 0.435 (95% CI, 0.184 to 1.030) . Most toxicities occured in two arms were grade 1/2, there is no grade 3/4 adverse events occured. In contrast to the control arm, no difference in safety events was found in the Endostar plus IMRT group. **Conclusion:** Endostar combined with concurrent IMRT for inoperable elderly local advanced NSCLC had a good safety and activity profile. One and two year survival rates were all increased, with a tendency of prolonging median survival time. Therefore the conclusion is worth to further confirmed in similar clinical study but with larger sample size.

Keywords: Endostar, IMRT, elderly NSCLC

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-012 CLINICAL OUTCOMES OF THE LARGEST UK COHORT OF CYBERKNIFE-DELIVERED STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR) FOR PRIMARY LUNG CANCERS

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Background: SABR is a definitive treatment option in patients diagnosed with an early stage lung cancer. It is a suitable alternative for patients of poor performance status who may be medically inoperable. The Cyberknife (CK) machine delivers high dose, hypofractionated regimes using extensive non-coplanar beams of radiation. This enables lesions to be treated with radiobiologically higher doses, maximising local tumour control. University Hospital Birmingham has delivered the most CK-based lung SABR for any stage lung cancer in the UK. Limited data exists for outcomes following CK treated lung cancers. At our institute we reviewed a cohort of patients with early stage lung cancer treated with CK over a 30 month period looking at overall survival and local control rates to ensure this was comparable to accepted SABR outcome statistics. **Method:** A retrospective analysis was performed on 88 patients with primary lung cancer treated with CK from June 2014 to December 2016. **Result:** From the 88 patients reviewed, 1 was excluded due to lack of follow-up data. Demographic data is presented in table 1. Median follow-up was 14 months (range 0.5 to 36). Local control (LC) was achieved in 93% of patients. The median progression free survival (PFS) interval was 15 months. Overall survival (OS) at 1 year was 90% and at 3 years 72%. The median overall survival was 14 months (range 0.5 to 36). During follow-up, 14 patients progressed. However, only 6 of these progressed within the treated lesion. There were no treatment-related deaths, nor grade 3 or 4 adverse toxicities documented. Table 1 Demographics

SEX	Male 52 (59%) Female 36 (41%)
AGE	Mean: 72 Years Range : 55- 87
ECOG PERFORMANCE STATUS	1 : 21 2: 33 3: 2 Not available: 32
TNM STAGING	T1aN0M0 : 4 T1bN0M0 : 32 T2aN0M0 : 46 T2bN0M0 : 6
HISTOLOGY	Adenocarcinoma : 8 Squamous: 9 NSCLC not differentiated: 2 Radiological diagnosis: 69
DOSE FRACTIONATION	50Gy/ 5# : 2 51Gy/ 3# : 1 54Gy/ 3# : 15 54Gy/ 5# : 1 55Gy/ 5# : 58 60Gy/ 8# : 11

Conclusion: These results have proven Cyberknife radiotherapy to be a safe and effective treatment for acquiring local disease control in early lung cancers. LC rates are in line with previously published outcomes for lung SABR. OS appears better at 3 years, but this does warrant further follow up.

Keywords: SABR, CyberKnife, lung cancer

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-013 EFFECT OF STEREOTACTIC RADIOTHERAPY (SABR) ON PULMONARY FUNCTION AND QUALITY OF LIFE: RESULTS FROM A TERTIARY ONCOLOGY UNIT

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Background: Surgical resection is generally accepted as the gold standard for managing early stage lung cancer. There remains, however, a subset of patients who do not proceed to surgery. Many of these patients are 'medically inoperable' due to comorbidities. Others may decline surgery or their tumour is deemed inoperable due to technical difficulties. In this subset, SABR has been shown to be an effective alternative treatment option. SABR involves multiple beams, which together deliver an ablative dose of radiation to a precise area. There is rapid dose fall-off which ensures sparing of nearby structures. Evidence suggests that SABR is not associated with a clinically relevant deterioration in quality of life (QoL). The negative impact on pulmonary function is also minimal. This audit aims to assess the effect of SABR on both pulmonary function and QoL of a cohort of patients undergoing treatment in the West Midlands. **Method:** The Queen Elizabeth Hospital, Birmingham delivers SABR to patients across the West Midlands. We followed a cohort of 45 patients who received SABR between September 2016 and April 2017 for early stage lung cancer. If patients had baseline PFTs, these were repeated between 3-13 weeks post treatment. Patients had their QoL assessed using the EORTC Quality of Life Questionnaire (QLQ-C30 version 3). This was recorded at baseline, early and late follow up (defined as 13-28 days and 30-75 days post treatment respectively). **Result:** To date, twenty patients have had baseline FEV1 and FVC which was repeated post treatment. Median baseline FEV1 was 1.52 (range 0.56-2.92) and median baseline FVC was 2.63 (range 1.25-4.89). Post treatment median FEV1 was 1.34 (range 0.60-2.61) and median FVC was 2.42 (range 1.40- 3.95). Using a Wilcoxon Signed Ranks test, there was no significant difference between pre and post treatment FEV1 or FVC (Z=-0.78,p=0.43 and Z=-1.0,p=0.31 respectively). Similarly, there was no difference in DLCO pre and post treatment (Z= -0.27,p=0.79) Thirty nine patients had their baseline QoL assessed. Of these, 36 had this repeated at early follow-up and 31 at late follow up. Median QoL score at baseline, early and late follow up was 66/100, 54/100 and 50/100 respectively. There was no significant difference in either early or late QoL compared to baseline (Z=-0.49,p=0.63 and Z=-0.15,p=0.88). **Conclusion:** Overall this study shows no significant difference in either PFTs or QoL in this cohort of patients undergoing SABR in Birmingham. These results compare favourably with other published data and are reassuring for our practice

Keywords: quality of life, Pulmonary Function, SABR

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-014 DOES HISTOLOGICAL SUBTYPE AFFECT OUTCOMES IN STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR) FOR LUNG TUMOURS?

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Background: The majority of patients offered lung SABR have a radiological diagnosis of primary lung cancer only. This is commonly due to poor performance status, multiple co-morbidities, poor lung function or medical inoperability rendering them unsuitable for lung biopsy. Local control rates (LCR) for SABR-treated lung lesions are in the order of > 90% at 12 months. Little data exists on whether histological subtype affects this or overall survival (OS). **Method:** We retrospectively analysed local control and survival data on all patients treated for primary lung cancer with SABR (using volumetric modulated arc therapy (VMAT) technique) at our tertiary centre over a 4-year period from May 2013 until February 2017. **Result:** 153 patients in total were treated, with follow-up data available for 135 patients. Baseline demographic

data and analysis are presented in table 1. Median follow-up was 13 months (range 0.5 to 45). The LCR in treated lesions for all patients was 95.2%. Squamous cell carcinomas (SCC) had a better LCR when compared to adenocarcinomas (100% vs 92.8%). Median OS for all patients was 13 months (range 0.5 to 45). By histological subtype, SCC had better OS when compared to adenocarcinomas (15.5 months vs 12.5 months). 35.7% of adenocarcinomas progressed either within the thorax or at distant sites compared to only 12.5% of SCC. However, in 93% of adenocarcinomas and 100% of SCC the original treated lesion did not progress. Those with no histology had LCR of 95% with a median OS of 12 months respectively.

Table 1

SEX	Male – 82 (53.6%) Female – 71 (46.4%)
AGE	Mean – 73 Range – 48-92
PERFORMANCE STATUS (PS)	PS 0 – 4 (2.6%) PS 1 – 66 (43.1%) PS 2 – 60 (39.2%) PS 3 – 6 (3.9%) Not recorded – 17 (11.1%)
DISEASE T-STAGE	T1a – 100 (63.4%) T1b – 29 (18.9%) T2a – 24 (15.7%)
HISTOLOGY	Adenocarinoma – 15 (9.8%) Squamous cell – 8 (5.2%) NSCLC not specified – 2 (1.3%) Large cell – 1 (0.7%) Carcinoid – 1 (0.7%) No histology – 126 (82.3%)
DOSE/FRACTIONATION	54Gy/3 – 38 (24.9%) 55Gy/5 – 103 (67.3%) 60Gy/8 – 12 (7.8%)
MEDIAN OVERALL SURVIVAL BY HISTOLOGY	Adenocarcinoma – 12.5 months (range 3 to 38) Squamous cell – 15.5 months (range 1 to 43) NSCLC not specified – no follow-up data available Large cell – 18 months (1 patient only) Carcinoid – 14 months (1 patient only) No histology – 12 months (range 0.5 to 45)
LOCAL CONTROL RATE BY HISTOLOGY	Adenocarcinoma – 92.8% Squamous cell – 100% NSCLC not specified – no follow-up data available Large cell – 100% Carcinoid – 100% No histology – 95.0%

Conclusion: Our data suggests a trend towards slightly better OS and LCR with SCC over adenocarcinomas. More adenocarcinomas progressed both locally and at distant sites than SCC did. This information may be useful prognostically and it suggests adenocarcinomas may need closer follow-up post-SABR. Overall, our LCR is in line with published data.

Keywords: SABR, early stage lung cancer, non-small cell lung cancer

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-015 OUTCOMES FOR STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR) FOR EARLY PRIMARY LUNG CANCERS: CYBERKNIFE VERSUS VMAT PLATFORM

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Background: SABR has become a commonly used treatment for early stage lung cancers, particularly in patients not suitable for radical surgery. It provides excellent local tumour control and is well-tolerated. At our institute, we have two platforms to deliver SABR; Linac-based volumetric modulated arc therapy (VMAT) and Cyberknife (CK). Little data exists directly comparing these two in terms of local control (LC) and overall survival (OS), thus, we performed an analysis to ascertain whether one platform outperforms the other. We have conducted lung SABR using VMAT since June 2013 and CK since June 2014. **Method:** We retrospectively analysed data on all early stage primary lung cancer patients treated with lung SABR from June 2013 to February 2017. Demographic and survival data was collected. **Result:** 241 patients were treated in total, 153 using VMAT and 88 using CK. 19 patients were excluded from analysis due to lack of follow-up data (18 VMAT, 1 CK). Median follow-up for all patients was 13 months (range 0.5 to 45). Age, sex and histological breakdown were similar for the two groups. The majority in both groups were treated based on a radiological diagnosis. In terms of staging, there were more T1 tumours treated with VMAT than CK due to our local departmental policy excluding tumours less than 2cm being considered for CK. LC was 95.2% for VMAT compared to 93% for CK at median follow-up. Median OS was 13 months for VMAT compared to 14 months for CK. We saw a higher proportion of disease progression (local or distant) in the VMAT group (25.8% versus 17.0%). Lung cancer related deaths were equal in both groups (8.9% VMAT versus 8.0% CK). Neither platform had any grade 3 or higher toxicities reported. **Conclusion:** We demonstrated both treatment modalities were well tolerated by patients and produced similar LC and OS outcomes. In those where the disease progressed, within the CK group a higher proportion of them progressed within the treated lesion, whereas in the VMAT group it was at other sites (ie new lung nodules or distant metastases). This could be due to staging and the fact the CK group featured significantly more T2 tumours. Overall, both treatment modalities gave comparable outcomes to surgery when looking at LC.

Keywords: SABR, CyberKnife, early stage lung cancer

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-016 PULOMONARY RESECTION AFTER CURATIVE INTENT CHEMORADIATION FOR NSCLC

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Background: In this study, we aimed to investigate the validity and clinical outcomes of lung resection after curative intent chemoradiation for locally advanced NSCLC. **Method:** The retrospective review of the prospectively recorded data of patients with NSCLC that was treated with curative intent induction chemoradiation followed by surgery between 1996 and 2016 was carried out. The patients undergoing segmentectomy or bigger resection with lymph node dissection after chemoradiotherapy were included into study. Patients received 2-6 cycles of chemotherapy and 45-70 Gy radiotherapy and were divided into two groups; Group 1: patients who received 60 Gy radiotherapy or less; Group 2: patients who received 61 Gy radiotherapy or more. We compared the chemotherapy drugs, doses, cycles, body mass index and performance status, type of lung resection, 90-day postoperative complications, mortality and long term survival between the two groups. **Result:** One hundred and forty two patients were included into study (group 1 n=88, group 2 n=54). All but 17 patients were male with a mean age of 56.5y (31-85y). Twenty patients underwent pneumonectomy and 122 patients received lobectomy (55 patients with extended resection, chest wall resection and sleeve etc). Complete pathological response was observed in 44(31%) patients (group 1= 29.5% (26/88), group 2= 33.3% (18/54), p=0.63. Postoperative morbidity rate was 42.2% (group 1=47.7% (42/88), group 2=33.3% (18/54), p=0.09. In addition, 90-day mortality rate was 6.3% (group 1=5.6%, group 2=7.4%, p=0.68). The overall survival 5-year survival rate was 54.1% that was 61% in Group 1 and 43.6% in Group 2, respectively (p=0.14). We found no relationships between the radiotherapy dose and the complete response rate, mortality, morbidity and survival. **Conclusion:** These findings reveal that lobectomy or pneumonectomy can be safely performed following high-dose chemoradiotherapy without affecting surgical outcomes. However, the positive or negative effect of high-dose radiotherapy on complete response and survival has not been proven.

Keywords: induction chemoradiation therapy, Surgery, Radiotherapy

P2.14: RADIOTHERAPY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.14-017 POSTOPERATIVE RADIOTHERAPY IN COMPLETELY RESECTED STAGE IIIA-N2 NON-SMALL CELL LUNG CANCER

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Background: Use of postoperative radiotherapy (PORT) in completely resected (R0) pathologic stage IIIA-N2 non-small cell lung cancer (NSCLC) remains controversial. To assess the impact of PORT, we analyzed on the patterns of failure and survival difference in these patients. **Method:** Consecutive 50 patients with pathologic stage IIIA-N2 NSCLC who underwent surgery with complete resection (R0) between Apr. 2004 and Dec. 2013 were retrospectively reviewed. Thirty-five(70%) patients were male and median age was 63 years (range, 35 - 82 years). Thirty-nine(78%) patients underwent lobectomy, 7(14%) bilobectomy, and 4(8%) pneumonectomy. Postoperative adjuvant therapy consisted of chemotherapy (ChT) alone in 26(52%) patients, ChT + PORT in 10(20%), PORT alone in 4(8%), and none in 10(20%). Radiation dose was ranged from 34 to 60 Gy with the median 55 Gy. Follow-up period was ranged from 4 to 132 months with median 42 months. Survival was calculated from the date of surgery. Kaplan-Meier method was used for survival calculation and their comparison was done using log-rank test. **Result:** The 3 and 5-year overall survival (OS) rate of all 50 patients was 70% and 58%, respectively and the median survival time was not yet reached. Both univariate and multivariate analysis showed age (> 70 yrs old) and ratio of node positive (LNR > 17%) were correlated with the poor OS. The locoregional recurrence was appeared in 19(38%) patients and distant metastasis in 27(54%). The median time to recurrence was 16 months (range, 1 - 87 months) in locoregional failure and that of distant metastasis was 20 months (range, 6 - 60 months). Lymphovascular space invasion (LVSI) was the only statistically significant factor correlating to the locoregional recurrence-free survival (LRFS) both in univariate and multivariate analysis. PORT did not improve both OS and LRFS. Three and 5-years OS in patients with PORT were 56% and 40%, in a while 76% and 68% in patients without PORT (P=0.166), respectively. Three and 5-years LRFS in patients with or without PORT was 80% and 80% versus 54% and 50% (P=0.105), respectively. We could find that the LNR over 17% (p=0.003), tumor extension (p=0.006), and LVSI (p=0.01) were more prevalent in patients group with PORT. **Conclusion:** In this analysis, the most important prognostic factor in the pathologic stage IIIA-N2 (R0) NSCLC patients was the age and positive lymph node ratio. Risk of locoregional recurrence was decreased with the use of PORT. However, this benefit was not leaded to the overall survival benefit.

P2.14-018 TREATMENT OUTCOME AND LUNG TOXICITIES OF VOLUMETRIC MODULATED ARC THERAPY IN THE TREATMENT OF INOPERABLE NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: Volumetric-modulated arc therapy (VMAT) has demonstrated the ability to deliver radiation dose precisely and accurately with a shorter delivery time and less MU compared to conventional intensity-modulated fixed-field treatment (IMRT) in the treatment of inoperable non–small-cell lung cancer (NSCLC). However, published data on clinical outcome and lung toxicities of VMAT in the treatment of NSCLC are scarce. The purpose of the present retrospective cohort study was to evaluate clinical outcome, acute and late pulmonary toxicities using VMAT (sequential/concurrent chemo) radiotherapy in inoperable NSCLC. **Method:** The clinical outcome, acute and late pulmonary toxicities of 134 consecutive inoperable NSCLC patients treated by VMAT with or without concurrent chemotherapy were retrospectively reviewed. Univariate and multivariate analysis on the dosimetric and characteristic factors associated with acute radiation pnuemonitis (RP) and pulmonary fibrosis were evaluated. **Result:** The average prescriptions dose to these patients were 5736.38±649.11 cGy (range from 5200 to 6400 cGy) with a median follow-up of 18.6 months (range, 2–45 months) for the enrolled 134 patients. The two-year progression-free survival (PFS) and overall survival (OS) for all patients was 18.2% and 38.4% with a median PFS and OS of 7.6 months and 18.6 months, respectively. There were 14 and 12 out of 134 patients experienced grade III/higher RP (10.45%) and pulmonary fibrosis (8.95%), respectively. Age, chemotherapy exposure, dose prescription, V10, V13, V20 and V30 were significantly associated with acute RP. Dose prescription was related to pulmonary fibrosis. Only V13 (p=0.02) and age (p=0.02) were independently associated with acute RP according to multivariate analysis. Based on regression analysis, the threshold for lung dosimetric metrics V10,V13,V20 andV30 were 50%,40%,28% and 18% in VMAT treatment of NSCLC to limit the RP rate <10%. **Conclusion:** VMAT can be delivered safely with acceptable acute and late toxicities for NSCLC. Lung dosimetric metrics were valuable in predicting acute RP. A threshold of 40% of Lung V13 in VMAT treatment of NSCLC was helpful to limit the RP rate <10%.

Keywords: non–Small-Cell Lung Cancer, Volumetric-modulated arc therapy, radiation pnuemonitis

P2.14-019 MAGNETIC RESONANCE (MR)-GUIDED ADAPTIVE STEREOTACTIC ABLATIVE RADIOTHERAPY FOR ADRENAL METASTASES

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Background: Stereotactic ablative radiotherapy (SABR) can result in high local control rates for adrenal metastases when biological doses of at least 100 Gy_{BED10} are delivered [Chance WW, 2017]. SABR is technically challenging due to respiration-induced displacements of the adrenals and adjacent organs at risk (OAR), both of which are poorly visualised using imaging techniques currently available at linear accelerators. MR imaging enables superior anatomical imaging of both the adrenals and OAR's. We implemented stereotactic MR-guided adaptive radiotherapy (SMART) using daily on-table re-optimization of pretreatment SABR plans using the anatomy-of-the-day. We studied the impact such daily plan re-optimization for adrenal metastases. **Method:** Since mid-2016, 13 patients with adrenal metastases from lung cancer have undergone video-assisted, respiratory-gated SMART delivery on the MRIdian system (ViewRay Inc.). This entails using visual feedback involving projection of both target volume and safety margins onto a monitor visible to patients. The radiotherapy system automatically shuts-off delivery when the target is outside pre-specified safety margins (3mm). The commonest fractionation scheme delivered was 5-fractions of 10 Gy (in 9 patients). Prior to each fraction, a 17-second MR scan in shallow breath-hold was performed with patient in treatment position, in which the GTV was rigidly registered to that on the baseline MR scan. Setup was performed on the gross tumor volume (GTV), and contour deformation was used to automatically generate OAR's according to the anatomy-of-the-day. Baseline SABR plans were recalculated on the anatomy-of-the-day (defined as 'predicted plans'), before being routinely re-optimized. **Result:** The median planning target volume (PTV = GTV + 3mm) was 35.1 cc (range 6.5 – 69.8 cc). Online plan adaptation improved PTV coverage in 78% of all fractions. Re-optimized plans exhibited significantly better sparing of OAR and achieved a reduction in volumes of stomach, bowel and duodenum receiving 33Gy, with respect to predicted plans. All patients completed the planned treatments using repeated breath-holds. The total on-table duration was approximately 50 minutes for each fraction. **Conclusion:** Breath-hold SABR delivery under MR-guidance is advantageous for adrenal tumors. Substantial variations in OAR's positions were observed at imaging prior to delivery of each fraction, leading to improved target coverage and OAR sparing when on-table plan re-optimization was performed.

Keywords: stereotactic radiotherapy, adrenal metastases, adaptive radiotherapy

P2.14-020 CLINICAL VALIDATION OF NTCP-MODELS FOR ESOPHAGUS TOXICITY IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH CONCURRENT CHEMORADIATION

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Background: Concurrent chemoradiation (CCRT) is the preferred treatment approach in inoperable non-small cell lung cancer (NSCLC) patients. However, CCRT increases the risk of acute esophagus toxicity (AET) compared to radiotherapy alone or sequential chemoradiation. To minimize the risk of AET, an international RT-dose constraint of either V50Gy or V60Gy <50% is used. However, clinical applicability of those models is not evident since assessment of the model accuracy and validity should be performed before generalizing to other populations. Therefore, the aim of this study was to clinically validate the two NTCP-models to predict acute esophagus toxicity in NSCLC patients treated with CCRT. **Method:** To validate the NTCP-models, clinical data of 274 inoperable NSCLC patients receiving CCRT using IMRT was used. The planned V50Gy and V60Gy and the prospectively scored grade ≥2 AET (CTC-AE) were retrieved and independently reviewed. The grade ≥2 AET probability for the V50Gy and V60Gy was calculated as; $[1/1+^{exp[-0.515 + (0.027*V50]}]$ and $[1/1+^{exp[-0.701 + (0.029*V60]}]]$. Validity of the model was assessed with the ability to predict the number of grade ≥2 AET events (calibration) and the ability to distinguish between those who develop grade ≥2 AET from those who do not (discrimination, area under the curve (AUC)). Furthermore, sensitivity and specificity for different cut-off points were determined. **Result:** From the 274 NSCLC patients, 125 (45.6%) patients developed grade ≥2 AET (93.8% grade 2, 6.2% grade 3), median V50Gy 23% (interquartile range 10.1-35.6%), median V60Gy 4.3% (interquartile range 0-20.5%). Calibration showed that the V50 overestimated the risk of developing grade ≥2 AET in low-risk patients while the V60 underestimated the risk of developing grade ≥2 AET in high-risk patients. Discrimination of both algorithms demonstrated a similar moderate fit (AUC 0.70 95%CI 0.64 to 0.76 and AUC 0.69 95%CI 0.63 to 0.76 for the V50Gy and V60Gy, respectively). For V50Gy, a cut-off point of more than 40% probability of developing grade ≥2 AET resulted in the most favorable sensitivity of 95.8% for grade ≥2 and 100% for grade 3, with specificity scores of 54.6% and 40.7% respectively. For V60Gy, a cut-off point of more than 60% resulted in the most favorable sensitivity of 95.1% for grade ≥2 and 100% for grade 3, with remarkably low specificity scores of 9.1% and 18.8%, respectively. **Conclusion:** The NTCP-models to predict acute esophagus toxicity in NSCLC patients both showed good predictive accuracy. For clinical practice, the V50Gy seems to be the most sensitive without compromising safety and efficacy.

Keywords: acute esophagus toxicity, epidemiology, Concurrent Chemoradiation

P2.15-001 NHWD-870, A NOVEL BET FAMILY BROMODOMAIN INHIBITOR TARGETING BRD2/3/4, PROVED TO BE EFFECTIVE AND PROMISING FOR TREATMENT OF SMALL CELL LUNG CANCER

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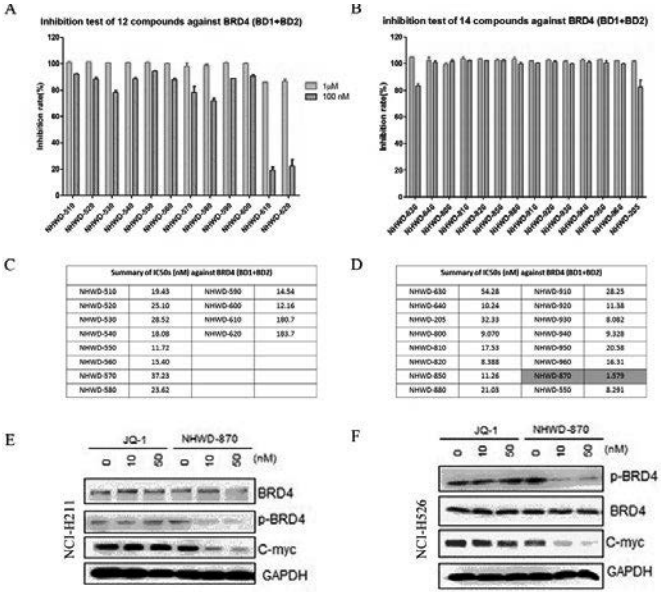
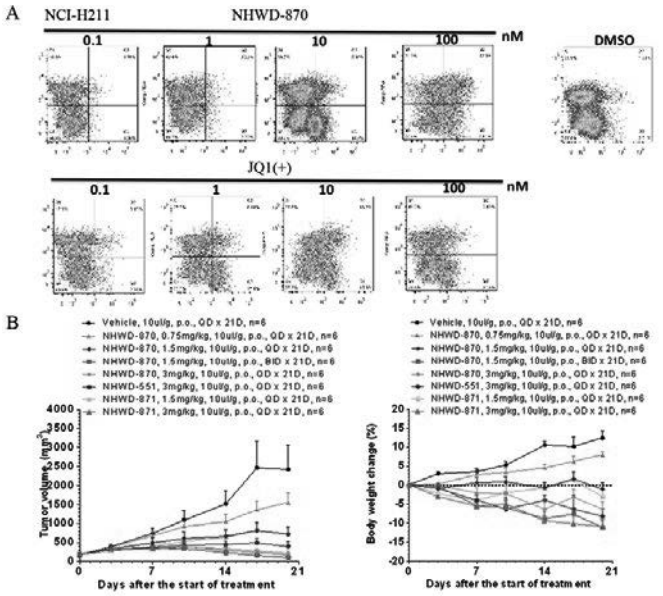
Background: Small molecule inhibitors targeting bromodomain and extraterminal domain (BET) protein is promising for cancer therapy. According to our previous study, BRD4 was highly expressed in small cell lung cancer (72%) and correlated with poor prognosis. **Method:** Series small molecular compound NHWD which design and modify by ourselves is a potent and selective BET family bromodomain inhibitor and only binds bromodomains of BRD2/3/4/T. We use the MTT in small cell lines to evaluate the activity and selected the best. And then potential pathway was demonstrated with Western blot and low cytometry. Finally, the activity of small compounds was conducted by xenograft and Patient Derived Xenograft (PDX). **Result:** Compare with JQ1 and other molecular compounds, NHWD-870 has the best effectiveness and powerful anti-cancer, and the IC50 was 1.579nM (figure 1). NHWD-870 exhibited robust single agent activity in cell viability assay across cell lines in vitro and xenografts of small cell lung cancer in vitro by downregulating the PDGFRβ, MEK1/2 and STAT1/MYC pathway (figure 1). Consistent with its broad spectrum of activities in invo, NHWD-870 has potent tumor suppressive efficacies in PDX model of small cell lung cancer (figure 2).





Conclusion: Further research will be conducted about series small molecular compounds from bench to beside.

Keywords: small cell lung caner, MEK1/2 signaling pathway, BET family bromodomain inhibitor

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P2.15-002 PULMONARY LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC): AN EXPERIENCE FROM EASTERN INDIAN HOSPITAL

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Background: Neuroendocrine tumors of lung are classified into four histological types (WHO-2015): typical carcinoid, atypical carcinoid, small-cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC). The Pulmonary LCNEC is considered as an orphan disease due to its low incidence. Our aim was to evaluate the clinical presentation and outcome of standard chemotherapy for LCNEC. All India Institute of Medical Sciences, Bhubaneswar, is an institute of national importnace situated in eastern India. No case of LCNEC has been reported from this part of India till date. **Method:** We retrospectively analysed data of patients from June 2014 June to May 2017 with special focus on pulmonary neuroendocrine tumors. We examined incidence of different histological types of pulmonary neuroendocrine tumors. We also analysed clinical characteristics of patients with pulmonary LCNEC and their treatment outcomes. **Result:** In this new Institution 263 Lung Cancer patients were diagnosed by bronchoscopic and transthoracic biopsies. There were 26 (10%) patients with pulmonary neuroendocrine tumors(NEC). Seven(2.7%) of them were LCNEC, 3(1%) carcinoid and 17 (7%) were SCLC. Median age of pulmonary LCNEC was 60 years with M:F ratio 5:2. Four of them were smokers. Median performance status (ECOG) was 2.5. Three patients presented with superior vena cava obstruction and 5 patients had central mass lesions. All the elligible patients with LCNEC were offered chemotherapy with Cisplatin 60 mg/m^2 IV on day-1 plus etoposide 120 mg/m^2 IV on days 1 to 3 in every 21days for initial 4 cycles as a standard treatment in addition to other supportive care. Two patients could not complete initial 4 cycles of chemotherapy due to progression of the diseases and drug intolerance. Four (57%) of the patients had partial response in initial chemotherapy and subsequent progression of disease. Two patients were offered Topotecan as second line chemotherapy but no significant response was observed. Overall survival of patients of LCNEC was 7 months (4-11). **Conclusion:** Incidence of pulmonary LCNEC is low but is increasingly encountered. Most of the patients were diagnosed at advanced stages. Overall survival was poor despite chemotherapy. There is no definite second line regimen recommended for LCNEC. There is a need for clinical trial with alternative modalities including targeted and immunological treatment for these types of lung cancer.

Keywords: Neuroendocrine tumor, LCNEC, Pulmonary Neuroendocrine tumor

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P2.15-003 A LONG NON-CODING RNA HOTTIP EXPRESSION IS ASSOCIATED WITH DISEASE PROGRESSION AND PREDICTS OUTCOME IN SMALL CELL LUNG CANCER PATIENTS

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Background: Small cell lung cancer (SCLC), which accounts for approximately 15% of lung cancer, is one of the most malignant diseases world-wide, with a high mortality. Despite progress in treatment of small cell lung cancer (SCLC), the biology of the tumor still remains poorly understood. Recently, we globally investigated the contributions of lncRNA in SCLC with a special focus on sponge regulatory network. Here we report lncRNA HOTTIP, which is specifically amplified in SCLC, is associated with SCLC proliferation and poor prognosis of patients. **Method:** RT-qPCR was used to investigate the expression of HOTTIP in SCLC tissues and cell lines. The role of HOTTIP in SCLC cell proliferation was demonstrated by CCK8 assay, colony formation assay, flow cytometry analysis and in vivo models of transplant tumor in mice through HOTTIP loss- and gain-of function effects. Western blot assay was used to evaluated gene expression in cell lines at protein level. RNA pull-down, Mass spectrometry and RNA binding protein immunoprecipitation (RIP) were performed to confirm the molecular mechanism of HOTTIP involved in SCLC progression. **Result:** We found that HOTTIP was overexpressed in SCLC tissues, and its expression was correlated with the clinical stage and the shorter survival time of SCLC patients. Moreover, HOTTIP knockdown could impair cell proliferation, affect the cell cycle and inhibit tumor growth of mice, while HOTTIP overexpression might enhance cell proliferation and cell cycle *in vitro* and *in vivo*. Mechanistic investigations showed that HOTTIP functions as an oncogene in SCLC progression by sponging miR-574-5p and affecting the expression of several protein-coding cancer driver genes, such as polycomb group protein EZH1 and EZH2. By in-depth study of mechanism, we identified Ago2 as an RNA-binding protein that binds to HOTTIP, which confirmed miRNAs interact with HOTTIP by the RNA-induced silencing complex (RISC). **Conclusion:** Our findings not only illuminate how HOTTIP confers an oncogenic function in SCLC pathogenesis, but also underscore a novel gene expression governing hallmarks in the disease.

Keywords: Predicting factor, small cell lung cancer, HOTTIP

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P2.15-004 UNDERREPRESENTATION OF ELDERLY PATIENTS WITH ED-SCLC AS CLINICAL TRIAL CANDIDATES (JCOG1201/TORG1528)

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Background: Since December 2013, we initiated a phase II/III trial [Japan Clinical Oncology Group (JCOG) 1201/Thoracic Oncology Research Group (TORG) 1528: UMIN000012605] for elderly patients with extensive-disease small-cell lung cancer (ED-SCLC). Aim of the study is to demonstrate that a carboplatin plus irinotecan regimen is superior to carboplatin plus etoposide in elderly patients with ED-SCLC. However, the patient accrual rate did not satisfactorily match our expectations a year from the time of initiation of our study. To define factors related to low accrual, we searched institutional records and analyzed. **Method:** We collected data of elderly

patients with ED-SCLC from each institution and investigated the total number of elderly patients with ED-SCLC, number of patients eligible/ineligible for the study, numbers of patients registered for the study, and the reasons for non-registration of even eligible patients. Doctor-reported questionnaires concerning elderly (≥71 years old) ED-SCLC patients diagnosed in their institutions were sent to chief or coordinate doctors at each institution in December 2014. **Result:** We received a response from 32 (84%) of 38 institutions. Approximately 260 patients were diagnosed as elderly patients with ED-SCLC in the last year. Only 100 patients (38%) were eligible for the JCOG 1201/TORG1528 trial. Reasons for ineligibility primarily included poor performance status (PS) (25%), low organ functions (25%), interstitial pneumonitis (19%) and double cancer (18%). Only 23 patients among the 100 eligible candidates accrued to the study. The primary reasons for non-accrual were delayed approval from the Institutional Review Board (IRB) of the individual institution (24%), physician preferences (23%), patient refusal (18%), and registration for other trials (12%). **Conclusion:** Our data demonstrated that 62% of ED-SCLC patients were ineligible for the protocol due to frailty with the most frequent reason being comorbidities such as poor PS and low organ functions. However, inactive institutions need to increase their efforts to register a greater number of eligible patients in addition to obtaining quicker IRB approval of protocol. Based on responses to questionnaires sent out as part of our investigation, in January 2016, the protocol was revised in terms of eligibility criteria to enhance patient accrual. Eligibility criteria for participation of elderly patients with ED-SCLC need to be formulated prudently so that patients are benefitted in routine clinical practice.

Keywords: irinotecan, elderly, ED-SCLC

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P2.15-005 POST-PROGRESSION SURVIVAL IS STRONGLY LINKED TO OVERALL SURVIVAL IN REFRACTORY SMALL-CELL LUNG CANCER PATIENTS WHO RECEIVED AMRUBICIN

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Background: The benefits of second-line chemotherapy on the overall survival (OS) of small-cell lung cancer (SCLC) patients might be confounded by subsequent therapies. In this study, we aimed to determine the influence of progression-free survival (PFS) and of post-progression survival (PPS) on OS after second-line chemotherapy in patients with refractory SCLC treated with amrubicin monotherapy. **Method:** We analyzed the data of 35 patients with refractory SCLC who were treated with amrubicin monotherapy as second-line chemotherapy between July 2005 and December 2015. The correlations of PFS and PPS with OS were statistically analyzed at the individual level using Spearman rank correlation and linear regression analyses. **Result:** The correlation between PPS and OS was strong ($r = 0.88, p < 0.05, R^2 = 0.87$), while that between PFS and OS was weak ($r = 0.60, p < 0.05, R^2 = 0.15$). The number of regimens administered after disease progression post-second-line chemotherapy was significantly associated with PPS ($p = 0.003$). **Conclusion:** OS is more strongly linked to PPS than to PFS in refractory SCLC patients who undergo amrubicin monotherapy as a second-line treatment. Moreover, receiving additional regimens after second-line treatment is a significant independent prognostic factor for PPS. Taken together, our results indicate that additional treatments administered after second-line chemotherapy favorably affect the OS of refractory SCLC patients treated with amrubicin monotherapy.

Keywords: small cell lung cancer, post-progression survival, second-line chemotherapy

P2.15: SCLC/NEUROENDOCRINE TUMORS -
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P2.15-006 THE EFFECTS OF PEGYLATED ARGINASE ON SMALL CELL LUNG CANCER IN VITRO AND IN VIVO

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Background: Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer cases. SCLC is characterized by frequent relapse, and current treatments lack tumor specificity. Arginase is an important enzyme in human, but it is deficient in some tumors. Arginine deprivation has become a potential therapeutic option in selected tumors. BCT-100 is a pegylated arginase which has demonstrated anticancer activity in arginine auxotrophic tumors, such as melanoma, hepatocellular carcinoma and acute myeloid leukemia. One of resistance mechanisms to arginase is overexpression of argininosuccinate synthetase (ASS1) and ornithine transcarbamylase (OTC). The aim of this study is to determine the effects of BCT-100 on SCLC *in vitro* and *in vivo*. **Method:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to detect cell viability of different SCLC cell lines after BCT-100 treatment. Western blotting was employed to evaluate the protein expression. Knockdown of OTC was performed using specific siRNA. Xenograft models were established in nude mice for testing the anticancer effect of BCT-100. **Result:** The IC_{50} values of BCT-100 in H69, DMS79, H187, H209, H446, H510A, H526, H841 and SW1271 cells were 462.9±112.2, >1000, 24.9±6.4, 8.6±0.8, 18.0±0.7, 18.2±4.0, 10.1±0.7, >1000 and 49.2±7.4 mU/mL respectively. Knockdown of OTC increased sensitivity to BCT-100 in H841 cells, partially mediated via apoptosis. Mitochondrial membrane depolarization was observed in BCT-100 treatment and cytochrome c and SMAC were released from mitochondria to cytosol. N-acetylcysteine (NAC), the reactive oxygen species (ROS) scavenger, could reverse the apoptosis induced by BCT-100 significantly. Besides, cell cycle specific proteins, cyclin A2, cyclin B1 and CDK4, were downregulated in a time-dependent manner. The tumor growth was inhibited and median survival of mice was prolonged in BCT-100 group in H446 and H510A xenograft models. Serum and intratumoral arginine level was sharply decreased, associated with G1 arrest and apoptosis in H446 and H510A xenografts. **Conclusion:** The SCLC cell lines with low expression of ASS1 and OTC were susceptible to BCT-100 treatment. ROS was involved in BCT-100 induced-apoptosis. BCT-100 showed potential anticancer activity in SCLC xenograft models.

Keywords: pegylated arginase (BCT-100), small cell lung cancer, Xenograft models

P2.15: SCLC/NEUROENDOCRINE TUMORS -
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P2.15-007 EXTENSIVE STAGE SMALL CELL LUNG CANCER: PATTERNS OF CARE AND OUTCOMES OF A SINGLE INSTITUTION OVER 15 YEARS

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Background: Survival outcomes for extensive stage small cell lung cancer (ES-SCLC) remain poor. The standard management of ES-SCLC is chemotherapy. For those achieving a good response consolidation thoracic radiotherapy and prophylactic cranial irradiation (PCI) is considered. This retrospective audit analysed patterns of care and survival for all patients with ES-SCLC treated at Prince of Wales Hospital (POWH) over 15 years. Factors correlating with survival were also analysed. A literature review was performed to benchmark our results. **Method:** We identified 187 patients diagnosed with SCLC at Prince of Wales Hospital between 2000 and 2014 from the departmental electronic patient information system (MOSAIQ, Elekta). Eligibility criteria were: age >18 years, histopathologically confirmed diagnosis of SCLC, extensive stage according to the two-stage Veterans' Affairs Lung Study Group staging criteria, and treatment at POWH. Median progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and log-rank test (IBM SPSS version 24). **Result:** Eighty-three patients fulfilled the eligibility criteria. Median age was 70 years. 42% of patients were female and 63.9% had an Eastern Cooperative Oncology Group performance status (PS) of 0-1. Median PFS and OS were 5.0 and 8.2 months respectively, comparable with published literature. There was correlation between PS (0-1 versus ≥2) and OS (p=0.025) but not PFS (p=0.16). 79.5% of patients received initial chemotherapy, 48.5% of these patients received 6 cycles, of which 89.4% was carboplatin and etoposide. Median time from date of diagnosis to start of chemotherapy was 12 days, with correlation between time to chemotherapy and OS (p=0.006) and PFS (p=0.003). 75.9% patients received radiotherapy of any kind, but only radiotherapy directed at the thorax was associated with improved OS (p=0.01) but not PFS (p=0.5). Five (6%) patients underwent consolidation thoracic radiotherapy, while 32.5% underwent palliative thoracic radiotherapy. Palliative whole brain radiotherapy was given to 11 (13.3%) patients and only 2 patients received PCI. 78.3% of patients had documented progression after treatment, with simultaneous loco-regional and distant progression the most common pattern. 66.2% of patients had treatment at progression, with most (86%) receiving palliative radiotherapy. **Conclusion:** Our current analysis demonstrates an association between survival outcomes and baseline PS, time to initiation of chemotherapy and receipt of thoracic radiotherapy for patients with ES-SCLC. The survival outcomes are comparable to the reported literature. This highlights the importance of early referral and treatment commencement for improved outcomes in ES-SCLC.

Keywords: small cell lung cancer, patterns of care, timing of treatment

P2.15: SCLC/NEUROENDOCRINE TUMORS -
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P2.15-008 GENOMIC ANALYSIS TO ASSESS A MOLECULAR SIGNATURE IN JAPANESE PATIENTS WITH PULMONARY HIGH GRADE NEUROENDOCRINE CARCINOMA

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Background: Pulmonary neuroendocrine carcinoma, including small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), and carcinoid tumor, is a highly malignant cancer with poor prognosis. Because of its rarity, the molecular

information available to investigate suitable therapeutic targets is insufficient, and little advancement has been made in the development of molecular-targeted therapies for these patients. This study aimed to determine a molecular signature of pulmonary neuroendocrine carcinoma by genomic analysis to explore therapeutic targets. **Method:** Surgically resected primary tumor specimens obtained between January 2014 and June 2016 from 15 patients with neuroendocrine carcinoma [SCLC, 8; LCNEC, 6; typical carcinoid (TC), 1; categorized based on WHO classification] were subjected to whole-exome sequencing (WES) and gene-expression profiling (GEP). Corresponding peripheral blood samples were collected as controls to identify tumor-specific genetic alterations in WES. Written informed consent was obtained from all patients. WES was performed on an Ion Proton system. An Agilent SurePrint G3 Human Gene Expression 8×60K v2 Microarray was used to detect tumor-specific gene expression. Oncogenic fusions were detected by targeted RNA sequencing. Copy number alterations were detected by integrating copy numbers resulting from WES and GEP. Promising oncogenic genetic alterations were selected using the OncodriveFML and Cancer Genome Interpreter. **Result:** Patient characteristics were: median age, 67 years; men, 67% (10/15); smokers, 93% (14/15); ratio of stage I/II/III/IV (%), 40/47/13/0. The median tumor mutational burden (TMB) in SCLC and LCNEC was 7.6 mutations (mt)/Mb (1.1–11.3) and 8.0 mt/Mb (3.5–12.6), respectively, which were significantly higher than that in lung adenocarcinoma (1.6 mt/Mb; $p = 0.0025$, $p = 0.009$), but not in lung squamous cell carcinoma (5.6 mt/Mb). One patient with TC showed low TMB (0.7 mt/Mb) and harbored a truncating mutation in *MEN1*, indicating a typical molecular signature of carcinoid tumor. The commonly altered genes (≥ 20%) were *TP53* [60%, mut, 8; downregulation (down), 1], *RB1* (53%, mut, 6; down, 2), *CCNE1* [27%, amplification (amp), 4], *APC* (27%, mut, 3; down, 1), and *BCL2* (20%, amp, 3). All genetic alterations detected in *TP53*, *RB1*, and *APC* were putative loss-of-functions. We observed no significant differences in frequency of alterations in the commonly altered genes between SCLC and LCNEC. One patient with LCNEC harbored EGFR-activating mutation, indicating possibility that this tumor was combined LCNEC with adenocarcinoma. **Conclusion:** This study revealed a molecular signature in Japanese patients with pulmonary neuroendocrine carcinoma, which could contribute to the development of novel molecular-targeted therapies.

Keywords: High grade neuroendocrine carcinoma, Genomic Profiling

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-009 LINC00173 MODULATES CHEMORESISTANCE OF SMALL CELL LUNG CANCER BY FUNCTIONING AS A COMPETING ENDOGENOUS RNA TO REGULATE ETK EXPRESSION

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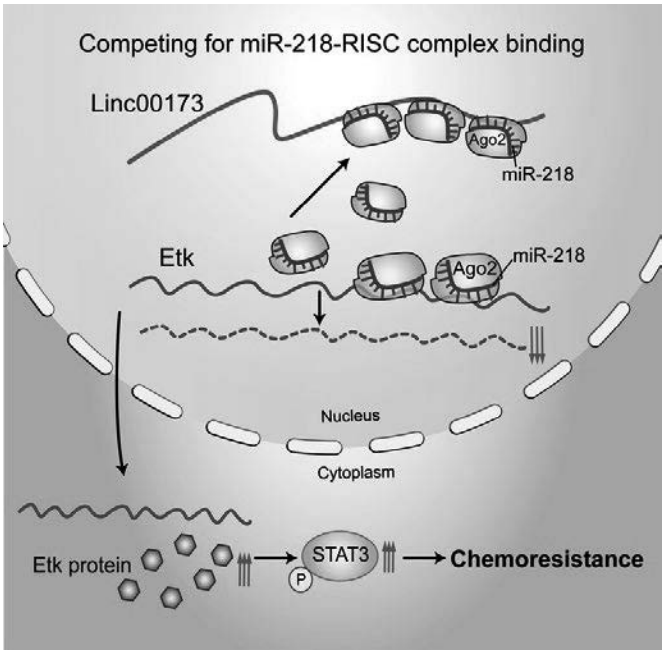
Background: Small cell lung cancer (SCLC) that constitutes of 15-18% of all lung cancers is a highly lethal malignancy. The functional effects of long noncoding RNAs(lncRNAs) in cancer have been widely recognized. Long intergenic non-protein coding RNA 173(Linc00173) was first identified in SCLC, and was found to be involved in chemoresistance. We aimed to explore the regulatory mechanisms of Linc00173 using drug-resistant cell lines and human tissues. **Method:** We used microarrays to compare expression profiles of lncRNAs in SCLC cell line and the drug-resistant subline and Linc00173 was identified. Linc00173 was examined in 60 SCLC patient samples by qRT-PCR assay. The functional roles of Linc00173 in SCLC were studied by overexpression and RNA interference approaches *in vitro* and *in vivo*. The localization of the genes were involved in competitive endogenous RNAs(ceRNAs) regulatory network was studied by separating cytoplasmic and nuclear RNA fractions from SCLC. Bioinformatic analysis, luciferase assays, RNA immunoprecipitation and pull-down assays were performed to elucidate the role of Linc00173 in mechanism of ceRNA. The positive Linc00173/Etk correlation was further verified by qRT-PCR assay and bivariate correlation analysis in clinical tissues and blood samples. **Result:** We found that Linc00173 expression was significantly associated with chemoresistance and the shorter survival time in SCLC patients. Downregulation of Linc00173 expression could impair cell proliferation and increased cell sensitivity to anticancer drugs, while upregulation of Linc00173 promoted the proliferation and induced multidrug resistance both *in vitro* and *in vivo*. Linc00173 overexpression enhanced the expression of Etk through competitively 'spongeing' miRNA-218 resulting in the activation of STAT3. Particularly, the ceRNA regulatory network of above genes was occurred in nucleus. Finally, the positive Linc00173/Etk correlation was found in SCLC tissues and blood samples. **Conclusion:**



Linc00173 was first identified to promote proliferation and chemoresistance of SCLC. It regulates levels of Etk by acting as 'sponger 'of miR-218. These genes may be novel indices for clinical diagnosis of tumor growth and chemoresistance in SCLC.

Keywords: chemoresistance, SCLC, Linc00173

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-010 ETK INTERACTING WITH PFKFB4 MODULATES CHEMORESISTANCE OF SMALL CELL LUNG CANCER BY REGULATING AUTOPHAGY

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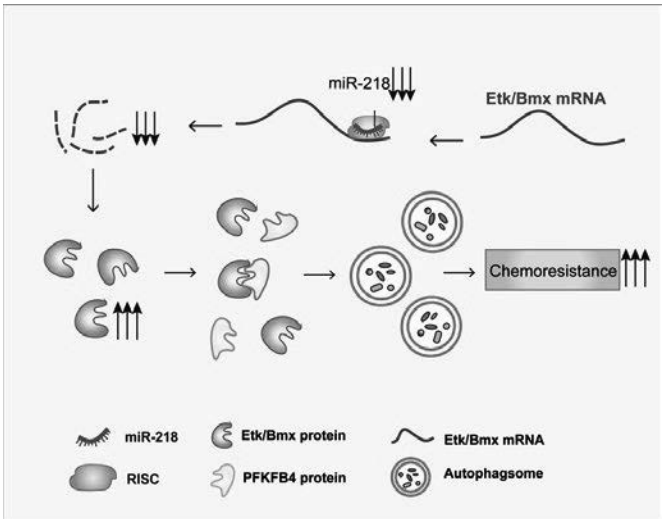
Background: Epithelial and endothelial tyrosine kinase(Etk), also known as Bone marrow X kinase (Bmx), was found to be critical in modulating chemoresistance of small cell lung cancer(SCLC) in our preliminary study. However, the molecular mechanisms of Etk leading to chemoresistance in SCLC remain obscure. **Method:** Knockdown of Etk by siRNAs was performed to evaluate autophagy change in SCLC. Subsequently, a microarray analysis identified PFKFB4 as a downstream molecule of Etk, and CoIP and GST-pull down was used to test protein interaction. We then explored whether PFKFB4 affected autophagy of SCLC. Gain or loss-of-function in vitro or in vivo was used to evaluate the effects PFKFB4 on chemotherapy sensitivity. The expression of PFKFB4 in SCLC tissues were measured by immunohistochemistry(IHC). Besides, luciferase assays, Western blot and CCK8 assay were performed to confirmed whether miR-218 regulates Etk and its effect on chemoresistance. As Etk shares conserved domains with Btk(Bruton's tyrosine kinase) family, we also explored whether ibrutinib, a Btk inhibitor used in leukemia, affected chemotherapy sensitivity of SCLC. **Result:** Etk affected autophagy in SCLC, and directly inhibition of autophagy sensitized cells to chemotherapy. PFKFB4 was found as a downstream molecule of Etk and they interacted with each other in protein level directly. Moreover, knockdown of PFKFB4 suppressed autophagy of SCLC. PFKFB4 affected chemoresistance of SCLC in vitro and in vivo, and high level of PFKFB4 was associated with poor therapeutic response and prognosis. Furthermore, miR-218 directly modulated Etk expression as a novel regulator and it affected chemoresistance in SCLC. We demonstrated that ibrutinib exhibited a synergistic effect with chemotherapy in SCLC. **Conclusion:**



Our results demonstrated for the first time that Etk interacts with PFKFB4 to modulate the chemoresistance of SCLC by autophagy and Etk is a direct target of miR-218. These genes may be predictive factors for the chemotherapy response as well as potential therapeutic targets in SCLC.

Keywords: chemoresistance, Etk, PFKFB4

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-011 THERAPEUTIC STRATEGIES AND GENETIC COMPARISONS IN SCLC AND LCNEC OF THE LUNG USING NEXT-GENERATION SEQUENCING

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Background: Small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) of the lung are highly malignant tumors and classified as variants of endocrine carcinoma and subdivided into pure or combined type. Clinical benefit of this stratification and strategy for target therapy has not been established in these tumors. **Method:** This study aimed to compare genetic and clinicopathological features between SCLC and LCNEC or pure and combined types, evaluate the usefulness of classification methodology, and explore the possibility of target therapy using next-generation sequencing (NGS). NGS custom panel was designed to cover 36 genes with median coverage percentage of 99.57% (80.89-100). As clinicopathological features, patients' characteristics and immunohistochemistry using 8 antibodies were evaluated. **Result:** In 13 SCLC and 22 LCNEC cases, 72 point mutations, 19 deletions, and 3 insertions were detected. As therapeutically targetable variants, mutations in *EGFR* (L858R), *KRAS* (G12D, G12A, G12V), and *PIK3CA* (E545K) were detected in 5 cases. One combined LCNEC cases harboring EGFR mutation (L858R) showed response to EGFR-tyrosine kinase inhibitor. However, these therapeutically targetable cases were not accompanied by specific features in immunohistochemistry or histology. And there was no significant genetic feature between SCLC and LCNEC or pure and combined types. **Conclusion:** Although even SCLC and LCNEC cases harbored therapeutically targetable mutations and potentially include the benefit for target therapy, they were not identifiable by clinicopathologic background. And there was not significant genetic difference between SCLC and LCNEC, including between pure and combined types. Classifying SCLC and LCNEC in same category is reasonable. However, distinguishing the pure type from combined type was not validated. Comprehensive genetic analysis should be performed to detect targetable variants in any type of SCLC and LCNEC.

Keywords: next generation sequencing, small cell lung cancer, large cell neuroendocrine carcinoma

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-012 ANALYSIS OF SMALL CELL LUNG CANCER WITH PARANEOPLASTIC LIMBIC ENCEPHALITIS

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Background: Section not applicable **Method:** The clinical data of 15 patients with small cell lung cancer(SCLC) combined with paraneoplastic limbic encephalitis(PLE) from 1980 to 2017 were collected from Peking Union medical college hospital. Their symptoms and laboratory data were analyzed and the prognosis of the patients was followed. **Result:** 1. PLE is a rare disease, the incidence rate in small cell lung cancer is about 0.842%.The data may be underestimated because of misdiagnose or missed diagnosis. 2. High incidence crowd of the disease is the middle-aged male smoker, The TNM stages of them are later than others. 3. Typical neurological symptoms include varying degrees of short-term memory loss, seizures and varying degrees of mental disorders; neurological symptoms usually occur before the onset of cancer or respiratory symptoms appear, an average of about 2 months be taken from onset to diagnosis. 4. Serum antibody (anti-Hu, GABA-R-Ab), cerebrospinal fluid, head MRI and EEG of the patients has abnormalities; Videography, especially CT is a good means of screening the primary tumor, pathology diagnosis mainly rely on bronchoscopy. 5. The treatment of primary tumors can be more effective in alleviating the nervous system symptoms than immunotherapy. **Conclusion:** Paraneoplastic limbic encephalitis is a rare paraneoplastic syndrome in nervous system caused by malignant neoplasms often characterized by facial neurological symptoms. The disease are usually associated with lung cancer (especially small cell lung cancer) .Its nervous system symptoms occur earlier than the tumor diagnosis. Early diagnosis and treatment for primary tumors will increase the benefit.

Keywords: Paraneoplastic limbic encephalitis, small cell lung cancer

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-013 DOXORUBICIN AND TOPOTECAN FOR RELAPSED/ REFRACTORY SMALL CELL LUNG CANCER (SCLC): A FPBCC CLINICAL TRIALS NETWORK PHASE I STUDY

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Background: Relapsed or refractory small cell lung cancer (SCLC) has a poor prognosis, with no good therapeutic options. Topotecan, a topoisomerase I inhibitor, and doxorubicin, a topoisomerase II inhibitor, are both active drugs in SCLC. We evaluated the safety and efficacy of a novel combination of oral topotecan and weekly doxorubicin, providing sequential topoisomerase I and II inhibition, in this setting. **Method:** Adult patients (>19 years) with relapsed or refractory SCLC who had received at least one prior chemotherapy regimen were included in the study. Patients received escalating doses of oral topotecan for five days (Days 1-5 of each cycle) every three weeks for a maximum of 5 cycles. The dosing cohorts were: DL1: 0.85 mg/m^2, DL2: 1.05 mg/m^2, DL3: 1.35 mg/m^2, DL4: 1.65 mg/m^2 and DL5: 2.30 mg/m^2. All patients received weekly doxorubicin 20 mg/m^2intravenously starting Day 6 of the first cycle and continued weekly for the duration of the study (maximum 15 weeks). The study design involved a standard 3+3 approach. In the absence of pre-specified criteria for dose limiting toxicities (DLT), patients were enrolled serially to escalated dose level cohorts. Patients received therapy until disease progression, undue toxicity or completion of the study. Primary objectives were safety and efficacy, dose limiting toxicity and response rate. **Result:** A total of 22 patients were enrolled in the study, of which 18 were evaluable for toxicity. Median age was 60.5 years, 72% were male and 95% were Caucasian. Most common adverse events observed were hematological toxicities. Grade 3/4 adverse events included: anemia (44%), thrombocytopenia (50%), neutropenia (44%), lymphopenia (33%), leucopenia (39%), transaminitis (17%), hypokalemia (11%), hypotension (5%) and dehydration (5%). There were no therapy-related Grade 5 toxicities. Incidence of DLT based on cohorts were: DL1: 0/3, DL2: 1/6 (Grade 4 Thrombocytopenia), DL3: 1/6 (AST Elevation) and DL4: 2/4 (Grade 4 Thrombocytopenia). Response rate was 16.6% (3/18) and disease control rate (SD + PR) was 33%. The median progression free and overall survival were 3.4 months and 5.8 months, respectively. **Conclusion:** The novel combination of oral topotecan and weekly doxorubicin was safe and showed promising efficacy in relapsed/refractory SCLC. The maximum tolerated dose of oral topotecan was 1.35 mg/m^2 when given concurrently with weekly doxorubicin. A phase 2 trial using this regimen is being developed.

Keywords: small cell lung cancer, topotecan, Doxorubicin

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-014 EXTENSIVE STAGE SMALL CELL LUNG CANCER: IS PRIMARY GROWTH FACTOR SUPPORT WARRANTED IN PATIENTS HAVING DOUBLET CHEMOTHERAPY?

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Background: Currently the chemotherapy protocol for extensive stage small cell lung cancer at Auckland Regional Cancer and Blood Service does not include a recommendation for the use of growth colony stimulating factor (G-CSF) support as either primary prophylaxis or in the secondary setting. The protocol does provide guidelines for treatment delay and dose reduction in the setting of haematological toxicity. Access to publicly funded pegfilgrastim (Neulasta) became available in New Zealand in May 2013. Individual physicians may choose to prescribe G-CSF prophylaxis for any patient they believe fits the funding criteria. We therefore

reviewed current clinical practice and outcomes in this patient population. **Method:** A retrospective audit of patients 18 years and over with a histologically confirmed diagnosis of extensive stage small cell lung cancer who were schedule to receive carboplatin with or without etoposide chemotherapy, from 1 January 2015 to 31 December 2015 was undertaken. Primary end point was rate of febrile neutropenia (FN) with secondary end points of G-CSF use, patient related risk factors for FN and dose reductions / delays. **Result:** 32 patients met the inclusion criteria, 29 of these received chemotherapy. The rate of FN in the entire population was 14% (4 episodes in 29 patients). One patient had 2 episodes of FN. The rate of FN in patients not receiving primary G-CSF was 13% (3 episodes in 23 patients). Six patients were administered G-CSF in the primary setting (20%, 6/29). One patient treated with primary G-CSF had FN (20%, 1/6). Two patients received G-CSF in the secondary setting. Risk factors for FN were commonly seen, including age >65 years (63%) chronic obstructive respiratory disease (41%) and multiple co-morbid conditions (22%). Treatment delays were experienced by 14 patients (48%) at some stage throughout their chemotherapy primarily due to haematological toxicity. Dose reductions occurred in 17 patients (58%). **Conclusion:** This retrospective audit confirms an overall rate of FN of 14%, in keeping with published data of moderate risk of neutropenia with carboplatin etoposide chemotherapy. In this retrospective study, primary G-CSF did not decrease this risk, but numbers are small. This population of patients commonly have risk factors for FN and many patients experience treatment delays. Given this and the importance of dose intensity in the treatment of small cell lung cancer, consideration for primary G-CSF support is warranted.

Keywords: audit, G-CSF support, Extensive small cell

P2.15: SCLC/NEUROENDOCRINE TUMORS -
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P2.15-015 NEGATIVITY FOR THYROID TRANSCRIPTION FACTOR 1 WAS CORRELATED WITH LESS NEUROENDOCRINE DIFFERENTIATION IN SMALL CELL LUNG CANCERS

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Background: The biological and clinical significance of thyroid transcription factor 1 (TTF-1) remains unclear in small cell lung cancer (SCLC). The purpose of this study was to clarify the clinicopathological characteristics of TTF-1-negative SCLC. **Method:** We retrospectively studied the associations between survival and the expression of TTF-1, and examined the association between the expression of TTF-1 and neuroendocrine markers (Synaptophysin, Chromogranin, and CD56), neuroendocrine cell-specific transcription factor (ASCL1, BRN2), and NF1B, which is an oncogene for SCLC. Formalin fixing and paraffin embedding (FFPE) and clinical data in SCLC patients were collected and used. The study was approved by the institutional review board. **Result:** Thirty-five patients were examined. Eleven patients were negative for TTF-1, and twenty-four patients were positive for TTF-1. The analysis demonstrated that overall survival was not statistically significant between patients with TTF-1-negative and those with TTF-1-positive SCLC. However, frequency of negativity of Synaptophysin and Chromogranin was greater in patients with TTF-1-negative SCLC than in those with TTF-1-positive SCLC based on immunohistochemical expression, and the difference was statistically significant. mRNA expression of ASCL1, NF1B, and serum ProGRP were significantly lower in patients with TTF-1-negative SCLC than in those with TTF-1-positive SCLC. We showed that TTF-1-negative SCLC showed less neuroendocrine differentiation. It is suspected that TTF-1-positive and -negative SCLC have different biological characteristics. **Conclusion:** TTF-1-negative SCLC was different in terms of aspects of neuroendocrine differentiation (negativity of Synaptophysin and Chromogranin, lower expression of ASCL1 and NF1B) compared to TTF-1-positive SCLC.

Keywords: small cell lung cancer, TTF-1, Prognosis

P2.15: SCLC/NEUROENDOCRINE TUMORS -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.15-016 CLINICAL SIGNIFICANCE OF TOPOISOMERASE-II EXPRESSION IN PATIENTS WITH RELAPSED HGNEC OF THE LUNG TREATED WITH AMRUBICIN

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Background: Amrubicin (AMR) monotherapy is one of treatment options in patients with relapsed high grade neuroendocrine carcinoma (HGNEC) of the lung. Although topoisomerase-II (Topo-II), a target of AMR, has been reported to be a predictive or prognostic marker for chemosensitivity and clinical outcomes in various types of malignancies, its role remains unknown in this population. **Method:** Eighty-four patients with relapsed HGNEC (consisting of small cell lung cancer [SCLC] and large cell neuroendocrine carcinoma [LCNEC]) who received AMR monotherapy between 2003 and 2015 were enrolled into this study. We retrospectively collected clinical data including histological type, anti-tumor effect, and survival data from medical records. The expression levels of Topo-II were examined by immunohistochemical staining in tumor specimens obtained from surgical resection or biopsy. **Result:** The majority of enrolled patients were men (89%) and had a histological type of SCLC (92%) with a median age of 70 years (range, 49-83 years). Twenty-three percent of patients had poor performance status of 2 to 4. Sixteen percent of patients exhibited Topo-II overexpression in the tumors. The overall response rates in patients with high and low expression of Topo-II were 38.5% and 25.7%, respectively ($p = 0.34$). In multivariate analysis, patients with high expression of Topo-II had significantly longer progression-free survival (Hazard Ratio [HR] 0.39, $p < 0.01$) and overall survival (HR 0.48, $p = 0.04$). **Conclusion:** Our findings suggest that Topo-II expression is associated with clinical outcomes in patients with relapsed HGNEC receiving AMR monotherapy.

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-001 LIPOSOMAL BUPIVACAINE (EXPAREL) REDUCES THORACIC SURGERY POST-OPERATIVE PAIN AND REDUCES LENGTH OF STAY, A RETROSPETIVE STUDY

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Background: Intercostal nerve blocks with a liposomal Marcaine formulation (Exparel) was reported to provide pain relief equivalent to an epidural in the immediate post operative period following a thoracotomy. We compared pain relief of thoracotomies that received an Exparel block to minimally invasive procedures in the immediate and extended post-operative period. **Method:** We reviewed the records of 166 patients who underwent thoracic surgery procedures with a thoracotomy or a video-assisted thoracoscopic surgery (VATS) and who received multilevel paravertebral nerve blocks with either Exparel or 1 % Marcaine with epinephrine. Pain scores and opiate use were routinely recorded by nurses for the first 48 hours as well as opiate use in the postoperative days (POD) 5 to 13 (by patients). Clinical variables, atrial fibrillation, pulmonary complications, and hospital length of stay (LOS) were also examined. Statistics included t-test for means, and Fisher exact for proportions. **Result:** Fifty patients underwent a VATS wedge resection with a paravertebral block with Exparel (VATS-E) and 53 patients underwent a VATS wedge resection with a paravertebral block with Marcaine (VATS-M). The pain score were lower for the VATS-E vs. the VATS-M patients ($p < 0.001$). 32 patients underwent a thoracotomy with an Exparel block (Thor-E) (30 lobectomies) and 15 patients had a VATS lobectomy with a Marcaine block (VATS-lobe-M). Thor-E patients expressed lower pain scores compared to VATS-M and VATS-lobe-M in the first 48 hours after surgery ($p<0.001$). Opiate use was also lower in the Thor-E patients compared to VATS-lobe-M patients, with 25% of the Thor-E patients not taking opiates by POD 5. Opiate use was not significantly different between Thor-E and VATS-E patients from POD5 to POD 13. The LOS was 3.2 days for Thor-E and 5.7 days for historic control thoracotomy lobectomy patients who received a Marcaine nerve block. **Conclusion:** Our study suggests that the pain relief provided by an Exparel block in thoracotomy patients compares favorably to that of VATS procedures in the immediate and extended postoperative period, and that Exparel paravertebral nerve blocks may also improve hospital length of stay.

Keywords: Post-op pain

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-002 ADEQUACY OF LYMPH NODE SAMPLING DURING LOBECTOMY IN A SMALL COMMUNITY TEACHING HOSPITAL

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Background: Current practice guidelines by the National Comprehensive Cancer Network (NCCN) recommend the complete dissection of at least three mediastinal nodal stations during lobectomy for lung cancer. Controversy exists concerning the adequacy of lymph node sampling (LNS) achieved by video assisted thoracic surgery (VATS) lobectomy for lung cancer and furthermore whether or not small volume centers could compare to the national benchmarks. Several large studies have shown conflicting evidence concerning the LNS yield in VATS vs thoracotomy. For thoracic surgeons in a rural community setting there may be warranted concern about the adequacy of lymph node dissection during VATS. This study aimed to assess the adequacy of lymph node sampling by VATS at our institution, a rural 300 bed community teaching hospital in western Massachusetts. **Method:** Retrospective review of clinical and pathological data were reviewed for 103 hospital admissions in patients undergoing lung Lobectomy performed from 2010-2016. Variables included age, sex, number of mediastinal nodes and node stations dissected. **Result:** 103 patients with 103 VATs Lobectomies, 49 males (ave age 64.6 yrs) and 55 females (ave age 67.5), had a mean number of mediastinal lymph nodes (MLD) of 10.98 and the mean number of dissected N1+N2 stations was 3.47. The mean N2 station yield averaged 2.93 stations. S1 was resected in 2/103cases (2%); S2, 10/103 (10%); S3, 0/103 (0%);

S4, 62/103 (64%); S5, 29/103 (30%); S6, 25/103 (25%); S7, 79/103 (81%); S8, 7/103 (7%); S9, 37/103 (38%); S10, 51/103 (53%); S11, 33/103 (34%); S12, 22/103 (23%); S13, 1/103 (1%). **Conclusion:** Recent data presented at Annual Meeting of the American Association for Thoracic Surgery (AATS) suggests VATS lymphadenectomy is inadequate 60% of the time. It was postulated that small volume centers and/or inexperienced general surgeons are contributing to this high percentage. This study agrees with previous data affirming the lymph node yield is adequate with VATs lobectomy. When compared to the current NCCN recommendations our institutions mean number of MLN and MLN stations dissected is similar or better to that of many larger volume centers across the nation and supports the adequacy of VATs Lobectomy in rural community hospitals.

Keywords: rural hospital, VATS, Lymph node dissection

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-003 DIAGNOSTIC LOBECTOMY FOR INDETERMINATE PULMONARY TUMOR

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Background: For tissue diagnosis of an indeterminate lung tumor with a strong suspicion of lung cancer, wedge resection is sometimes difficult because of tumor size or location. Intra-operative needle aspiration biopsy can be considered when tumor biopsy via flexible bronchoscopy (FB), or using transthoracic needle aspiration biopsy (TTNA), fails to prove malignancy in tumors with a high rate of false negatives. There are numerous lesions where an easy wedge resection or TTNA cannot be carried out, and lobectomy followed by thorough pathological examination is required. **Method:** From April in 2010 through December in 2015, 30 patients with indeterminate lung tumors who underwent lobectomy (including 2 upper segmentectomy in the left upper lobe) followed by thorough pathological examination were reviewed. Right middle lobe lesion was excluded in this study. **Result:** Sixteen were men and 14 were women. The median age of the patients was 67 years with a range of 24 to 85 years). According to the size and location of the lesion, each case was classified in two patterns: deep nodule (18 patients, locates centrally, inner two thirds from the lung surface) or mass (12 patients, greater than 30mm in diameter). Tumor located in the right upper lobe/ right lower lobe/ left upper lobe/ left lower lobe in 13 (deep nodule/mass: 8/5) / 4 (deep nodule/mass: 3/1) / 7 (deep nodule/mass: 4/3) / 6(deep nodule/mass: 3/3) patients, respectively. Preoperative examination was chest computed-tomography/F-18 FDG PET/transbronchial biopsy through bronchofiberscopy in 30/24/19 patients, respectively. Pathological diagnosis were as followings: 25 primary lung cancer (13 adenocarcinoma, 1 adenosquamous cell carcinoma, 1 mucoepidermoid carcinoma, 4 bronchiolo-alveolar varcinoma, 1 pleomorphic carcinoma, 1 small cell carcinoma, 4 squamous cell carcinoma) / 1 inflammatory myoblastic tumor/ 1 metastatic carcinoma/ 1 organizing pneumonia/ 1 caseous granuloma/ 1 Non Tuberculous Mycobacteriosis(Mycobacterium xenopi). Pathological stages of primary lung cancer were stage IA/IB/IIB/IIIA/IV in 6/1/3/2/1/3 patients, respectively. Operative time was 110~304 minutes (median: 182.5 min), and intra-operative blood loss was 0~530ml (median: 60 ml). Post-operative drainage were 2~18 days (median: 3 days) and post-operative hospital stay was 5~23 days (median: 10 days). Post-operative complications of Clavien-Dindo grade grater than or equal to II occurred in 6 patients (II/III: 3:3), all of them resolved conservative therapy. **Conclusion:** Diagnostic lobectomy followed by thorough pathological examination were carried out safely with acceptable range of postoperative complications.

Keywords: indeterminate pulmonary tumor, lobectomy, pulmonary resection

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-004 ALTERNATIVE SUBPREURAL LYMPH FLOW PATHWAYS IN HUMAN LUNG – A HUNDRED CASES EXPERIENCE AND ANALYSIS

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Background: Pulmonary lymph flows are predominantly regarded to run along bronchi. In addition, limited resections such as segmentectomy are increasing recently. However there are some cases suggesting alternative lymph pathways, such as the skip metastases. We herein observed pleural lymph flows by the indocyanine green (ICG) fluorescence method with a near-infrared camera device in patients who underwent lung resections. **Method:** After thoracotomy, we injected ICG to subpleural spaces of the lung lobe that planned to resect in 100 cases. Intraoperative fluorescence images were observed in real time using a near-infrared camera. Patients with pleural involvement were excluded. **Result:** In 58 out of 100 cases, ICG movements were observed in subpleural space. In 18 cases, ICG flowed into adjacent lobes over the interlobular line. In 5 cases, ICG flowed into the mediastinum directly. Subpreural lymph flow detection rates were significantly lower in patients with smoking pack-year >40 than those with pack-years <40. **Conclusion:** In our study, in more than half of the cases, pleural lymph flows were observed and there were lymph flows that flowed into the mediastinum directly. In addition, the reduction of subpleural lymph flows in smokers with >40 pack-year suggests that smoking might modify lymph flow patterns. In the future, these findings may help us to select appropriate procedures for patients with possible skip metastasis.

Keywords: Lung remodeling, Subpleural lymph flow, skip metastasis

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-005 IS THERE ANY ONCOLOGICAL CONCERN ABOUT PREOPERATIVE BIOPSY FOR RESECTABLE LUNG CANCER PATIENTS?

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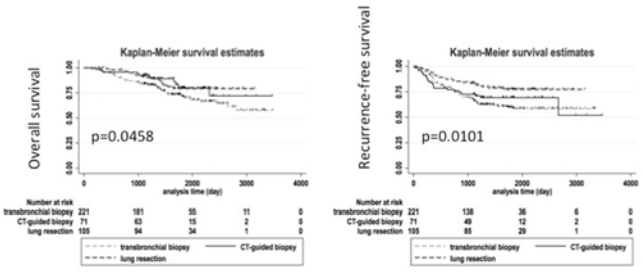
Background: Preoperative trans-bronchial biopsy and/or computed tomography (CT)–guided biopsy inevitably disrupt lung structure and might disseminate tumour cells into airway, vessels or the pleural cavity. Because preoperative diagnostic intervention may potentially disperse tumour cells, it may affect relapse and/or prognosis. **Method:** The data from the consecutive patients with cTanyN0M0 lung cancer who underwent surgery between January 2006 and December 2012 at our institute were extracted by chart review and analysed retrospectively. Prognostic factors of overall and recurrence-free survival were compared among the groups (the trans-bronchial biopsy group, the CT-guided biopsy group and the intra- or postoperative-diagnosis group) by using the univariate and multivariate Cox proportional hazard model. A stepwise backward elimination method with a probability level of 0.15 was used to select the most powerful sets of outcome predictors. A p-value <0.05 was considered statistically significant. **Result:** Data from 397 patients were available for analysis (the trans-bronchial biopsy group: 221, the CT-guided biopsy group: 71 and the intra- or postoperative-diagnosis group: 105). Solid tumour size was larger in the trans-bronchial biopsy and/or the CT–guided biopsy than the intra- or postoperative-diagnosis group ($p = 0.0001$). In the crude analysis, the trans-bronchial biopsy group and the CT-guided biopsy group showed higher probability of pleural dissemination ($p = 0.048$) and showed worse prognosis than the intra- or postoperative-diagnosis group (overall survival: $p = 0.0458$, recurrence-free survival: $p = 0.0101$). However, the method of diagnosis was not identified as an independent risk factor for pleural dissemination and overall and recurrence-free survivals by multivariate analyses.



Conclusion: Preoperative diagnostic intervention did not affect relapse and/or prognosis in this study cohort. Preoperative diagnostic intervention is recommended if necessary.

Keywords: diagnosis, outcome, non-small cell lung cancer

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-006 LOCKING OF THE SCAPULA AFTER LOBECTOMY WITH RIB RESECTION

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Background: Locking of scapula is rare complication of rib resection or thoracotomy. The patients experience severe pain and restriction of movement in their shoulder, and they are treated conservatively or surgically. **Method:** A 72-year-old woman underwent right upper lobectomy and extended combined resection of the posterior chest wall (via a standard posterolateral thoracotomy and resection of the 2nd to 4th ribs), to treat a stage3A lung cancer. Chest wall reconstruction was not performed. Her immediate postoperative course was uneventful, she was discharged from our hospital on 7th operative day. One year after operation, severe pain appeared in her right shoulder while she put on her underwear. She was referred to our hospital. **Result:** Physical examination revealed that resting pain was not so severe, but the range of shoulder motion was restricted due to severe pain. We suspected that the inferior angle of the scapula was caught inside the 5th rib. Chest x-ray showed that scapula prolapsed into the intrathoracic cavity through the resection site in the right chest wall (figure). The manipulative closed reduction was successful, then her symptoms were resolved. We advised her to pay attention to her right shoulder movement especially in over 90 degrees abduction. Five month later, no recurrences were observed.

Conclusion: As to rib defects like this case, the necessity of the reconstruction is controversial because the defect is completely covered by scapula. Moreover scapular prolapse into the intrathoracic cavity is rare and implants have a potential to infection. We conclude that the partial resection of the inferior angle of the scapula should have been performed at her operation in order not to be caught inside the rib.

Keywords: thoracotomy, scapula locking, rib resection

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-007 TWO CASES OF VATS RESECTION FOR ENDOBRONCHIAL PROTRUDED TUMORS

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Background: We report two rare cases of complete resection for endobronchial protruded tumors. **Method:** Case 1; a-46-year old man with a history of several pneumoniae consulted us because of chest X-ray abnormality. A chest-CT showed atelectasis at medial segment of the right lung with bronchial obstruction. Case 2; a-68-year-old woman was referred to our hospital for persistent couch. Enhanced CT scan showed an endobronchial tumor at basal segment of the right lung with peripheral atelectasis. **Result:** In case 1, bronchoscopic findings showed a smooth-surfaced polypoid tumor which occluded the medial bronchi of the right lung. An endobronchial biopsy was performed, and it suspected mucoepidermoid carcinoma. He underwent a right middle lobectomy with VATS. The tumor grew as an endobronchial polyp with 25mm in a diameter. On Histopathological findings, the tumor consisted of epithelial cells and myoepithelial cells with tubular or alveolar formation, and it diagnosed epithelial-myoepithelial carcinoma. In bronchoscopy in case 2, the basal segment bronchi were obstructed by a whitish endobronchial tumor, and it caused obstructive pneumonia. A biopsy from the tumor showed no evidence of malignancy. A right lower VATS lobectomy was performed. The tumor showed endobronchial growth without fibrous capsules. Spindle cells with mild atypia were scattered in the tumor. With immunohistological examinations (positive for smooth muscle actin and desmin, negative for estrogen receptor), the tumor was diagnosed as bronchial leiomyoma. **Conclusion:** Epithelial-myoepithelial carcinoma belongs to carcinomas of salivary-gland-type. Bronchial leiomyoma, arising from bronchial smooth muscle, should be distinguished from benign metastasizing leiomyoma. These tumors are usually covered with normal bronchial epithelium. Endobronchial biopsy is necessary for histological diagnosis. Bronchoscopic examination followed by surgical resection is recommended for endobronchial protruded tumors.

Keywords: VATS, endobronchial tumor

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-008 COLLAPSED LUNG INDEX TEN MINUTES AFTER THORACOTOMY AND PRE-OPERATIVE PULMONARY FUNCTION TESTS

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Background: The lung is still pneumatized and we cannot take a broad view of the chest cavity. As for surgeons, the prediction of lung prolapse is valuable for surgical manipulations. We estimated the degree of the collapsed lung ten minutes after thoracotomy (collapsed lung index; CLI). We also evaluated the relationship between CLI and pre-operative pulmonary function test. **Method:** From December 2016 to June 2017, we included 38 patients undergoing video-assisted thoracoscopic surgery (VATS) without pleural adhesion. CLI was determined as the degree of collapse of the lung ten minutes after opening the first thoracic port. CLI definition was as follows; Grade 1: the distance between visceral pleura and chest wall was less than 1cm, Grade 2: the distance was less than 3cm, Grade 3: the distance was less than 5cm, Grade 4: the distance was more than 5 cm and the lung parenchyma was partially deflated, and Grade 5: the lung was completely collapsed. We also checked the relationship between CLI and pre-operative pulmonary function test of the patients. **Result:** The patients are 47 years old to 83 years old. They consist of 25 males and 13 females. The numbers of CLI Grade 1 were 0 cases, Grade 2 were 4 cases, Grade 3 were 18 cases, Grade 4 were 14 cases, and Grade 5 were 2 cases. VATS were easily undergone with broad surgical view Grade 4 and Grade 5. The 42% of the cases are included in CLI Grade 4 and Grade 5. The mean value of %VC was 102.6 %, FEV1.0G was 76.8 %, and FEV1.0% was 100.3 % in Grade 4 and Grade 5 patients. The preoperative pulmonary function tests were better in Grade 4 and 5 than the other Grades. **Conclusion:** We proposed CLI to estimate the surgical views at the beginning of VATS. The preoperative pulmonary function will predict the surgical field. We are waiting for some methods to deflate the lung in CLI Grade 1, 2, and 3 to Grade 4 or 5. The complete collapsed lung should make a good contribution for Single port VATS.

Keywords: Prediction from pulmonary function test, Collapsed Lung Index, SinglePort VATS

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-009 STRATEGY FOR ONCOLOGIC EMERGENCY IN THORACIC DISEASE

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Background: No large series of oncologic emergencies in thoracic surgery has been reported. Such patients are usually in critical condition and need immediate intervention of various types. Here, we present the surgical interventions that have occurred in our experience with oncologic emergencies. **Method:** We retrospectively analyzed 28 patients with oncologic emergencies who underwent surgical intervention at our hospital in 2002-2016. The mean patient age was 76 years, and there were 19 (68%) males and 9 (32%) females. The primary disease was primary pulmonary carcinoma in 13 cases, including adenocarcinoma and squamous cell carcinoma in 4 and 6, respectively, other-organ carcinomas in 12, and mediastinal tumors in 3. Airway stenosis was the complaint in 19 (68%), including hemoptysis in 2, superior vena cava syndrome in 3 (11%), infectious diseases in 2 (7%), tumor bleeding in 2 (7%), and pneumothorax in 2 (7%). **Result:** The goal of surgery was a radical operation in 8 (29%), biopsy in 3 (11%), and palliative therapy in 17 (60%) patients. The surgical procedure was lobectomy in 4 patients, bronchoplasty in 4, wedge resection in 3, pneumonectomy in 1, tumor removal in 2, pleural decortication in 1, excisional biopsy in 4, airway intervention (stent or laser cauterization) in 11, and tracheostomy in 6. The mean hospital stay was 32±39 (range 3–155) days. The outcome was hospital death in 7 (25%) and discharge in 21 (75%). Of the discharges, 3 (11%) patients were transferred to another hospital, and 18 (64%) were sent home. The mean survival was 743±743 (range 3–3798) days. Of the 21 discharges, 7 (25%) patients are alive, including 4 (14%) who are cancer-free and 3 (11%) with cancer. As treatment, radical surgery was more effective than conservative therapy. **Conclusion:** The oncologic emergencies experienced in thoracic surgery included obstruction/stenosis, bleeding, infection, and rupture. Stenosis comprised the majority and was caused by tumor growth in the airway and compression and invasion by tumors. Good outcomes were expected in patients with slow-growing tumors who underwent laser cauterization or airway stent placement.

Keywords: thoracic disease, oncologic emergency

P2.16-010 REMOVING THE CHEST TUBE ON THE FIRST DAY AFTER SURGERY DOES NOT CONTRIBUTE TO THE EARLY DISCHARGE FROM THE HOSPITAL

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Background: Postoperative chest tube drainage is essential in pulmonary surgery. After chest tube removal, the patient can be discharged from the hospital promptly. Therefore, it should be a close relationship between hospital stay and drainage duration. Removing chest tube in the early postoperative period leads to reduction of pain and early discharge from the hospital. However, there are few reports about removal chest tube on the first day after surgery. In this study, we examined cases where chest tube was removed on the first day after surgery. **Method:** From January to December 2016, 48 patients with lung cancer underwent lobectomy in our institute. They were consisted of 35 males, 13 females, and median age was 72 (53-87) years old. Among them, chest tube was removed on the postoperative day (POD) 1 in 24 patients (Group 1) and on the POD2 in 24 patients (Group 2). Patients complicated of postoperative lung fistula and infection were excluded. **Result:** Patients were discharged from the hospital on 5.4 days after surgery in Group 1 and on 5.6 days in Group 2. There was no significant difference between them (p=0.48). The CRP values on POD1, 2, and 3 were 5.49±2.38, 12.0±4.71, and 11.6±6.12 mg/dl in Group 1, and 7.27±3.28, 15.5±6.31, 12.9±5.87 mg/dl in Group 2, respectively (p=0.03, p=0.03, p=0.46). In addition, the period until CRP peaked out was 2.5 days in Group 1, and 2.1 days in Group 2. Group 2 showed obviously short period until CRP peaked out (p=0.03). **Conclusion:** Removing the chest tube on the first day after surgery will not lead to an early hospital discharge, conversely it will prolong the inflammatory response such as CRP.

Keywords: pulmonary surgery, early discharge, chest tube

P2.16-011 UNSUSPECTEDLY DETECTED ISOLATED FIBRINOGEN DEFICIENCY IN A PATIENT WITH LUNG ADENOCARCINOMA AFTER SURGERY

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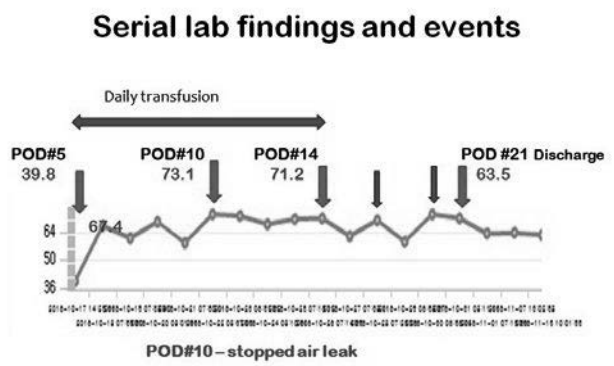
Background: Isolated fibrinogen deficiency is rare disease in Korean; especially extremely rare in patient with preoperative normal level of PT/aPTT. **Method:** I present a 62-year-old female patient who was admitted with lung cancer (adenocarcinoma, RUL, cT2aN0M0). She underwent VATS right upper lobectomy with mediastinal lymph node dissection. During operation, there was no need for transfusion (EBL 200cc) and no evidence of hemodilution. **Result:** On the first postoperative day (POD), PT was prolongated over 100 seconds (INR was over than 10). Coagulating factors were evaluated and isolated fibrinogen deficiency was diagnosed. As serum level of fibrinogen was fallen below 40mg/dL, spontaneous bleeding such as subcutaneous hemorrhage on trunk and persistent minor air leakage was observed. Bleeding tendency and air leak was improved since repeated transfusion of cryoprecipitate made the serum level of fibrinogen over 60 mg/dL. On POD 24, she was discharged without complication, however, she still had low level of fibrinogen. Although she was stable without any signs of spontaneous bleeding and prolongation of PT, the serum level of fibrinogen was still low around 60mg/dL at last visit in out-patient clinic which needed intermittent transfusion of cryoprecipitate.



Conclusion: She refused genetic evaluation for fibrinogen deficiency and I still don't know what caused isolated fibrinogen deficiency in this patient, which could lead to a critical situation. To prevent any other disaster caused by this, I think there needs countermeasure for this.

Keywords: lung adenocarcinoma, Surgery, fibrinogen deficiency

P2.16-012 DOES PERCUTANEOUS ULTRASOUND PREDICT TUMOR SITE AND INTERNAL TUMOR PROPERTIES?

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Background: The lung contains a large volume of air and have thus been unsuitable for observation with ultrasound. However, recent advancements in ultrasound have enabled the diagnosis of pneumothorax and tumor invasion of the chest wall, and fine-needle aspiration of tumors abutting the pleura can now be performed using ultrasound. Here, we investigated whether ultrasound is capable of predicting internal tumor properties. **Method:** TOSHIBA aplio 400 was used. Of 64 patients with tumor lesions undergoing preoperative ultrasound at our hospital between June 2015 and April 2017, we investigated 42 patients in whom internal tumor properties were visualized before surgery. There were 27 men and 15 women; 37 patients had malignant and 5 had benign lung tumors. Solid components were present in the tumor in 25 patients, liquid components in 3, a cavernous lesion in 9, a ground-glass opacity (GGO) lesion in 4, and pulmonary sequestration in 1. The tumor diameters ranged from 0.7 to 10.4 cm (median, 2.4 cm), and the distances from the lung surface ranged from 0 to 8.9 cm (median, 0.57 cm). **Result:** Ultrasound was useful for identifying an anomalous vessel originating from the aorta in a case with pulmonary sequestration. According to internal tumor properties, lesions containing a large volume of air (cavernous or GGO lesions) were visualized as hyperechoic areas, while many solid lesions appeared hypoechoic with a hyperechoic periphery on images. The posterior echo was enhanced in tumors containing liquid components and also in many cases with benign tumors. Thus, ultrasound is potentially useful for determining whether tumors are malignant or benign before surgery. **Conclusion:** Although ultrasound was not capable of visualizing the internal tumor structures in all cases, the internal tumor structure, if visualized by ultrasound, could be assessed. Moreover, ultrasound has the potential for differentiating benign from malignant tumors. Our results suggest that ultrasound merits future study, with further accumulation of cases.

Keywords: percutaneous ultrasound, lung tumor

P2.16-013 PERIPHERAL OR CENTRAL LUNG NODULES: HOW DO THORACIC SURGEONS DEFINE IT?

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Background: "Peripheral" is ubiquitously used in thoracic surgery literature, but definitions differ. Our purpose was to ascertain opinions of thoracic surgeons on CT images and assess the frequency of peripheral nodules according to their definitions. **Method:** We developed a survey and obtained an IRB exemption. Surgeons were asked to choose one of methods A-D to define the peripheral pleura: A=costal pleura, B=costal and mediastinal pleura (diaphragmatic pleura also on coronal and sagittal views), C=costal and fissural pleura, D=any pleural surfaces on: Question#1) axial images, Question#2) coronal images, Question#3) sagittal images. Question#4 asked whether the peripheral lung was: 1, 2, or 3 cm, outer 1/3, outer 1/2 or outer 2/3. Question#5 asked whether the measurement from the nodule to the pleura started at the inner edge, center, or outer edge of the nodule. By applying the possible choices to a database of 76 patients with documented lung cancer we determined the frequency of peripheral cancers for each combination. **Result:** Ten thoracic surgeons participated, all had different answers. The most frequent response to Question#1 was Method A (n=4), Question#2 Method A (n=5), and Question#3 Method B (n=4). The most frequent answer for Question#4 was the outer 1/3 of the lungs (n=6), and for Question#5, the outer border of the nodule, closest to the relevant pleura (n=5). The frequency of nodules classified as peripheral according to these answers ranged from 13% (10/78) to 91% (71/78). **Conclusion:** There was no consensus. Standardization and rationale for this would be highly useful.

Keywords: lung cancer, peripheral lung nodule, Thoracic Surgery

P2.16-014 DECONSTRUCTING SURGICAL DECISION MAKING

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Background: With the increase in number of individuals undergoing CT screening, lung cancers are now being detected at an earlier stage. Curative treatment can thus be performed on these patients, resulting in better lung cancer survival. Effective surgical decision making depends upon the degree of knowledge and experience the treating surgeon has about the outcome of actions, ability to assess risk and its subsequent impact. Use of a gnostic expert system would increase cost-effectiveness and efficiency. Our objective is to garner experts' tacit knowledge about surgical

decision making in a form of probability function. **Method:** Nine surgeons with extensive experiences in thoracic surgery were presented with a set of hypothetical cases, specified by indicators for surgical treatment (lobectomy or limited resection). Their choice of surgery and probability of performing limited resection were recorded for each case. Probabilities were translated into a logistic probability function for limited resection by 1) taking logits of the probabilities: Y=log[P/(1-P)], then 2) applying a general linear model for the mean of Y, $\hat{Y}=\beta_1+\beta_2X_2+\beta_3X_3+\beta_4X_4+\beta_5X_5+\beta_6X_6+\beta_7X_7+\varepsilon$. Standardized coefficients were computed and ranked to determine the effect of each indicator on limited resection. **Result:** Across the 24 cases, the median probabilities of limited resection among experts ranged from 0.0% to 100.0%, their case-specific IQR had values from 5 to 90 (Q3-Q1) percentage points, and ranges had values from 10-100(max-min) percentage points. Considering the expert-specific median probabilities, five out of eight experts favored lobectomy (median probabilities of limited resection ≤12.5%). Two other experts had median probabilities of 42.5% and 49% while the remaining expert favored limited resection (median probability 65%). The effect of each indicator on preferring limited resection over lobectomy varied between surgeons. Overall, distance from relevant pleura and nodule size were important factors for considering limited resection. **Conclusion:** There was great inter-surgeons variability on surgical decision making. Garnering experts'tacit knowledge on surgical decision making will enhance efficiency of health care and potentially change surgical practice.

Keywords: lung cancer treatment indicators, surgical decision making, probability function

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P2.16-015 LOG DATA OF DIGITAL DRAINAGE SYSTEM IS A POTENTIAL PREDICTIVE FACTOR OF PLEURODESIS EFFICACY FOR POSTOPERATIVE AIR LEAK AFTER PULMONARY RESECTION

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Background: Digital drainage system (DDS) has been recently recognized as a useful device in postoperative chest drainage. However, there is no past study predicting the efficacy of pleurodesis using DDS for postoperative air leak. The aim of this study is to identify predictive factors of the efficacy of pleurodesis including the observed data in DDS log. **Method:** The 857 patients underwent pulmonary resection and were made use of DDS for chest drainage postoperatively from January 2015 to December 2016. We retrospectively reviewed clinical database and log data of DDS, and compared the patient who stopped postoperative air leak by single pleurodesis with the patient who needed two or more pleurodesis. Fisher's exact test was used to compare categorical values, and Mann-Whitney U test was used to analyze continuous values. The cut-off values were decided by receiver operating characteristic curve. **Result:** The 40 patients underwent pleurodesis for postoperative air leak. The median age was 70 years (range, 51 to 86), and 83% of patients were men. The most common type of surgery was lobectomy (90%). Postoperative air leaks in the 23 patients (58%) were stopped by single pleurodesis, and those in the 17 patients (42%) needed pleurodesis more than two times to stop air leak. The predictive factors to stop air leak by single pleurodesis were lower air leak flow at the time of pleurodesis (P = 0.02), and lower average of air leak flow for 24 hours before pleurodesis (P = 0.05). The cut-off value of air leak flow was 100 ml/min, and average of air leak flow for 24 hours was 130ml/min. **Conclusion:** Air leak flow at the time of pleurodesis and the average for 24 hours in DDS log were useful predicters of stopping air leak by single pleurodesis.

Keywords: pleurodesis, digital drainage system, air leak

P2.16: SURGERY -
TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.16-016 SURGICAL TREATMENT OF INDETERMINATE LUNG NODULES

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Background: Recently, the improvement of ability of Computed tomography (CT) scans permits us to identify a large number of small peripheral, undefined pulmonary lesions that require a diagnosis. Although the large majority of these cases are benign, diagnostic approaches to discriminate benign nodules from malignant nodules remain most-unsatisfactory.So we often have to perform thoracoscopic resection with the primary objective of diagnosis. In this study, we examined the clinicopathological findings in the cases of indeterminate pulmonary nodules in which thoracoscopic or open excisional biopsy was performed. **Method:** From a single institutional database, a total of 253 patients diagnosed with lung cancer or suspected lung cancer underwent resection between January 2014 and March 2017. In 155 patients, a histological diagnosis was not obtained preoperatively. This study was intended for 108 patients diagnosed with lung cancer after surgery among the 155 indeterminate pulmonary nodules. **Result:** Out of 155, 108 patients were diagnosed as primary lung cancer by intraoperative frozen section or postoperative pathological examination. Twenty-six patients were diagnosed as metastatic lung tumors, and 21 patients were diagnosed as other, such as benign inflammatory changes. Surgical resection of indeterminate lung nodules (mean diameter 20.6mm, range 3 to 53 mm) were performed in 108 primary lung cancer cases, which represented 52.4% of the 206 resections for lung cancer performed during the study period. There were 57 men and 51 women with an average age of 70.6 years old (47-91 years old). A biopsy needle (13cases) or wedge resection (61cases) was used to the methods of intraoperative diagnosis. The remaining 34 cases performed a final pathological examination after surgery without intraoperative diagnosis. Nineteen small pulmonary nodules that include ground-glass attenuation required preoperative computed tomography-guided lipiodol marking to identify the position of a nodule. The postoperative stage was 0 in 17 patients (16%), IA in 66 (61%), IB in 11 (10%), IIA in 1 (1%), IIA in 3 (3%), IIIA in 8 (7%), and IV in 2 (2%). **Conclusion:** The small pulmonary nodules that include ground-glass attenuation are tricky to diagnose. When CT findings are highly suggestive of lung cancer, we think that positive lung biopsy under thoracoscopic surgery is necessary to detect lung cancer.

Keywords: Video-assisted thoracic surgery, lung cancer, pulmonary nodules

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P2.16-017 SURGICAL TREATMENT OF BRONCHIAL CARCINOID TUMORS: EVALUATION OF SURVIVAL AND PROGNOSTIC FACTORS. A SINGLE-CENTER EXPERIENCE

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Background: Pulmonary carcinoids (PC) are rare malignant neuroendocrine tumors with indolent course. It is estimated that PC overall encompass 1% to 5% of all lung neoplasms. The surgical resection is the preferred treatment modality but the indolent nature of the disease makes interpretation of survival numbers problematic. **Method:** Aims: We report a single institution experience with PCs over a 17-year period to gain a better understanding of prognostic factors related to the management of these rare tumors. Material and Methods: Patients who underwent operations for primary pulmonary carcinoid tumor at National Tuberculosis and Lung Diseases Research Institute in Warsaw, Poland between 1998 and 2015 were identified from the database. Their medical records were reviewed for clinical presentation, tumor spread, pathology, treatment modalities, and survival. **Result:** There were 329 cases of PCs: 217 (66%) typical (TC) and 112 (34%) atypical (AC) carcinoids, with a median follow-up time of 7,6 years. There were 230 females (69,9%) and 99 males (30,1%). The most common symptoms were cough (38,7%), dyspnea (15,9%) and hemoptysis (14%). No patients showed a carcinoid syndrome. There was no correlation between smoking status and PCs. The majority of patients were in stage I disease (67,4%), only 6,4% in stage III and IV (6,4%). Involvement of lymph nodes was present in 49 cases (14,9%), N1 -34 (10,3%) and N2 – 15 (4,6%). Infiltration of bronchial or vessel margin (R1) was revealed in 10 cases (3%). Surgical treatment consisted of: 247 lobectomies (75,1%), 30 pneumonectomies (9,1%), 36 bilobectomies (10,9%), 5 anatomic segmentectomies (1,5%), 8 wedge resections (2,4%), 3 – bronchoplastic procedures without lung resection (0,9%). Radical mediastinal lymphadenectomy was added in all cases. The number of death among the patients with TC and AC was 7 (6,3%) and 31 (14,3%) respectively. Kaplan-Meier 1-, 5-, 10- and 15-year overall survivals for the entire group were 98,8%, 92,8%, 86,8% and 78,6% respectively. **Conclusion:** • PCs are tumors with an excellent prognosis, even in the presence of metastases in lymph nodes and positive surgical margin. • None of the symptoms and stage of tumors as well as the distance of the tumor from the surgical margin did not affect significantly the overall survival. • The age of patients, the type of operation and performance status (ECOG score) had vital importance for overall survival. • Surgical resection is the best and adequate therapy for PCs with high overall survival and disease-free survival but long-time observation is necessary.

Keywords: Surgical treatment, bronchial carcinoid

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P2.16-018 PHRENIC NERVE INJURY AFTER LUNG SURGERY: AN UNDERESTIMATED PROBLEM

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Background: Inadvertent phrenic nerve injury (PNI) during lung cancer surgery is not well-studied. It is not always easy to make a clear-cut diagnosis with routine methods. Very few cases have been reported in literature. The aim of our study is to find an easily accessible and precise way to diagnose PNI and then to evaluate the incidence and its impact in early-stage lung cancer patients undergone minimally invasive surgery. **Method:** The first step was to examine the extent of diaphragm elevation in patients with invasive thymomas in whom phrenic nerve was certainly divided. The distance between the diaphragm and the apex of the chest was calculated on chest X-Ray before (DB: Distance before) and after (DA: Distance after) surgery. The following formula was used: [(DB-DA)/DB]x100. The result (mean+SD) was

used as criteria for diagnosing PNI. The second step was to study PNI in early-stage lung cancer patients undergone VATS lobectomy using the above criteria. **Result:** Diaphragm elevation was found to be 24.24 +/- 6.2% in 22 invasive thymoma-patients and therefore, 30% was adopted as criteria for the diagnosis of PNI. Among 567 consecutive patients with early-stage lung cancer recruited from January 2014 to December 2016, 43 (7.6%) were diagnosed to have PNI (Table 1). No correlation was detected between PNI and location of the lesion or extent of lymph node dissection. Neither was there any difference in post-operative complications or length of hospital stay. But comparing spirometry data before and 6 months after surgery, reduction in FEV1, FVC, and DLCO was significantly greater in patients with PNI. **Conclusion:** We found an easily accessible way to diagnose precisely PNI in lung cancer patients receiving VATS lobectomy. Inadvertent PNI during minimally invasive surgery seems to be underestimated, and it is associated with significant reduction in pulmonary function of the patient.

Keywords: Thoracic Surgery, Phrenic nerve injury, lung cancer

	Patients with PND	Patients without PND	P-value
Case	43 (7.58%)	524 (92.4%)	
Gender			
male	17 (40%)	243 (46%)	0.387
female	26 (60%)	281 (54%)	
Age	62.1±9.4	59.6±9.3	0.085
Co-morbidity			
HBP	13 (30%)	143 (27%)	0.404
DM	8 (19%)	57 (11%)	
COPD	2 (4.6%)	15 (2.9%)	
CHD	0 (0%)	7 (1.3%)	
Arrhythmia	4 (9.3%)	14 (2.6%	
History of MT	1 (2.3%)	17 (3.2%)	
Location			
RU	20 (47%)	199 (38%)	0.412
RM	2 (4%)	64 (12%)	
RL	5 (12%)	93 (18%)	
LU	9 (21%)	89 (17%)	
LL	7 (16%)	79 (15%)	
Side			
left	16 (37%)	168 (32%)	0.488
right	27 (63%)	356 (38%)	
Lobe			
upper	29 (67%)	288 (55%)	0.508
lower/middle	14 (33%)	236 (45%)	
T stage			
T1/Tis	29 (68%)	314 (60%)	0.494
T2	13 (30%)	180 (34%)	
T3	1 (2%)	30 (6%)	
N stage			
N0	36 (84%)	415 (79%)	0.678
N1	3 (7%)	35 (7%)	
N2	4 (9%)	74 (14%)	
Lymphadenectomy			0.211
sns	21 (49%)	205 (39%)	
snd	22 (51%)	319 (61%)	
LOH (days)	6.51+3.78	6.35±4.05	0.802
PO-morbidity	1 (2.3%)	48 (9.1%)	0.125
Spirometry			
FEV1 Pre-operation	2.53±0.57	2.40±0.58	0.346
FVC Pre-operation	3.16±0.71	2.95±0.76	0.246
DLCO Pre-operation	19.22±4.43	18.50±6.60	0.644
Rate of decline in FEV1%	36.1±19.5	19.5±16.7	0.000
Rate of decline in FVC%	35.3±19.1	17.4±14.6	0.000
Rate of decline in DLCO%	22.5±9.7	14.9±12.1	0.009

HBP: High blood pressure
DM: Diabetes mellitus
COPD: Chronic obstructive pulmonary disease
CHD: Coronary heart disease
Sns: systemic limph node sampling
Snd: systemic limph node dissection MT: Malignant tumor
BPF: Bronchopleural fistula
CPAP: Continuous positive airway pressure
PE: Pulmonary embolism
RNLP: Recurrent laryngeal nerve paralysis

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P2.16-019 IMPROVING SURVIVAL WITH A LYMPH NODE (LN) COLLECTION KIT FOR NON-SMALL CELL LUNG CANCER (NSCLC) RESECTIONS

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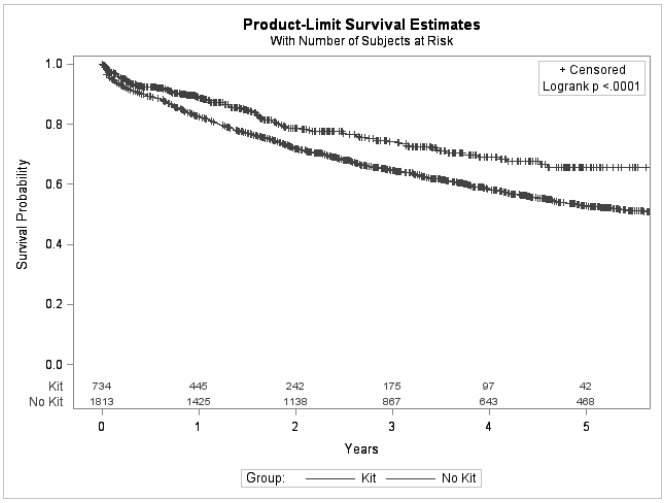
Background: Poor pathologic nodal staging impairs overall survival (OS) after curative-intent surgical resection of NSCLC. We implemented a LN collection kit and previously demonstrated how it improves pathologic nodal staging. We now report its survival impact. **Method:** Using a prospective step-wedge design, kits were implemented for curative-intent surgical resections from 2009-2017 in 11 hospitals within 4 contiguous US Dartmouth Hospital Referral Regions. OS was analyzed with the Kaplan-Meier method. Crude (HR) and adjusted (aHR) hazard ratios with 95% confidence intervals (CI) are presented from Proportional Hazards Models adjusted for clustering by surgeon. Covariates in adjusted models include: age, sex, histology, tumor grade, extent of resection, T and M categories, and number of comorbidities. **Result:** The LN kit was used in 734 of 2,547 (29%) resections. All demographic and clinical characteristics, including age, sex, race, health insurance coverage and preoperative stage distribution were similar between kit and non-kit cases. Aggregate 1, 3, 5-year OS: 89%, 74%, 66%(kit) vs. 83%, 65%, 53% (non-kit) ($p < 0.0001$, Fig.1).

Clinical stage stratification (kit v non-), 5-year OS: I, 68% vs. 58%, (p-value=0.0038); II, 68% vs. 40%, (p=0.0045); III, 57% vs. 42%, (p=0.0412). Pathologic stage stratification (kit v non-) 5-year OS: I, 72% vs. 59% (p=0.0082), II, 60% vs. 44% (p=0.0403); III, 48% vs. 36%, p =0.0179). For both clinical and pathologic Stage IV, survival did not differ. Kit cases had a 30% lower hazard of death compared to non-kit cases: HR 0.67 (CI[0.55,0.80], p<0.0001) and aHR: 0.70 (CI[0.54,0.92], p<0.0001). Results remained statistically significant after multiple sensitivity analyses excluding sub-lobar resections, 60-day mortality, non-adopting surgeons, and excluding the 48 months of retrospective baseline control data (aHR: 0.28 to 0.73). Operating time, perioperative complication rates, and duration of hospitalization were similar between groups.



Conclusion: Intraoperative specimen collection with a LN kit improves long-term NSCLC survival.

Keywords: Lung cancer survival, curative-intent resection, early stage lung cancer

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P2.16-020 SURGICAL STRATEGY FOR SYNCHRONOUS MULTIPLE LUNG CANCER WITH GROUND GLASS OPACITY

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Background: With the recent advances of diagnostic imaging modalities such as high-resolution computed tomography (HRCT), the detection rate of multiple synchronous lung cancer with ground-glass opacity (GGO) has increased. In clinical practice, preoperative pathological diagnosis of GGO lesions by transbronchial biopsy is difficult. It is necessary to develop the optimal surgical strategy that achieves both accurate diagnosis and curative resection. We recently encountered three cases of synchronous multiple lung cancer with GGO. **Method:** Case 1: A 68-year-old male had abnormal shadows detected on chest computed tomography (CT). HRCT showed a 3.5cm-in-diameter part-solid nodule in the right upper lobe (RUL), a 2.5cm-in-diameter part-solid nodule in the right lower lobe (RLL), and a 1.5cm-in-diameter pure ground-grass nodule (GGN) in the left lower lobe (LLL). Thoracoscopic right upper lobectomy and right S6 segmentectomy was performed. The histopathological diagnosis of the RUL tumor was well-to-moderately differentiated adenocarcinoma and RLL tumor was well differentiated adenocarcinoma. These tumors were found to harbor different epidermal growth factor receptor (EGFR) gene mutation. The LLL tumor is followed up by CT scan. Case 2: A 71-year-old female had an abnormal shadow incidentally detected on chest radiography. HRCT showed a 1.0cm-in-diameter pure GGN in RUL and a 3.0cm-in-diameter part-solid nodule in left upper lobe (LUL). To achieve a minimal invasive approach for bilateral lesions, we planned to perform staged bilateral surgery that the limited resection precedes the anatomical resection. Thoracoscopic wedge resection of RUL was performed as the first operation, then thoracoscopic left upper lobectomy was performed as the second. The histopathological diagnosis of both tumors were well-to-moderately differentiated adenocarcinoma with different EGFR mutation status. Case 3: A 68-year-old female had abnormal shadows detected on chest CT. HRCT showed a 1.5cm-in-diameter pure GGN in RUL and a 1.0cm-in-diameter pure GGN in LLL. Thoracoscopic wedge resection of LLL was performed as the first operation, then thoracoscopic right S3 segmentectomy was performed as the second. The histopathological diagnosis of the LLL tumor was well-to-moderately adenocarcinoma and the RUL tumor was well differentiated adenocarcinoma. **Result:** All three cases had an uneventful postoperative course with no evidence of recurrence. **Conclusion:** In case of multiple tumors, we decide surgical procedures based on the size, number, location, and radiological findings of the tumors. We select combination surgery with anatomical resection and limited resection, and avoid bilobectomy if possible. Additionally, the thoracoscopic approach for multiple lung cancer seems to be a good option to perform minimally invasive surgical procedures.

Keywords: Thoracoscopic surgery, ground-glass opacity, multiple lung cancer

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P2.16-021 MALIGNANT MELANOCYTIC NEOPLASM: A RARE PRESENTATION OF A LARGE MEDIASTINAL MASS

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Background: Malignant melanocytic neoplasm is a highly malignant tumour derived from melanocytes. It occurs most commonly in the skin and mucous membranes while occurrence in the mediastinum is extremely rare. **Method:** Section not applicable **Result:** Section not applicable **Conclusion:** We report a case of a young female who presented with shortness of breath and chest tightness. Further imaging revealed a large anterior mediastinal mass with compression of the pulmonary vessels and a few lung nodules. A Chamberlain procedure was performed and showed a highly pigmented lesion. The histology returned as malignant melanocytic neoplasm. She was then started on pembro.

Keywords: Melanoma, Surgery, mediastinal mass

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P2.16-022 INITIATIVE FOR EARLY LUNG CANCER RESEARCH ON TREATMENT: PILOT IMPLEMENTATION

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Background: We have initiated a new *multi-center, international collaborative cohort* study, the Initiative for Early Lung Cancer Research for Treatment (IELCART), which focuses on identifying optimal treatment for early stage lung cancer An issue under discussion is the extent of surgery (i.e., sublobar resection and no mediastinal lymph node resection) in order to decrease the length and morbidity of the surgical procedure, preserves pulmonary function, and increases the likelihood of resection of future new occurrences of lung cancers. The role of Stereotactic Body Radiation (SBRT), and for certain cases, Watchful Waiting (WW) also needs to be better delineated. Increasingly, the power of large prospective databases collected in the context of clinical care is being recognized as providing important information. **Method:** Based on an extensive literature review, scientific articles, and a series of focus sessions with patients and treating physicians, a common protocol has been developed. Relevant data forms were developed for both physicians and patients, both for pre- and post-surgery to account for potential confounders. These forms have been tested and entered into a web-based data collection system that also includes relevant imaging data. Initial enrollment focused on surgery. **Result:** Initial enrollment was limited to surgical clinics of 8 surgeons and a total of 174 patients (94 women, 80 men) agreed. Average age was 67.5 years and pack-years of smoking was 31.4. Patients stated that the internet was the most frequent source of information (35%), while family/friends, medical literature were used much less frequently (each <20%). Factors influencing the patient pre-treatment choice was that the physician thought it was best (93%) or what would provide the best outcome (87%); only 38% got a second opinion. The surgeon's choice of procedure depended mainly on the location (75%), size of the nodule (64%), and the ability to have negative parenchymal margin (40%), with other considerations being much less likely (<26%). There was good agreement between patients' and surgeons' perceptions of the procedure, although the patients not fully prepared about the post-treatment consequences of surgery. Patients also thought that support groups were important in patients' decisions on what was the best surgery. **Conclusion:** These results together with quality of life information and focus sessions suggest that more support in the post-operative phase of the treatment would be beneficial. Within the next 3 years, we anticipate to have statistically meaningful results to start to compare outcomes of alternative treatments.

Keywords: comparative effectiveness, radiation therapy, Surgery

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P2.16-023 CHANGES OF THE PULMONARY ARTERY AFTER RESECTION OF STAGE I LUNG CANCER

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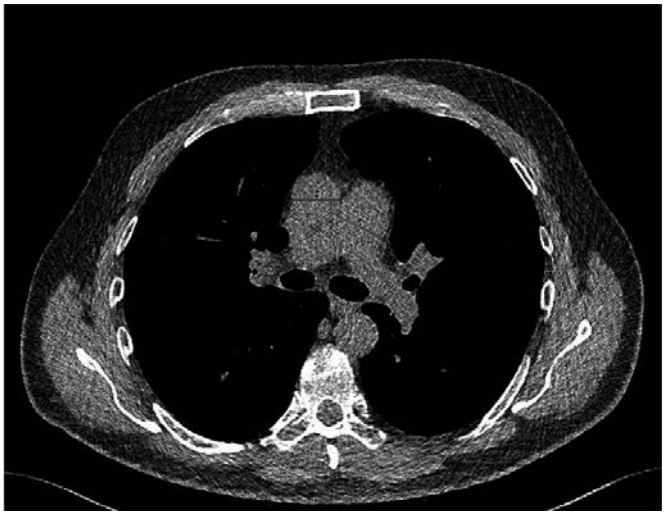
Background: Radiologists focus on the anatomic changes in the lung itself when interpreting postoperative surveillance CT scans, but the anatomic and physiologic

effects of lung resection on the other organs of the thorax, specifically the pulmonary artery (PA), have not been well studied. Potential variations in PA size over time have been recognized as predictors of post-surgical complications and the development of pulmonary hypertension. **Method:** The International Early Lung Cancer Action Program (I-ELCAP) database was queried for lung cancer patients who underwent lobectomy and had both preoperative and postoperative CT imaging. Case-specific details were previously recorded in the database as per I-ELCAP protocol. All surgeries were performed by general thoracic surgeons. All CT imaging for each patient was reviewed by a fellowship-trained chest radiologist.



Result: Among the 142 subjects who underwent lobectomy, the median follow-up time from the pre-surgical CT to the last reviewable CT was 53.2 months (IQR: 27.9-100.4 months). The average increase in the size of the main pulmonary artery (mPA) was 1.5 mm (19.9 mm to 21.4 mm, $P < 0.0001$). There was also a significant increase between the pre-surgical CT and the initial postoperative CT which was on average 12.6 months later from 19.9 mm to 20.7 mm ($P = 0.0002$). Considering patients with and without CT evidence of emphysema, the 82 with emphysema had a smaller average change of the main PA between the pre-surgical and the last reviewable CT than the 60 without emphysema (1.0 mm vs. 1.8 mm, $P = 0.08$). **Conclusion:** Patients undergoing lobectomy appear to be at increased risk for enlargement of their pulmonary artery diameters after surgery. These results show that a focus on all the organs in the thorax, not just the lungs themselves, is important when evaluating postoperative lung resection CTs.

Keywords: pulmonary hypertension, lung cancer surgery, post-surgical complications

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P2.16-024 EFFECT OF RESECTION OF STAGE 1 LUNG CANCER ON LUNG VOLUME

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Background: The anatomic and physiologic effects of lung resection for early stage lung cancer patients have not been extensively reported. We hypothesize that patients who have undergone lobectomy or wedge resection will have reduced lung volume on the affected side immediately after surgery while the lung volume on the opposing side may increase to compensate. **Method:** The Mount Sinai database was queried for stage 1 lung cancer patients who underwent lobectomy or wedge resection and had both pre-operative and postoperative CT imaging. Surgeries were performed by thoracic surgeons. The lung volumes on all CT scans were measured using previously published research software including actual volumes for each lung (left and right) at each time point as well as a set of volumes normalized to the overall chest volume in order to compensate for differences in inspiration. **Result:** In the cohort of 21 patients who met the above criteria, the median follow-up time from the date of surgery to the most recent CT was 44.6 months (IQR: 23.5-94.7 months). The median age was 63 and the median pack years was 40. There were 2 patients for which only one post-op scan was successfully analyzed; the remaining cases all had two postop scans. In 20 of the 21 patients, the lung volume on the side where the surgery occurred was reduced in the first postop CT scan (average reduction in volume of 5.6%). The change in volume of the contralateral side (not undergoing surgery), was highly variable, with 11 cases showing an increase in volume on both post-op scans, 2 cases showing a decrease, and 8 cases showing an increase in volume at the first postop scan followed by a decrease in volume on the second post-op scan. **Conclusion:** Stage 1 lung cancer patients undergoing resection have reduced lung volume on the side of surgery, however there was marked variability in the contralateral lung suggesting that the extent to which patients compensate post operatively is complex and dependent on many factors.

Keywords: lung volume, post-surgical complications, Chest CT

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P2.16-025 ACCURACY OF MULTIDISCIPLINARY EVALUATION OF SMALL SOLITARY PULMONARY NODULES IN A PORTUGUESE PRIVATE HOSPITAL

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Background: A solitary pulmonary nodule (SPN) is a common and increasing clinical problem, mainly due to the lung cancer (LC) screening programs and easier access to complementary diagnostic tests. Differential diagnosis is broad and often challenging for decision making, particularly in small and not accessible lesions. The process of selecting the right strategy must address the probability of malignancy, nodule characteristics observed on CT/PET-CT, patient preferences and institutional-related expertise. The aim of this study was to evaluate the accuracy of the multidisciplinary lung cancer tumour (MLCT) board team in the management of SPN. **Method:** We retrospectively reviewed all SPN patients who underwent surgical resections between January 2015 and March 2017. All patients were evaluated at a MLCT meeting. We characterised demographic, clinical and radiological features, surgical procedure, histology and outcomes. **Result:** We included 73 patients, 37 male (50.7%), with a mean age of 63.3±10.2, 64.4% smokers (current or former) and none with asbestos/radon exposure. Twenty-five patients (34.2%) had previous history of cancer and 5 (6.8%) of tuberculosis. Emphysema was present in 21 patients (28.8%). Fifty-six were solid SPN (6–20 mm) and 17 subsolid SPN (9-18 mm): 15 with solid component (2-13.5 mm) and 2 pure ground glass nodules (10 and 12.3 mm). Of the 73 patients, 11 (15.1%) had a definitive histological result before the surgical intervention: 10 LC and 1 metastasis. Among patients without diagnosis (n=62), frozen section was performed in 45 patients (61.6%): 31 of these (70%) were malignant disease (25 LC and 6 metastasis) and 14 were benign lesions. In this group, we performed 17 lobectomies, 15 anatomic segmentectomies and 13 wedge resections. All patients with LC underwent mediastinal lymph node dissection (MLND). Among the 25 patients with LC, 7 were adenocarcinoma in situ and 18 invasive lesions (17 in stage I). In the other 17 cases without previous diagnosis, a direct surgery was performed, based either on the location of the lesion, size or clinical suspicion. Twelve of these patients (70.6%) were confirmed to have LC in the final pathology evaluation (all invasive LC in stage I). They underwent an upper bilobectomy, 10 lobectomies, 3 anatomic segmentectomies, all with MLND, and 3 wedge resections. No major complications were reported. **Conclusion:** This study suggests that surgery is a safe strategy in the diagnosis and treatment of SPN without previous diagnosis.

Keywords: solitary pulmonary nodule, Surgery, multidisciplinary evaluation

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P2.16-026 SURGICAL TREATMENT FOR METASTATIC LUNG TUMORS FROM VARIOUS SARCOMAS

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Background: Sarcomas are known to be malignant and aggressive tumors, and often develop multiple pulmonary metastasis. Although systemic therapy is a treatment of choice for metastatic lung tumors, effective treatments have not yet been established. Surgical resection for metastatic lung tumors is a therapeutic option to control the disease, while it is not a curative therapy. **Method:** Between 2006 and 2014, 129 sarcoma patients who underwent pulmonary metastasectomy in Okayama University Hospital 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 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 of sarcoma were performed without major complication, indicating 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: Surgery, metastatic lung tumor, sarcoma

P2.16-027 COMPARISON OF SINGLE CHEST TUBE VERSUS DOUBLE CHEST TUBE DRAINAGE AFTER LUNG RESECTION FOR THE TREATMENT OF NON-SMALL CELL LUNG CANCER

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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 efficacy of chest drainage after lung resection using single chest tube versus two chest tubes in patients with non-small cell lung cancer (NSCLC). **Method:** Single-centre prospective randomized trial including patients who underwent anatomical lung resection for NSCLC between February 2016 and may 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 mmHg was used, switched on the 1st postoperative day to -8 mmHg. Chest tubes were removed in the absence of air leak for more than 24 hours, and the chest tube output <250 mL/day. **Result:** There were 357 patients enrolled, including 219 men, mean age 64.43 years (range: 22-84) and 138 women, mean age 64.06 years (range: 24-85). One chest tube was used in 176 patients, including 50 cases of VATS lobectomy and 126 cases of open lobectomy. Two chest tubes were used in 181 patients, including 35 patients after VATS lobectomy and 146 after open lobectomy. In the single chest tube group there was significantly shorter air leak time (4.25 vs. 4.5 day; p = 0.001, drainage time (3.6 vs 4.7 day; p = 0.0001), and postoperative hospital stay (6.15 vs 7.5 day; p <0.0011. Multivariate regression analysis demonstrated that time of chest tube drainage after cessation of the air leak depends on the volume of chest tube output in the first 6 hours (p = 0.00001) and the time of air leak (p = 0.0014), regardless of the number of drains. **Conclusion:** Single chest tube after anatomical lung resections is associated with shorter air leak, shorter drainage time, shorter hospital stay compared to two chest tube drainage. Routine use of single chest tube is safe and effective treatment.

Keywords: Lung cancer, digital chest drainage system, chest tube, air leak, pulmonary lobectomy.

P2.16-028 ARE WE DOING THE RIGHT THING? OVERALL SURVIVAL & INTERMEDIATE OUTCOMES FOLLOWING LUNG METASTASECTOMY

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Background: The ability to constantly metastasize remains a truly challenging obstacle for cancer patients . Historically in the past , any local surgical treatment in patients with systemic malignant disease is considered without any prognostic benefit , this has since evolved with many studies confering huge success rates with excellent prognostic benefits . We hereby report our experience over the last 5 years at Wellington Regional Hospital , Cardiothoracic unit . **Method:** A retrospective study was undertaken in series of cancer patients with colorectal , melanoma , breast , sarcoma & renal metastatic disease undergoing pulmonary metastasectomy , from year 2011 to 2015 . These data was identified & stratified into groups using hospital patient database & ORSOS theatre database **Result:** Total of 61 patients had pulmonary metastatectomies in 5 years , of which 14 were done via VATs wedge resection .Population age between 34 to 86 years old with a M: F ratio of 2:1 . Average age was 63 years . A further 4 patients had multiple metastatectomy on ipsilateral side . 45 patients were non-smoker in this cohort . Average in-hospital stay was 7.83 days , with 3 patients requiring post op ICU admission . 47 patients had pre-op epidural catheter for pain management . Complications include 6 patients needing to return to theatre for suspicion of lung torsion , bronchopleural fistula , haemothorax and 3 patients had torrential air leaks .No major complications noted . Majority had colorectal & melanoma metastases . No mortality at 30 days . 87% survived at 1 year . Total of 38 patients are still alive at present . **Conclusion:** Using MDM as a tool , these carefully selected surgical patients underwent pulmonary metastasectomy for metastatic diseases which confers continual prognostic & survival advantage in this group . Overall 1 year survival seems resonable & surprisingly excellent given the overall bad prognosis of metastatic disease in general .

Keywords: metastatectomy , NSCLC , wedge resection

P2.17-001 PULMONARY INFLAMMATORY MYOFIBROBLASTIC TUMOR WITH TPM4-ALK TRANSLOCATION

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Background: ALK is a receptor tyrosine kinase that was discovered in anaplastic large cell lymphoma in the form of a fusion protein. To pick-up the patients with ALK-rearrangements is important to select the individual therapy as ALK inhibitor for mainly lung adenocarcinoma. There are several fusion partners with ALK 3' region. **Method:** A 35-year-old woman with a short-breath and cough was referred and admitted taking a therapy for lung tumor in our hospital. By the bronchoscopic biopsy, she was suspected pulmonary IMT, but correct diagnosis was not indicated. Right upper wedge lobectomy was done. By the pathological examination of the permanent surgical resected tissue, the final diagnosis was pulmonary IMT. **Result:** The immunohistochemistry of ALK by using the iAEP method was positive. We extracted the RNA from frozen surgical resected tumor tissue, and prove the TPM4-ALK by 5' RACE and RT-PCR. The preoperative bronchial biopsy specimen was also found positive for anti-ALK immunohistochemistry with iAEP method. **Conclusion:** The molecular therapeutic drug was expected as personalized therapy for the tumor with ALK translocation as oncogenic driver. We should examine the ALK protein expression and translocation about the cases of lung cancer and IMT by using adequate ALK immunohistochemistry system. We experienced a case of pulmonary IMT with TPM4-ALK translocation.

Keywords: Pulmonary inflammatory myofibroblastic tumor, ALK translocation, 5'RACE

P2.17-002 PULMONARY AND MEDIASTINAL PARAGANGLIOMAS: RARE ENDOTHORACIC MALIGNANCIES WITH CHALLENGING DIAGNOSIS AND TREATMENT

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Background: Tumors originating from chromaffin cells are located in 90% of cases in the adrenal gland and called pheochromocytomas, while in 10% of cases have an extra-adrenal origin (paraganglionic cells scattered throughout the body) and are termed paragangliomas. Endothoracic paragangliomas can arise in the lung and mediastinum, may have neuroendocrine activity, secreting catecholamines, or be non-functional, incidental, in asymptomatic patients or causing mass effect symptoms. Even if rare and with low grade of malignancy, they can present an aggressive behaviour, developing local infiltration of surrounding organs and distant metastases. A correct pathological diagnosis and radical surgical treatment are fundamental to obtain clinical recovery. We report our experience with three cases of endothoracic paragangliomas, in order to point out difficulties in diagnosis and problems related to surgical treatment. **Method:** From January 2009 to December 2016, we treated 3 patients (2 women, 1 man), mean age 67 years, with histological diagnosis of paraganglioma: 2 pulmonary, 1 mediastinal. All patients were asymptomatic for catecholamine-secreting syndromes; the two cases with pulmonary localization showed no other symptoms, while the mediastinal one had cough and dyspnea, due to compression by the mass, and blepharospasm. Imaging diagnosis was based on chest CT scan in pulmonary cases, chest CT and MRI scan for the mediastinal mass, which allowed to define vascularization and relationships with adjacent structures. No patient had preoperative histological diagnosis. Intraoperative pathological examination of the two pulmonary forms was suggestive for malignancy (extensive necrosis, high proliferative index, hypervascularization), thus a right pulmonary wedge resection was performed in one case, a right upper lobectomy in the other one. The hypervascularized mediastinal lesion, located in the middle mediastinum, tenaciously adherent to the superior vena cava, the aortic arch, the right branch of the pulmonary artery and the trachea, was completely removed after challenging isolation and section of numerous vascular pedicles. **Result:** Postoperative course was uneventful in all cases. No patient received adjuvant treatments. At a median follow-up of 35 months (range: 6-90 months), two patients are alive, without local or distant recurrence; one patient (with pulmonary involvement) died 6 months after surgery, due to disease progression. **Conclusion:** Endothoracic paragangliomas, rare and often asymptomatic tumors, are of difficult diagnosis and should be considered malignant tumors, due to the potential aggressive behaviour of cases with high mitotic index and the frequent possibility of recurrence. After complete excision, long-term prognosis is generally good. However, even after surgical removal, a close and periodical follow-up is mandatory.

Keywords: pulmonary and mediastinal paragangliomas, diagnosis, treatment

P2.17-003 IS COMPLETE RESECTION MANDATORY FOR MEDIASTINAL GERM CELL TUMOR WHICH SHOWS SEVERE ADHESION TO GREATER VESSELS?

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Background: Surgical resection for mediastinal germ cell tumors is one of important modality to cure. But it sometimes shows severe adhesion to greater vessels, complete resection without vessel replacement is difficult. But, no viable cells are found in the resected specimen in many cases. Is vessel replacement really needed for this situation? The aim of this study is to confirm whether complete resection is really needed for mediastinal germ cell tumor. **Method:** The data of 13 patients with resected mediastinal germ cell tumor were retrospectively analyzed for recurrence. **Result:** Median follow up period was 72.2 months. All cases were male. Mean age was 33.1 years old. Pathological diagnosis was mature teratoma in 5 cases, seminoma in 5 and non-seminomatous malignant germ cell tumor in 3. Seven cases received preoperative chemotherapy. Mean tumor size before surgery was 7.1cm. Median sternotomy was performed in 10 cases and posterolateral approach in 3 cases. Mean operative time was 225 minutes and blood loss was 228 g. Mean postoperative in-hospital duration was 8.2 days. There were not any life-threatening postoperative complications. Macroscopic residual tumor (R2) was found in 5 cases; 2 mature teratoma and 2 seminomas and a germ cell tumor because of severe adhesion to aorta. Four cases received adjuvant therapy. But in R2 case; 2 of mature teratoma and a seminoma without viable cell did not receive adjuvant therapy. Only a case of non-seminoma with complete resection, which did not achieve negative tumor marker preoperatively, showed distant metastases 4 months later after surgery. **Conclusion:** The surgery for mediastinal germ cell tumor in selected situation can show good survivability without recurrence. To balance the invasiveness and curability, minimizing the extent of surgery; not performing greater vessel replacement is one of choice.

Keywords: mediastinal germ cell tumor, complete resection, vessel replacement

P2.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - TUESDAY, OCTOBER 17, 2017 - 09:30-16:00

P2.17-004 SALVAGE SURGERY FOR PULMONARY METASTASES IN PATIENTS WITH TESTICULAR GERM CELL TUMORS

S. Kikuchi[1], Y. Sekine[1], K. Sugai[1], T. Kawamura[1], S. Ueda[1], Y. Saeki[1], N. Kobayashi[1], Y. Goto[1], Y. Minami[1], M. Onizuka[1], T. Kojima[2], K. Kawai[2], H. Nishiyama[2], H. Ichimura[3], Y. Sato[1]

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Background: Germ cell tumors of testicular origin are the most common malignancy in young males. The lungs and the retroperitoneal space are frequently the initial sites of metastatic disease. Salvage surgery is an important treatment modality for residual post-chemotherapy pulmonary masses. We analyzed the prognostic predictors of survival in the patients after pulmonary metastasectomy. **Method:** Between September 1989 and December 2015, 32 patients underwent pulmonary resection of thoracic metastases following cisplatin-based chemotherapy. Germ cell tumors of mediastinal origin were excluded. These patients' records were subsequently reviewed. **Result:** All patients underwent high orchidectomy and cisplatin-based chemotherapy. The primary tumor histology demonstarated 2 seminomas and 30 nonseminomatous germ cell tumors. Twenty-three patients (72%) received two or more chemotherapy regimens. International Germ Cell Cancer Collaborative Group classification, TNM factors, and serum tumor marker level at diagnosis were not associated with prognosis after pulmonary metastasectomy. The mean age at pulmonary surgery was 31.9 years. The surgical procedures included wedge resection in 23 (72%) and segmentectomy/lobectomy in 9 (28%). There were no perioperative deaths and major postoperative complications. The overall 5-year survival rate was 73% after an average follow-up of 55 months. The pathology of residual pulmonary masses revealed viable tumor cells in 12 patients (38%), necrosis alone in 18 patients (56%), and mature teratoma alone in 2 patients (6%). Preoperative increased lactic dehydrogenase (LDH) levels were significantly associated with the viable tumor cells of residual masses. The size of pulmonary metastases has not been found to be statistically related to malignant tumor cells. A significantly poor survival was observed using univariate analysis in patients with preoperative high free-βHCG (p=0.012), high intact HCG (p=0.031), high LDH (p<0.001), removing 5 or more lung metastases(p=0.012), and viable tumor cells of residual masses (p=0.026). **Conclusion:** We conclude that pulmonary resection in metastatic testicular tumors is a safe and effective treatment strategy. Increased tumor marker levels, free-βHCG/intact HCG or LDH, removing 5 or more lung metastases, and viable tumor cells of residual masses were identified as prognosis-related criteria for a poor prognosis.

Keywords: pulmonary metastasis, testicular germ cell tumors, salvage surgery

POSTER SESSION 3 | WEDNESDAY, OCTOBER 18, 2017

P3.01: ADVANCED NSCLC - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-001 COMPARISONS OF TWO PLASMA EGFR PLATFORMS (DDPCR AND COBAS) IN PATIENTS WITH RADIOLOGICAL METASTATIC LUNG CANCER

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Background: The treatment for stage IV non-small cell lung cancer relies on molecular diagnosis on tumor DNA for guiding systemic therapy. Liquid biopsy provides a timely and non-invasive way of detecting potential therapeutic targets and spares the need of performing a confirmatory biopsy procedure in patients with a positive result. **Method:** We report local experience on epidermal growth factor receptor (EGFR) mutations detected by two platforms (droplet digital polymerase chain reaction (ddPCR) technique and Cobas EGFR v2) on cell free tumor DNA from radiological stage IV lung cancer patients, guiding first- and second-generation EGFR tyrosine kinase inhibitor (TKI) therapy. All these patients who had either plasma EGFR platforms done from Nov 2015 to May 2017 are retrospectively identified and analyzed. **Result:** 97 patients identified. 11 out of 39 (28.2%) and 16 out of 58 (27.6%) has detectable EGFR mutation in plasma by using ddPCR and Cobas techniques respectively. Much higher detection rate is noted in never smokers (23/46, 50.0%) compared with chronic/ever smokers (4/41, 9.8%) and is highly statistically significant for difference (p-value: <0.001). The types of EGFR mutations detected are as follows: ddPCR method: 4 (36.4%) del 19, 7 (63.6%) L858R. Cobas method: 5 (31.3%) del 19, 9 (56.3%) L858R, 2 (12.5%) G719X. 20 (74.1%) patients were eventually put on 1st or 2nd EGFR-TKI as first line treatment and, among those, 17 (85%) attained partial response as the best treatment response and the median PFS and OS of is not reached. Among the 56 patients who obtained tissue biopsy/cytology along the course of disease, 6 (10.7%) of which carries histology (3 squamous cell carcinoma, 1 peripheral nerve sheath tumor, and 1 small cell carcinoma and 1 large cell tumor neuroendocrine tumor) that›s not normally sent for EGFR molecular testing, as well as 11 (19.6%) patients having NSCLC-NOS histology only. **Conclusion:** ddPCR and Cobas EGFR v2 platforms have similar detection rate and chance of avoiding the need of a confirmatory tissue biopsy. A simple clinical history of smoking status determines the yield of a positive result. Plasma liquid biopsy provides a non-invasive and promising way for treatment initiation in radiological lung cancer.

Keywords: Cobas EGFR v2, ddPCR, liquid biopsy

P3.01: ADVANCED NSCLC - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-002 CONCURRENT EGFR T790M SECONDARY MUTATION AND EMT IN A LUNG ADENOCARCINOMA PATIENT WITH EGFR TKI DRUG RESISTANCE

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Background: Almost all EGFR-mutant lung cancers develop resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs). Several mechanisms for this acquired resistance have been identified, including development of an EGFR T790M mutation, MET amplification, hepatocyte growth factor (HGF) overexpression, loss of PTEN expression, epithelial to mesenchymal transition (EMT) and transformation to small cell lung cancer. **Method:** We presented a lung cancer patient with EGFR exon 19 deletion who was resistant to EGFR TKI treatment during disease progression. The original lung tumor started to enlarge and bred a secondary growing nodule adjacently. A left upper lobectomy plus systematic mediastinal lymphadenectomy by VATS was performed after a whole body evaluation which had no sign of extrapulmonary abnormalities. The pathological examination, genetic sequencing, and histological staining of E-cadherin and Vimentin were performed on the TKI resistant postoperative specimens. **Result:** The original lung tumor was confirmed to be adenocarcinoma according to the typical morphology and positivity of TTF1 and CK7. The secondary lung tumor has sarcomatoid histology showing a more spindle-like mesenchymal morphology with CK and Vimentin positivity. Next generation sequencing (NGS) test confirmed that the original lung adenocarcinoama retained EGFR exon 19 deletion but was also found T790M mutation in EGFR exon 20. The secondary sarcomatoid carcinoma retained EGFR exon 19 deletion as well. Besides, sarcomatoid carcinoma had genetic mutation on FANCL and BCL2L2, and amplification on CDK4, MDM2, APFRP1, GNAS, CIC, FANCE, Notch4 and AKT2. In addition, in comparison with adenocarcinoma from biopsy and postoperative specimens, the second growing sarcomatoid tumor is strongly positive for Vimentin and nearly negative for E-cadherin, indicating that sarcomatoid histology probably underwent EMT. **Conclusion:** The clinical implication of this case provides significant insights into our understanding that two or more mechanisms might be involved simultaneously in the EGFR TKI resistance. Therefore, if possible, it is necessary to perform tumor biopsies after the development of resistance to identify the best treatment options for patients.

Keywords: drug resistance, EGFR-TKI

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-003 STUDY OF THE RELATIONSHIP BETWEEN EGFR MUTATION STATUS AND BONE METASTASIS IN ADVANCED LUNG ADENOCARCINOMA

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Background: To investigate the relationship between EGFR mutation status and bone metastasis in lung adenocarcinoma. **Method:** We collected the data of 331 patients with advanced lung adenocarcinoma, and the status of EGFR mutation was detected by RT-PCR. Follow-up these patients was performed. **Result:** 331 cases of advanced lung adenocarcinoma, EGFR mutation rate was 52.2%. The incidence of bone metastases (54.9%) and brain metastases (29.4%) with EGFR mutant patients was higher than that wild type. Compared with the number of metastases, EGFR mutant bone metastases were more than 2 and more, and the proportion of wild type single-site metastasis was more. The median survival of bone metastases in advanced lung adenocarcinoma was 14.7 months. EGFR gene mutant group, bone metastasis group median survival in 18.2 months, no bone metastasis group median survival in 21.8 months. In the wild-type group, the median survival of the bone metastases group was 11.5 months, and the median survival in the non-bone metastases group was 15.5 months. **Conclusion:** EGFR mutations in patients with advanced lung adenocarcinoma are more likely to develop bone metastasis and brain metastasis.

Keywords: lung adenocarcinoma, EGFR, bone metastasis

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-004 THE UNDERESTIMATED ROLE OF BRONCHIAL WASHING FLUID IN THE DETECTION OF EGFR MUTATION FROM LUNG CANCER PATIENTS

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Background: The aim of the current study was to examine the clinical application of BWF samples in detecting epidermal growth factor receptor (EGFR) mutations in a large sample set of NSCLC patients. **Method:** In diagnostic bronchoscopic examinations, before or after biopsy to target lesions, subsequent bronchial washing by saline was performed. Thereafter, EGFR mutation testing for both supernatant and sediment of BWF and histologic tissues was performed via amplification refractory mutation system real-time PCR (ARMS RT-PCR) assay. **Result:** A total of 127 cases of histologic and corresponding BWF samples of patients underwent bronchoscopy for suspected lung malignant tumor lesions on chest radiography were successfully obtained. Of these, 72 cases were pathologically confirmed to be NSCLC based on forceps biopsy samples and EGFR mutations were identified in 26 cases. In 70 of 72 cases, the results of EGFR mutation status were concordant for BWF and histologic samples, and the concordance rate was 97%. In 13 cases that were not pathologically diagnosed with NSCLC with forceps biopsy samples but other samples, five cases (38.46%) with EGFR mutated-type were detected by BWF. The overall EGFR mutation concordance rate between supernatant and sediment specimens was 100%. The detection of EGFR mutations with supernatant/sediment of BWF samples showed a sensitivity of 86.5%, a specificity of 100%. **Conclusion:** This study demonstrates a clear comparison of supernatant/sediment of BWF samples and histologic tissues for EGFR mutation testing with largest clinical samples to date. Both supernatant and sediment of BWF samples showed high credibility and concordance via highly sensitive PCR analysis. BWF is considered a simple, rapid and effective alternative for histologic samples in EGFR mutation testing.

Keywords: EGFR mutation, Bronchial washing fluid, NSCLC

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-005 ASTRIS: A REAL WORLD STUDY OF OSIMERTINIB TREATMENT IN PATIENTS WITH EGFR T790M POSITIVE ADVANCED NSCLC; INTERIM ANALYSIS

S. Kim[1], B.C. Cho[2], D. Kim[3], K. Park[4], M. Tiseo[5], M.R. Migliorino[6], A. Santo[7], J. Lee[8], D. Vicente[9], A. Paredes[10], E. O'Hanrahan[11], H. Freitas[12], M. Provencio[13], Y. Chen[14], P. Cheema[15], A. Milner[16], J. Rigas[17], Y. Wu[18], F. De Marinis[19]

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Background: Osimertinib is a third-generation, CNS active EGFR-TKI that potently and selectively inhibits both EGFR-sensitizing and EGFR T790M resistance mutations in non-small cell lung cancer (NSCLC). We report interim clinical and molecular diagnostic testing results from a predefined interim analysis of the ongoing ASTRIS study (NCT02474355). **Method:** Patients (pts) received osimertinib 80 mg once daily. Eligible pts had advanced NSCLC that had progressed on prior EGFR-TKI therapy and with a T790M mutation determined by local validated molecular test, WHO performance status (PS) 0–2, acceptable organ and bone marrow function and no history of interstitial lung disease or QTc prolongation. Asymptomatic, stable CNS metastases were permitted. The primary efficacy outcome was overall survival; other outcomes included local test methods, specimen type, EGFR mutations identified, investigator-assessed response rate (RR), progression-free survival and time to treatment discontinuation. Safety data are also reported. **Result:** From 18 Sept 2015 to the planned 3 Nov 2016 data cut-off (DCO), 1217 pts received osimertinib 80 mg once-daily across 14 countries with a median age 64 yrs (27–92 yrs), 67% female, 61% White, 37% Asian, 87% WHO PS 0/1, 44% prior chemotherapy, 45% prior radiotherapy. All pts tested positive for T790M; T790M was reported alone in 185 pts (15%). The most common testing methods were PNA-Clamp 317 pts (27%), Qiagen therascreen 254 pts (22%), and Roche cobas 204 pts (17%). Exon 19 deletion was the most common co-occurring mutation with T790M (57%), followed by L858R (27%). Tissue or cytology specimens were used in 720 pts (59%), plasma in 433 pts (36%), and other specimens in 64 pts (5%). At DCO, the median duration of exposure was 3.8 months (<1–13.2 months) with a median follow-up time of 4.1 months (<1–14 months). In pts evaluable for response, the investigator-assessed RR was 64% (569/886; 95% CI 61, 67). Adverse events (AEs) leading to dose modification and treatment discontinuation were reported in 122 pts (10%) and 54 pts (4%), respectively. Serious AEs were reported in 165 pts (14%) and AEs leading to death in 28 pts (2%). **Conclusion:** ASTRIS is the largest reported global study of osimertinib in pts with T790M-positive NSCLC identified by a wide array of molecular testing methods and from various specimen types. Considering this breadth of T790M testing, the clinical activity of osimertinib is like that observed in the clinical trial program and no new safety signals were identified.

Keywords: osimertinib, EGFR-TKI, T790M

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-006 OSIMERTINIB IN PRETREATED EGFR T790M-POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS WITH LEPTOMENINGEAL CARCINOMATOSIS

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Background: Leptomeningeal carcinomatosis (LC) is a detrimental complication of non-small cell lung cancer (NSCLC). Osimertinib is the current standard therapy for pretreated *EGFR* T790M-positive NSCLC patients. However, the efficacy of osimertinib for these patients with LC is unknown. **Method:** Retrospective case series of 5 patients with pretreated *EGFR* T790M-positive NSCLC who developed LC and received osimertinib therapy in an Expanded Access Program was reviewed. We evaluated the clinical outcomes of these patients. **Result:** Four female patients and one male patient (age, range 51-67) with *EGFR* T790M-positive NSCLC and LC received osimertinib therapy at a starting dose of 80 mg/day. *EGFR* T790M mutation was detected in three re-biopsied specimens and two plasma samples. Four patients had Eastern Cooperative Oncology Group performance status (PS) ≧ 2. One patient received whole-brain radiotherapy after commencing osimertinib therapy. Osimertinib dose escalation to 160 mg/day or 160 mg every other day was administered to 3 patients who did not respond to standard dose therapy. Radiologically decreased leptomeningeal enhancement was seen in 3 out of 4 evaluable patients, and improvement of clinical symptoms was recorded in 2 patients. Two patients died of aspiration pneumonia, and one died of hypoxic respiratory failure of unknown cause. Osimertinib therapy is ongoing in two patients at 80 mg/day for 9 and 10 months, respectively, with good tolerability. **Conclusion:** Osimertinib is well tolerated even in patients with poor PS. Clinical benefits were seen in some patients, and the optimal dose should be explored.

Keywords: leptomeningeal carcinomatosis, osimertinib, Prognosis

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-007 HETEROGENEOUS RESISTANCE MECHANISMS IN REBIOPSIES FROM EGFR-MUTATED NSCLC: TRANSFORMATION TO SCLC; FGFR3 AND T790M MUTATIONS

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Background: Patients with epidermal growth factor receptor (EGFR) gene-mutated NSCLC initially show substantial clinical benefit from EGFR Tyrosine-Kinase Inhibitors (TKIs), but will ultimately develop resistance with a median progression-free survival of 9-15 months. However, the type and timing of TKI-resistance cannot be predicted and several mechanisms may occur simultaneously/subsequently during TKI-treatment. We present a patient case with advanced non-small cell lung cancer (NSCLC) of adenocarcinoma subtype (ADC) with EGFR-mutation and Erlotinib-treated Different mechanisms of TKI-resistance were detected in tumor biopsies during treatment time. **Method:** The patient was a 49 year-old, previously healthy, Caucasian male with metastatic ADC. A diagnostic biopsy from hepatic metastasis, cytology from metastatic pleural effusion at first progression during TKI-therapy and a biopsy from new liver metastasis at second progression were analyzed by histology, immunohistochemistry and targeted next-generation sequencing (NGS) of hot-spot mutations in 50 cancer-related genes (Ion AmpliSeq Cancer Hotspot Panel v.2, Ion Torrent, Thermo Fisher Scientific). **Result:** CT-scans revealed tumor in the right upper lobe with mediastinal infiltration and multiple pulmonary and hepatic metastases, stage T4N2M1b. Diagnostic liver biopsy revealed ADC (mucin-producing, CK7- and TTF1-positive epithelial acinar structures), which concomitantly harbored an EGFR exon 19-mutation (p.E746_A750delELREA) and a previously unreported 2 bp microdeletion in the fibroblast growth factor receptor 3 (FGFR3; p.D785fs*31) gene. The patient received first-line Erlotinib but progressed after 7 weeks with metastatic pleural effusion, in which transformation to small cell lung cancer (SCLC) and maintenance of EGFR-mutation and FGFR3-mutation was identified. The progression was treated with standard Carboplatin-Etoposide regimen for SCLC together with Erlotinib continuation. The second progression 7 months later was a new liver-metastasis with persistence of the original EGFR- and FGFR3-mutated ADC-phenotype and additional emergence of the Erlotinib-resistant T790M EGFR-mutation. The patient rapidly deteriorated and deceased. **Conclusion:** Thus, in this advanced EGFR-mutated NSCLC rapid onset and heterogeneous mechanisms of TKI-resistance occurred at different times of metastatic disease:

1. Concomitant FGFR3-mutation prior to and during TKI-treatment as potential intrinsic resistance-mechanism;

2. Transformation to SCLC at 1st progression during TKI-therapy;

3. Acquisition of T790M EGFR-mutation at 2nd progression.

This suggests a continuous variation of TKI-resistant cells' genetic and phenotypic behavior. Therefore, re-biopsies are important to provide the current status of the disease and better define subsequent treatment options. "Liquid biopsies" may potentially help identify heterogeneous genetic resistance-mechanisms; however assessment of mechanisms such as SCLC-transformation needs tissue biopsies

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-008 ASSOCIATION BETWEEN ICOTINIB EFFICACY AND CIRCULATING TUMOR CELL LEVELS IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Advanced non-small cell lung cancer(NSCLC) studies indicated a potential association between chemotherapy efficacy and circulating tumor cells (CTC) counts in peripheral blood. The icotinib efficacy and circulating tumor cells (CTC) counts in non-small cell lung cancer remain unknown. The aim is to investigate association between the icotinib efficacy and CTC counts in advanced NSCLC patients. **Method:** A total of 74 advanced NSCLC patients consented to provide 5ml of peripheral blood before systematic therapy, and divided into two groups (those with high CTC counts and those with low CTC counts) based on the patients median CTC counts. All the patients were treated with icotinib, and the icotinib efficacy and prognoses were compared. **Result:** The treatment efficacies were 46.88% (15/32) and 23.81% (10/42) for the low CTC group and the high CTC group, respectively. The median overall survival was 22.0 months (95%CI: 19.6-28.7 months) for the low CTC group and 18.3 months (95% CI: 15.3-25.4 months) for the high CTC group. The median progression-free survival was 11.6 months (95% CI: 8.7-15.6 months) and 7.2 months (95% CI: 3.4-8.7 months) for the low group and the high CTC group, respectively. **Conclusion:** The CTC counts can be used as a important biomarker for therapy monitoring the icotinib effect on patients with advanced NSCLC. Efficacy and prognosis of icotinib and CTC counts were considered important, and the CTC counts could be used to predict the efficacy of icotinib and prognosis of advanced NSCLC. The change in CTC count levels can be used as a biomarker for evaluating the prognosis of patients with advanced NSCLC.

Keywords: icotinib, non-small cell lung cancer, Circulating tumor cells

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-009 CLINICAL EFFICACY OF ICOTINIB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER HARBORING EGFR EXON 18 E709X MUTATIONS

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Background: EGFR exon 18 E709X mutation is only reported in small case numbers of non-small cell lung cancer (NSCLC) in the literature, and their influences on the effectiveness of icotinib have not been fully understood. The study of this aim is to investigate the efficacy of icotinib in patients with NSCLC that carrying EGFR exon 18 E709X mutation. **Method:** Three cases of EGFR exon 18 E709X mutations were retrospectively analyzed until the progress of the disease or the emergence of the side effects and clinical efficacy was observed after months of followed-up. **Result:** The median progression-free survival (PFS) of three cases with EGFR exon 18 E709X (E709_T710>D, E709A, E709K plus L858R) was 3.1 months, patients with complex mutations showed a better PFS than those with single mutations (7.2 months vs. 2.7 months, P=0.225). Clinical efficacy of icotinib with advanced NSCLC harboring EGFR exon 18 E709X mutation (ORR: 66.67%, DCR: 66.67%). **Conclusion:** Icotinib is effective in patients with exon 18 E709X mutations. Patients with complex mutations benefited more from icotinib than those with single mutations.

Keywords: icotinib, E709X, uncommon mutation

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-010 HIGH PROBABILITY AND FREQUENCY OF EGFR MUTATIONS IN NON-SMALL CELL LUNG CANCER WITH BRAIN METASTASES

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Background: Lung cancer is the leading cause of cancer death in men and women worldwide. Brain metastasis (BMs) of NSCLC is the most important cause of death. This study aimed to explore the association of epidermal growth factor receptor (EGFR) mutations and brain metastases (BMs) in non-small cell lung cancer (NSCLC). **Method:** We analyzed 50 NSCLC patients with BMs and 50 match-paired NSCLC patients with no brain metastases (NBMs). The EGFR mutation status of primary lesions was detected using the amplification refractory mutation system (ARMS) polymerase chain reaction. **Result:** The BMs patients had a higher frequency of EGFR mutations than the NBMs patients (52.0% vs. 22.0% respectively, P<0.001), in both adenocarcinoma (60.5% vs 30.6%, P=0.003) and squamous carcinoma (37.5% vs. 0%, P=0.04). The incidence of BMs in patients with EGFR mutations was higher than in patients with wild-type EGFR (70.3% vs. 38.1%, P=002). **Conclusion:** NSCLC patients with BMs had a higher incidence of EGFR mutations and those with mutant EGFR had a higher frequency of BMs. EGFR mutations may promote brain metastasis growth of NSCLC.

Keywords: non-small cell lung cancer, Epidermal growth factor receptor, brain metastases

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-011 COMPARISION OF EGFR AND ALK-DRIVEN LUNG ADENOCARCINOMA WITH BRAIN METASTASES FOR PROGNOSTIC FACTORS IN CHINESE PATIENTS

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Background: Brain metastases are often seen in Eastern-Asian lung adenocarcinoma in which most common oncogenic driver mutations are *EGFR* sensitive mutations or *EML4- ALK* fusions, occurring in about 60% patients. Elucidation of *EGFR* and *ALK*-driven mutation prognostic factors in patients with brain metastases has important clinical implications. **Method:** Lung adenocarcinoma harboring *EGFR* mutations or ALK fusions were studied for their occurrence of brain metastases and relevant prognostic factors. **Result:** Of 602 lung patients with lung adenocarcinoma, 516 had *EGFR* mutations and 86 had *EML4-ALK* fusions. *EGFR*-mutation patients had much more brain metastases than *ALK*-fusion patients, whether at first diagnosis (40.1% vs 28%, *P*=0.03) or followed up two years (63.8% vs 42.7%, *P*<0.01). Brain metastasis is a significant indicator for poor survival in the *EGFR*-mutation patients (*P*<0.001), but not in the *ALK*-fusion patients (*P*=0.79). In the EGFR-mutation patients, late occurred brain metastases (after one year) predicted better survival (*P*=0.001). Meanwhile,

female or young age was associated with better survival in the brain metastatic patients with ALK fusions ($P<0.05$). Moreover, multivariate analysis indicated that tyrosine kinase inhibitor (TKI) treatment, no symptomatic brain metastases and cranial radiotherapy were the significant indicators for better survival in both *EGFR*-mutation and *ALK*-fusion patients ($P<0.05$). Although there was no difference in overall survival between EGFR mutation and *ALK* fusion patients with brain metastases ($P=0.23$), in the TKI-treating subgroup ALK-fusion patients had longer survival time than *EGFR*-mutation patients(NR vs. 36 months, $P=0.15$). Furthermore, in the *EGFR*-mutation patients with brain metastases erlotinib was associated with better survival compared with gefitinib as first-line treatment (38 months vs 34 months, $P=0.03$) **Conclusion:** *EGFR*-mutation and *ALK*-fusion lung adenocarcinoma patients with brain metastases have distinct clinical characteristics and prognostic factors. However, while doing targeted treatment *ALK*-fusion indicated better survival than EGFR-mutation in the patients with brain metastases.

Keywords: lung adenocarcinoma, brain metastases, EGFR , ALK .

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-012 SYMPTOM IMPACT OF FIRST-LINE DACOMITINIB VERSUS GEFITINIB IN EGFR-POSITIVE NSCLC: RESULTS FROM A RANDOMIZED PHASE 3 STUDY

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Background: Patients with non-small-cell lung cancer (NSCLC) experience high disease burden due to many cancer-related symptoms (eg, cough, dyspnea, pain, and fatigue). Decreasing tumor burden may reduce/delay symptoms and favorably impact global health-related quality of life (HRQoL). Dacomitinib is an irreversible, small-molecule inhibitor of EGFR/HER-1, HER-2, and HER-4 tyrosine kinases. In a global, multicenter, randomized, open-label phase 3 study (NCT01774721) for first-line treatment of NSCLC, dacomitinib improved the primary objective of progression-free survival per independent radiologic review (median, 14.7 vs 9.2 months; hazard ratio, 0.59; 95% confidence interval [CI], 0.47–0.74; $P<0.0001$) over gefitinib. Median duration of treatment was longer with dacomitinib than with gefitinib (67 vs 52 weeks, respectively).[1] A secondary objective was to explore HRQoL. Here, we report the impact of dacomitinib and gefitinib treatment on core lung cancer symptoms. **Method:** Patients were randomized 1:1 to receive oral dacomitinib (45 mg) or gefitinib (250 mg) once daily. Disease-related symptoms were measured using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 (QLQ-C30) and Lung Cancer 13 (QLQ-LC13). Scores were summarized by the mean and 95% CI for each group and plotted over 30 cycles and at the end of treatment; the number of cycles (n=30) chosen for this analysis was not prespecified. Mean changes from baseline (cycle 1, day 1 [C1D1]) were reported for each group. **Result:** Between 9-May-2013 and 20-March-2015, 452 patients were randomly assigned to dacomitinib (n=227) or gefitinib (n=225). Baseline scores were similar between treatment arms. On-study completion rates were high, with >90% of patients answering all questions for most treatment cycles. Statistically significant improvements from baseline (95% CI excludes 0; no adjustment for multiplicity) for most cycles were seen in fatigue, pain, dyspnea, and cough in both arms. Improvements were reported as early as C1D8. Clinically meaningful improvements (≥10 points score change) were recorded for pain in chest (23/30 cycles) and cough (28/30 cycles) with dacomitinib and for cough (22/30 cycles) with gefitinib; hence, improvements appear to be more frequent with dacomitinib. Symptom burden at end of treatment was generally higher than during treatment. As treatment duration was longer with dacomitinib, key lung cancer symptom improvements were seen for a longer time in patients treated with dacomitinib. **Conclusion:** Dacomitinib, along with gefitinib, demonstrated favorable clinical benefit and improvements in key NSCLC symptoms. These findings are important when considering choice of therapy. **Reference** 1. Mok T, et al. *J Clin Oncol*. 2017;35(Suppl):abstract LBA9007.

Keywords: EGFR-mutated NSCLC, Dacomitinib, Patient-reported outcomes

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-013 CNS METASTASES IN EGFR MUTATION POSITIVE NSCLC: IMPACT ON HEALTH RESOURCE UTILIZATION

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Background: EGFR mutation positive (EGFRm) NSCLC patients commonly progress in the CNS. We reviewed CNS disease development and its impact on resource utilization and outcomes in EGFRm patients who received first-line EGFR TKI. **Method:** s: A retrospective review was completed of all advanced EGFR+ patients referred to the BC Cancer Agency and treated with a first/second-generation EGFR TKI from 2010-2015. Baseline characteristics, systemic treatment and CNS management was collected. Comparison was made between the CNS positive (CNS+) and negative (CNS-) patients' health resource utilization from median time of CNS+ diagnosis to death/last follow-up (8.9 m) and for no CNS metastases group, 9 months preceding death/last follow-up, using the Chi squared test and t-test. **Result:** 499 patients were identified. Baseline characteristics: Female 68%, median age 66 (30-90), adenocarcinoma 89%, Asian 51%, never/former/current smoker 67/24/9%, exon 19/21/other/not specified 57/37/3/3%. 229/499 patients (46%) developed CNS+; 39% at diagnosis, 61% during the course of disease. Systemic treatment: first-line EGFR TKI 95%, first-line platinum doublet 5%; 40% (202/499) second-line EGFR TKI 24%, second -line platinum doublet 56%, single agent chemo 13%, osimertinib 7%, third-line therapy 47%. CNS+ management: surgery+/-WBXRT 13%, WBXRT alone 73%, SRS+/-WBXRT 5%, no CNS directed therapy 9%. Median time from diagnosis to CNS+ was 7.6 m. Median time from development of CNS+ diagnosis to death was 8.9 m. Median OS was 24m in CNS+ versus 33m in CNS- (p<0.001).

Events in 9m preceding death or last follow-up (consistent with median time from CNS+ to death)	No CNS Metastases n=270	CNS Metastases n=229	p value
Average number of clinic visits	8.53	12.71	<0.001
Average number of hospitalizations	0.43	0.76	<0.001
Average number of CNS imaging investigations	0.52	2.65	<0.001
Average number of ER visits	0.03	0.14	0.001
Palliative Care Unit admission	22 (8%)	22 (10%)	0.64
Hospice admission	9 (3%)	43 (19%)	<0.001

Conclusion: The incidence of CNS+ in EGFRm patients is high and associated with increased Health Resource Utilization. Prevention or delay of CNS+ with newer systemic therapy options may result in decreased interactions with health care providers, which may translate into lower resource utilization and cost savings.

Keywords: Health Resource Utilization, CNS disease, EGFRm NSCLC

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-015 DIFFERENTIAL OUTCOMES BETWEEN FIRST AND SECOND GENERATION TKIS IN PATIENTS WITH ACTIVATING EGFR MUTATIONS IN NSCLC

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Background: Both first and second generation EGFR tyrosine kinase inhibitors (TKIs) have efficacy in NSCLC with activating EGFR mutations (EGFRM+). Previous studies showed a differential benefit of second generation TKIs based on mutational subtypes but failed to show a difference in overall survival (OS). We aimed to characterize the patterns of use and outcomes of first and second generation TKIs and describe any differences with mutation subtype in the real world setting. **Method:** A retrospective review of all advanced EGFRM+ NSCLC patients treated with TKIs between the years 2010-2015 at the British Columbia Cancer Agency was performed. All time to event analyses were performed from date of diagnosis of metastatic disease. Multivariate regressions were performed to examine for associations of OS, treatment and mutation subtypes. **Result:** 500 patients were eligible for analysis: 283 patients had an exon 19 deletion (del19), 185 had an exon 21 L858R mutation and 32 were not specified or have mutational variants such as G719var. Patient characteristics in the del19 vs. L858R group were similar: 69%/66% were female, 66%/71% were never smokers, 90%/89% were adenocarcinoma, 20%/20% had CNS metastases at diagnosis, 85%/84% had de novo metastatic disease and 41%/37% received ≥2 lines of therapy (all p>0.05). The del19 cohort had less Asians (46% vs 58%, p=0.02) and were younger (median age 63 vs. 69, p=0.02) compared to L858R group. In the del19/L858R cohorts, 81%/19% and 84%/16% received a first and second generation TKI respectively. 43% of patients receiving a second generation TKI required a dose reduction to manage the toxicity and one patient discontinued the medication. OS in the entire cohort was 26 months, with the del19 group surviving longer compared to the L858R cohort (27 vs. 22 months, p<0.01). In multivariate analysis, factors associated with improved OS were del19 (HR0.7, p<0.01 95%CI0.6-0.9), treatment with a second generation TKI (HR0.6, p=0.01 95%CI0.5-0.9) and absence of CNS metastases (HR0.7, p<0.01 95%CI0.5-0.9). First line treatment with a second generation TKI was associated with better OS compared to a first generation TKI (HR0.6, p=0.04 95%CI0.3-1.0). This was statistically significant only in the del19 subgroup (HR0.4, p=0.04 95%CI0.2-1.0). **Conclusion:** Use of a second generation TKI

in EGFRM+ advanced NSCLC is associated with improved OS in multivariate analyses controlling for other prognostic factors. This was significant in the entire group and in the del19 cohort, supporting the use of mutational subtype to guide therapy decisions.

Keywords: EGFR Tyrosine Kinase Inhibitors, non small cell lung cancer, EGFR mutation

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-016 FACTORS ASSOCIATED WITH SYMPTOMS IMPROVEMENT AND HRQOL FOR FIRST-LINE EGFR-TKIS IN NSCLC: A MULTICENTER PROSPECTIVE SMILE STUDY

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Background: First-line epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) offer an advantage compared to doublet chemotherapy in progression free survival, tolerability, and quality of life (QOL) in EGFR-mutated advanced non-small cell lung cancer (NSCLC) patients. In Taiwan, gefitinib, erlotinib and afatinib are all reimbursed as first-line therapy. It provides a rare opportunity to investigate factors associated with the extent of symptoms and QOL improvement in real-world patient population. **Method:** We conducted a multicenter, prospective, observational study to evaluate the QOL and disease-related symptoms at baseline, 2, 4, and 12 weeks in EGFR-mutated advanced NSCLC patients with first-line EGFR TKI treatment. QOL was assessed by the instrument of Functional Assessment of Cancer Therapy-Lung questionnaire (FACT-L) and Treatment Outcome Index (TOI) derived from FACT-L. Symptoms assessment was evaluated by the Lung Cancer Subscale (LCS). The mean change from baseline of QoL and LCS score was analyzed by paired t-test. **Result:** The average age was 65.1± 12.5 (range 31.4–92.9) years old, with a larger proportion of females (62.6%) than males, and more never-smokers (74.0%) than ever-smokers. Patients were treated with gefitinib 250 mg (72.4%), erlotinib 150 mg (18.9%) or afatinib 40 mg (8.7%). For FACT-L, the total score was increased by 4.0 ± 15.49 at week 2, 4.9 ± 18.31 at week 4, and 4.1 ± 20.44 at week 12 (all p<0.001). Similarly, increased TOI of 2.4 ± 11.61 (p<0.001), 3.1 ± 13.48 (p<0.001), and 2.4 ± 14.35 (p=0.009) were observed at week 2, 4, and 12, respectively. For LCS, it was slightly increased by 1.7 ± 4.59 at week 2, 2.0 ± 5.48 at week 4, and 1.9 ± 5.35 at week 12 (all p<0.001). In general, subgroup analyses indicate that patients with more than 2 metastatic sites and ex-smokers were associated with clinically meaningful improvement in terms of LCS (change in LCS ≥ 2 points). Other subgroup analyses show that patients with characteristics such as at least 3 metastatic sites, ex-smoker, PS of 1, and treatment with gefitinib group, were associated with improved QOL in terms of TOI and FACT-L. **Conclusion:** In EGFR mutated NSCLC patients, first-line EGFR-TKI treatment was associated with improvement in disease-associated symptoms and QOL. Patients with 2 or more metastatic sites and ex-smokers were associated with symptoms and QOL improvement. In addition, PS of 1 and treatment with gefitinib were associated with clinical meaningful improvement in global QOL.

Keywords: EGFR TKI, gefitinib, quality of life

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-017 CLINICAL OUTCOMES OF PATIENTS WITH EGFR T790M + NSCLC ON OSIMERTINIB

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Background: Osimertinib (AZD9291) is a third-generation EGFR TKI specific against T790M resistance mutations in patients with metastatic EGFR-mutant (EGFRm+) NSCLC after prior first-line TKI therapy. We aimed to evaluate the clinical efficacy of osimertinib in patients treated under the AZD9291 Early Access Program (EAP) at our local institution. **Method:** This retrospective study included 57 patients who were enrolled on the AZD9291 EAP between Jul 2015 and Nov 2016 after being tested T790M+ on tumor (by direct Sanger sequencing or Roche COBAS EGFR mutation test v2) and/or plasma (cfDNA) specimens (by Lung Colon Panel v2 or ARMS PCR). Of these patients, 52 were treated with osimertinib. Tumor responses were independently assessed by radiologists using RECIST 1.1 criteria. DOR, PFS and OS were estimated by Kaplan-Meier method. **Result:** The median age at diagnosis was 58 years (range: 35-76), 80.7% patients were non-smokers, 89.5% had ECOG 0-2, 96.5% had adenocarcinoma subtype and 87.8% had either EGFR exon 19/ exon 21 mutations. Median line of therapy when osimertinib was administered was third-line (range 2nd – 9th), and 30 (53%) had brain metastasis at osimertinib initiation. RR by RECIST 1.1 was 46% (95% CI 32.2 – 60.5%) (4 CR + 20 PR) with median DOR of 8.7 months. With median follow-up of 6.2 months from osimertinib initiation, median PFS was 10.3 months (95% CI 7.52 to 15.87 months). For the 52 patients treated with osimertinib, EGFR T790M mutation was tested on the following specimens: tumor-only (n=43), plasma-only (n=25), and both (n=17). In patients with paired tumor/plasma T790M testing, 4/17 had concordant results (RR 75%), while 13 patients with discordant results [T790M+ in 8 tumor-only: RR 25% (95% CI 3.2% - 65.1%) or in 5 plasma-only: RR 40% (95% CI 5.3% - 85.3%)] had overall RR 31% (95% CI 9.1% – 61.4%). ECOG status was associated with PFS by univariable analysis, with higher ECOG 2-4 associated with shorter PFS (HR=6.54, 95% CI: 2.48 to 17.26; p<0.001) than ECOG 0-1. Line of osimertinib treatment and presence of brain metastases at osimertinib initiation were not associated with clinical outcome. **Conclusion:** Osimertinib is effective in patients with advanced EGFR T790M+ NSCLC after progression on prior EGFR TKI, regardless of presence/ absence of CNS metastasis or line of therapy. Notwithstanding ongoing optimization of plasma-based assays, T790M tumor-plasma discordance in our patient cohort is likely a reflection of overall burden of T790M subclones, and may represent a potential negative predictive biomarker of response to osimertinib.

Keywords: EGFR T790M, osimertinib, NSCLC

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-018 MUTATION ABUNDANCE AFFECTS THE THERAPEUTIC EFFICACY OF EGFR-TKI IN PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA: A RETROSPECTIVE ANALYSIS

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Background: To detect the mutation abundance and sites of epidermal growth factor receptor (EGFR), and to investigate their influence on the therapeutic efficacy of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) in patients with advanced non-small cell lung cancer (NSCLC). **Method:** A total of 2,417 NSCLC patients with EGFR gene mutations were retrospectively analyzed using an amplification refractory mutation system (ARMS). Of 861 patients, 407 patients had exon 19 deletions and 454 patients had exon 21 (L858R) site mutations of the EGFR gene. Next we analyzed the mutation abundance of lung adenocarcinoma patients who received EGFR-TKI therapy and complete follow up. 194 patients diagnosed with stage IIIB or stage IV lung adenocarcinoma with an ECOG score of 0-3 were enrolled. The primary endpoint was to determine associations between progression-free survival (PFS) and mutation abundance or mutation sites after EGFR-TKI therapy. The secondary endpoint was to evaluate the objective response rate and effects when EGFR-TKI was administered as the first-line treatment, as well as risk factor analysis for PFS. **Result:** Of the 194 enrolled patients, the median PFS was 9.3 months (95% CI, 8.2–10.8 months). The PFS was significantly different with EGFR gene mutation abundance after EGFR-TKI therapy (P = 0.014). The median PFS was significantly longer when the cut-off value of EGFR mutation abundance of exon 19 or exon 21, exon19 was > 26.7% and 61.8%, respectively. For patients who received EGFR-TKI as first-line treatment, the median PFS was significantly longer in the high mutation abundance group than in the low mutation abundance group (12.7 m vs 8.7 m, P = 0.002). However, there was no significant correlation with gender, age or smoking status and PFS. **Conclusion:** The PFS benefits were greater in patients with a higher abundance of exon 19 mutations in the EGFR gene after EGFR-TKI treatment.

Keywords: mutation abundance, lung adenocarcinoma, EGFR

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-019 CANADIAN MULTICENTRE VALIDATION STUDY OF PLASMA CIRCULATING TUMOUR DNA FOR EPIDERMAL GROWTH FACTOR (EGFR) T790M TESTING

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Background: Plasma detection of EGFR T790M mutations in circulating tumour DNA (ctDNA) of advanced lung cancer patients with acquired resistance to EGFR tyrosine kinase inhibitor (TKI) has been proposed as alternative to tumor re-biopsy. This national validation study across Canadian centres aimed to establish the sensitivity and specificity of plasma detection of T790M as a clinical test using digital droplet (dd)

PCR and next generation sequencing (NGS) assays. **Method:** Canadian patients at 7 centres undergoing screening for ASTRIS (NCT02474355) were invited to participate in this companion blood-based study. Patients with acquired resistance to EGFR TKI consented to collection of blood samples and demographic data. Samples were analysed using ddPCR and/or NGS platforms available at 4 molecular diagnostic laboratories across Canada. Concordance between the results of plasma T790M assayed in these 4 laboratories with reference tissue/plasma testing conducted for ASTRIS was assessed. **Result:** 63 patients participated; the median age was 64 years (range 31-87), 69%(40/58) were Asian; 55%(33/60) were male. All patients received prior EGFR TKI, 17%(10/60) also received prior chemotherapy. Reference testing for EGFR T790M for ASTRIS eligibility identified positive T790M(+) results for 31(49%), negative(-) for 30(48%) and indeterminate(i) results for 2(3%) patients. One laboratory tested all 63 patient samples using both ddPCR and NGS (Oncomine Lung cfDNA assay), another laboratory tested 18 samples using ddPCR and NextSeq, a third tested 10 samples using ddPCR and COBAS EGFRv2, and a fourth tested 6 samples using Ion Torrent PGM. A total of 188 tests were performed including 91 by ddPCR, 87 NGS and 10 COBAS assays. Combining test results for each patient, 60%(38/63) of patient plasma samples were T790M+, 23(37%) were T790M-, and 2(3%) were inconclusive. Of 31 patients with reference T790M+ results from ASTRIS, 23(74%) had T790M detected in plasma, 6(19%) did not (T790M-), and 2(7%) had indeterminate (T790Mi) plasma results. For 30 patients with T790M- reference results from ASTRIS, 13(43%) had plasma T790M+ and 17 plasma T790M- results. The 2 patients with T790Mi by reference testing both had T790M+ results from plasma. Altogether, 47%(15/32) of patients deemed to have T790M-/i tumours by reference testing were found to have T790M+ results by plasma in this multicentre study. Combining results from both tissue and plasma testing, 73%(46/63) of study patients had T790M+ results. **Conclusion:** Plasma ctDNA testing in this multicentre Canadian study identified a significant number of additional patients eligible for osimertinib therapy beyond routine biopsy tissue testing for *EGFR T790M*.

Keywords: Circulating Tumor DNA, plasma T790M, osimertinib

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-020 CLINICAL FEATURES OF PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) HARBOURING EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS IN BRUNEI

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Background: Brunei is indifferent to its neighbouring South East Asia countries whereby the highest cancer mortality rate is attributed to lung cancer. *EGFR* mutations are present in a subset of patients with non-squamous NSCLC that predict a favourable response to *EGFR* tyrosine kinase inhibitor (TKI) therapy. Thus far, the prevalence of *EGFR* mutations in Brunei patients with NSCLC remains unknown. This study was conducted to characterise non-squamous NSCLC patients with *EGFR* mutations in Brunei. **Method:** Retrospective data collection from clinical case notes of patients with non-squamous NSCLC diagnosed from January 2010 to March 2017 was undertaken at The Brunei Cancer Centre to determine the frequency of *EGFR* mutations and correlation with clinico-pathological variables. The progression-free survival (PFS) of *EGFR* mutated patients on *EGFR* TKI and the overall survival (OS) of patients with mutated and wild type *EGFR* were estimated and compared using Kaplan-Meier curves and log-rank tests. **Result:** *EGFR* mutation status was evaluable in 71 out of 191 lung adenocarcinoma cases. The overall mutation frequency was 43.7 % with a mean age of 63.3 years. *EGFR* mutations were significantly more common in female (71%) and never smokers but 33.3% of patients with *EGFR* mutations were current smokers. The most prevalent *EGFR* mutation was exon 21 point mutation (L858R) (43.3%) followed by exon 19 deletion (40.0%). 87% of patients with *EGFR* mutations received *EGFR* TKI therapy and the objective response rate (ORR) was 65.2%. The median PFS for patients on *EGFR* TKI was 7 months and there was no significant differences between the two most common mutations. The median PFS of patients treated with *EGFR* TKI upfront and after first line chemotherapy was 8 and 6 months (p=0.045) respectively. Although not statistically significant (p=0.232), our result showed a trend of improvement in median OS for *EGFR* mutated patients (29 months) compared to wild type (17 months). **Conclusion:** This is the first study to reveal the clinical characteristics of patients with *EGFR* mutated non-squamous NSCLC in Brunei. The prevalence of *EGFR* mutation in our study is high and comparable to other Asian NSCLC patients. Interestingly, PFS rate on *EGFR* TKI observed in our population was inferior to published studies despite the high ORR and this warrants further exploration. Nevertheless, *EGFR* mutation analysis should be performed in all patients with non-squamous NSCLC to identify the subset of patients who may benefit from *EGFR* TKI.

Keywords: EGFR, NSCLC, BRUNEI

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-021 A MULTICENTER, NON-INTERVENTIONAL STUDY ON REAL WORLD EGFR TESTING AND IN PATIENTS WITH IIIB/IV NSCLC IN NORTHERN CHINA

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Background: EGFR mutation plays a dominant role in the precise treatment of non-small cell lung cancer (NSCLC), and EGFR-TKIs has been recommended for patients with positive EGFR-sensitive mutation as a standard regimen in clinical practice. In China, application of EGFR-TKIs without knowing EGFR mutation status has been a common phenomenon due to various reasons including the vast territory, uneven distribution of medical resources, differences level of testing technology and others. Therefore, we prospectively conducted a real-world investigation to understand the actual situation of EGFR testing in Northern China, and identify the underlying causes affecting EGFR detection, in order to provide references to improve the standardized treatment.(NCT02620657) **Method:** The patients with IIIB/IV NSCLC who were firstly diagnosed or postoperative recurrence between 2014-1-1 and 2014-12-31 in 28 research centers of Northern China were analyzed. The primary endpoint was testing rate,the secondary endpoints were factors affecting EGFR testing, EGFR mutation status, detection methods and the survival outcomes of patients. **Result:** Among 2809 patients, 2250(90.78%) were adenocarcinoma, 208(7.40%) were squamous carcinoma, 51(1.82%) were other pathologic types. Testing rate was 42.54%(1195/2809) and was significantly related to city level (first-tier cities vs. new first-tier cities vs. second-tier cities vs. third-tier and above cities : 69.04% vs. 38.08% vs. 34.05% vs. 14.11%, P < 0.001), smoking status (never smoking vs. ever smoking vs. smoking: 45.42% vs. 51.10% vs. 33.37%, P<0.001), ECOG PS(0 vs.1vs.2vs.≥3:47.93%vs. 44.48vs.34.89%vs.20.37%, P=0.011), pathological type (adenocarcinoma vs. squamous carcinoma: 44.94% vs.19.23%, P=0.003) and medical insurance situation (social basic medical insurance vs. new rural cooperative medical insurance vs. own expense: 44.98% vs. 36.49% vs. 29.55%, P=0.001). EGFR sensitive mutation rate was 46.44%, the most common subtype was 19Del(42.16%), followed by L858R(40.00%), Exon 20 insertions(1.62%) and other subtypes(16.20%). The most common methodology is ARMS(63.77%), the second common one is DNA sequencing(5.36%). The 1-year and 2-year survival rate in patients receiving EGFR testing was 73.6%and 51.9%, compared with 64.3% and 43.7% respectively in patients without EGFR testing. **Conclusion:** There were regional differences in EGFR testing rates among IIIB/IV NSCLC patients in Northern China. The intention of doctors and patients, medical insurance coverage and differences technical level are major factors affecting the testing rate of EGFR. Approaches should be taken to improve the situation, such as strengthening the training, expanding the coverage of medical insurance, and relying on commercial gene detection companies, and further standardize the molecularly pathological diagnosis and treatment of NSCLC.

Keywords: testing frequency, Epidermal growth factor receptor, non-small cell lung cancer

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-022 PROGNOSTIC VALUE OF CLINICAL, IMMUNE AND BIOCHEMICAL MARKERS IN EGFR-MUTANT NSCLC PATIENTS TREATED WITH FIRST-LINE EGFR TKIS

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Background: Sensitizing Epidermal Growth Factor Receptor (*EGFR*) mutations confers a better prognosis and predicts a favorable response to treatment with *EGFR* tyrosine kinase inhibitors (TKIs) in patients with advanced non-small cell lung cancer (NSCLC). We sought to determine the prognostic utility of a comprehensive panel of clinical, immune and biochemical markers in *EGFR*-mutant advanced NSCLC patients treated with first-line EGFR TKIs. **Method:** A retrospective analysis was conducted on a cohort of NSCLC patients treated at our institution. Only patients who met the following criteria were included: NSCLC with *EGFR* mutations, diagnosed with Stage 4 disease at initial diagnosis or incurable disease recurrence, and received first-line EGFR TKI treatment. Statistical analysis on descriptive and survival data was performed using IBM SPSS Statistics, version 20. **Result:** We identified 74 patients based on predefined criteria. The mean age of the patients was 63.8 years with 38 (51.4%) female patients and 36 (48.6%) male patients, 51 (68.9%)

were never smokers and 39 (52.7%) harbored *EGFR* exon 19 deletion. 15 (22.7%) out of 66 patients with available data had high serum LDH (median: 456 U/L; normal range: 250-580 U/L). In addition, 19 (25.7%) had brain metastasis, 12 (16.2%) had liver metastasis and 12 (16.2%) had adrenal metastasis at stage 4 diagnosis. These represent the descriptive data of the variables that were later identified to carry prognostic significance. The median PFS and OS for this cohort of patients were 12 and 30 months respectively. On our multivariable Cox-PH regression analysis, old age (>=60; HR = 2.35; 95% CI = 1.18-4.69, **p-value = 0.015**), female gender (HR = 2.05; 95% CI = 1.05-4.00, **p-value = 0.036**) and high LDH levels (HR = 2.45; 95% CI = 1.04-5.81, **p-value = 0.041**) retained their association with unfavorable PFS and only high LDH levels (HR = 2.84; 95% CI = 1.25-6.49, **p-value = 0.013)** is an independent prognostic indicator of unfavorable OS. Total leukocyte count, hemoglobin levels, absolute neutrophil, lymphocyte and platelet counts at diagnosis were not statistically significant for PFS or OS. **Conclusion:** We identified old age, female gender and high serum LDH levels as independent prognostic predictors of progression-free survival on multivariable analysis. The strong association between elevated LDH and unfavorable overall survival is in line with recent published studies. Further studies confirming the prognostic utility of these markers are necessary to potentially develop a prognostic scoring system that can guide risk stratification in patients with *EGFR* mutations treated with EGFR TKIs.

Keywords: NSCLC, Prognostic biomarkers, EGFR mutation

P3.01: ADVANCED NSCLC -
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P3.01-023 FIRST-LINE AFATINIB FOR NON-SMALL CELL LUNG CANCER IN REAL WORLD PRACTICE

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Background: The efficacy of first-line afatinib was demonstrated for epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) in large randomized trials, and it has been approved and reimbursed in South Korea since year 2014. This study evaluated clinical outcomes of afatinib in real world practice. **Method:** Patients treated with first-line afatinib for advanced EGFR-mutant NSCLC in Samsung Medical Center (Seoul, South Korea) from October 2014 to December 2016 were included into the analyses. **Result:** In total, 165 patients were analyzed. One hundred fourteen had *deletion in exon* 19, 37 L858R, and 14 patients had uncommon EGFR mutations including 4 de novo T790M. Median progression-free survival (PFS) was 19. 1 months (95% CI: 12.3- 25.9 months). There was difference in median PFS according to EGFR mutation type: deletion in exon 19 (19.1 months), L858R (15.8 months), de novo T790M (4.7 months), and uncommon EGFR excepting for T790M (not yet reached) (P = 0.01). Though 112 patients (67.8%) had to reduce afatinib dose from 40 mg per day into 30 mg or 20 mg per day due to adverse events, it did not impair its efficacy in terms of PFS (23.5 months in a reduction group vs. 12.4 months in no reduction group). Among 29 patients with evaluable follow-up brain MRI for non-irradiated brain metastatic lesions, significant response was documented in 22 cases (75.9%). Out of 20 patients who were biopsied again at disease progression (excluding one case with de novo T790M), T790M appeared in 7 the repeat-biopsied specimens (35.0%). **Conclusion:** In the real practice in South Korea, first-line afatinib showed comparable or better efficacy data compared with previous clinical trials.

Keywords: afatinib, EGFR, non-small cell lung cancer

P3.01: ADVANCED NSCLC -
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P3.01-024 CHARACTERIZATION OF PD-L1 EXPRESSION AND ITS PREDICTIVE AND PROGNOSTIC SIGNIFICANCE IN EGFR-MUTANT NSCLC PATIENTS TREATED WITH EGFR-TKIS

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Background: Not all the patients with EGFR-mutant non-small cell lung cancer (NSCLC) could benefit from EGFR-TKIs and both the predictive and prognostic markers remain undetermined. Previous study demonstrated that EGFR activation could up-regulate the PD-L1 expression and then contribute to immune escape, indicating the critical role of PD-L1 in EGFR-driven lung tumors. Therefore, we aimed to investigate the predictive and prognostic significance of PD-L1 expression in EGFR-mutant NSCLC treated with EGFR-TKIs. Characterization of PD-L1 expression in this populations were also explored. **Method:** We analyzed a cohort of 73 NSCLC patients with EGFR mutations. PD-L1 expression were assessed by immunohistochemistry and staining > 5% of tumor cells were considered as positive. Published studies that assessed the predictive or prognostic value of PD-L1 expression in EGFR-mutant NSCLC patients treated with EGFR-TKIs were included. **Result:** 19 (26.0%) patients had positive PD-L1 expression. Positive PD-L1 expression was significantly associated with non-adenocarcinoma histology in this population (*P* = 0.028). Two cases with positive PD-L1 expression had KRAS mutation while none of those with negative PD-L1 expression harbored KRAS mutation (11.8% vs. 0%, *P* = 0.109). Five publications had reported both the predictive and prognostic value of PD-L1 expression in EGFR-mutant NSCLC patients treated with EGFR-TKIs. The pooled analysis including the current study showed that overall survival (OS) was significantly shorter in PD-L1 positive group than in PD-L1 negative group (HR, 1.92; 95% CI, 1.15-3.22; *P* = 0.01). However, positive PD-L1 expression was not correlated with progression-free survival (PFS: HR, 0.82; 95% CI, 0.51-1.30; *P* = 0.39). **Conclusion:** Positive PD-L1 expression tends to correlate with non-adenocarcinoma histology and KRAS mutation in EGFR-mutant NSCLC. Positive PD-L1 expression was significantly associated with better OS instead of PFS in EGFR-mutant NSCLC patients treated with EGFR-TKIs.

Keywords: PD-L1, EGFR mutation, non-small cell lung cancer

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-025 TREATMENT OUTCOMES OF ADVANCED LUNG ADENOCARCINOMA WITH UNKNOWN EGFR GENE STATUS: A RETROSPECTIVE ANALYSIS OF 140 PATIENTS

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Background: Limited data are available on treatment experience of advanced lung adenocarcinoma with unknown EGFR gene status (UN-EGFR-GS). We studied the demographic profile and treatment outcomes of advanced lung adenocarcinoma patients, which the EGFR gene status was unknown. **Method:** Retrospective study of patients with UN-EGFR-GS advanced lung adenocarcinoma over a 5-year period at a tertiary hospital in China. Patients diagnosed with stage IIIB or IV were included for analysis during 2010 and 2014. **Result:** In total, 140 patients were included, females and males constituted 48.6% (n=68) and 51.4% (n=72), respectively. The mean age was 58y. Among the 113 patients, 79 were non-smokers and 61 were smokers. Majority of patients had stage IV disease (90.0%), only 14 patients had stage IIIB disease. Most of the patients performance status (PS) score were 0 or 1 (n=128). Ninety-two patients were advanced stage when diagnosed and 48 patients were relapsed disease once received surgical resection. Nineteen patients received adjuvant chemotherapy, which were not relapsed in 6 months after finishing last cycle. In the140 patients, eighty-six had EGFR-TKIs ever, the rest were had chemotherapy only and never received EGFR-TKIs ever. The common regimens of first-line treatment were pemetrexed plus platinum (n=44), gemcitabine plus platinum (n=40), and paclitaxel plus platinum (n=18). Other drugs included docetaxel, novelbine. Twenty patients received EGFR-TKIs as first-line treatment. The commonest second-line treatment was oral EGFR-TKIs (n=47). Nineteen patients received EGFR-TKIs as third-line treatment and four received EGFR-TKIs as fourth-line treatment. At the end of follow-up (2016-7), 104 patients were dead and 36 patients were alive or lost follow up. The median survival of this whole cohort was 19.9m.Those who had a chance taken EGFR-TKIs lived longer than never; the median overall survival was 20.5 months and 16.4 months, respectively. EGFR-TKIs was associated with an improvement of overall survival, respectively in univariate analysis (p=0.027) and multvariate analysis (p=0.007). PS score was also associated with survival, respectively in univariate analysis (p<0.01) and multvariate analysis (p<0.01). The overall survival was not associated with sex (p=0.336), and smoking (p=0.414), TNM stage (p=0.565), age (p=0.100). The overall survival was also not associated with the chemotherapy drugs used in the first-line treatment. **Conclusion:** EGFR-TKIs have efficacy improved overall survival in patients with UN-EGFR-GS advanced lung adenocarcinoma, compared with conventional chemotherapy only. Oral EGFR-TKIs appear to be useful for this group of patients.

Keywords: advanced lung adenocarcinoma, unknown EGFR gene status, treatment outcomes

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-026 ANALYSIS OF LONG-TERM RESPONSE TO FIRST-LINE AFATINIB IN THE LUX-LUNG 3, 6 AND 7 TRIALS IN ADVANCED EGFRM+ NSCLC

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Background: In patients with advanced *EGFR* mutation-positive (*EGFR*m+) NSCLC,

first-line afatinib significantly improved PFS and objective response rate (ORR) versus platinum-doublet chemotherapy in the phase III LUX-Lung (LL) 3 and LL6 studies, and PFS, time-to-treatment failure (TTF) and ORR versus gefitinib in the phase IIb LL7 study. Here, we present post-hoc analyses of efficacy, safety and patient-reported outcomes (PROs) in afatinib long-term responders (LTRs) in LL3/6/7. **Method:** Treatment-naïve patients with stage IIIb/IV *EGFR*m+ NSCLC who were randomized to 40mg/day afatinib in LL3/6/7 and remained on treatment for ≥3 years were defined as LTRs. In these patients, we assessed efficacy and safety outcomes, as well as PROs measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire and the EQ-5D™ health status self-assessment questionnaire; these included scores on the EORTC Global Health [GH]/QoL scale (0–100), EORTC Performance Functioning scale (PF; 0–100), EQ Visual Analogue Scale (VAS; 0–100) and EQ-5D UK utility scale (EQ UK utility; 0–1). **Result:** In LL3/6/7, there were 24/229 (10%)/ 23/239 (10%)/ 19/160 (12%) afatinib-treated LTRs; 6/9/14 remained on treatment at time of analysis. Baseline characteristics were similar to the overall study populations, except for the proportion of women (LL3/6 only [LTRs versus overall]: 92/78% vs 64/64%) and Del19+ patients (LL3/6/7: 63–79% vs 49–58%). In LL3/6/7, 4–11% of LTRs had brain metastases at enrolment. Median (range) duration of treatment in LL3/6/7 LTRs was 50 (41–73)/56 (37–68)/42 (37–50) months. Due to few deaths, median OS could not be estimated. Median follow-up for OS in LL3/6/7 was 64.6/57.0/42.1 months. ORR among LTRs in LL3/6/7 was 70.8% (complete response: 4.2%; n=1)/78.3% (13.0%; n=3)/89.5% (5.3%; n=1). The frequency of afatinib dose reductions due to treatment-related AEs, and the frequency/duration of subsequent treatments were similar to the overall LL3/6/7 populations. In afatinib-treated LTRs in LL3/6/7, PROs appeared stable between ~Week 24 to ~Week 160, with slight improvements after ~3 years afatinib treatment versus scores at the start of treatment. **Conclusion:** In LL3/6/7, 10%–12% of afatinib-treated patients were LTRs. Afatinib was well tolerated among these patients. Long-term treatment was independent of tolerability-guided dose adjustment or presence of brain metastases at time of enrolment, and had no detrimental impact on subsequent treatment. In afatinib-treated LTRs, PROs were not negatively affected by long-term treatment, and were slightly improved after ~3 years of treatment versus scores at treatment initiation.

Keywords: long-term responders, PROs, afatinib

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P3.01-027 TET2 MUTATION AS A NOVEL MECHANISM OF ACQUIRED RESISTANCE TO EGFR TKIS IDENTIFIED BY A MUTATIONAL PROFILING USING NGS

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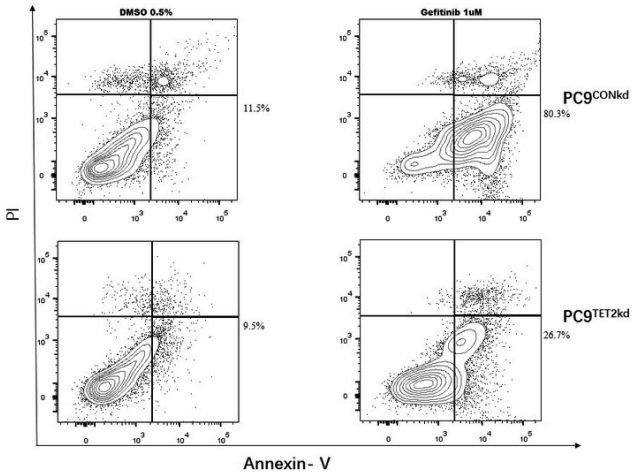
Background: Overcoming acquired resistance to EGFR TKIs remains challenging, identification of actionable genetic alterations conferring drug-resistance can be helpful for guiding the subsequent treatment decision. In our previous study, we performed mutational profiling in a cohort of 83 NSCLC patients using targeted next generation sequencing (NGS) and identified *TET2* mutations in 12% of patients. This study aims to further explore the role of *TET2* mutation in acquired EGFR-TKIs resistance in NSCLC cell lines with mutant EGFR. **Method:** CRISPR/Cas9 system was used to knock out *TET2* gene in NSCLC cell line PC-9. Quantitative real-time PCR was performed to detect mRNA levels of *TET2* gene, and western bot was performed to detect the expression levels of *TET2* protein, thus cell line of *TET2* silencing can be selected; positive for Annexin V and/or propidium iodide by flow cytometry was used to determine apoptotic rate. Bisulfite sequencing PCR (BSP) and real-time PCR for detection of EGFR promoter methylation status and mRNA expression. **Result:** By applying combined analyses of gene expression, apoptotic rate, and biochemical analyses of EGFR inhibitor responsiveness, we identified homozygous loss of *TET2* to segregate EGFR-dependent cells. We show that in EGFR-dependent cells, *TET2 l*oss partially uncouples mutant EGFR from downstream signaling and activates EGFR, thereby contributing to erlotinib resistance.



Conclusion: Our study is expected to provide new ideas and put forward corresponding relevant tactics for patients with secondary resistance to the first-generation EGFR TKIs.

Keywords: TET2 mutation, EGFR TKIs, aquired resistance

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P3.01-028 EFFICACY OF OSIMERTINIB FOR BRAIN METASTASIS IN ADVANCED NSCLC: DATA FROM SINGLE CENTER IN ASTRIS TRIAL

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Background: CNS (central nervous system) involvement is common in advanced NSCLC (non-small cell lung cancer). Osimertinib has shown activity in CNS in preclinical studies and phase II, III trials (AURA2, AURA3). We reported the efficacy of CNS metastases from an open label, multinational, multicenter, real world treatment study (ASTRIS, NCT02474355) in patients with T790M-positive advanced NSCLC who have progressed on or after prior epidermal growth factor receptor-tyrosine-kinase inhibitors (EGFR-TKI) therapy. **Method:** Patients with T790M-positive (from tissue, plasma or other fluids) advanced NSCLC received osimertinib 80mg once daily. Of the 88 patients who were enrolled in ASTRIS at Yonsei Cancer Center, 10 patients who did not have baseline brain workup and 15 patients without CNS metastases at the beginning of study were excluded from this analysis. A subgroup analysis was conducted in patients with CNS metastases at the baseline, as assessed by neuroradiologist, to define CNS overall response rate (ORR), duration of response (DOR), and progression-free-survival (PFS) by RECIST(Response Evaluation Criteria in Solid Tumors) v1.1. The CNS full analysis set (cFAS) included patients with ≥ 1 measurable and/or non-measurable CNS metastasis present on baseline scan; the CNS evaluable for response set (cEFR) included only patients with ≥ 1 measurable CNS metastasis. **Result:** Among the 63 patients who had CNS metastases at baseline, fifty-four (61.4%) patients were included in the subgroup analysis as cFAS, except for the 9 patients who did not follow up brain image during ASTRIS. In patients without brain metastases at the time of initiation of osimertinib (n=15), no experienced CNS progression during ASTRIS. CNS ORR was 81.3% (95% confidence interval [CI] 73.2-89.4) in the cEFR and 40.7% (95% CI 30.4-50.9) in the cFAS. In the cEFR and cFAS, median CNS DOR was "not reached" vs 40.1 weeks (95% CI 36.95-43.25). The median CNS PFS was not reached in both cFAS and cEFR. CNS ORR of 33.3%(95% CI 11.7-64.9) and 42.2% (95% CI 28.9-56.7) were observed for patients with CNS metastases within 3 months brain radiation and without prior radiation or ≥ 3months brain radiation, increasing to 75.0% (95% CI 28.9-96.6) and 83.3%(95% CI 54.0-96.5) respectively, for patients with measurable CNS disease only. CNS ORR of T790M-positive patients in tissue and plasma were 37.5%(95% CI 21.1-57.4) and 46.4% (95% CI 29.5-64.2) in the cFAS, vs 100%(95% CI 55.7-100.0) and 70.0%(95% CI 39.2-89.7) in the cEFR. **Conclusion:** Osimertinib had good CNS efficacy irrespective of radiation history in T790M-positive advanced NSCLC.

Keywords: Brain metastasis, osimertinib, NSCLC

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P3.01-029 TRANSIENT ASYMPTOMATIC PULMONARY OPACITIES (TAPOS) DURING OSIMERTINIB TREATMENT AND ITS CLINICAL IMPLICATION

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Background: Osimertinib is an oral, potent, irreversible 3rd generation EGFR tyrosine kinase inhibitor(TKI) approved for the treatment of T790M positive non-small cell lung cancer (NSCLC) patients who failed 1st or 2nd generation EGFR TKIs. Interstitial lung disease (ILD) is a rare complication with osimertinib, accounting for 1-3%. Recently, relatively high incidence of transient asymptomatic pulmonary opacities (TAPOs) which are different from ILD has been described (Noonan et al, JTO 2016). However, its clinical implication has not been fully determined yet. **Method:** We retrospectively analyzed 75 EGFR mutant NSCLC patients treated with osimertinib at Samsung Medical Center. Serial CT findings were reviewed by radiologist (Dr. HY Lee) and TAPO was classified according to its radiologic pattern. We also analyzed the correlation of TAPO with clinical outcomes. **Result:** Among 74 patients, TAPO was found in 15 (20.3%). The median time to TAPOs development was 23.5 weeks (1 – 72 weeks) and the median duration of TAPOs was 6.0 weeks (5 – 24 weeks) during continued osimertinib treatment. The most common radiological patterns of TAPO include cryptogenic organizing pneumonia and/or simple eosinophilic pneumonia (SEP). There was no significant difference in patient characteristics between TAPO positive and negative group. The duration of exposure to osimertinib is longer in TAPO positive than negative group (25.2 months vs 14.0 months, p=0.016). The progression free survival (PFS) and overall survival (OS) was numerically longer in patients with TAPO positive than negative group (PFS : 15.0 m *vs* 12.5 m, p= 0.201/ OS : 37.0 m *vs* 24 m, p=0.155) **Conclusion:** TAPOs are frequently observed with osimertinib

treatment and may be mistaken for isolated pulmonary progression or ILD. Given the lack of serious clinical deterioration, it is reasonable to continue osimertinib with regular CT scan follow-up. For further clinical validation of TAPOs, long-term and large studies are warranted.

Keywords: transient asymptomatic pulmonary opacities, osimertinib

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P3.01-030 CNS METASTASES IN EGFR MUTATION POSITIVE (EGFRM) NSCLC PATIENTS: THE PROGNOSTIC RELEVANCE OF PRESENTING SYMPTOMS

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Background: The overall survival (OS) of patients with EGFR mutation positive (EGFRm) lung cancer has changed dramatically due to the combined benefit of targeted systemic therapy, local management of oligometastatic disease and incorporation of judicious use of radiotherapy. We reviewed EGFRm NSCLC patients who were diagnosed with CNS metastasis to determine the prognostic importance of the initial CNS presentation. **Method:** A retrospective review was conducted of EGFR+ referred to the BC Cancer Agency between 2010 and 2015, treated with a first/second-generation EGFR TKI who developed CNS metastases (CNSm). Baseline characteristics, presenting symptoms and CNS-targeted treatment data was collected. Cox regression was conducted to determine the prognostic implications of the most common clinical presentations on OS. **Result:** 229 patients were identified; 90 presented with CNSm and 139 developed CNSm during the course of their disease. Method of CNSm detection: CT only 61%, MRI only 8%, CT and MRI 30%, PET 1%. 80% of patients were symptomatic at CNSm diagnosis. Baseline characteristics: female 66%, median age 62 (34-90), Asian 51%, exon 19/exon 21/rare mutation/not specified 56/39/3/2%. CNS management: 13% surgery+/- whole brain radiotherapy (WBRT), 73% WBRT alone, 5% stereotactic radiosurgery (SRS)+/-WBRT, 9% no CNS directed therapy. OS was 21.6 months in patients who presented with CNSm vs. 27.1 months in those who developed CNSm during the course of disease (p=0.39). On multivariate analysis, the only presenting symptom associated with increased risk of death was cognitive dysfunction.

	Frequency of symptom at presentation	**Univariate Analysis**		**Multivariate Analysis**	
		HR	P value	HR	P value
Cognitive Dysfunction	19%	1.26	0.01	1.21	0.04
Motor Dysfunction	18%	1.04	0.69		
Balance and Ataxia	11%	1.04	0.46		
Cranial Nerve Changes	8%	0.94	0.65		
Headache and Dizziness	30%	0.94	0.41		
Nausea and Vomiting	13%	0.92	0.48		
Visual Disturbance	10%	0.99	0.97		
Speech and Aphasia	10%	1.19	0.16		
Seizures	7%	0.75	0.09	0.78	0.13
Leptomeningeal disease	12%	1.25	0.04	1.20	0.10

Conclusion: The most common symptoms at initial presentation of CNSm in EGFRm patients were headache and dizziness, cognitive dysfunction and motor dysfunction. In multivariate analysis, only cognitive dysfunction was associated with poorer survival. Clinicians should have a low threshold for CNS screening based on the varied clinical symptoms experienced by patients

Keywords: CNS disease, clinical presentation, EGFRm NSCLC

P3.01: ADVANCED NSCLC -
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P3.01-031 CTDNA ASSESSMENT OF EGFR MUTATION STATUS IN CHINESE PATIENTS WITH ADVANCED NON–SMALL-CELL LUNG CANCER IN READ WORLD SETTING

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Background: EGFR mutation in plasma circulating free tumor-derived DNA (ctDNA) by ARMS methods has been widely used in clinical settings in China. However, the prevalence of EGFR mutations in ctDNA was still unknown in the real world. This large-scale study (NCT02623257) aimed to explore the prevalence of EGFR mutations and determine the correlation of EGFR mutation status with clinical characteristics. **Method:** Plasma DNA samples from 721 patients with stage III/IV NSCLC who received ≤1 line chemotherapy were collected from 65 hospitals. EGFR mutations were tested by ARMS method. The EGFR mutation rate was calculated and the associations between EGFR mutant and patients' demographic data, disease status as well as treatment pattern were explored. **Result:** EGFR mutations were detected in 176 of 721 (24.4%) patients, 165 of 620 (26.6%) in adenocarcinoma and 8 of 85 (9.4%) in squamous carcinoma. 138 (19.1%) harbored sensitizing mutations (66 19del, 62 L858R, 7 G719X, 2 L861Q, and 1 S768I) alone, 20 (2.8%) had resistance mutations (13 T790M, 7 Ins20) alone, 2 (0.3%) had a combination of activating mutations, and 16 (2.2%) had a combination of activating and resistance mutations. Twenty-eight (3.8%) patients were detected de novo T790M mutation either existed alone or combination, but no difference of clinical characteristics was observed. Higher detection rate was observed in 566 chemotherapy-naïve patients than in 155 patients received 1st line chemotherapy (27.2% versus 14.2%; p<0.001). Of which, the mutation rate of exon 19 deletion was 11.3% for naïve patients and 8.4% for the patients with 1st line chemotherapy; while the mutation rate of L858R decreased most obviously from 11.9%(naïve) to 1.9%(1st line). We also noticed 117 patients had ≥ 2 organ metastases and the mutation rate was 35.0% in these patients. Multivariate analysis showed female, chemotherapy native, or patients with ≥2 metastatic organs had higher percentage of EGFR mutation. Additionally, in 194 patients who had the follow-up treatment records, 34 of 49 patients (69.4%) with sensitive EGFR mutations received EGFR-TKI, 96 of 136 (70.6%) patients without sensitive EGFR mutation received chemo±radiation. **Conclusion:** Using plasma samples to detect EGFR mutation is feasible. ctDNA based EGFR mutation test could be a surrogate when tissue biopsy is not available due to limited tissue availability and procedural feasibility.

Keywords: ctDNA, ARMS, EGFR

P3.01: ADVANCED NSCLC -
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P3.01-032 PRELIMINARY STUDY OF LUNG CANCER ADENOCARCINOMA WITH DE-NOVO EGFR T790M MUTATION IN PERSAHABATAN HOSPITAL-JAKARTA, INDONESIA.

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Background: De-novo EGFR T790M mutations are rare, occurs less than 5% in the world and resistant to EGFR-TKI treatment. In Persahabatan Hospital, patients with De novo EGFR T790M mutations are given systemic chemotherapy with or without radiotherapy. No data on clinical profiles and 6 months survival rate in this group. the purpose of this preliminary study is to evalaute clincal profiles and 6 months survival of EGFR-T790M mutation in lung adenocarcinoma in Persahabtan Hospital Jakarta Indonesia. **Method:** Subjects was recruited consecutively from lung cancer Adenocarcinoma with De-novo EGFR T790M mutations. EGFR mutation is routinely assesed in lung adenocarcinoma in Persahabatan Hospital using PCR-High Resollution Melting, RFLP Analysis and direct sequencing. Subjects' clinical characteristics (race, age, gender), smoking habits, family history of malignancy, occupation, date at diagnosis (through anatomic pathology examination), complete diagnosis, stage, performance status, metastasis, chemotherapy and radiotherapy, RECIST evaluation, date of death were recorded. **Result:** Fourteen subjects were elligible and included in this study of which 9 subjects were male (64,2%), 5 subjects female (35,7%). Smoking status were 8 subject were smoker (57,1%), never smoke (35,7%), ex smokers (7,14%). Two subjects (14.2%) has family history of malignancy. All subjects were stage 4 with 42.8% pleural effusion (6 subjects), 21.4% pleural effusion and bone metastasis (3 subjects), 21.4% (3 subjects) with distant lymph nodes metastasis, 7.2% brain metastasis (1 subjects), 7.14% brain and bone metastasis. Mutation in ONLY exon 20 T790M 85,7% (12 subjects); double mutation did exist with Exon 19 ins/del and exon 20 T790M (1 subject); exon 19 ins/del and exon 20 T790M (1 subject); exon 21 L861Q and exon 20 T790M in 1 subject. Systemic chemotherapy were done in 9 subjects (64,3%), systemic chemotherapy and radiotherapy were done in 5 subject (35,7%). Six months survival rates in this group was 50%; and 1 year survival were 21,42%; Interestingly 4 subjects (28,6%) survived more than 1 year. **Conclusion:** De-novo EGFR T790M mutations are rare (< 5%). The presence double mutation ie. De-novo EGFR T790M mutations and other

activating EGFR mutation did exist. these group has variable clinical responses with chemotherapy and warrant further investigation.

Keywords: advanced NSCLC, EGFR T790M, De-novo

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P3.01-033 DETECTION OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS WITH PLASMA SAMPLE COMPARED WITH TUMOR TISSUE BIOPSY IN ADVANCED LUNG ADENOCARCINOMA

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Background: Personalized treatment based on the molecular markers in tissue of patients have crucial role in clinical practice. However, Obtaining Tumor tissue samples are not always available, and rebiopsy is not easy to do. The liquid biopsy with blood samples will be a good alternative diagnostic method. We compared the detection rate of EGFR mutation detection techniques between matched tumor tissue and peripheral blood sample in patients with lung adenocarcinoma. **Method:** We collected the paired samples from plasma and paraffin-embedded tumor tissue in patients before EGFR-TKIs treatment or after progression of EFGR-TKIs treatment. EGFR mutation analysis was done by two detection methods. One is the PNAClampTM (Clamp) which is the PNA-based PCR clamping that selectively amplifies only the mutated target DNA sequence as minor portion in mixture with the major wild type DNA sequences. The other is the PANAMutyperTM EGFR kit (Mutyper), which use PNA clamping-assisted fluorescence melting curve analysis to perform mutation detection and genotyping. The tissues were tested by Clamp method, and blood was tested in two ways. We compared the sensitivity of EGFR mutation detection techniques from tumor tissue and plasma circulating tumor DNA in patients. **Result:** Total patients were thirty two (17 male, 15 female) with advanced stage, mean age was 62.8 years-old, all patients were adenocarcinoma, and fifteen patients were never smoker. EGFR mutation positive rate of tissue was 31.3%. In plasma samples, there were 21.9% in Clamp method and 31.3% in Mutyper method. EGFR plasma detection rate of Mutyper was higher than Clamp. Two patients who showed wild type in tissue Clamp method have EGFR 19 deletion by Mutyper method. Both patients were female never smoker. In two cases, T790M was detected only in tissue but not in liquid biopsy. The overall concordance and degree of agreement between two samples were better in Mutyper (75%, gamma=0.872, p<0.001) than Clamp (71.3%, gamma=0.824 p=0.003). **Conclusion:** The plasma detection rate and the degree of agreement of Mutyper test were better than Clamp test. This method can be useful to detect EGFR mutation in circulating cell-free DNA sample. Liquid biopsy is an excellent resource, and had additional effect in choosing available drug for EGFR rich lung cancer population.

Keywords: EGFR mutation. Liquid biopsy. Lung adenocarcinoma

P3.01: ADVANCED NSCLC -
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P3.01-034 LIQUID BIOPSY FOR EGFR GENOTYPING USING CELL-FREE DNA AND EXTRACELLULAR VESICULAR DNA OF PLEURAL EFFUSION IN PULMONARY ADENOCARCINOMA PATIENTS

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Background: Pleural effusion is a highly efficient sample for liquid biopsy due to cancer cell enriched components. Liquid biopsy for EGFR genotyping is mostly being done using cell-free DNA. Extracellular vesicles (EVs) are known to carry oncogenic double stranded DNA that is considered as a noble biomarker. We set up to investigate the liquid biopsy using cell-free (cf) DNA and extracellular vesicular (EV) DNA of pleural effusion for EGFR genotyping in pulmonary adenocarcinoma patients. **Method:** Forty nine pleural effusion samples of pulmonary adenocarcinoma patients were evaluated. Non-cellular components after removing cell pellets by centrifuge (400g, 10 min, 4°C) were used for liquid biopsy and EVs were isolated by ultracentrifuge method (200,000g, 1 hr, 4°C). EV DNA and cf DNA were extracted separately and EGFR genotyping was done by PNA-clamping method. For the analysis of T790M detection, cell block slides were used as rebiopsy sample, when compared with liquid samples. **Result:** Among 31 EGFR-TKI naïve patients with known tissue EGFR genotyping, liquid biopsy using effusion EV DNA showed 100% matching with tissue EGFR genotyping in 19 EGFR mutant cases and detected 3 more EGFR mutant cases in tissue wild type (WT) patients, while liquid biopsy using effusion cf DNA missed 2 cases of tissue-based EGFR mutant patients and found 2 more EGFR mutant cases in tissue WT patients. In 18 patients with acquired resistance to EGFR-TKI, EGFR genotyping using effusion EV DNA detected T790M mutation in 13 of 18 (72.2%) patients, while 11 of 18 (61.1%) patients were detected by using effusion cf DNA, respectively. In contrast, only 3 patients were found to have T790M when using cell block slides. **Conclusion:** Liquid biopsy using pleural effusion is particularly effective for EGFR genotyping than conventional cytology or cell block sample. Liquid biopsy using effusion EV DNA is highly promising for EGFR genotyping, especially detecting T790M mutation, when compared with cf DNA.

Keywords: extracellular vesicular DNA, liquid biopsy, EGFR genotyping

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P3.01-035 POST-MARKETING OBSERVATIONAL STUDY OF JAPANESE PATIENTS WITH EGFR MUTATION-POSITIVE (EGFRM+) NSCLC TREATED WITH DAILY AFATINIB (FINAL REPORT)

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Background: This is a prospective, post-marketing surveillance study (NCT02131259) to evaluate safety and effectiveness of the irreversible ErbB family blocker, afatinib, which is approved in Japan for the treatment of inoperable/recurrent *EGFR*m+ NSCLC. **Method:** Patients with inoperable/recurrent *EGFR*m+ NSCLC received afatinib at the approved dose (20–50 mg/day) and were observed following treatment initiation for 52 weeks/until premature discontinuation. Data were included for all patients who received afatinib during the investigational period of this study, thus minimizing patient selection bias. The incidence/severity of adverse drug reactions (ADRs)/serious ADRs (sADRs) was the primary endpoint. Other endpoints included effectiveness (objective response rate [ORR]) and the incidence/severity of ADRs of special interest (diarrhea, rash/acne, nail effects [NEs] and interstitial lung disease [ILD]). **Result:** As of February 2017, 1,602 patients were included in the analysis (59% female, 81% aged <75 years, 86% ECOG PS 0–1, 83% BMI <25 kg/m^2). 97% of patients had adenocarcinoma, and 64%/26% had *EGFR* Del19/L858R mutations. 70% had ≥1 line of prior chemotherapy; 48%/30% had prior gefitinib/erlotinib. Afatinib starting dose was 40 mg in 77% of patients. 95% had ADRs (36% grade ≥3). The most frequently reported ADRs (all grade/grade 3–4) were diarrhea (78%/15%), rash/acne (59%/6%), stomatitis (31%/4%), and NEs (38%/4%). ILD (all grade/grade 3–4/grade 5) occurred in 4%/2%/1% of patients. Median (range) time to initial onset was 5.0 (1–316) days for diarrhea, 11.0 (1–406) days for rash/acne, 9.0 (1–327) days for stomatitis, 38.0 (1–526) days for NEs, and 35.5 (3–329) days for ILD. Four patients (<1%) had creatinine elevation following grade ≥3 diarrhea. Dose reductions/permanent discontinuations occurred in 8%/7% of patients following diarrhea, 6%/4% following rash/acne, 3%/2% following stomatitis, 5%/2% following NEs, and <1%/4% following ILD. 33% of patients experienced sADRs. ADR frequency was associated with starting dose (96%/91% with 40/<40 mg afatinib), but was not unfavorably impacted by age, ECOG PS, number of prior chemotherapies, or previous EGFR TKIs. ORR with afatinib was higher in EGFR TKI-naïve patients than those who had previously been treated with EGFR TKIs (68% versus 21%). **Conclusion:** Consistent with previous studies, afatinib was effective in inoperable/recurrent *EGFR*m+ NSCLC, particularly as first-line targeted treatment (ORR ~70%). ADRs were predictable and generally manageable. ADR frequency was not notably affected by age, ECOG PS or number of previous therapies. In clinical practice, patients should be closely monitored and ADRs, particularly diarrhea and ILD, treated early to prevent sADRs.

P3.01: ADVANCED NSCLC -
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P3.01-036 A PHASE IIIB OPEN-LABEL, SINGLE-ARM STUDY OF AFATINIB IN EGFR TKI-NAÏVE PATIENTS WITH EGFRM+ NSCLC: AN INTERIM ANALYSIS

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Background: In the Phase III LUX-Lung (LL) 3 and LL6 trials, first-line afatinib significantly improved PFS vs platinum-doublet chemotherapy in patients with *EGFR*m+ NSCLC (independent review; LL3: 11.1 vs 6.9 months, HR=0.58; p=0.001;

LL6: 11.0 vs 5.6 months, HR=0.28; p<0.0001). In the Phase IIb LL7 trial, afatinib significantly improved PFS and TTF vs gefitinib in patients with *EGFR*m+ NSCLC harboring common *EGFR* mutations (PFS, independent review: 11.0 vs 10.9 months, HR=0.73; p=0.017; TTF: 13.7 vs 11.5 months, HR=0.73, p=0.0073). Here we report interim analysis results of a large Phase IIIb study of afatinib in a broad population of EGFR TKI-naïve patients with *EGFR*m+ NSCLC. **Method:** In this Phase IIIb trial with a similar setting to 'real-world' practice, EGFR TKI-naïve patients with locally advanced/metastatic *EGFR*m+ NSCLC were recruited from centers in China, Hong Kong, India, Singapore and Taiwan and received afatinib 40mg/day until investigator-assessed progression or lack of tolerability. Primary endpoint: number of patients with serious adverse events (SAEs). Secondary endpoints included: number of patients with afatinib-related AEs; time to symptomatic progression (TTSP). Other assessments included PFS (investigator review). **Result:** At data cut-off (13 Feb 2017) 479 patients were treated with afatinib (median age: 59.0 years; female: 52.4%; common [(Del19 and/or L858R) with or without uncommon]/uncommon only *EGFR* mutations: 86.0%/14.0%; ECOG PS 0/1: 19.8%/78.1%; brain metastases: 19.2%; 0/1/≥2 lines of prior chemotherapy: 59.7%/30.1%/10.2%. 24.8% of patients required dose reductions to 30mg; 6.1% had further reductions to 20mg. Median (range) treatment time was 9.7 months (0.2–38.6). SAEs were reported in 115 (24.0%) patients and afatinib-related SAEs in 29 (6.1%) patients. Grade ≥3 afatinib-related AEs occurred in 122 (25.5%) patients; diarrhea (n=50; 10.4%) and rash/acne (n=38; 7.9%) were the most common (≥5%). 18 (3.8%) patients discontinued treatment due to afatinib-related AEs. Median TTSP (15.3 months [95% CI: 13.4–17.5]) was 3 months longer than PFS (12.1 months [10.8–13.7]), suggesting afatinib may be continued beyond progression, and both were longer in patients with common (with/without uncommon) vs uncommon only *EGFR* mutations (PFS: 12.6 vs 9.1; TTSP: 15.8 vs 10.0 months). **Conclusion:** The safety data of afatinib from this interim analysis of a large-scale population of EGFR TKI-naïve *EGFR*m+ NSCLC patients are consistent with LL3/6/7 and confirm that most afatinib-related AEs are manageable and result in few treatment discontinuations. Afatinib also demonstrated encouraging efficacy in patients with common and uncommon *EGFR* mutations. Data from larger patient populations will be evaluated in further analyses of this trial.

Keywords: afatinib, EGFR, NSCLC

P3.01: ADVANCED NSCLC -
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P3.01-037 UNDERSTANDING MECHANISMS OF RESISTANCE TO OSIMERTINIB BY CIRCULATING TUMOR DNA GENOTYPING IN ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Epidermal growth factor receptor (EGFR) T790M mutation is the most common mechanism for resistance to first- and second-generation EGFR tyrosine kinase inhibitors (TKI). Osimertinib has been demonstrated to overcome EGFR T790M non-small cell lung cancer (NSCLC). However, most of these patients eventually developed resistance after 10 months. Here we performed a comprehensive next generation sequencing (NGS) using circulating tumor DNA (ctDNA) to study resistance mechanisms in patients with advanced NSCLC who had developed resistance to osimertinib, and to provide potential opportunities for treatment. **Method:** 10 advanced NSCLC patients were enrolled in this study after progression from first-generation EGFR-TKI treatment. Patients received osimertinib with 80mg daily, the response rate and progression-free survival (PFS) was assessed during treatment. 10ml peripheral blood was collected from patients after progression from osimertinib, and ctDNA genotyping was performed by next-generation sequence (NGS). **Result:** There were 3 patients received gefitinib and 7 patients received erlotinib before osimertinib therapy. All patients confirmed a partial response (PR) on osimertinib, the median PFS was 13.3 months. The initial gene mutation patterns before osimertinib therapy could be classified into two groups: L858R/Exon 19 Deletion (19Del) +T790M, and L858R/19Del+T790M unknown or wild-type. However, after progression from osimertinib, mutation patterns varied from groups. In the L858R/19Del+T790M group, two of six patients detected with L858R/19Del+T790M+C797S, two patients with L858R (+T790M) +HER2 amplification, and two patients with only 19Del+T790M; In the L858R/19Del+T790M unknown or wild-type group, there was only one patient detected with L858R/19Del+C797S mutation, the other three patients detected with only L858R mutation. For the C797S-mutated patients, it showed that T790M and C797S mutation presented in the same allele (cis) in two patients, while in both trans and cis in one patient. Other EGFR mutations were also detected, such as A750P, L792F, E709K, A1013V, L718V, and EGFR amplification. **Conclusion:** Genotyping of ctDNA in osimertinib resistant patients showed that the resistance might be related to specific gene mutation, e.g., EGFR C797S and HER2 amplification. Our findings provide insight that resistance to osimertinib might be different between T790M-mutated patients and T790M wilt-type patients. Combination therapy of osimertinib with other agents may be candidate to overcome the acquired mutation.

Keywords: ctDNA, NSCLC, EGFR-TKI

P3.01: ADVANCED NSCLC -
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P3.01-038 IMPACT ON OS AND PFS OF 2ND AND 3RD GENERATION TKI IN EGFR MT+ AND ALK+ PATIENTS: RESULTS OF THE NOWEL NETWORK

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Background: EGFR TKI treatment is standard of care in patients with metastasized NSCLC carrying an activating EGFR mutation. Targeted therapies achieve a higher ORR, OS, PFS and a better quality of life than chemotherapy. With the advent of 2nd and 3rd generation TKI´s effective in 1st generation TKI resistant tumors, we wanted to study the impact of these drugs on the outcome of patients in a real life setting in 3 lung cancer centers. **Method:** 1473 patients from three cancer centers diagnosed with non-squamous cell NSCLC stage IV (UICC 7) were examined. Methods for the mutation testing was performed according to the German Oncopedia guidelines using either Sanger Sequencing or COBAS ® or Next Generation Sequencing. **Result:** 964/1473 (65%) consecutive patients with non-squamous cell NSCLC were studied for the presence of tumor mutations. The EGFR mutation rate was 16% (147/943), and the ALK-translocation rate 4% (26/695). Median OS in EGFR mt+ patients was 27 months (n=147) compared to 11 months (n=796) in patients with EGFR WT (p<0.000). Median OS in EGFR mt+ patients depending on the center was 27 (n=95) vs. 28 (n=38) vs. 16 (n=14) months respectively (center 1 vs. center 2 vs. center 3). Median OS in ALK mt+ patients was 24 months (n=19) in center 1 and 11 months (n=5) in center 2 (p<0.025). The ORR in the CR/PR group was 54.2% for patients treated with chemotherapy and 77% for patients treated with TKI on 1st line therapy. The chance to reach a CR/PR is 2.83 higher for patients on TKI than for patients on chemotherapy (p<0.02). The use of 3rd generation TKI Osimertinib (n=19) lead to a significantly higher OS (n=19, median OS 67 months) than the use of only 1st and 2nd generation TKI (n=119, median OS 23 months, p<0.000). The hazard ratio for patients treated without Osimertinib was 4.66 [95% CI 2.006-10.81] (p<0.000). Patients treated with 3rd gen TKI had significantly longer PFS (11 months, n=7) than patients treated without (5 months, n=20) (p<0.037). Similarly, use of 2nd and 3rd generation ALKi impacted significantly on median OS: Crizotinib alone (n=8) 17 months, Crizotinib followed by Ceritinib and/or Brigatinib/Alectinib (n=12) median OS not reached and 3 months for other therapies (n=6) (p<0.000). **Conclusion:** Small differences in OS were observed, depending on the treatment centers, but the use of multiple EGFR and ALK-I impacted highly significantly on the outcome of patients with EGFR and ALK-alterations in a real life setting.

Keywords: 3rd generation TKI, advanced NSCLC, EGFR

P3.01: ADVANCED NSCLC -
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P3.01-039 SEQUENTIAL AFATINIB-OSIMERTINIB THERAPY IN EGFR MUTATION-POSITIVE (EGFRM+) NSCLC: ANALYSIS OF TIME ON TREATMENT AND OS

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Background: Acquired resistance to EGFR TKIs necessitates further treatment for patients with *EGFR*m+ NSCLC. In the LUX-Lung 7 (LL7) trial, afatinib significantly improved PFS, TTF and ORR vs gefitinib. Particularly encouraging OS was observed across both treatment arms in patients who received a subsequent third-generation EGFR TKI (afatinib vs gefitinib, median: not reached vs 48.3 months). Osimertinib has demonstrated activity against tumors harboring the T790M mutation; this mutation is known to be the main mechanism of acquired resistance to afatinib. Here, we assess the outcomes of first-line afatinib followed by subsequent osimertinib treatment, in patients with *EGFR*m+ NSCLC. **Method:** Patients with common (Del19/L858R) *EGFR* mutations who were randomized to receive first-line afatinib (40mg/day in LL3/6/7) or gefitinib (250mg/day in LL7) and received subsequent osimertinib treatment were included in the analysis. We retrospectively assessed time on osimertinib treatment following afatinib or gefitinib, and OS in patients treated with sequential afatinib-osimertinib or gefitinib-osimertinib, in LL7 alone (afatinib and gefitinib arms) and in a pooled analysis of LL3/6/7 (afatinib arm only). **Result:** In LL7 (data cut-off: 5 December 2016), 24 and 19 patients in the afatinib and gefitinib arms,

respectively, received subsequent osimertinib. Approximately 30% of these patients received osimertinib as second-line treatment following afatinib/gefitinib. Baseline characteristics of osimertinib-treated patients were generally similar to the overall LL7 population and between treatment arms. Median time on study drug was longer in both the afatinib-osimertinib and gefitinib-osimertinib groups versus the overall afatinib and gefitinib study populations (16.5 and 17.9 vs 13.7 and 11.5 months). Median time on osimertinib treatment was 31.5 vs 15.2 months (afatinib vs gefitinib; HR=0.41; 95% CI=0.13–1.30). Median OS was not reached in both arms. Three-year survival rates were 96% vs 89% (afatinib vs gefitinib). In the combined analysis of LL3/6/7, 34 afatinib-treated patients received subsequent osimertinib, with 26.5% receiving osimertinib as second-line treatment. Median time on osimertinib treatment was equal to that of the LL7 analysis (afatinib arm; 31.5 months); median OS was again not reached and three-year survival rate was 97%. **Conclusion:** The long duration of osimertinib treatment and OS observed in this analysis suggest that sequential afatinib-osimertinib therapy is remarkably effective in patients with *EGFR*m+ NSCLC and warrants further assessment. Based on these data, we hypothesize that afatinib's broad and durable inhibition of the ErbB family delays and/or suppresses onset of acquired resistance and passenger aberrations, facilitating longer duration of treatment with subsequent osimertinib.

Keywords: afatinib, EGFR, NSCLC

P3.01: ADVANCED NSCLC -
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P3.01-040 REAL-WORLD MANAGEMENT OF PATIENTS WITH EGFR MUTATION-POSITIVE NSCLC IN THE US

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Background: Clinical trials have demonstrated the efficacy and safety of EGFR tyrosine kinase inhibitors (TKIs), as first-line therapy in patients with metastatic non-small-cell lung cancer (NSCLC) whose tumours harbour activating mutations in the *EGFR* gene. However, there are limited data in the real-world setting describing TKI use among patients with *EGFR*-mutated NSCLC. **Method:** A retrospective non-interventional study was conducted using the Flatiron Health database, a longitudinal database containing electronic health record data, of patients seen in over 265 United States cancer clinics (~800 sites of care). Adult patients with histologically confirmed stage IIIB or IV NSCLC, with documented *EGFR*-mutated disease (del 19 or L858R), and who had received the first sequence of systemic therapy between January, 2011 and March, 2016 were included. Patient demographic and clinical disease characteristics were analysed and time-to-next treatment (TTNT) was used as a surrogate measure for progression-free survival. If validated in time, overall survival data will be presented. **Result:** Overall 20,924 adult patients with advanced NSCLC were identified, of whom 12,148 (58.1 %) were tested for *EGFR* mutations. Among these, 1,919 (15.8 %) patients had a positive *EGFR* result with 1,412 patients carrying del 19 or exon 21 mutations. Of these, 886 patients were treated with regimens in the first-line setting. Median age was 69.0 years; 67.7% were female; 55.5% were Caucasian; 54.3% were non-smokers; 97.5% had non-squamous histology and 57.3% received at least one subsequent treatment. Most patients received a TKI (71.8%) and 28.2% received other therapy. There were no differences observed in a patient's type of insurance and the type of treatment (TKI or chemotherapy) that they were likely to receive. Patients treated with an EGFR TKI had a significantly longer median TTNT [erlotinib (13.2 months [95% CI 12.2–14.4; p=<0.001]) afatinib (12.6 months [95% CI 8.6–16.2; p=<0.001]), gefitinib (not evaluable; due to small sample size n=9) than those treated with other anti-cancer agents (4.6 months [95% CI 4.0–5.4]). **Conclusion:** These real world data mirror the results shown in randomised clinical trials, with the exception of patients being generally older. Importantly, patients who did not receive a TKI had significantly shorter TTNT. A large proportion of patients (42%) are not being tested for *EGFR* mutations, although there was an improvement over time. The reasons for not testing all eligible patients for *EGFR* mutations should be investigated further.

Keywords: Erlotinb, Real-world data, Flatiron Health database

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-041 THE ROBUSTNESS OF ALLELE-SPECIFIC QPCR ASSAYS FOR DETECTION OF EGFR MUTATIONS IN PLASMA CELL-FREE DNA FROM NSCLC PATIENTS

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Background: The analysis of *EGFR* mutations in plasma cell-free DNA (cfDNA) may become an auxiliary tool in the molecular diagnosis of advanced NSCLC patients from whom sufficient tumor tissue/cells specimens cannot be obtained. We evaluated the diagnostic performance of the two most common real-time PCR-based platforms for detection of *EGFR* mutations in plasma cfDNA that we use in our routine laboratory practice. **Method:** *EGFR* mutations were analyzed in plasma cfDNA collected from 107 NSCLC patients (non-SQC type, stages I-IV) before treatment (n=80) or at the time of progression on EGFR-TKIs (n=27) using two IVD-marked assays: 'Cobas EGFR Mutation Test v2' (Roche) and 'Therascreen EGFR Plasma RGQ PCR Kit' (Qiagen). **Result:** The overall concordance between *EGFR* mutation status in plasma cfDNA and paired tumor tissue samples was 62% (46% for Cobas and 32% for Therascreen test) for all patients regardless the NSCLC stage. The concordance increased to 88% (83% for Cobas and to 56% for Therascreen) when only samples from advanced NSCLC patients were evaluated. Accordingly, the Cobas test showed higher positive percent agreement between cfDNA and tissue results (PPA=83%) than did the Therascreen test (PPA=56%). Both test showed 100% negative percent agreement. The T790M mutation was detected in 26% cfDNA samples from patients upon progression on EGFR-TKIs. In 12 (44%) cases with progressive disease, the plasma cfDNA was the only specimen available for *EGFR* mutation analysis. **Conclusion:** In our laboratory setting, Cobas test demonstrated superior diagnostic performance over Therascreen assay in detection of *EGFR* mutations in plasma cell-free DNA from advanced NSCLC patients. Since analysis of mutated *EGFR* cfDNA in plasma is troublesome laboratory procedure, we recommend to validate the true diagnostic performance of each commercial assay in a specific laboratory conditions despite its IVD certification. The study is on-going.

Keywords: EGFR mutations, plasma cell-free DNA, non-squamous NSCLC

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-042 EFFICACY & TOLERABILITY OF AFATINIB IN NSCLC PATIENTS PRIOR EXPOSURE TO 1ST GENERATION EGFR TKI: THAILAND MULTICENTER STUDY

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Background: The Compassionate-Use-Program (CUP) was available in Thailand for requesting afatinib during 2012-2014 for patients whom had failed at least one-line of platinum-based-chemotherapy and progressed following at least 6 months on 1st-generation EGFR-TKIs. This is a multicenter-retrospective-study in Thailand aimed to explore the efficacy and tolerability of afatinib in this group of patients. **Method:** Full medical-records of 79 patients from 7 institutions were reviewed. Clinical and tumor characteristics were analyzed using descriptive statistics. The efficacy in brain metastases was explored. Survival curves were constructed using the Kaplan-Meier method. All analysis was done in Stata version14. **Result:** Sixty-eight percent of patients were younger than 65 years old, 60% were female, and 67% received more than 2 of prior-regimen. EGFR-mutation was tested in 75% of patients; comprise of 86% common-mutations, 14% uncommon-mutations. Eleven patients had *T790M* acquired-resistance in combination with sensitive-mutation before receiving afatinib. One patient had De-novo-*T790M*. The mOS, mPFS, and mTTF were 11.5, 3.9, and 5.1 months, respectively. Eighteen patients had brain-metastases at enrollment and 6 patients had new brain-metastases during afatinib treatment. The mOS, mPFS, and mTTF were not statistically different among new brain-metastases or pre-existing brain-metastases. There was no dose-reduction in 38%, 1 dose-reduction 44%, 2 dose-reductions 12%, and 3 dose-reductions 6% of patients. The mean dose for every patient was 35 mg. Time-to-first-dose-reduction significantly affected the mPFS and mTTF as shown in Table. Furthermore, number of prior-treatment more than 2 was the significant factor causing first-dose-reduction within 1 month and age younger than 65 years-old was the significant factor causing first-dose-reduction within 2 and 3 months in multivariate and univariate model, respectively.

Time to 1st dose reduction	OS		PFS		TTF	
	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P*-value
> 1 month <= 1 month	1 1.59 (0.74-3.41)	0.23	1 1.52 (0.82-2.82)	0.19	1 1.45 (0.77-2.74)	0.25
>2 month <= 2 months	1 1.54 (0.72-3.3)	0.27	1 2.11 (1.14-3.92)	0.02	1 1.63 (0.88-3.04)	0.12
>3 months <= 3 months	1 2.31 (0.98-5.45)	0.06	1 2.67 (1.38-5.20)	0.004	1 2.12 (1.09-4.12)	0.03

Conclusion: The mOS, mPFS, and mTTF of our study were comparable with LUX-Lung1 study. Number of prior-treatment and age were the significant factors causing

dose-reduction. Taken together with time-to-first-dose-reduction also affected the survival of patients.

Keywords: Lung cancer, Afatinib, Compassionate-Use-Program

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-043 IMPACT OF ERBB MUTATIONS ON CLINICAL OUTCOMES IN AFATINIB- OR ERLOTINIB-TREATED PATIENTS WITH SCC OF THE LUNG

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Background: In LUX-Lung 8 (LL8), second-line afatinib (an irreversible ErbB family blocker) significantly improved OS (median 7.9 versus 6.8 months; HR [95% CI]: 0.81 [0.69-0.95]; p=0.0077), and PFS (2.6 versus 1.9 months; 0.81 [0.69-0.96]; p=0.0103) versus erlotinib in lung SCC (N=795). Comprehensive genetic analysis in LL8 patients assessed whether afatinib efficacy varied according to genetic aberrations in cancer-related genes, including ErbB family mutations. **Method:** Tumor genetic analysis (TGA) was performed using Foundation Medicine FoundationOne™ next-generation sequencing (NGS). The cohort was enriched for patients with PFS >2 months, reflecting a range of responsiveness to EGFR-TKIs. EGFR expression was assessed by immunohistochemistry (IHC) in a largely separate cohort. Cox regression analysis correlated PFS/OS with genetic mutations (individual/grouped) and EGFR expression. **Result:** Of 440 patients selected for TGA (PFS >2 months: n=320; ≤2 months: n=120), samples from 245 were eligible (afatinib: n=132; erlotinib: n=113). In the selected TGA population, PFS/OS outcomes were improved in the afatinib versus erlotinib arm. Baseline characteristics were similar in TGA and IHC cohorts and LL8 overall. In the TGA subset, 53 patients (21.6%) had ≥1 ErbB family mutation (EGFR: 6.5%; HER2: 4.9%; HER3: 6.1%; HER4: 5.7%). Beyond the benefit seen for afatinib in the overall population, in afatinib-treated patients, PFS/OS were longer when ErbB mutations were present (PFS: 4.9 versus 3.0 months; OS: 10.6 versus 8.1 months). Conversely, survival outcomes in erlotinib-treated patients were similar with/without ErbB mutations. Presence of HER2 mutations predicted favorable PFS/OS with afatinib versus erlotinib. The Table shows outcomes in patients with/without ErbB family mutations, and by EGFR expression levels (afatinib: n=157; erlotinib: n=188). **Conclusion:** These data are provocative and suggest that NGS may enable identification of lung SCC patients who would derive additional clinical benefit from afatinib. Differential outcomes with respect to ErbB mutations for afatinib and erlotinib are hypothesized to reflect afatinib's broader mechanism of action.

Subgroup	**n**	**Afatinib vs erlotinib**			
		PFS		**OS**	
		HR (95% CI)	**pinteraction**	**HR (95% CI)**	**pinteraction**
ErbB mutation-positive ErbB mutation-negative	53 192	0.56 (0.29–1.08) 0.70 (0.50–0.97)	0.718	0.62 (0.35-1.12) 0.76 (0.56-1.03)	0.683
EGFR mutation-positive EGFR mutation-negative	16 229	0.64 (0.17–2.44) 0.67 (0.50–0.91)	0.981	1.01 (0.32–3.16) 0.72 (0.54–0.95)	0.529
HER2 mutation-positive HER2 mutation-negative	12 233	0.06 (0.01–0.59) 0.72 (0.54–0.97)	0.006	0.06 (0.01–0.57) 0.76 (0.58–1.00)	0.004
HER3 mutation-positive HER3 mutation-negative	15 230	0.52 (0.16–1.72) 0.69 (0.51–0.94)	0.692	0.84 (0.27–2.59) 0.73 (0.56–0.97)	0.998
HER4 mutation-positive HER4 mutation-negative	14 231	0.21 (0.02–1.94) 0.67 (0.50–0.91)	0.909	0.22 (0.05–1.04) 0.75 (0.56–0.99)	0.272
EGFR IHC positive EGFR IHC negative	292 53	0.74 (0.56–0.97) 0.76 (0.41–1.40)	0.985	0.82 (0.63–1.06) 0.75 (0.41–1.40)	0.882
EGFR amplification present EGFR amplification absent	17 228	0.72 (0.18–2.90) 0.68 (0.50–0.92)	0.994	0.50 (0.15–1.65) 0.76 (0.58–1.00)	0.413
HER2 amplification present HER2 amplification absent	9 236	0.94 (0.20–4.38) 0.68 (0.50–0.91)	0.861	1.10 (0.27–4.48) 0.72 (0.54–0.94)	0.388

Keywords: NSCLC, Squamous cell carcinoma, afatinib

P3.01-044 ERLOTINIB VS CHEMOTHERAPY IN EGFR MUT+ NSCLC: OS IN THREE PHASE III TRIALS ADJUSTING FOR POST-PROGRESSION TREATMENT CROSSOVER

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Background: In EURTAC, ENSURE and OPTIMAL, first-line erlotinib was associated with higher response rates and improved PFS versus chemotherapy in *EGFR* Mut+ NSCLC. OS benefit was not observed, possibly due to high crossover. We present statistical analyses of OS adjusting for crossover in the three studies. **Method:** Rank Preserving Structural Failure Time (RPSFT) analysis is a retrospective statistical methodology that estimates the effect of active treatment and then removes that effect from the control patients, during the period of active treatment. Separately, post-hoc OS analyses were conducted on non-randomized subgroups of patients who received a single line of therapy, chemotherapy only or erlotinib only; or a sequence, chemotherapy followed by TKI or erlotinib followed by chemotherapy. Impact of sequencing on OS was evaluated (Kaplan-Meier methodology). **Result:** RPSFT analyses (Table) show OS was numerically longer with erlotinib versus chemotherapy in EURTAC and ENSURE. OS was not longer with erlotinib in OPTIMAL, possibly due to low treatment adherence in the erlotinib arm, where >50% of patients refused chemotherapy or did not complete four cycles. In the non-randomized analyses, patients receiving erlotinib as the sole treatment had longer OS versus patients treated with only chemotherapy, in all three studies. Patients who received erlotinib followed by chemotherapy had longer OS versus patients who received chemotherapy followed by erlotinib in EURTAC and ENSURE. Patients who received chemotherapy followed by erlotinib in OPTIMAL had longer OS than patients who received erlotinib then chemotherapy, again possibly due to erlotinib patients refusing the full extent of post-progression chemotherapy. **Conclusion:** RPSFT analysis showed increased OS between erlotinib and chemotherapy in EURTAC and ENSURE versus the original ITT analysis. Similar impact in OPTIMAL was not apparent. Post-hoc analysis of non-randomized subgroups (patients treated with a single therapy) showed longer OS for erlotinib versus chemotherapy, notwithstanding caveats of such an approach.

OS (RPSFT analysis)				
Study	**Treatment Group**	**N**	**Median OS, months**	**HR (95% CI)**
EURTAC	Erlotinib	86	22.9	0.64 (0.44, 0.95)
	Chemo	88	15.4	
ENSURE	Erlotinib	110	26.3	0.47 (0.32, 0.69)
	Chemo	107	17.1	
OPTIMAL	Erlotinib	82	22.7	1.78 (1.21, 2.64)
	Chemo	72	30.5	

Influence of sequencing on OS in patients who crossed over (Kaplan-Meier analysis)				
Study	**Treatment Group**	**N**	**Patients crossing over, %**	**Median OS, months**
EURTAC	Erlotinib/chemo	49	57	24.9
	Chemo/TKI	72	82	22.6
	Erlotinib alone	37		17.2
	Chemo alone	16		1.6*
ENSURE	Erlotinib/Chemo	69	63	27.0
	Chemo/TKI	89	83	25.6
	Erlotinib alone	41		23.2
	Chemo alone	18		22.9
OPTIMAL	Erlotinib/ Chemo	49	60	26.8
	Chemo/TKI	52	72	31.4
	Erlotinib alone	33		18.6
	Chemo alone	20		11.2
*There were 5 deaths and 5 censored observations that occurred in the first two months				

Keywords: Rank Preserving Structural Failure Time analysis, overall survival, Erlotinib

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-045 CORRELATION OF EGFR MUTATION DETECTION IN CTDNA BY TWO DIFFERENT PLATFORMS IN ADVANCED NSCLC PATIENTS FROM A SINGLE INSTITUTION

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Background: Circulating-free tumor DNA (ctDNA) has emerged as a sensitive and feasible non-invasive blood-based approach alternative to tissue biopsies to screen for genetic drivers in advanced non-small cell lung cancer (NSCLC) patients. Recently, the COBAS Mutation Test has been FDA-approved for the detection of *EGFR* mutation (*EGFR*m) in peripheral blood but other approaches are currently used in clinical practice. Here, we aimed to correlate two different platforms for *EGFR*m monitoring ctDNA in an enriched cohort of tissue-genetically phenotyped EGFRm advanced NSCLC patients. **Method:** Blood samples were prospectively obtained from an enriched cohort of *EGFR*+ advanced NSCLC patients. Formalin-fixed paraffin-embedded (FFPE) tumor was characterized by NGS (Ion AmpliSeq Lung Cancer Research Panel v.2) in all patients at diagnose. Plasma ctDNA derived from peripheral whole blood was evaluated by COBAS *EGFR* Mutation Test v2 and a Peptide Nucleic Acid (PNA) probe–based real-time polymerase chain reaction blinded to baseline tumor genotype. Diagnostic accuracy and concordance of both blood techniques was used for direct comparison with respect to the molecular status of FFPE tissue. **Result:** A total of 80 matched pairs of peripheral blood samples from 40 patients were collected. Baseline tissue NGS reported mutations at exon 19 del (n=23), exon 21 (n=10), exon 18 (n=2), exon 20 (n=2) and T790M (n=3). Four wild-type *EGFR* tumors were used as controls. Blood samples were obtained at diagnose (n=12) and during tyrosine-kinase inhibitor (TKi) treatment for monitoring (n=28). Overall, concordance between both blood-based techniques with respect tissue-NGS was 100% (4/4) for negative controls and 55% (20/36) for positive tissue-NGS samples. Detection based on PNA and COBAS was negative in 60% (24/40) and 32.5% (13/40) patients respectively. Among 19 samples negative by PNA at monitoring, COBAS allowed plasma *EGFR*m detection in 11 patients. At baseline, the only two negative samples patients by both techniques were found in patients with localized brain disease. Six patients had detectable driver T790M mutation; among three patients with T790M+ in tissue, COBAS allowed detection in plasma in one patient whereas none was identified with PNA. The other three patients had acquired T790M mutations identified only in blood, all by COBAS. **Conclusion:** In this prospective blinded validation cohort, both methods retained high specificity. However, major differences between techniques were observed for longitudinal monitoring of *EGFR*m in blood.

Keywords: NSCLC, ctDNA, EGFR mutations

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-046 LONGITUDINAL ANALYSIS OF PLASMA CTDNA IN EGFR-MUTANT NSCLC: SWOG S1403 TRIAL OF AFATINIB WITH OR WITHOUT CETUXIMAB

P. Mack[1], J. Miao[2], K. Banks[3], R. Burich[1], K. Politi[4], V. Raymond[3], D. Dix[3], R. Lanman[3], J. Moon[2], M.A. Melnick[5], A. Truini[4], M. Redman[2], S. Goldberg[5], D.R. Gandara[1], K. Kelly[6]

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Background: Detection of actionable mutations using circulating tumor DNA (ctDNA) isolated from patient plasma is now accepted as clinical practice in NSCLC. Nevertheless, the full extent to which longitudinal plasma analysis can be utilized to guide clinical decision-making has yet to be realized. We prospectively incorporated serial next-generation sequencing (NGS) of ctDNA into the ongoing SWOG S1403 clinical trial (NCT02438722) of afatinib+cetuximab vs afatinib in treatment-naïve NSCLC patients with EGFR-mutant tumors. **Method:** Time points for specimen collection were pre-treatment, after two months of therapy on Cycle 3 Day1 (C3D1) and at progression. Objectives were to: 1) determine the prognostic and predictive significance the EGFR mutant allele frequency (MAF) at each time point; 2) correlate changes in MAF over time with regard to patient outcome, and 3) identify putative emergent resistance mechanisms and companion mutations. Specimen analysis was conducted using the Guardant360 73-gene digital NGS panel. **Result:** To date, 53 patients with advanced EGFR-mutant NSCLC have contributed baseline samples. Of these, 46 had ctDNA detectable at baseline (87%). 39 of these 46 (85%) had detectable, tissue-identical EGFR mutations, for an overall EGFR detection rate of 74% (39/53). A positive finding for EGFR amplification (Amp) in plasma correlated with high ctDNA MAF: median for Amp **16.9** vs nonAmp **0.9** (range/n: 11.6-43.7/10 vs 0.11-7.7/17; **p<0.0001**). Of patients with detectable EGFR mutation at baseline, 27 had analyzable ctDNA collected at C3D1. Of these, 26/27 showed decreasing MAFs on-treatment (mean for baseline: **9.8** vs C3D1: **0.14**; p<0.0001), with 20 cases having no detectable EGFR mutation at C3D1 (mean of 7 positives at C3D1: **0.55**). At progression,

samples were collected from 14 patients and 10 had EGFR mutations detectable, with T790M present in 3. Another patient had an FGFR3 fusion at PD, but no previous draws were available to determine if it was emergent. **Conclusion:** Longitudinal analysis of plasma ctDNA in S1403 patients demonstrated significant treatment-induced changes in mutation burden and identified resistance mechanisms at progression. EGFR gene amplification, as assessed in plasma, was significantly associated with increased ctDNA MAFs. Patients showed a significant, one-to-two orders of magnitude decline in EGFR MAF after two months of therapy, with **74%** dropping below detectable levels. At progression, EGFR mutation detection rates increased, often concomitantly with a putative emergent resistance factor. Accrual to S1403 is ongoing and patient treatment and outcomes remain blinded. The prognostic and predictive utility of baseline and therapy-induced changes in ctDNA MAF kinetics will be determined at study unblinding.

Keywords: EGFR mutation, liquid biopsy, ctDNA

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-047 ERLOTINIB INDUCED ECTROPION FOLLOWED BY PAPULO-ERYTHEMATO SKIN RASH

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Background: Erlotinib is a thyrosine kinase inhibitor which prevents epidermal growth factor receptor(EGFR) by blocking intracellular phosphorylation. Various cutaneous side effects have been associated with EGFR inhibitors. We present a case with ectropion and conjunctivitis followed by erythemato papulopustular skin rash. **Method:**

A 72 year old male who has suffered from non small cell carcinoma (adenocarcinoma)of lung stage IV since one year ago came to our clinic with bilateral ectropion and conjunctivitis. He has received erlotinib 150 mg/d since three to four months ago. **Result:**

We prescribed supportive care and symptomatic treatment and discontinued erlotinib for one week due to the severity of eye disease. It resolved gradually after two weeks but erythemato papulr rash appeared **Conclusion:** EGFR inhibitors are one of the most important treatment modalities among patients with lung adenocarcinoma.Cutaneous side effects of these agents are reported frequently. Eye disease including ectropion is a rare adverse effect of these factors. We describe this case to consider the newly diagnosed eye edverse effect of this important agents.

Keywords: Erlotinib, adenocarcinoma, ectropion

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-048 CBL MUTATIONS AS POTENTIAL MEDIATORS OF EGFR TKI RESISTANCE EFFECTIVELY TREATED WITH SITRAVATINIB

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Background: Third generation EGFR inhibitors are efficacious in patients with NSCLC harboring *EGFR* sensitizing mutations. Acquired resistance includes alternative mechanisms of EGFR activation and activation of other signaling pathways. Here we report a patient with a *CBL* mutation as a potential mechanism of acquired resistance to 3rd generation EGFR TKI effectively treated with sitravatinib, a spectrum-selective RTK inhibitor of TAM receptors (comprised of TYRO3, AXL, and MER), PDGFRA, KIT, and MET. **Method:** In Study 516-001, a phase 1/1b study of sitravatinib in patients with advanced solid tumor malignancies, patients are selected based on mutations in targeted pathways. Eligible genetic alterations include inactivating mutations of *CBL*, which encodes an E3-ubiquitin ligase that regulates degradation of activated RTKs that include EGFR, TAM receptors, PDGFRA, KIT, and MET and which account for ~2-3% of NSCLC. Based on overlap of sitravatinib and *CBL* RTK targets and supporting cancer cell line and tumor model data, we hypothesize that inactivating *CBL* mutations predict response to sitravatinib. **Result:** After Phase 1, patients were enrolled by mutational profile, and here we report on a patient enrolled into the *CBL* mutation cohort. The patient is a 77 year-old female, lifelong non-smoker with metastatic lung adenocarcinoma characterized by *EGFR* exon19del initially treated with erlotinib with a partial response (PR) of 9 months. Upon disease progression (PD), a new *EGFR* T790M mutation led to treatment with rociletinib (an experimental inhibitor of EGFR T790M) with stable disease for 11 months. Upon PD she was treated with osimertinib without response. She then received carboplatin/pemetrexed with a PR. Brief erlotinib re-challenge resulted in PD, with post-progression NGS revealing loss of *EGFR* T790M, presence of the original *EGFR* exon19del, and a new *CBL* C384R, a mutation located in the RING domain and predicted to result in the loss of CBL ligase adaptor function resulting in sustained activation of relevant RTKs. The patient then started sitravatinib treatment in Study 516-001. After 36 days on-study, restaging demonstrated PR, which was later confirmed with a maximum decrease in unidimensional target lesion measurement of 77%. She remains on-study. **Conclusion:** Loss of function mutations in *CBL* represent a unique class of mutations that may be responsible for acquired resistance to 3rd generation EGFR TKI. Sitravatinib has demonstrated clinical activity in a patient with NSCLC characterized by *EGFR* exon19del and *CBL* C384R mutations. The clinical trial with sitravatinib is currently enrolling patients with *CBL* loss of function mutations. (NCT02219711).

Keywords: CBL, RTK inhibitor, NSCLC

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-049 T790M MUTATION DETECTION, CLINICAL CHARACTERISTICS AND IMPACT IN NSCLC PATIENTS TREATED WITH EGFR TYROSINE KINASE INHIBITORS

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Background: All EGFR mutated lung cancers will eventually develop acquired resistance to first-line EGFR tyrosine kinase inhibitors (TKi). The most common cause is the EGFR T790M point mutation. Recent studies demonstrated the utility of liquid biopsies (LB) as initial detection strategy. The mutation may be indicative of a more indolent disease and plasma positivity seems to be related to more extensive disease. **Method:** Retrospective evaluation of T790M status and clinical characteristics of patients with advanced or recurrent non-small cell lung cancer (NSCLC) who progressed under EGFR-TKi was performed at our institution. The T790M mutation was assessed in circulating cell-free DNA (cfDNA) in plasma as initial strategy; if negative, a tumor biopsy (TB) was obtained. Samples were analyzed using Cobas® EGFR Mutation Test v2. The purposes of this study were: to explore the feasibility of T790M mutation detection in our practice; to evaluate objective response rate (ORR) and progression-free survival (PFS) on first-line TKi therapy according to T790M status and clinical characteristics. **Result:** We identified 29 patients. Regarding the pre-treatment activating EGFR mutations, 59% (n=17) harbored an exon 19 deletion, 38% (n=11) the L858R mutation and one case had both mutations (two primaries). All patients were treated with EGFR-TKi, 90% (n=26) in the first-line treatment setting. The T790M mutation was positive in 18 patients (12 plasma+ and 6 plasma-/tissue+). The remaining 11 negative results, 7 were assessed only by plasma and the other 4 were confirmed on TB. The resistance mutation was more frequent in patients with EGFR exon 19 deletions (71%, 12/17). In patients with a positive T790M result, those with extra-thoracic disease had detectable T790M mutation in plasma in the majority of cases (86%, 12/14), while all patients with exclusive intra-thoracic disease (n=4) had negative result in plasma. Patients who developed a T790M mutation had a longer PFS under first-line TKi, but not statistically significant (14 months in T790M+ [CI 95% 7.8-20.2] vs. 9 months [CI 95% 6.8-11.2] in T790M-, p=0.201) with similar ORR (55.6% in T790M+ vs. 45.5% in T790M-, p=0.597). **Conclusion:** The evaluation of EGFR T790M mutation is feasible in LB (cfDNA) in patients progressing under EGFR-TKi, but TB is recommended in the negative cases. The likelihood of detection of T790M in

plasma is greater in patients with extra-thoracic disease, probably related with higher disease burden. Tumors which develop T790M tend to have a more indolent course, but the conclusion is limited due to the small sample size.

Keywords: T790M mutation, circulating cell-free DNA (cfDNA), EGFR tyrosine kinase inhibitor

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-050 A REAL WORLD TREATMENT STUDY OF OSIMERTINIB: ASTRIS STUDY KOREAN SUBGROUP ANALYSIS

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Background: ASTRIS (NCT02474355) is an open-label, single-arm, multination, real world treatment study, investigating the safety and efficacy of osimertinib in patients with T790M-positive advanced non-small cell lung cancer (NSCLC), who have previously received EGFR-TKI. We report the first results of Korean subset from ASTRIS which is the largest real world treatment study of osimertinib to date. **Method:** Eligible patients had advanced NSCLC harbouring a T790M mutation determined by local validated molecular tests, received prior EGFR-TKI therapy, acceptable organ and bone marrow function and no history of interstitial lung disease (ILD) or QTc prolongation. Enrollment of patients with asymptomatic, stable CNS metastases were permitted. Patients received osimertinib 80 mg once daily. The primary efficacy outcome was overall survival; other outcomes included investigator-assessed response rate (RR), progression-free survival (PFS) and time to treatment discontinuation (TTD). Safety assessment was also conducted. Data cut-off (DCO) was 3 November 2016; results from 1,217 patients in the global study have been presented previously (ASCO 2017 Abstract 9036). **Result:** A total of 371 patients received at least one dose of osimertinib from 30 Korean sites (full analysis set); at DCO, 319 patients (81.4%) were ongoing and median follow-up time was of 3.1 (0–8) months. Baseline patients' characteristics were median age 61.1 (27–85) years old, female 65.5%, PS 0/1 88%, prior chemotherapy 47%, prior radiotherapy 48%. Tissue was the most common specimen source to test T790M mutation as well as other EGFR mutations (287/371, 77.4%) and plasma was the next (39/371, 13.1%). Fifty two patients (13.3%) had discontinued treatment; median duration of exposure 3.3 (0–7) months, 30 pts (7.7%) had disease progression and 24 patients (6.5%) died. In patients evaluable for response, defined as at least one dose of osimertinib and one response assessment, the investigator-assessed RR was 72.1% (212/294; 95% CI 66.6 – 77.2). Due to limited follow-up period, OS, PFS, and TTD were immature to analyze. Adverse events (AEs) leading to dose modification and treatment discontinuation were reported in 26 patients (7%) and 14 patients (3.8%), respectively. Serious AEs were reported in 50 patients (13.5%) and AEs leading to death in 8 patients (2.2%). ILD/pneumonitis-like events were reported in 9 patients (2.4%), and QTc prolongation (>470ms) in 5 patients (1.3%). **Conclusion:** At DCO for the 1st interim analysis of ASTRIS, Korean subgroup results demonstrated similar clinical activities (RR) to that observed in the osimertinib clinical trial program with no new safety signals.

Keywords: T790M, osimertinib, Korean

P3.01: ADVANCED NSCLC -
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P3.01-051 DRAMATIC RESPONSE TO AFATINIB IN EGFR-MUTANT LUNG ADENOCARCINOMAS AFTER RESISTANCE TO FIRST-GENERATION EGFR INHIBITORS: A BRIEF REPORT

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Background: T790M inhibitor, a third-generation epithelial growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), was significantly superior to chemotherapy for *EGFR*-mutant patients with advanced non-small-cell lung cancer (NSCLC) harboring *T790M* mutation after resistance to the first-generation EGFR-TKIs. However, for those without acquired *T790M* mutations or *MET* amplification, few data showed whether the second-generation EGFR-TKI could overcome resistance to the first-generation EGFR-TKIs. **Method:** *EGFR* mutation was detected by amplification refractory mutation system (ARMS) technology. Overexpression of MET was determined by immunohistochemistry (IHC), and *MET* amplification was detected by FISH. Next generation sequencing (NGS) was used to test tumor tissues before and after resistance to TKIs. **Result:** Patient 1 was a 53-year-old Asian male, who underwent surgery followed by adjuvant chemoradiotherapy with an 11 months of disease-free survival. A biopsy was performed and revealed an activating deletion mutation in exon 19 of the *EGFR*. He started gefitinib 250mg once daily and achieved an initially good partial response (PR) followed by continuously stable disease for a progression-free-survival (PFS) about 29 months. A rebiopsy showed that exon 19 deletion mutation still existed without an acquired *T790M* mutation or *MET* amplification. He refused to receive chemotherapy so we prescribed afatinib 40mg daily. He then achieved a dramatic PR 23 days later which was confirmed 1.5 months after that. We sent tumor tissue of the patient before and after TKI therapy for NGS, the result showed a decreasing abundance of *EGFR* exon 19 deletion without *T790M* mutation, *MET* amplification and *Her2* mutation/amplification. Patient 2 was a 63-year-old Asian female harboring *EGFR* exon 20 insertion (A763-Y764 ins), who received first and second lines of chemotherapy with short PFSs. He was enrolled in the trial of allitinib (AST-1306) as the third line therapy with the best response of stable disease(SD) and the PFS of 7 months. A later rebiopsy showed the strong overexpression of MET, but the forth-line therapy crizotinib failed. He then received chemotherapy as the-fifth line therapy, 4 cycles later he progressed. So he started afatinib 40mg daily. His symptoms were relieved significantly 5 days later, and PR was confirmed 1.5 months later. **Conclusion:** Afatinib might overcome resistance to the first-generation EGFR-TKIs for *EGFR*-mutant patients with advanced NSCLC without acquired *T790M* mutation or *MET* amplification. Further investigations are warranted.

Keywords: EGFR-TKI resistance, afatinib, NSCLC

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P3.01-052 THE PREVALENCE AND GENOTYPE DISTRIBUTION OF DUAL IN CIS EGFR MUTATIONS IN CHINESE ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The prevalence of EGFR mutation has been well elucidated in different ethnicities. Recently, increasing attention has been given to dual *EGFR* mutations. However, less attention has been invested in dual *in cis EGFR* mutations. Until now, none of retrospective or prospective research has focused on dual *in cis EGFR* mutations except case reports. **Method:** In this real world study, we performed capture-based ultra-deep targeted sequencing on circulating tumor DNA to identify and investigate the prevalence and genotype distribution of dual *in cis EGFR* mutations in 3,000 Chinese advanced NSCLC patients. This cohort consisted of both treatment-naïve and previously treated patients. Ten milliliter of peripheral blood was collected from every patient and a minimum of 50ng of ctDNA was needed for library construction. The panel covered critical exons and introns of 168 genes (160kb of human genomic regions). **Result:** 1,266 patients harbored *EGFR* mutant in this cohort; among them, 501 patients harbored 19 deletions, 489 harbored L858R, and the remaining harbored other *EGFR* mutations. We identified 1.5% patients (19/1,266) harboring dual *in cis EGFR* mutations. Among them 37% (7/19)carried two rare EGFR mutations and the remaining 63% (12/19) carried *EGFR* L858R in combination with a rare mutation. No patient carried *EGFR* 19 del in combination with other rare mutations was identified in this cohort, suggesting *EGFR* 19del is a stronger oncogenic driver than *EGFR* L858R (p=0.000197, Fisher's exact test). For patients carried two rare mutations, both mutations were either located on exon 18 or exon 21. The allelic fractions (AF) of both mutations were similar. The AF of either *EGFR* mutations was the maximum AF in all patients, demonstrating the clones harboring *EGFR* mutations were major clones. Interestingly, 1 patient carried additional *KRAS* mutation and 2 patients had *EGFR* amplification. **Conclusion:** *In cis* dual *EGFR* mutation was rare (1.5%) in EGFR mutant Chinese advanced NSCLC patients. *EGFR* L858R was significantly more likely to couple with a rare *in cis* dual mutation than 19 del. *EGFR* 19del might be a stronger oncogenic driver than *EGFR* L858R.

Keywords: dual in cis EGFR mutations, Advanced Non-Small Cell Lung Cancer, Chinese

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P3.01-053 DETECTION OF COMMON EGFR MUTATION IN CYTOLOGICAL SMEARS USING REVERSED DOT BLOT (RDB) HYBRIDIZATION METHOD

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Background: Epidermal growth factor receptor (EGFR) mutation can predict the response to EGFR tyrosine kinase inhibitor (TKI) in non small cell lung cancer (NSCLC). In this study, we determined the limit of detection of different methods, such as sequencing, restriction frament length polymorphism (RFLP), high resolution melting (HRM) and reversed dot blot (RDB) hybridization to detect for EGFR mutation detection. **Method:** Mutation detections of exons19 and 21 in EGFR gene were performed using sequencing, restriction fragment length polymorphism (RFLP) and high resolution melting (HRM) analysis method. Moreover, we also developed Reversed Dot Blot(RDB) method hybridization as an alternative procedure. Genomic DNA of H1975, HCT116 cell line as well as specially designed oligonucleotides were used to determine the limit of detection of these procedures. We also determine the sensitivity and specificity of RDB method compared to existing methods. **Result:** Limit of detection of each method was determined by titration of mutant allele in wildtype background. HRM analysis and RFLP were able to detect mutation in samples containing 6.25% to 12.5% mutated DNA.Limit of detection of RDB method was around 12.5%. Analysis of 40 patients had shown that the specificity for to detect mutations in exon 19 and 21 was 100% and 89.5% and the sensitivity for both exon was 62.5%. **Conclusion:** RDB method maybe used as an alternative method to standard procedure such as sequencing. This method is specific, but need further improvement to increase its sensitivity.

Keywords: EGFR mutation, lung cancer, pleural effusion

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P3.01-054 URINARY CT-DNA TESTING OF EGFR COMMON MUTATION IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The existence of circulating tumor DNA (ct-DNA) in urine as a noninvasive and alternative sample to tissue biopsy has been promising. However, it still has some challenges. Common mutations of epidermal growth factor receptor (*EGFR*), such as L858R in exon 21 mutation has been used to predict lung cancer treatment response to tyrosine kinase inhibitors (TKI). The study aimed to demonstrate that DNA from urine can be detected using simple methods with high sensitivity, enabling early Non-Small Cell Lung Cancer (NSCLC) detection from these noninvasive samples. **Method:** Cytological smear and urine samples from 59 NSCLC patients had been collected and processed to obtain genomic DNA. EGFR common mutations in exon 21 were analyzed using polymerase chain reactions (PCR) and restriction fragment length polymorphism (RFLP) methods that having analytical sensitivity of detecting 3% EGFR mutant alleles. Diagnostic sensitivity and specificity test was used to evaluate the feasibility of urine as source of noninvasive samples compared with cytological samples. **Result:** We were able to detect EGFR exon 21 L858R mutations in 17 of 59 (28,81%) urine samples while 27 of 59 (45,76%) cytological samples were EGFR positive mutations. Agreement between urine and cytological slide was 45.76%. Diagnostic sensitivity and specificity were 22,22% and 65.62% respectively. **Conclusion:** EGFR mutation of lung cancer patients were detected from urine using RFLP methods. In this study, mutation rate in urine (28,81%) was similar to mutation rate from plasma (22%) of Asian Lung cancer patients as described Han, B et al 2015. However, poor sensitivity (22.22%) and specificity (65.62%) of urinary ctDNA L858R analysis may not lead to treatment decision. More in-depth studies focusing on urine collection techniques and more sensitive technology may lead to useful application of urine as an alternative noninvasive liquid biopsy sample for NSCLC detection.

Keywords: EGFR, RFLP, urine

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P3.01-055 THE USEFULNESS OF LIQUID BIOPSY FOR CTDNA IN PATIENTS WITH EGFR-MUTANT NSCLC DURING AND AFTER TREATMENT WITH EGFR-TKIS

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Background: Non-small-cell lung cancer (NSCLC) patients with activating mutation of epidermal growth factor receptor (EGFR) gene inevitably develop disease progression to EGFR-tyrosine kinase inhibitors (TKIs). T790M gatekeeper mutation accounts for approximately 60% of the acquired resistance, and osimertinib, third generation EGFR-TKI, is effective against such tumors. Demonstration of T790M requires second biopsy, which is inconvenient and sometimes hazardous. Liquid biopsy of circulating tumor DNA (ctDNA) in the plasma is a non-invasive alternative, but clinical relevance of this method is yet to be fully elucidated. **Method:** NSCLC patients with EGFR mutation undergoing 1st- or 2nd-generation EGFR-TKI treatment are monthly or bi-monthly monitored for plasma ctDNA EGFR mutations, including T790M, by Cobas EGFR mutation test® via 10 ml blood sampling. The treatment could be changed on the attending physicians' discretion, including osimertinib in patients with documented T790M mutation, with continuation of the monitoring. The primary endpoints are T790M positivity rate of ctDNA among patients with tissue-confirmed T790M mutation, and T790M positivity rate of ctDNA at landmark points, such as radiological progression, clinical deterioration or second biopsy of the tumor. The secondary endpoints include EGFR mutation detection rate of plasma ctDNA at landmark points, the interval of tissue and plasma T790M detections, and response rate and progression-free survival in patients treated with osimertinib according to plasma/tissue T790M status. **Result:** From Oct 2016 to Mar 2017, 121 eligible patients were enrolled. The median age 73 years (range, 42-92), 42 male (34.7%), PS 0, 1 and 2 were 64 (52.9%), 54 (44.6%) and 3 (2.5%) respectively. EGFR mutation types were 61 patients (50.4%) del 19, 55 (45.5%) L858R and 5 (4.0%) others. 80 (66.1%) were never smokers. At the time of EGFR-TKI initiation, 82 (67.8%) had advanced and 39 (32.2%) had recurrent diseases. 65 (53.7%) had any prior therapy, including 21 (14.8%) with prior cytotoxic chemotherapy. Used EGFR-TKIs were gefitinib 50 (41.3%), erlotinib 40 (33.1%), and afatinib 31 (25.6%). Newly-diagnosed/on TKI therapy at enrollment was 18 (14.9%)/103 (85.1%). The median follow-up is 12[鈴木1] months. So far, plasma T790M was detected in 8 patients. **Conclusion:** This observational study will elucidate the clinical usefulness and limitations of monitoring of ctDNA for T790M mutation in the real-world setting.

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P3.01-056 INTRACRANIAL ACTIVITY OF OSIMERTINIB IN NAÏVE EGFRM T790M(-)AND TREATED EGFRM T790M(+) NSCLC PATIENTS WITH ASYMPTOMATIC BRAIN METASTASES

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Background: Osimertinib is an effective, irreversible EGFR-TKI selective for EGFR-TKI-sensitizing (EGFRm) and T790M$^+$ resistance mutations. Intracranial activity of osimertinib has been reported in T790M$^+$ patients; however its activity in EGFR-TKI naïve setting has not been investigated yet. Here, we present preliminary data of a phase II study assessing the intracranial activity of osimertinib in EGFRm NSCLC patients with asymptomatic brain metastases as 1st line therapy for naïve patients and as 2nd line therapy for EGFRm patients who progressed on EGFR TKI and harbor T790M$^+$. Dose escalation from 80 mg QD to 160 mg QD was allowed in cases of brain progression. **Method:** A phase II, open label, two arm study is presented. Treatment-naïve (arm A) advanced NSCLC with sensitizing EGFRm and previously treated (arm B) with 1st or 2nd-generation EGFR TKIs (gefitinib, erlotinib or afatinib) in whom T790M$^+$ was diagnosed were enrolled to this study. Intracranial response was assessed by brain MRI scans every 6 weeks and systemic evaluation by PET-CT scan every 3 months unttil progression. The study plans to enroll 20 patients in each arm aiming to reach a statistical power of 0.8. **Result:** As of May 31 2017, 22 patients were enrolled; 15 patients in arm A and 7 patients in arm B, age 67.8±10.4 years, 14 females and 8 males. Preliminary outcome analysis is presented for 16 patients with a median follow up of 6.1 months (range 1.4-11.4 months). On May 31st 2017 data cut-off was performed. The Intracranial response rate (ICRR) was 81% (13/16 pts); 82% (9/11 pts) in arm A and 80% (4/5 pts) in arm B. Time to response was 6 weeks (1st MRI) in all responding patients. Intracranial disease control rate (IDCR) was 81% (13/16 pts) for the current follow up time of 6.1 months; median PFS not reached. Dose escalation was performed in 2 cases and data is not mature yet. Toxicity profile is similar to previous reported data. **Conclusion:** Osimertinib shows a promising intracranial response rate in naïve EGFRm NSCLC patients (82% ICRR) and in 2nd line T790M (+) setting with 80% ICRR. This study is still recruiting.

Keywords: osimertinib, NSCLC, EGFR

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P3.01-057 COMPARISON OF EGFR MUTATIONS IN MATCHED TUMOR TISSUES, CELL BLOCKS, PLEURAL EFFUSIONS AND BLOODS WITH NSCLC, BY PANA MUTYPER AND PNA CLAMPING

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Background: There has been a marvelous paradigm shift in the diagnosis and management of lung cancer, with the discovery of driver mutations that can be targeted by specific inhibitors. Personalized therapy is driving the demand for mutation testing in cancer. Especially, molecular testing of lung adenocarcinoma for the epidermal growth factor receptor (EGFR) is now considered one of the most important standard of care with other driver mutations. However, sampling tumor tissue other than surgical resection has inevitable limitations. It may be difficult to obtain enough DNA for EGFR mutation test if biopsy tissue was inadequate. There is a promising ctDNA detection technology, that is PANA Mutyper technology, which is a novel technology that integrates PNA clamp and PANA S-melting. We investigated

effectiveness of both methods for the detection of EGFR mutation. **Method:** Ninety patients with malignant pleural effusion of lung cancer were enrolled. EGFR mutations were assessed by PANA Mutyper and PNA clamping using tumor tissues, cell blocks, pleural effusions, and bloods separated by serum and plasma. The diagnostic performance of both methods was investigated. **Result:** Among the 90 patients with malignant pleural effusion of lung cancer, 56 patients were adenocarcinoma of lung, 11 were squamous carcinoma of lung, and 17 were small cell lung cancer. PANA Mutyper using bloods showed that 70% sensitivity, 100% specificity, 100% positive predictive value and 83% negative predictive value comparing to the combination of PANA Mutyper and PNA clamping through tumor tissues, cell blocks and pleural effusions (p=0.014). **Conclusion:** PANA Mutyper using bloods had a diagnostic performance for the detection of EGFR mutations in NSCLC that was comparable to that of tumor tissues, cell blocks and pleural effusions. The diagnostic performance of PANA Mutyper was better than that of PNA clamping. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014R1A2A1A11052422).

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P3.01-058 IMPACT OF DIFFERENT TIMING OF RADIOTHERAPY IN PATIENTS WITH BRAIN METASTASES FROM EPIDERMAL GROWTH FACTOR RECEPTOR-MUTANT NSCLC

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Background: To perform a retrospective analysis of patients with brain metastases (BM) from epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) to evaluate the preferred treatment timing of EGFR-tyrosine kinase inhibitors (TKIs) in this population. **Method:** Of 94 initial or recurrent patients diagnosed BM from EGFR-mutant NSCLC between Jan 1, 2012, and Jun 31, 2016, 30 received upfront brain RT followed by EGFR-TKI, 39 EGFR-TKI combined with concurrent brain RT, and 25 upfront EGFR-TKI then brain RT. Disease-specific-graded prognostic assessment was similar among all 3 groups. The primary endpoint was overall survival (OS), and the second endpoint was intracranial progression-free survival. **Result:** Although the median OS was not significantly different among the upfront RT, concurrent treatment, and upfront EGFR-TKI groups (29.0 vs 24.0 vs 17.0 months; P=0.186), however, it was longer in the upfront RT group compared with the upfront EGFR-TKI group (P=0.035). On subgroup analysis, the exon 19 deletions patients had longer OS than the exon 21 mutations patients in upfront EGFR-TKI group (23.0 vs 15.0 months; P=0.048), but the upfront RT (34.0 vs 23.0 months; P=0.186) and the concurrent treatment groups (24.0 vs 13.0 months; P=0.827) did not. 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 upfront RT compared with those receiving concurrent treatment or upfront EGFR-TKI (not reached vs 40.0 vs 9.0 months; P=0.003). **Conclusion:** The present study suggests that the use of upfront brain radiotherapy, and the deferral of EGFR-TKI may result in superior OS in patients with brain metastases from EGFR-mutant NSCLC. Also, upfront brain radiotherapy management could significantly reduce the risk of intracranial progression. A prospective, multi-institutional, randomized trial of upfront EGFR-TKI then RT versus upfront RT followed by EGFR-TKI is urgently needed, especially based on different subgroup population.

Keywords: non-small cell lung cancer, Epidermal growth factor receptor, brain metastases

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P3.01-059 FIRST EXPERIENCE WITH OSIMERTINIB IN PATIENTS WITH NEWLY DEVELOPED T790M MUTATION PREVIOUSLY TREATED WITH EGFR – TKIS IN CROATIA

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Background: EGFR T790M mutation is responsible for 50 to 60% cases of resistance to first and second generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) in patients who have lung cancer with an activating EGFR mutation. **Method:** We administered osimertinib 80 mg once daily in 11 patients with advanced lung cancer who had radiologically documented disease progression after previous treatment with first and second-line EGFR tyrosine kinase inhibitors. **Result:** We treated 11 patients with osimertinib with stage IV lung adenocarcinoma. Three patients were males and eleven were females, median age 64 (raging from 54 to 82). Seven patients were never smoker, and four were ex-smokers. Ten patients had initially deletion 19 in EGFR gene and one had L858R in exon 21 and then developed T790M mutation. In all patients T790M was proven from tumor tissue. Majority of patients were ECOG 1. All patients were previously treated with first or second line EGFR TKIs (erlotinib, gefitinib or afatinib) and had radiologically documented disease progression. Two patients received osimertinib in 2nd line setting, three patients in third line setting, 3 in fourth, one in fifth, one in seventh and one even in tenth line setting. Median time to response was 4 weeks (raging from 3 to 7). All11 patients had partial response (PR) with progressive disease in only one patient after 12 months of treatment. Median duration of response is at the moment 12.5 months, (4 to 60). No significant side effects were observed. **Conclusion:** Osimertinib is highly active in patients with lung adenocarcinoma which harbor EGFR T790M mutation who had had disease progression during prior therapy with EGFR tyrosine kinase inhibitors. Efficacy in Croatian population is similar to previously observed. There were no serious side effects of treatment.

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P3.01-060 THE CLINICAL UTILITY OF CTDNA GENE ANALYSIS IN LUNG CANCER

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Background: Next-generation sequencing (NGS) of cell-free circulating tumor DNA (ctDNA) enables a non-invasive option for comprehensive genomic analysis of lung cancer patients. In this study, we evaluated the impact of ctDNA sequencing on outcomes and treatment strategy. **Method:** In this retrospective study, data was collected from files of advanced non-small cell lung cancer (NSCLC) patients at the Thoracic Cancer Unit, Rabin Medical Center, Israel, between 2014-2017. Plasma samples were analyzed by a commercial test (Guardant360™), using massively parallel paired-end synthesis to sequence a targeted 68-73 gene panel. **Result:** 116 consecutive NSCLC patients were included in this study. Median age at diagnosis was 63 years, 74% had adenocarcinoma. 41% performed ctDNA analysis before 1st line therapy (Group A) and 59% on progression (Group B), among them 41% after progression on EGFR TKIs (Group B1) and 59% on other treatments (Group B2). ctDNA analysis yielded actionable mutations (*EGFR*, *ALK*, *RET*, *BRAF*, *MET*, *ERBB2* (HER2)) in 40.5%: 31% in group A, 47% in group B, 71% in group B1 and 30% in group B2. Treatment decision was taken toward targeted therapy subsequent to NGS in 26%.

Genetic alterations frequencies among groups A, B, B1 and B2			
Group A 19 individual mutations	Group B 52 individual mutations	Group B1 34 individual mutations	Group B2 18 individual mutations
EGFR Sensitizing 52.5% (10/19)	EGFR Sensitizing 42% (22/52)	EGFR Sensitizing 59% (20/34)	MET 55.6% (10/18)
MET 16% (3/19)	MET 27% (14/52)	EGFR T790M 23% (8/34)	ERBB2 16.7% (3/18)
ERBB2 10.5% (2/19)	EGFR T790M 15% (8/52)	MET 12% (4/34)	RET 16.7% (3/18)
BRAF V600E 10.5% (2/19)	ERBB2 8% (4/52)	ERBB2 3% (1/34)	EGFR Sensitizing 11.1% (2/18)
RET 10.5% (2/19)	RET 6% (3/52)	ALK 3% (1/34)	
	ALK 2% (1/52)		

Response assessment (RECIST) to targeted therapy showed complete response in 4%, partial response in 44%, stable disease in 37% and progressive disease in 15%. Response rate was 44% for group A, 50% for group B, 60% for group B1, 37.5% for group B2. Total objective response rate was 48% and disease control rate was 85%. Overall survival was evaluated for 40%, median was 14.4 months for patients who received targeted therapy vs 13.6 months for patients who received standard treatment. **Conclusion:** Comprehensive ctDNA testing revealed treatment options for 40.5% of patients analyzed. The highest impact was seen in progressors on EGFR therapy. These positive results emphasize the utility of liquid biopsy analysis to guide clinicians to select the most efficacious therapy for each patient.

Keywords: liquid biopsy, non-small cell lung cancer, next generation sequencing

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P3.01-061 ENDOSTAR COMBINED WITH RE-CHALLENGED GEFITINIB IN PREVIOUS TREATMENT FAILED NSCLC: A RETROSPECTIVE STUDY

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Background: To investigate the efficacy of gefitinib combined with recombinant human endostatin (endostar) as a salvage therapy in patients who failure to benefit from gefitinib in previous treatment of advanced non-small cell lung cancer (NSCLC) due to resistance with T790M mutant negative or unknown. **Method:** Patients with pathologically confirmed stage IV NSCLC who had failed of disease control by gefitinib were retrospectively reviewed. In total, twenty patients were enrolled incluing two

patients with squamous disease, eighteen patients were adenocarcinoma. The median age was 61.6, ranging from 43 to 75. After acquired gefitnib treatment resistance, six patients were tested their tumor samples by re-biopsy and confirmed T790M negative. Fourteen patients refused to re-biopsy, therefore the T790M status were unknow among them. In our analysis, from September 2009 to May 2014, all patients met the selection standards above received endostar (15 mg/day, i.v. day 1-7, 21 days per cycle) additionally and keep taking gefitinib after preious treatment failure. The efficacy and toxicities of the combined treatment were observed. **Result:** Two patient achieved partial response (PR) (10%) , twelve patients had stable disease (SD) (60%) , six of those patient had progressive disease (PD) (30%) . The objective response rate (ORR) was 10% and the disease control rate (DCR) was 70%. Median progression free survival was 4.2 months (95% CI, 3.21 - 5.19 months) , whereas median OS time was 8.0 months (95% CI, 4.96 - 11.04 months). The results of efficacy accessed in terms of DCR, PFS and OS were not correlated with the sex, age, performance status (PS) score, histologic types or the treatment duration of gefitinib. **Conclusion:** After the failed attempting of gefitnib treatment, the combination of Endostar with gefitinib treatment could stabilize disease in T790M negative or unknown patients, and prolonged their survival time with tolerable toxicities.

Keywords: gefitinib, Endostar, non-small cell lung cancer

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P3.01-062 THE PERCEIVED VALUE OF AVOIDING BIOPSY: PATIENTS' WILLINGNESS TO PAY FOR CIRCULATING TUMOUR DNA T790M TESTING

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Background: Plasma detection of circulating tumour DNA (ctDNA) with T790M mutation in the context of EGFR tyrosine kinase resistance has been shown to have high concordance with tissue biopsy specimens. In a public healthcare system, patients' perceived value of a test and willingness to pay can inform policy decisions regarding implementation and funding of a novel technology. **Method:** As part of screening for the ASTRIS clinical trial (NCT02474355), Canadian patients were invited to participate in a national validation study of blood-based ctDNA T790M testing. Eligible patients had acquired resistance to EGFR TKI and consented to collection of blood samples, demographic data, and completion of a structured interview measuring their perceived value of blood-based ctDNA testing as an alternative to tumour biopsy. They were asked about their willingness to pay for testing using both open-ended and iterative bidding approaches. The study was supported by a grant from AstraZeneca. **Result:** 60 patients were accrued to the study. Median age of the cohort is 64 years (range 31-87); 69% are Asian (40/58); 55% (33/60) are male. All patients had received prior EGFR kinase inhibitor treatment, with 67% (45/60) receiving gefitinib. 17% of patients also received chemotherapy (10/60). A median of 1 prior line of therapy had been received (range 1-6). All patients preferred to have the blood test over repeat tumour biopsy. Patients estimated a mean reasonable price to pay for the test of $954; median $300 (range 0-10,000; IQR 150-800). Patients were personally willing to pay a mean of $281; median $100 (range 0-2500; IQR 33-350). **Conclusion:** In a public health system that covers the cost of standard diagnostic tests, Canadian patients indicated a willingness to pay out of pocket for peripheral blood detection of ctT790M. Patients have high perceived value of ctDNA and prefer it to tumor biopsy.

Keywords: EGFR mutation positive lung cancer, T790M detection, Value of novel diagnostics

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-063 CONCOMITANT EGFR MUTATION AND ALK REARRANGEMENT IN NON-SMALL-CELL LUNG CANCER

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Background: The concomitance of epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*) rearrangement defines a new molecular subtype of non-small-cell lung cancer (NSCLC). We investigated the factors associated with the efficacy of targeted therapy and resistance mechanisms in *EGFR/ALK* co-altered NSCLCs. **Method:** *EGFR* mutation was identified with direct sequencing or Scorpion amplification refractory mutation system (ARMS). Relatively low *EGFR*-mutant abundance is considered as sequencing (-)/ARMS (+), while high abundance as sequencing (+). *ALK*-positive is assessed with any of the 3 methods: fluorescence in situ hybridization (FISH), rapid amplification of cDNA ends -coupled polymerase chain reaction and sequencing or Ventana immunohistochemistry (IHC). Next-generation sequencing was employed to analyze genetic profiles in patients with specimens before and after targeted therapy. **Result:** From December 2011 to December 2016, sixteen patients were identified with concomitant *EGFR/ALK* co-alterations, accounting for 0.6% (16/2632) in NSCLC patients, 1.8% (16/867) in *EGFR*-mutant and 8.6% (16/185) in *ALK*-positive patients. Five ALK-IHC (-)/FISH (+)/EGFR (+) patients with EGFR-TKIs experienced 3 PR, 1 SD and 1 waitiing for response evaluation, with median PFS of 11 months. Three with relatively low *EGFR*-mutant abundance achieved PR with crizotinib, while three with relatively high *EGFR*-mutant abundance obtained 2 PR and 1 SD with EGFR-TKIs. Spatial and inter-tumoral heterogeneity was observed in one *EGFR/ALK* co-altered patient. (Figure 1B) Two patients with T790M, one with Met pathway activation and two with loss of *EGFR* mutation were found after resistance to EGFR-TKIs. One with KRAS mutation was found pre- and post-EGFR-TKIs. *ALK*_F1174C mutation was observed in one patient after progression to crizotinib and *ALK*_G1202R mutation after resistance to ceritinib.

(See Figure 1 next page.)

Conclusion: *ALK* protein expression, *EGFR* mutation abundance and tumor heterogeneity were associated with efficacy of targeted treatment for *EGFR/ALK* co-altered patients. Most mechanisms resistance to EGFR-TKIs and crizotinib were similar to those in typical *EGFR* mutation and *ALK* rearrangement respectively.

Keywords: co-altered, EGFR mutation, ALK rearrangement

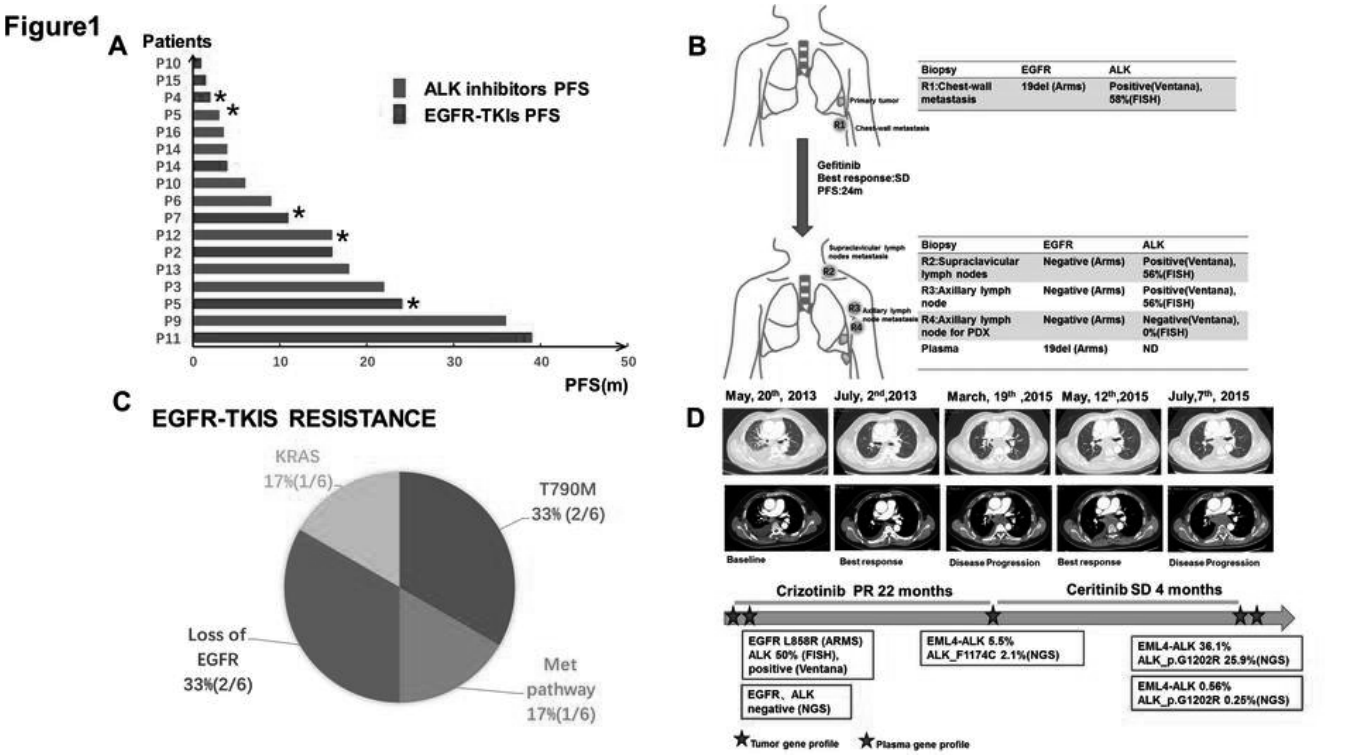

Figure 1 A The PFS of EGFR-TKIs and crizotinib in EGFR/ALK co-altered patients. B The gene profile of pre and post EGFR-TKI in different regions in one EGFR/ALK co-altered patient. C The potential resistance mechanism of EGFR-TKIs in EGFR/ALK co-altered patients. D The resistance mechanism to crizotinib in EGFR/ALK co-altered patients
*** Patients continue with targeted drugs**

P3.01: ADVANCED NSCLC -
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P3.01-064 DETECTION OF EGFR MUTATIONS IN CIRCULATING TUMOR DNA USING PLASMA SAMPLES: CLINICAL VALIDATION OF COBAS EGFR MUTATION TEST V2

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Background: Detection of EGFR mutations in circulating tumor DNA using plasma samples is non-invasive and safety method. Cobas EGFR mutation test v2 with tumor tissue has been approved for detection of EGFR mutations to offer EGFR-TKI therapy in Japan. Recently, cobas test v2 using plasma samples at disease progression after prior EGFR-TKI therapy was approved for detection of T790M mutation. However, diagnostic accuracy of this test using plasma samples has not yet known in clinical practice. **Method:** This study is a single-center retrospective study. Between May 2016 and June 2017, we obtained 70 plasma samples from 53 advanced NSCLC patients harboring EGFR mutation in our hospital, and evaluated concordance rate of tissue and plasma EGFR mutation status using sensitivity and specificity. All plasma samples were tested using cobas EGFR mutation test v2. **Result:** 70 samples were classified into three cohorts, diagnostic cohort(n=22), continuing response cohort(n=10), and acquired resistance cohort(n=38) by clinical setting. In diagnostic cohort, sensitivity for major mutations was 89%(ex19=100%, L858R=83%, respectively). In all cohorts, sensitivity for major mutations was 70%(ex19=80%, L858R=65%, respectively). T790M detection was evaluated in acquired resistance cohort, sensitivity was 67%, and specificity was 74%, respectively. **Conclusion:** The cobas EGFR mutation test v2 using plasma samples had good accuracy for detection of EGFR mutation in diagnostic setting. On the other hand, there was moderate accuracy for T790M detection in acquired resistance setting.

Keywords: liquid biopsy, cobas EGFR mutation test v2, T790M

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-065 ADVANCED NSCLC WITH EGFR MUTATIONS IN ELDERLY PATIENTS. SINGLE-CENTRE EXPERIENCE

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Background: Along the past 10 years determination of EGFR mutational status has becoming part of the standard clinical practice for NSCLC patients. It is also acknowledged that median age of NSCLC patients is progresively increasing and nowadays a significant percentage are elderly when diagnosed. The aim of this paper is to analize the characteristics of NSCLC-EGFR-mutated patients that were 75 years or older at diagnosis and assess their survival. **Method:** EGFR-mutated patients with advanced NSCLC treated betweeen June/2010 and June/2016 in our Department were analyzed. The subgroup of those >75 years have been reviewed for assessment. **Result:** Out of the 73 patients with EGFR mutation, 22 (30.1%) were 75 years or older. Median age was 80.5 y (75-86). Performance status: 0 3p, 1 8p, 2 10p, 3 1p. Gender: male 36.4%, female 63.6%. Stage IIIb 18.2%, IV 81.8%. 20p (90.9%) received therapy, all with a TKI (erlotinib, gefitinib or afatinib). The other 2p refused therapy. Median survival was 16 moths (m) (range 1-31). It was greater for patients with PS 0-1 (31m) and for females (32m) vs male (8m). No significant differences existed by stage or TKI. Lnadmark 2-year survival was 18.2% and 3-year 4.5%. These figures were lower than the corresponding for younger patients (median 21 months, 2-y 35.3%, 3-y 13.7). **Conclusion:** A significant percentage of NSCLC with EGFR mutation were older than 75 years. They tended to be more females and slightly worse PS than youger patients. Survival was also lower. These patients merit an specific approach, careful evaluation and follow-up.

Keywords: EGFR mutation, Elderly patients

P3.01-066 CNS METASTASES OF PULMONARY ADENOCARCINOMA HARBORING EGFR-ACTIVATING MUTATIONS: A MULTIDISCIPLINARY APPROACH, INCLUDING EGFR-TKIS

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Background: The incidence of CNS metastases among patients (pts) with pulmonary adenocarcinoma harboring EGFR-activating mutations seems to be increasing, probably related to their prolonged overall survival. A multidisciplinary approach, including radiation therapy, surgery and EGFR-TKIs, is absolutely essential for the management of these pts. We aimed to study the effectiveness of this multidisciplinary approach of CNS metastases in pts not previously treated with EGFR-TKis. **Method:** It is a retrospective, uni-institutional study, and all pts were consecutively identified and treated between 2009 and 2017. Eligible pts had to be diagnosed with pulmonary adenocarcinoma harboring EGFR-activating mutations (Sanger sequencing performed in either archived, or new, formalin-fixed and paraffin-embedded samples). CNS involvement was diagnosed based on CT scans, MRI and/or cerebrospinal fluid findings. All studied pts were treated with EGFR-TKIs (erlotinib or gefitinib) and other multimodality therapies including radiation therapy (whole brain or stereotactic radiosurgery), metastasectomy and/or intrathecal methotrexate, based on the decision of the multidisciplinary team. **Result:** 35 pts were studied, with a median age 63 y.o. (35-90), being 26 (74%) female, 19 (54%) never-smokers, and 26 (74%) ECOG-PS 0-2. All pts received an EGFR-TKI (erlotinib or gefitinib), and 26 also were treated with radiation therapy, 11 were submitted to surgery, 2 to stereotactic radiosurgery and 1 received IT-MTX; 4/35 were treated with an EGFR-TKI only. Median treatment time with an EGFR-TKI was 7.6 mo. Median progression-free survival (mPFS) was 8.2 mo and the median overall survival (mOS) was 11.9 mo. Among those 25 pts whose tumors were diagnosed with an exon 19 deletion, mPFS was 8.2 mo. and mOS 11.9 mo., and among those 9 pts with L858R mutation, mPFS was 10.8 mo. and mOS 13.8 mo. **Conclusion:** Those pts diagnosed with pulmonary adenocarcinoma harboring EGFR-activating mutations treated with a multidisciplinary approach (including an EGFR-TKI) may derive promising PFS and OS results. The approach must be individualized, considering patient characteristics, tumor biology aspects and also the available healthcare resources.

Keywords: brain metastases, lung cancer, EGFR

P3.01-067 TP53 MUTATIONS COULD INVOLVED IN EGFR-TKI PRIMARY RESISTANCE IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Activating mutations in the epidermal growth factor receptor (EGFR) are strongly predictive of EGFR-tyrosine kinase inhibitor (TKI) activity in non-small cell lung cancer (NSCLC). However, primary resistance to EGFR-TKIs occurs in approximately 20-30% of NSCLC patients with EGFR mutations, acquired resistance is inevitable. The aim of study is to discover unknown resistant mechanisms and contribute to more precisely administrate advanced and metastatic NSCLC with EGFR mutations. **Method:** 60 NSCLC patients with EGFR sensitive mutation were enrolled this study. All of patients received EGFR-TKI treatment. 21 of patients were primary resistance and 39 acquired resistance according to Jackman standard. Tumor tissues of all of patients were collected before EGFR-TKIs treatment, and rebiopsy tissues were gained after acquired resistance in 39 NSCLC patients. Whole exome sequencing were performed in Illumina HiSeq2000 platform. The captured sequencing data was further processed to identify somatic mutations, including single nucleotide variants (SNVs), short insertions/deletions (indels) and copy number variations (CNVs). **Result:** In primary resistance patients, 13 patients occurred rapid progress (PFS ≤60 days) were put into group 1, and other 8 patients with PFS within 90-180 days were into group 2; in acquired resistance patients, 9 patients were observed long-term clinical benefit (PFS≥540 days) were into group 3; remaining 30 patients with PFS between 180 to 540 days were into group 4. Median PFS were 29, 95, 761 and 311 days from group 1 to 4, respectively. More signaling pathways were activated in group 1, relative to other groups, including bypass activation, downstream signal activation, apoptotic pathways disturbance and EMT activation. Meanwhile, the activation of more signaling pathways were found in samples after acquired resistance compared with paired baseline samples. In all of baseline samples, 60.0% patients harbored TP53 mutations, and these mutations distributed in exon 2,4,5,6,7,8 and 11, respectively. Interestingly, TP53 mutations of 23% patients were in exon 6 in group 1, mutations in exon 5 occurred in 33.3% patients with long-term clinical benefit (group 3). Patients with exon 6 mutation had more shorter PFS than those with exon 5 mutation (105 days vs 284 days). **Conclusion:** For patients resistant to EGFR-TKI, more signal pathways were activation, and the heterogeneity of tumor cloning were complicated. TP53 mutations in different exons may have distinct effect on response to EGFR-TKI of patients with EGFR sensitive mutation.

Keywords: TP53 mutation, non-small cell lung cancer, EGFR-TKI

P3.01-068 INVESTIGATION OF LOW PLASMA/TISSUE EGFR CONCORDANCE IN RUSSIA: FOLLOW-UP TO THE IGNITE GLOBAL DIAGNOSTIC STUDY

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Background: IGNITE was a large multi-national, non-comparative, non-interventional diagnostic study whose objective was to in part determine the concordance in EGFR mutation status between tissue/cytology and plasma testing in the real world setting[1]. Locally advanced or metastatic NSCLC patients were enrolled from 9 countries in Asia-Pacific including Russia. A very significant difference was observed in performance of plasma testing in Russia (PPV=39.3%) vs. Asia Pac (PPV=92.5%) vs tissue results with only 51/84 ctDNA EGFR mutation positive results from Russian labs confirmed by the corresponding tissue result. No single lab appeared to contribute predominantly to the questionable overall performance. 1. Han, B et al.; 'Determining the prevalence of EGFR mutations in Asian and Russian patients (pts) with advanced non-small-cell lung cancer (aNSCLC) of adenocarcinoma (ADC) and non-ADC histology: IGNITE study' (ELCC 2015 Abstract No. 96O). **Method:** 142 of the 941 evaluable plasma samples from Russia were selected to include originally discordant samples and a similar number of concordant positive and concordant negative samples. All samples were shipped to an experienced lab and re-tested for TKI sensitizing mutations using the QIAamp Circulating Nucleic Acid Kit and the Therascreen® EGFR Plasma RGQ PCR test (Qiagen). The central laboratory was blinded to the origin of the samples and original EGFR mutation result. **Result:** Adhering to package insert defined criteria for the internal control, 38 of 112 (34%) of cases were re-classified (19 to pos. and 19 to neg.). By independent clinical laboratory interpretation of the results, 55 of 142 (39%) cases were re-classified (25 to pos. and 30 to neg.). A marked improvement was seen in concordance with the local tissue result after re-testing from 38% to 69% with the false positive rate decreasing from 18.8% to 3.6%. Re-classification of 17 (81%) original 'false positive' and 17 (35 %) original 'false negative' plasma results validates the original tissue results and appropriate collection and handling of plasma. **Conclusion:** Low concordance between original tissue and plasma EGFR status for the TKI sensitizing mutations observed in the Russian cohort from the IGNITE study was primarily due analytical issues in plasma test methodology. The contribution of the specific analytical process (extraction, testing or analysis) could not be determined. This follow-up study has been communicated back to the Russian laboratories resulting in the appropriate validation and proficiency programs being put in place to ensure quality plasma EGFR ctDNA testing.

Keywords: Global Diagnostic Study, IGNITE Study Follow-up, Plasma EGFR ctDNA testing

P3.01-069 THREE TREATMENTS FOR EGFR-MUTANT NON-SMALL-CELL LUNG CANCER WITH BRAIN METASTASES

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Background: Brain metastases (BM) are a common cause of morbidity and mortality in patients with non-smallcell lung cancer (NSCLC). EGFR-TKIs, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and chemotherapy are treatment options available. But the optimal management, the combination or sequence, remains undefined. This study evaluated the efficacy of EGFR-mutant NSCLC patients with BM receiving multiple regimens and analyze the prognostic factors. **Method:** We retrospectively studied 45 EGFR-mutated NSCLC patients with BM, who had received EGFR TKIs,radiation therapies (WBRT or SRS) and pemetrexed based chemotherapy successively between 2010 and 2015 at Zhejiang Cancer Hospital. Patient follow-up by telephone was done until January 2016. Treatment response was evaluated and survival data were collected and analyzed. **Result:** Among the 45 patients, 22(48.9%) had an EGFR exon 19 deletion and 23(51.1%) had an EGFR exon 21 L858R mutation. Thirty (66.7%) patients received upfront radiation therapies (RT). 28 patients (62.2%) were treated with pemetrexed based chemotherapy as the first line treatment while 17 (37.8%) received first line EGFR TKIs instead. The median overall survival (OS) from diagnosis of BM was 28.0 months for the whole cohort (95% CI, 17.3-38.7 months). Patients with the exon 19 deletion had a longer median OS than patients with the exon 21 L858R mutation (not reached vs. 23.2 months, P=0.031). There was no difference in OS between the upfront RT group and the deferral group (26.5 vs. 28.0 months, P=0.57), and similar results were found between the first line chemotherapy group and the TKIs group (28.0 vs. 23.2 months, P=0.499). Patients with a higher GPA score

showed better survival. In multivariate analysis, the prognosis was correlated with EGFR mutation type (P=0.017). Patients with extracranial metastases showed the strongest trend toward decreased OS, although it did not reach statistical significance (P = 0.070). **Conclusion:** Applying three treatments can significantly improve OS of patients, especially those with EGFR exon 19 deletion. Different sequences of treatments and timing of RT need further studies to identify the optimal treatment model.

Keywords: Epidermal growth factor receptor, Tyrosine kinase inhibitors, brain metastases

P3.01: ADVANCED NSCLC -
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P3.01-070 A PHASE II STUDY OF FRUQUINTINIB IN COMBINATION WITH GEFITINIB IN STAGE IIIB/IV NSCLC PATIENTS HARBORING EGFR ACTIVATING MUTATIONS

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Background: Seveal studies have demonstrated targeting EGFR mutations and tumor angiogenesis simultaneously has synergistic effect in the 1st line setting in EGFR mutant NSCLC. However, in JO25567 trial, the ≥grade 3 hypertension incidence with combination therapy was much higher (60%) when compared to historic incidence of hypertension with bevacizumab (10-15%). Considering relatively shorter half-lives for small molecule tyrosine kinase inhibitors, it might be a better choice to combine EGFR TKI and VEGFR TKI when it comes to hypertension management. Fruquintinib is a potent and highly selective oral kinase inhibitor targeting VEGFR and it has demonstrated favorable benefit-to-risk profile in third line treatment in NSCLC patients.Thus it is important to assess safety, tolerability and efficacy of this new combination in the 1st line setting in EGFR mutant NSCLC patients. NCT02976116 **Method:** This is a single arm, open-label, multi-center study. All patients will receive gefitinib continuously at 250 mg qd. Fruquintinib will be given at 4 mg as starting dose for 3 weeks followed by 1 week off in the first 4-week cycle. Fruquintinib dose can be escalated to 5 mg with the same 4-week cycle if no ≥grade 3 adverse event (AE) or ≥grades 2 liver dysfunction occurs in the first cycle. Treatment continues until disease progression, unacceptable toxicity, or patient withdrawal. The primary objective is to assess the safety and tolerability of this combination. Key eligibility criteria include: histologically or cytologically confirmed NSCLC, ECOG PS 0-1, no prior systematic treatment, no brain metastasis. Key exclusion criteria include: known T790M mutation and bleeding history within 1 month before enrollment. **Result:** As of Jun 20, 2017, 9 patients have been enrolled and received at least one dose of fruquintinib and gefitinib. Six patients had L858R mutations, and three patients had exon 19 deletions. All patients reported AEs, but only one patient (11.1%) had grade 3 proteinuria. No SAE was reported. The most common AEs were increased ALT (3 [33.3%] patients), increased AST (3 [33.3%] patients), increased TBIL (3 [33.3%] patients), proteinuria (3 [33.3%] patients) and rash (3 [33.3%] patients). Fruquintinib dose reduction occurred in 3 patients due to grade 3 proteinuria, grade 2 increased ALT and grade 2 hemoptysis, respectively. **Conclusion:** The study is ongoing. As of the cut-off date, no unexpected toxicities were identified. The combination of fruquintinib and gefitinib showed an expected and manageable preliminary safety profile. Additional patients and follow-up data are required to further confirm the full potential of this combination treatment.

Keywords: Fruquintinib, non-small cell lung cancer, gefitinib

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-071 RANDOMIZED PHASE 1B/3 STUDY OF ERLOTINIB + RAMUCIRUMAB IN UNTREATED EGFR MUTATION-POSITIVE STAGE IV NSCLC: PHASE 1B OUTCOMES

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Background: Despite the likelihood of an initial response to an EGFR TKI, NSCLC patients with an activating *EGFR* mutation eventually develop disease progression. Anti-angiogenic agents in combination with an EGFR TKI may provide additional benefit in *EGFR*-mutant NSCLC, but additional studies are needed to confirm the benefit. **Method:** This ongoing phase 1b/3 study (NCT02411448; RELAY) enrolled patients with previously untreated stage IV NSCLC, ECOG PS 0-1, and an activating *EGFR* mutation (exon 19 deletion or exon 21 L858R substitution). In part A (phase 1b), patients received ramucirumab (anti-VEGFR2 antibody) 10 mg/kg intravenously on day 1 of a 14-day cycle and oral erlotinib at 150 mg/day. Treatment continued until disease progression or unacceptable toxicity. The primary objective of part A was to assess safety and tolerability, in terms of dose-limiting toxicities (DLTs) during the first two cycles of therapy, and to determine the recommended dose for Part B (phase 3). Data cutoff was 31-May-2017. **Result:** Fourteen patients were enrolled and treated in part A. Two patients discontinued prior to completion of cycle 2, due to non-DLT adverse events of grade 2 interstitial pneumonia and grade 1 hemoptysis and were therefore not eligible for DLT assessment. Of the 12 DLT-evaluable patients (Japan, n=6; US/Europe, n=6), median age was 72 years (range 51-83), 83% were female, and 75% had ECOG PS of 1. Median duration of therapy was 64.3 weeks (interquartile range [IQR] 19.5-89.0) with ramucirumab and 68 weeks (IQR 44-95) with erlotinib. Treatment-emergent adverse events (TEAEs) occurred in all patients, most commonly rash (100%), diarrhea (92%), paronychia (67%), hypertension (58%), and dry skin (58%). Ten (83%) patients experienced grade 3 TEAEs (hypertension [n=4], rash [n=3], diarrhea [n=2], neutropenia, conjunctivitis, elevation of alanine aminotransferase [DLT; resolved within 4 days], and elevation of aspartate aminotransferase). No serious or grade 4-5 adverse events occurred. Median PFS was 17.1 months (95% CI 8.8-NR; 50% censored) and the PFS survival rate at 21-months was 46.9%. Five patients remain on study treatment. **Conclusion:** Ramucirumab plus erlotinib demonstrated encouraging clinical activity with no unexpected toxicities in Part A. Randomization into Part B began in January-2016, maintaining the dose of ramucirumab at 10 mg/kg Q2W with oral erlotinib at 150 mg/day.

Keywords: vascular endothelial growth factor receptr VEGFR, first-line treatment, EGFR mutant NSCLC

P3.01: ADVANCED NSCLC -
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P3.01-072 DACOMITINIB VERSUS GEFITINIB FOR FIRST-LINE TREATMENT OF ADVANCED EGFR+ NSCLC IN JAPANESE PATIENTS (ARCHER 1050)

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Background: Second-generation EGFR tyrosine-kinase inhibitor dacomitinib has shown encouraging activity as first-line therapy in patients with *EGFR*-activating mutation-positive (*EGFR*+) advanced NSCLC. We performed the first randomized, open-label phase 3 trial comparing dacomitinib with gefitinib as first-line therapy (NCT01774721) which demonstrated a clinically meaningful and statistically significant benefit of dacomitinib versus gefitinib (PFS per IRC: HR, 0.59 [95%CI, 0.47–0.74]; 1-sided *P*<0.0001; median PFS, 14.7 vs 9.2 months). We present results from Japanese patients enrolled in this ongoing study. **Method:** Patients with newly diagnosed stage IIIB/IV recurrent NSCLC harboring an *EGFR*-activating mutation (exon 19 deletion or exon 21 L858R ± exon 20 T790M) were randomized 1:1 to once-daily oral dacomitinib 45 mg or gefitinib 250 mg until disease progression or discontinuation. Patients with CNS mets excluded. Stratification was by race and *EGFR* mutation subtype. The primary endpoint was progression-free survival (PFS) per blinded independent review committee (IRC). **Result:** Among 452 patients enrolled in ARCHER 1050, 81 were Japanese. Slight imbalances in baseline characteristics were observed (Table). PFS and duration of response improvement in Japanese patients was consistent with global results.

Japanese Intention-to-Treat Population			
	Dacomitinib (n = 40) n (%)	**Gefitinib (n = 41) n (%)**	**Unstratified HR [95% CI] 1-sided p-value**
Male	15 (37.5)	20 (48.8)	
Age, years <65	19 (47.5)	15 (36.6)	
≥65	21 (52.5)	26 (63.4)	
Smoking status Never smoked	19 (47.5)	24 (58.5)	
Ex-smoker	20 (50.0)	16 (39.0)	
Smoker	1 (2.5)	1 (2.4)	
ECOG PS 0	28 (70.0)	21 (51.2)	
1	12 (30.0)	20 (48.8)	
	Median, months	**Median, months**	
PFS per IRC	18.2 (95% CI, 11.0–31.3)	9.3 (95% CI, 7.4–14.7)	0.54 (95% CI, 0.31–0.95) P=0.0141

Japanese Intention-to-Treat Population			
	Dacomitinib (n = 40) n (%)	**Gefitinib (n = 41) n (%)**	**Unstratified HR [95% CI] 1-sided p-value**
PFS per INV	18.3 (95% CI, 14.6–22.1)	10.2 (95% CI, 7.3–16.9)	0.61 (95% CI, 0.36–1.04) P=0.0334
DoR per IRC in responders	# of responders=30 17.5 (95% CI, 10.2–34.3)	# of responders=31 8.3 (95% CI, 5.6–12.9)	0.44 (95% CI, 0.22–0.84) P=0.0056
CI, confidence interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; INV, investigator assessment.			

Objective response rates per IRC were similar (dacomitinib, 75.0% [95%CI, 58.8–87.3]; gefitinib, 75.6% [95%CI, 59.7–87.6]; 2-sided *P*=0.9579). Overall survival data are not mature. All 81 patients received study treatment. No grade 4/5 adverse events (AEs were observed with dacomitinib, while 3 grade 4 AEs and 1 grade 5 AE (disease progression) occurred with gefitinib. The most common grade 3 AEs were dermatitis acneiform (27.5%) and paronychia (22.5%) with dacomitinib and alanine aminotransferase increased (12.2%) and abnormal hepatic function (7.3%) with gefitinib. No new safety signals were identified. **Conclusion:** Dacomitinib significantly improved PFS and duration of response over gefitinib in first-line treatment of Japanese patients with advanced *EGFR*+ NSCLC, with a manageable safety profile.

Keywords: Dacomitinib, Non-small-cell lung cancer, EGFR mutation

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-073 TPX-0005 WITH AN EGFR TYROSINE KINASE INHIBITOR (TKI) OVERCOMES INNATE RESISTANCE IN EGFR MUTANT NSCLC

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Background: Overexpression of several receptor tyrosine kinases (RTKs) substitutes EGFR signaling in EGFR-mutant NSCLC. The MET ligand hepatocyte growth factor (HGF) provides an alternative signaling mechanism for EGFR by inducing inter-receptor cross talk with EphA2, CUB domain-containing protein-1 (CDCP1) or AXL. SHP2, a non-receptor protein tyrosine phosphatase is central in signal transduction downstream of RTK signaling and in Src activation. We previously demonstrated that STAT3 and Src-YAP1 signaling limits EGFR TKI efficacy in EGFR-mutant NSCLC. We are now exploring the possibility of multiple RTK activation through a Src-YAP1-mediated transcriptional program. We are evaluating whether combined EGFR inhibition with TPX-0005, a novel orally available multikinase inhibitor and potent Src/FAK and JAK2 inhibitor, can be more efficient than EGFR inhibition alone in EGFR-mutant NSCLC cells. **Method:** We studied the mRNA expression levels of stromal HGF and tumor RTKs, AXL, CDCP1, MET, and EphA2, as well as SHP2, and clinical outcome in baseline samples of 64 EGFR-mutant NSCLC patients treated with first-line EGFR TKI. We combined in vitro approaches to explore whether gefitinib or osimertinib combined with TPX-0005 can abolish STAT3 and Src-YAP1 and downregulate the expression of RTKs. **Result:** High levels of AXL, CDCP1 and SHP2 mRNA expression were associated with worse outcome to EGFR TKI in 64 EGFR-mutant NSCLC patients. Median progression-free survival (PFS) was 14.5 and 23.4 months for patients with high and low AXL mRNA, respectively (p=0.0359). Median PFS was 9.1 and 20.2 months for patients with high and low CDCP1 mRNA, respectively (p=0.0179). Tumoral EPHA2 and MET or stromal HGF levels did not affect PFS. Median PFS was 11.4 and 24.1 months for patients with high and low SHP2 mRNA, respectively (p=0.0094). The combination of gefitinib/osimertinib with TPX-0005 resulted in highly synergistic suppression of cell viability and reduced colony formation in two EGFR-mutant cell lines. The combination abolished the EGFR inhibition-induced STAT3 and YAP1 phosphorylation, as confirmed by western blotting and immunofluorescence. The results of TaqMan quantitative-PCR assay revealed that gefitinib/osimertinib plus TPX-0005 reduced the mRNA levels of AXL, CDCP1 and MET, an effect that could not be obtained with EGFR inhibition alone. In vivo experiments are ongoing. **Conclusion:** AXL and CDCP1 are adverse predictive markers of PFS in EGFR-mutant NSCLC patients. STAT3 and Src-YAP1 signaling limits the efficacy EGFR TKI. Combined EGFR inhibition with TPX-0005 (currently in phase I clinical testing) is a particularly attractive strategy

Keywords: EGFR-mutant NSCLC, EGFR TKI, TPX-0005

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-074 GENOMIC ANALYSIS OF TUMOR AND PLASMA IN T790M MUTANT POSITIVE EGFR LUNG CANCER PATIENTS BEFORE AND AFTER OSIMERTINIB TREATMENT

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Background: Osimertinib is a third-generation, central nervous system active epidermal growth factor receptor (EGFR) – tyrosine kinase inhibitor (TKI) that potently and selectively inhibits both EGFR-sensitising and EGFR T790M resistance mutations. Osimertinib is approved for EGFR mutation positive non small cell lung cancer (NSCLC) patients who develop EGFR T790M resistant mutation and resistant to prior EGFR TKI. Osimertinib resistance pattern and clinical outcome after osimertinib treatment are undergoing intensive investigation. **Method:** Seventy-one EGFR-TKI resistant patients received osimertinib in the AURA study in one medical center. We excluded patients treated as first-line or who do not have detectable T790M mutation. We collect available data of pre-osimertinib treatment plasma and tissue and post-osimertinib plasma, tissue samples and tested for EGFR, HER2, K-ras, B-raf, mutations, ALK fusion and cMET or HER2 gene amplification. Clinical and pathological characteristics before and after osimertinib treatment were collected. **Result:** Of the 53 T790M-positive patients, 6 did not progress. Three and 18 patients discontinued osimertinib due to side effect or progression, respectively; 26 received osimertinib beyond progression (1.1 to 20.5 months); 7 patients received osimertinib combination after progression. Fourteen patients are still alive. Median progression-free survival(PFS), overall survival(OS) and post-progression survival (PPS) were 11.1 months, 16.9 months and 5.0 months, respectively (only progression patients). In 47 progressive patients, post progression EGFR plasma tests were available in 40 patients. T790M was detected by BEAMing in 12 patients (4 patients combined with C797S) and not detected in 28 patients (70%). OS and PPS was longest for patients with no detectable EGFR activating mutation and T790M in the plasma before and/or after osimertinib treatment. Patients who lost detectable T790M but maintained activating EGFR mutation in the plasma had shortest osimertinib PFS. Post progression tissue sample or pleural effusion tumor cells were available in 22 patients. Two patients developed small cell transformation, one patient developed squamous cell carcinoma. Post progression tissue or effusion genomic tests were performed (N= tested patient number) and showed T790M+ in 9 patients(N=18), C797S in 2 (N=12), cMET amplification in 5 (N=10), B-Raf V600 mutation in 1 (N=13), K-ras mutation in 1 (N=13) and no ALK, ROS1 and RET fusions. **Conclusion:** Heterogeneous resistance mechanisms develop after osimertinib treatment, in tumors retain T790M or losing T790M. Patients who have no detectable activating EGFR mutations in the plasma had best survival outcomes. Loss of T790M but maintainance activating EGFR mutations in the plasma correlated with short osimertinib PFS.

Keywords: EGFR, Resistance, osimertinib

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-075 AFATINIB DOSE ADJUSTMENT: EFFECT ON SAFETY, EFFICACY AND PATIENT-REPORTED OUTCOMES IN THE LUX-LUNG 3/6 TRIALS IN EGFRM+ NSCLC

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Background: Afatinib 40mg/day is approved globally for first-line treatment of *EGFR* mutation-positive (*EGFR*m+) NSCLC. Afatinib is available in several tablet strengths (20/30/40/50mg), and tolerability-guided dose adjustment schemes are well established. Here, we evaluate the impact of afatinib dose reduction on safety (AEs), pharmacokinetics, PFS and patient-reported outcomes (PROs) in the Phase III LUX-Lung (LL) 3 and 6 trials. **Method:** Treatment-naïve patients with stage IIIB/IV *EGFR*m+ NSCLC in LL3/6 received either 40mg/day afatinib or chemotherapy. In case of any treatment-related grade ≥3 AEs or selected prolonged grade 2 AEs, afatinib dose was reduced by 10mg decrements (minimum dose 20mg/day). In this post-hoc analysis of all afatinib-treated patients in LL3/6 (n=229/n=239), we compared incidence and severity of common AEs before and after dose reduction, afatinib plasma concentrations in patients who reduced to 30mg versus those remaining on 40mg, and PFS in patients with/without dose reductions in the first 6 months of treatment. PROs were measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire and the EQ-5D™ health status self-assessment questionnaire, and pooled data from both trials were assessed before/after dose reduction; these included scores on the EORTC Global Health/Quality of Life scale (GH/QoL; 0–100), EORTC Performance Functioning scale (PF; 0–100), EQ Visual Analogue Scale (VAS; 0–100) and EQ-5D UK utility scale (EQ UK utility; 0–1). **Result:** Dose reductions occurred in 122/229 (53.3%) patients in LL3 and 67/239 (28.0%) in LL6; >80% of dose reductions occurred in the first 6 months of treatment. Dose reductions decreased the incidence of treatment-related AEs (grade ≥3 AEs before/after dose reduction: LL3, 73%/20%; LL6, 81%/12%), and were more likely among patients who had higher afatinib plasma concentrations prior to subsequent dose reduction (Day 22). On Day 43, geometric mean afatinib plasma concentrations were comparable between patients who had dose reduced (n=59; 23.3ng/mL) and patients who remained on 40mg (n=284; 22.8ng/mL). Median PFS was comparable between patients with or without dose reductions in the first 6 months (LL3: 11.3 versus 11.0 months; HR [95% CI] 1.25 [0.91–1.72]; p=0.175; LL6: 12.3 versus 11.0 months; 1.00 [0.69–1.46]; p=0.982). There were no clinically meaningful changes in PROs following afatinib dose reduction: GH (40/30mg: 59.1/66.9; n=136); PF (79.4/83.0; n=136); EQ VAS (70.1/75.1; n=135); EQ UK utility (0.70/0.78; n=135). **Conclusion:** Tolerability-guided dose adjustments effectively reduced afatinib-related AEs without negatively affecting therapeutic efficacy and PROs.

Keywords: dose adjustment, PROs, afatinib

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-076 QTWIST ANALYSIS TO COMPARE THE BENEFIT OF GEFITINIB VERSUS PEMETREXED PLATINUM FOR PATIENTS WITH EGFR MUTATED NSCLC

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Background: In an open-label, Phase 3 randomized study (Clinical trial registry of India: CTRI/2015/08/006113), Gefitinib was found to be superior to Pemetrexed-Platinum in terms of progression-free survival in patients with EGFR mutated NSCLC. In this analysis, we aimed to assess the benefit of gefitinib over Pemetrexed platinum using quality-adjusted time without symptom or toxicity analysis method. **Method:** In this phase III, randomized study EGFR activating mutated patients were randomized in 1:1 fashion to either receive pemetrexed-carboplatin followed by maintenance pemetrexed or gefitinib till progression. Patients post progression received the treatment received in other arm if they were fit. These patients were followed up until death. Toxicity during the whole course of treatment was documented in accordance with CTCAE version 4.02 criteria. For QTWiST analysis, the overall survival and progression-free survival were documented. The overall survival was partitioned in 3 health states. These were TOX, TWiST, and REL. TOX state comprised of time in months spent by the patient in grade 2 or above toxicity post randomization but before the first progression. TWiST state comprised of time in months spent by the patient post randomization but before the first progression without grade 2 or above toxicity. REL state was defined as the time in months spent post the first progression until death. RStudio will be used for analysis. The data will be censored for this analysis on 30th June 2017. The restricted mean of all three health states would be calculated using non-parametric 500 boot straps. The time spent in each state will be weighted by a corresponding health-state utility coefficient for QTWiST calculation. A threshold utility analysis will be performed using utility values between 0-1. Where 0 represents a health state similar to death and 1 represents a perfect health state. **Result:** The restricted mean health state duration in months for each state with its 95% CI for each arm, the difference between the 2 arms for each health state with its 95%CI and corresponding p-value will be provided. The results of threshold utility analysis with the corresponding QTWiST difference between the 2 arms with p-value would be presented. **Conclusion:** LBA: Not applicable

Keywords: EGFR mutation, NSCLC, QTWiST

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-077 EFFECTIVENESS OF METHYLNALTREXONE BROMIDE IN OPIOID-INDUCED CONSTIPATION IN ADVANCED NSCLC PATIENTS

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Background: Methylnaltrexone Bromide (MB) is a selective antagonist of opioid binding at the mu-receptor (μ or MOR receptor). Constipation is a quite common side effect in Non-Small-Cell-Lung-Cancer (NSCLC) patients receiving opioids for chronic pain, usually due to skeletal metastases. We set out to investigate if MB is effective in those patients who received opioids and complained of constipation. **Method:** Sixty-eight NSCLC patients with a life expectancy of at least three months were recruited for our study after providing written consent. All patients received either fentanyl as a transdermal patch, in its inhaled form or per os. Patients were randomized (1:1) to four weeks of treatment with either MB 12mg/0.6ml (n=22) administered subcutaneously (sc) or a placebo, on alternate days. We recorded the number of patients who defecated within four hours of the MB or placebo injection, and the number of patients needing a second dose of MB or placebo within six hours from the first dose. We recorded the side effects of this treatment. Patients were not allowed to use other laxatives. **Result:** In the MB group after one injection, fifty one patients (75%) had a bowel movement within four hours compared to nine placebo patients (13%), p=0.02. Fifteen patients in the MB group had a bowel movement after two or more doses of MB, raising the percentage of patients who responded to MB to 96%. The more severe the constipation, the higher the response with MB. The overall rate of adverse events was similar in the MB (43%) and placebo groups (42%). In the MB group, the most commonly reported adverse events were abdominal pain (16%), flatulence (16%), vomiting (11%), and nausea (13%). Most treatment related adverse events were rated as mild or moderate by the patients. Discontinuation due to adverse events occurred in 5% and 6% of patients in the MB and placebo groups, respectively. **Conclusion:** Methylnaltrexone Bromide has been shown to be superior to placebo in achieving defecation within a short time, in NSCLC patients with opioid-induced constipation, The more severe constipation, the higher the response with MB. There were no serious adverse events. We conclude that Methylnaltrexone Bromide is effective, safe and superior to other commonly used laxatives.

Keywords: Opioids, Constipation, Methylnaltrexone Bromide

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-078 OUTCOME OF STAGE IIIB NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS – A SINGLE TERTIARY CENTER EXPERIENCE

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Background: The optimal treatment strategy for Stage IIIB NSCLC patients with a T4N0-1 tumor is a matter of debate. In prospective combined modality series including surgery, the median overall survival (OS) is approximately 24 months. We hypothesized that results comparable to regimens including surgery can be achieved with concurrent chemoradiation in this patient group. **Method:** In our retrospectively collected database of NSCLC patients, all patients with T4 (mediastinal invasion) N0-1 NSCLC receiving concurrent chemoradiation were included. One patient had a recurrence after previous pneumonectomy. All patients were given 3 cycles of chemotherapy (cisplatin and etoposide). Radiotherapy (RT) was started at the 2nd course of chemotherapy. OS was calculated from date of diagnosis (Kaplan-Meier method). Toxicity was scored according to CTCAEv3.0. **Result:** 42 patients (8 female, 34 male) with a median age of 62.5 ± 9 years (44-80 years) were included from January 2005 until December 2009. Stage distribution: 86% T4N0 (n=36), 14% T4N1 (n=6). The maximal tumor dose was 66 Gy using conventional fractionation. The median prescribed mean lung dose was 15 ± 4.4 Gy (5.03 -19.9 Gy). Acute toxicity: 1 patient experienced grade 3 dyspnea during RT. Grade 3 dysphagia occurred in 5 patients (12%) during RT requiring tube feeding in 3 of these patients (7%). Dysphagia persisted later than 1 month after RT in 1 patient (2%). Grade 3 dysphagia only occurred in patients treated concurrently. Grade 3 cough occurred in 1 patient during RT, no patient experienced grade 3 cough 1 month after RT. 2 patients died within 3 months after start of RT, one due to myocardial infarction, one of unknown causes. Severe late toxicity was not present: no grade 3 complications more than 3 months after the end of radiotherapy. With a median follow-up of 42 months, the median OS for the whole group is 34 months (95% CI 24-43 months). 2-year OS survival is 55%. **Conclusion:** Concurrent accelerated chemoradiation using an individualized dose prescription is a valid treatment strategy for stage IIIb, T4N0-1 NSCLC patients yielding very promising OS results with low toxicity.

Keywords: NSCLC

P3.01-079 EVALUATING THE ROLES OF NEOADJUVANT AND ADJUVANT CHEMOTHERAPY FOR TREATING PATIENTS WITH STAGE IIIA (N2) LUNG CANCER

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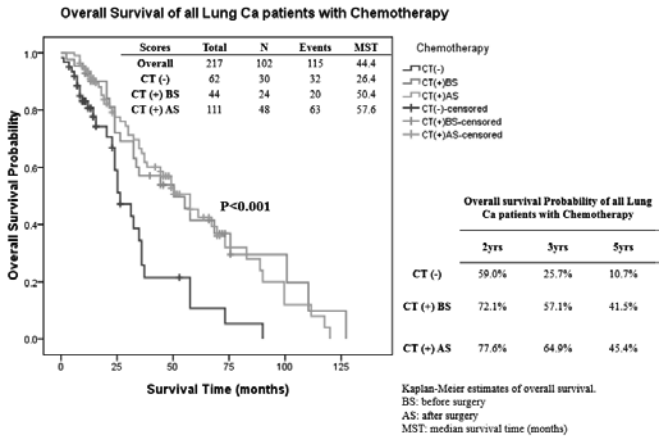
Background: The survival benefit of systemic chemotherapy has been demonstrated for treating patients with stage IIIa (N2+) lung cancer. The NCCN guideline recommends induction chemotherapy with or without irradiation followed by surgery for those patients if no disease progression was noted after induction therapy. However, there are also studies revealed the survival benefit of adjuvant chemotherapy for patients with N2+ IIIa disease. The current study compared the survival results of neoadjuvant (before surgery, BS) and adjuvant (after surgery, AS) chemotherapy plus surgical resection for the patients with non-small cell lung cancer with N2+ stage IIIa disease. **Method:** There were 217 patients with Stage IIIa N2+ who ercieved surgery resection in the recent decade in our hospital, with a mean follow-up duration of 44 months. The overall survival time was evaluated and compared between these three groups of patients

Result:



There were 62, 44 and 111 patients without chemotherapy(C/T) (Nil) or C/T given as neoadjuvant (BS) and adjuvant (AS) setting respectively. There were more patients with advanced age in the Nil and AS groups and more patients with AS group have received sublobal resection (p<0.01 respectively) as compared to the patients of BS group. The mean survival duration after surgery for the patients of AS and BS groups was 57.6 and 50.4 months respectively which was signinficantly longer than those patients of Nil group (MST: 26.4 months : p<0.001 respectively). Multivariate analysis revealed the addition of chemotherapy as a single prognostic factor of the patients. However, there was no significant difference of survival duration between the patients of AS and BS groups. **Conclusion:** Chemotherapy given both as adjuvant or neoadjuvant setting can provide a survival benefit for the patients with stage IIIa N2+ non-small cell lung cancer after surgery. No statistical difference was observed about the survival duration for these two groups of patients.

Keywords: chemotherapy, NSCLC, Advanced NSCLS

P3.01-080 OVERALL SURVIVAL (OS) OF PATHOLOGICAL N2 NON-SMALL CELL LUNG CANCER (NSCLC) AFTER SURGICAL RESECTION

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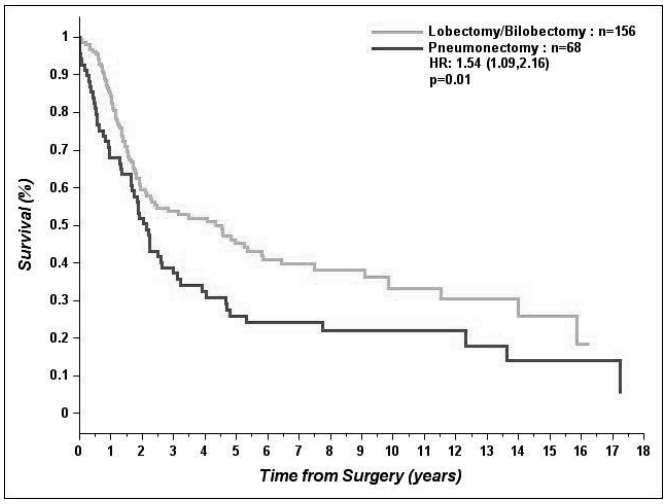
Background: Despite complete pre-operative staging, incidental N2 disease is still found during surgical resection of NSCLC. Proceeding with resection versus aborting the operation to treat with definitive chemotherapy and radiotherapy is controversial. The aim of the current study was to evaluate survival of pathological N2 disease after complete resection. **Method:** The *Institut de Cardiologie et Pneumologie de Quebec* Biobank was queried for all patients with pathological N2 NSCLC who underwent complete (R0) surgical resection either by lobectomy, bilobectomy or pneumonectomy between January 2000 and February 2017. Survival was examined using the Kaplan-Meier method with log rank analysis. Significance was set at p≤0.05. **Result:** We identified 224 eligible patients; 119 (53%) were male, mean age was 63±9, there were 143 (64%) adenocarcinoma and 60 (27%) squamous cell carcinoma. Regarding surgical modality, 156 (70%) patients underwent lobectomy or bilobectomy and 68 (30%) pneumonectomy. The 30-day mortality of the cohort was 3% (5 pneumonectomy and 2 lobectomy). During 17 years of follow-up, 142 (63%) patients died, including 87 (61%) in the lobectomy/bilobectomy group and 55 (39%) in the pneumonectomy group. Among all deaths, 105 (74%) were cancer-related. Median OS of the entire cohort was 2.6 y (CI 1.9-4.4). In the univariate analysis cox model, median OS was shorter for pneumonectomy than lobectomy/bilobectomy (2,1 years [1,6-2,6) vs 4,4 years [2,2-5,8]), HR 1.54 (CI 1.09 – 2.16, p=0.01; figure 1). However, when only considering cancer-related deaths, the difference was not statistically significant (p=0.95). Figure 1: Overall survival of pathological N2 according to type of resection.



Conclusion: In our institutional database study, median OS after surgical resection of N2 NSCLC was 2.6y. Pneumonectomy is indicated as cancer cure treatment however, major efforts should be made to decrease peri-operative morbidity and mortality.

P3.01-081 OVERALL SURVIVAL (OS) OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) AFTER NEGATIVE INVASIVE MEDIASTINAL STAGING

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Background: According to current guidelines, invasive pre-operative staging should be performed with endoscopic ultrasound in NSCLC in suspected N2 disease. Due to its higher negative predictive value, in case of PET positive, CT enlarged mediastinal lymph nodes or central tumors, mediastinoscopy remains indicated when EBUS staging is negative. The aim of the current study was to evaluate OS of patients with locally advanced NSCLC who underwent surgical resection after negative EBUS and mediastinoscopy. **Method:** The *Institut de Cardiologie et Pneumologie de Quebec* Biobank was queried for all patients with high probability of N2 disease or central tumors with negative EBUS and mediastinoscopy that underwent complete surgical resection (R0) between March 2009 and February 2017. Survival was examined using the Kaplan-Meier method with log rank analysis. Significance was set at p≤0.05. **Result:** We identified 88 eligible patients (Table 1); 56 (64%) were male, mean age was 65±9 and 50% of the cases were adenocarcinoma. Regarding surgical modality, 1 (1%) patient underwent sublobar resection, 65 (74%) lobectomy or bilobectomy and 22 (25%) pneumonectomy. Among these, there were 11 (13%) pathological N2 cases. There was no 30-day mortality. During 8 years of follow-up, 30 patients died, including 20 (31%) in the lobectomy/bilobectomy group compared to 9 (41%) in the pneumonectomy group. We then identified 16 (80%) cancer-related deaths in the lobectomy/bilobectomy and 7 (78%) in the pneumonectomy group. Median OS of the entire cohort was 5.7 years, with no difference between groups (HR 1.29, CI 0.58-2.87, p=0.53). Table 1: Demographics of Locally advanced NSCLC Cohort

Characteristic	Lobectomy/ Bilobectomy (n=65) N(%)	Pneumonectomy (n=22) N(%)	Total (87) N (%)	p value
Sex Male Female	44 (68) 21 (32)	11 (50) 11 (50)	55 (63) 32 (37)	0.200
Histology Squamous Adenocarcinoma Other	21 (32) 34 (53) 10 (15)	10 (45.5) 10 (45.5) 2 (1)	31 (36) 44 (50) 12 (14)	0.549
Mean age (years)	65.8 ± 8.2	63.4 ± 6.8	65.4 ± 8.1	0.216
Pathological stage IA IB IIA IIB IIIA IIIB	10 (15) 13 (20) 12 (18) 10 (15) 19 (30) 1 (2)	0 4 (18) 3 (14) 9 (40) 5 (23) 1 (5)	10 (11) 17 (20) 15 (17) 19 (22) 24 (28) 2 (2)	0.075

Conclusion: In our institutional database, patients locally advanced NSCLC had 13% incidence of pathological N2 disease and the OS was 5.7y. Our data supports surgical complete resection either by lobectomy or pneumonectomy in this group of patients with locally advanced disease.

Keywords: mediastinal staging, pneumonectomy and lobectomy

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-082 SURGICAL REBIOPSY IN ADVANCED NON-SMALL CELL LUNG CANCER RESISTANT TO PREVIOUS CHEMOTHERAPY

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Background: To optimize the personalized medicine for advanced non-small cell lung cancer (NSCLC), sufficient tumor tissue is mandatory to analyze molecular and genetic profile. The demand for repeat biopsy in NSCLC is increasing, it is more difficult to obtain specimen after initial treatment. The aim of this study was to evaluate the impact of surgical rebiopsy in advanced NSCLC. **Method:** From Jan 2014 to Mar 2017, 146 consecutive patients underwent surgical rebiopsy for NSCLC which was resistant to prior chemotherapy. Their medical record were reviewed retrospectively. **Result:** There were 60 male and 86 female patients with mean age of 57 years (range 30-83). Adenocarcinoma was most common histologic type (n=142, 93%). Among them, 107 patients represent EGFR mutation before chemotherapy, deletion in exon 19 (n=73) was most frequently observed. Before surgical rebiopsy, 121 patients (83%) were treated with EGFR-TKIs. The mean number of change in chemotherapy regimen was 2 (range 1-6) and 24% of patients underwent more than 3 different chemotherapy before rebiopsy. The median time between initial treatment and rebiopsy was 17.4 months (IQR 9-25). Surgical rebiopsy was possible in all cases. One hundred and seven patients (73%) underwent pleura biopsy, 22 underwent lung resection and 12 patients underwent both pleural and lung resection. Most procedure underwent video-assisted thoracic surgery (n=136, 93%), 10 patients required mini-thoracotomy. Median postoperative hospital stay was 4 days (IQR, 3-6) and the 30-day mortality was 2.7%. All specimens were confirmed as NSCLC and adequate for mutational and genetic analysis except 2 patients. One patient was failed to mutational analysis, other patients was failed to genetic sequencing due to low tumor volume. After surgery, 129 patients can resume chemotherapy. Of those, 85 patients were enrolled clinical trial or treated with new target agent. Thirty nine patients were treated with cytotoxic chemotherapy and 5 patients continued with prior target agent. **Conclusion:** Surgical rebiopsy can detect changes in cancer characteristics and may be used in therapeutic decision making in advanced NSCLC resistant to previous treatment.

Keywords: non-small cell lung cancer, rebiopsy

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-083 CLINICAL CHARACTERISTICS AND SURVIVAL OUTCOMES FOR NON-SMALL CELL LUNG CANCER PATIENTS WITH EPIDERMAL GROWTH FACTOR RECEPTOR DOUBLE MUTATIONS

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Background: Multiple randomized clinical trials have demonstrated that epidermal growth factor receptor (EGFR) exon 19 deletion (19Del) and exon 21 L858R mutation (L858R) are highly correlated with sensitivity to epidermal growth factor receptor tyrosine kinase inhibitorsinhibitor (EGFR-TKIs)TKI) treatment in non-small -cell lung cancer (NSCLC). A mutation in exon 20 (T790M) is reportedly associated with resistance to EGFR-TKIs. However, there are few studies have focused on those patients harboring double mutations in these three3 mutation sites. **Method:** Between March 2007 toand November 2016, 2546 Chinese patients with non-small cell lung cancer,NSCLC underwent EGFR mutation detections in tumor tissues at three3 medical institutions and were enrolled in this retrospectivelyretrospective study. Clinical characteristics of these patients, including the response to EGFR-TKIs and progression -free survival outcomesoutcome for EGFR-TKIsTKI treatment (PFS-TKIs) of these patientsTKI), were analyzed. **Result:** Forty-five patients (45/2546, 1.7%) harbored double mutations of 19Del, L858R, and T790M. Patients with EGFR double mutations were more likely to be non-smoker, PS smokers, have a performance status of 0-1, have adenocarcinoma, and be at stage III-IV. Twenty-four patients with EGFR double mutations received EGFR-TKIsTKI therapy. The objective response rate (ORR), disease control rate (DCR)), and median PFS-TKIsTKI were 25% (6/24), 62.5% (15/24) and 5.95 months, respectively. The ORR, DCR, and median PFS-TKIsTKI in patients with double mutations of 19Del and T790M were 50% (4/8), 75% (6/8)), and 16.5 months, respectively. In those patients with 19Del and L858R, the ORR, DCR, and median PFS-TKIsTKI were 18.2% (2/11), 45.5% (5/11)), and 3.3 months, respectively. The ORR, DCR, and median PFS-TKIsTKI were 0% (0/5), 80% (4/5)), and 3.0 months, respectively, in patients with concomitant mutations of L858R and T790M. **Conclusion:** The ORR, DCR, and median PFS-TKIsTKI in patients harboring EGFR double mutations were lower than in patients with a single EGFR -activating mutation. The differences ofin ORR and DCR were statistically insignificant between the three3 groups. Patients with double mutations of 19Del and T790M had longer PFS-TKIs than patients in the other two2 groups.

Keywords: non-small cell lung cancer, EGFR, Double mutations

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-084 ANALYSIS ON ALTER0303 TRIAL: ACECS LEVEL MAY CORRELATE WITH METASTASES BURDEN AND PREDICT PFS OF ANLOTINIB IN ADVANCED NSCLC

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Background: Activated circulating endothelial cells (aCECs) have been indicated as a potential biomarker for cancerous angiogenesis in varieties of malignancies. Furthermore, several studies have exhibited aCECs were related with progression-free survival (PFS) and overall survival (OS) in anti-angiogenesis therapy. Anlotinib is a TKI of VEGFR1/2/3, FGFR1-4, PDGFR α/β, and c-Kit. As a third-line and above treatment on advanced NSCLC, Anlotinib has shown an affirmatory efficacy in ALTER0303 controlled trial. Herein we investigated the connection between aCECs and PFS, OS and metastases burden in the trial. **Method:** Blood samples were collected at baseline (pre-therapeutically), the 7th, 15th, 21th, 42th, 63th day of Anlotinib or placebo. aCECs was measured by Flow Cytometry. Receiver-operating characteristics (ROC) analysis was used to determine a cutoff value of baseline aCECs counts to divide them into high and low groups. The predicting value of aCECs for PFS was investigated by univariate survival analysis. Chi-square test for baseline aCECs counts and patients' clinical characteristics before Anlotinib or placebo treatment was performed. **Result:** aCECs were obtained in 78 patients (Anlotinib n=49). No significant difference in baseline characteristics was found between two arms (P>0.05). High baseline aCECs count was statistically in connection with more metastatic lesions (>3) (c^2= 4.905,P=0.027). 49 Anlotinib treated patients were divided into 35 and 14 according to the ratio of minimal aCECs counts at every time point and baseline (aCECs min/baseline), as <1 and ≥1. Median follow-up was 8.6 months. Patients with min/baseline<1 had longer median PFS than ones with min/baseline>1 (193 vs.124 days, HR=0.439, 95%CI 0.211-0.912, P=0.023. shown in Table1). However, no significant relation between PFS and aCECs min/baseline was found in control arm.

Table 1.Comparison of Progression Rate in Various aCECs min/baseline

	N	Progression Rate %			Log Rank χ^2	P-value
		3 months	6 months	9 months		
aCECs min/baseline≥1	14	36.5	52.4	84.1	5.149	0.023
aCECs min/baseline<1	35	20.4	26.7	47.3		

Conclusion: Decreased aCECs during an initial period of Anlotinib therapy may predict longer PFS and baseline aCECs count may be related with the number of metastatic lesions.

Keywords: aCECs, Anlotinib, ALTER0303

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-085 A PHASE 2 TRIAL OF APATINIB IN ADVANCED NON-SQUAMOUS NSCLC: UPDATED DATA AND CLINICAL BENEFIT OF CONTINUING APATINIB AFTER INITIAL PROGRESSION

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Background: Apatinib exerts anti-tumor effects by selectively inhibiting VEGFR-2. A single-arm Phase 2 study of apatinib monotherapy in advanced non-squamous NSCLC patients showed promising response across multiple therapy lines (P3.02C-025, WCLC 2016 Abstracts). Here we report the updated efficacy and safety data, as well as the clinical benefit of continuing apatinib beyond initial progression. **Method:** Forty patients with previously heavily treated advanced non-squamous NSCLC were enrolled to receive apatinib until progression, unacceptable toxicity, withdrawal or death. After study discontinuation, apatinib monotherapy or combined therapy was allowed for patients on disease progression at the discretion of the investigators and under the consent of patients. **Result:** The cutoff date was March 12, 2017. The treatment duration of apatinib was 82 (43, 127) days with a mean dosage of 477.0 ± 85.3 mg/day. Thirty-eight patients were available for tumor response evaluation, and the best overall response rate (ORR) and disease control rate (DCR) were 21.1% and 76.3%, respectively. The median progression-free (PFS) and overall survival (OS) were 3.32 (95% CI, 2.37–4.86) and 9.26 (95% CI, 5.36–not estimable) months, respectively.

Common adverse events (AEs) were hand-foot-skin reaction (HFSR) (30.0%), proteinuria (27.5%), hypertension (17.5%) and aphthous stomatitis (22.5%). Severe AEs included Grade 3 HFSR (5%), hypertension (5%) and thrombocytopenia (5%). Results of preliminary subgroup analyses indicated that age, gender, PS score, treatment line and having a driver gene mutation had no significant effects on ORR, DCR and survival. After initial progression following apatinib treatment, 9 patients received apatinib alone or combined therapy with docetaxel, gefitinib or erlotinib (Table). One PR and 6 SD were achieved. Encouragingly, 8 patients had treatment duration over 4 months.

Table: Patients continued apatinib alone or combined therapy after progression

No.	Regimens after progression	Dose of apatinib (mg)	Best efficacy	Treatment duration (months)	Reason for discontinue treatment
1	Apatinib plus Docetaxel	500	PR	13.11	Second progression
2	Apatinib plus Gefitinib	250	SD	7.98	Lost to follow-up
3	Apatinib plus Gefitinib	375	SD	7.82	Death
4	Apatinib plus Gefitinib	500	SD	5.82	Lost to follow-up
5	Apatinib plus Erlotinib	500	SD	4.27	Lost to follow-up
6	Apatinib	375	SD	5.13	Second progression
7	Apatinib	500	NE	4.44	Second progression
8	Apatinib	250	SD	4.24	Death
9	Apatinib	500	NE	0.33	Death

Conclusion: This updated analysis further confirmed the efficacy and safety of apatinib for heavily treated advanced non-squamous NSCLC. Continuing apatinib monotherapy or combined therapy could bring clinical benefit.

Keywords: non-small cell lung cancer, Apatinib, Treatment beyond disease progression

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-086 BIOMARKER TESTING TRENDS AND TREATMENT PATTERNS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS IN THE UNITED STATES

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Background: The CAP/IASLC/AMP molecular testing guidelines recommend ALK and EGFR testing on patients with lung adenocarcinoma, regardless of clinical characteristics. While PD-L1 testing has recently become available, a potential challenge to implement this testing is limited tissue availability. NGS may address this issue but there are limited published data assessing the impact of PD-L1 testing on NSCLC biomarker testing and treatment patterns using large real-world data sources. The objective of this study is to describe real-world biomarker testing and treatment patterns in the United States (US). **Method:** Flatiron Health's database is a longitudinal, demographically and geographically diverse database containing EHR data. The database includes over 265 cancer clinics (~800 sites of care) representing more than 1.7 million active US cancer patients. Patients with ≥2 visits after Jan 1, 2011, ≥18 years of age, treated in first line (1L), and stage IIIB/IV NSCLC diagnosis from Jan 2012 - Mar 2017 were included in this analysis. Results were stratified by year of diagnosis (2012-2015 vs. 2016+). **Result:** Of 21,514 patients identified, the majority (80%) were diagnosed with de novo disease and 76% presented with non-squamous histology. PD-L1 testing rates were higher in those diagnosed in 2016+ compared to 2012-2015 (36% vs. 7%). A larger proportion of patients were tested for at least one biomarker in 2016+ (75%) vs. 2012-2015 (65%). The use of NGS also doubled (10% in 2012-2015 vs. 21% in 2016+) during this time period. For all patients, biomarker positivity rates varied by biomarker (PD-L1: 34%, EGFR: 17%, ALK: 4%, ROS1: 2%, KRAS: 30%) and by histology with the exception of PD-L1. The percentage of patients who initiated 1L systemic therapy, prior to receiving their first positive biomarker test results, ranged from 17% to 27% depending on the biomarker test. **Conclusion:** The introduction of PD-L1 testing has coincided with an increase in the proportion of patients being tested for a biomarker, as well as an increase in NGS. NGS has previously been shown to be associated with the longest turn-around time, and up to 27% of patients initiate systemic therapy prior to receiving positive biomarker test results. Additional research to understand the resource implications and clinical outcomes of initiating systemic therapy prior to test results (rather than delaying therapy) is underway.

Keywords: non-small cell lung cancer, Real world, biomarker testing

P3.01: ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.01-087 IMPACT FACTOR ANALYSIS FOR EFFICACY AND PROGNOSIS OF ANLOTINIB IN NSCLC AS THIRD-LINE TREATMENT: DATA FROM TRIAL ALTER 0303

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Background: Anlotinib hydrochloride is a novel TKI targeting the VEGFR, FGFR, PDGFR and c-Kit. With the capability of inhibiting the tumor angiogenesis and tumor cell itself, anlotinib had showed significantly improvement in OS (9.63 vs. 6.30 months, HR=0.68, 95%CI 0.54-0.87, p=0.0018) and PFS (5.37 vs. 1.40 months, HR=0.26, 95%CI 0.21-0.33, p<0.0001) in ALTER 0303 study for refractory cancer, a randomized, double-blind, placebo-controlled Phase III trial in China. Here, we report the main impact factors affecting the efficacy and prognosis of anlotinib based on the data from ALTER0303 to elucidate the most benefit population. **Method:** Analyzed data were collected from 294 patients that were enrolled in ALTER0303 trial and received anlotinib treatment between 4th March 2015 and 15th August 2016. The statistical analysis was conducted using SPSS19.0 software, in which the measuring and enumeration materials were described with Mean±SD and frequency/percentage respectively, Kaplan-Meier method was used for survival curves in survival analysis. Independent impact factors of OS and PFS were identified by univariate and multivariate analysis in Cox proportional hazards regression model (Significant level, α=0.05). **Result:** Several factors were discovered to be associated with the efficacy of Anlotinib treatment. The impact factors were presented in Tab1.

Tab1. Impact factors for PFS and OS analyzed by Cox proportional hazards regression model

	Independent risk factor	Independent protective factor
PFS	Ratio of granulocytes to lymphocytes at PD (HR=1.07, 95%CI 1.041-1.100, p<0.0001) Elevated ALP level (HR=1.553, 95%CI 1.142-2.112, p=0.005) Baseline sum of longest diameters of target lesions (HR=1.004, 95%CI 1.001-1.006, p=0.007)	Elevated TSH level (HR= 0.555, 95%CI 0.422-0.730, p<0.0001) Hypercholesteremia (HR=0.720, 95%CI 0.534-0.971, p=0.031) Hypertension (HR=0.482, 95%CI 0.370-0.628, p<0.0001) Hand-foot skin reaction (HR=0.489, 95%CI 0.373- 0.643, p<0.0001) Elevated LDL level (HR=0.630, 95%CI 0.437-0.909, p=0.014) Age (HR=0.987, 95%CI 0.975-0.999, p=0.039)
OS	Ratio of granulocytes to lymphocytes at PD (HR=1.116, 95%CI 1.081-1.151, p<0.0001) Baseline sum of longest diameters of target lesions (HR=1.006, 95%CI 1.003-1.008, p<0.0001) ECOG PS≥2 at PD (HR=2.245, 95%CI 1.704-3.508, p<0.0001)	Elevated TSH level (HR=0.725, 95%CI 0.524- 1.005, p=0.053) Hypertriglyceridemia (HR=0.601, 95%CI 0.440-0.821, p<0.0001) Rash (HR=0.581, 95%CI 0.369-0.916, p=0.019) Female (HR=0.713, 95%CI 0.533-0.953, p=0.022)

Conclusion: This analysis explored the possible impact factors of PFS and OS in Anlotinib treatment. Moreover, we provide real data for the prediction of Anlotinib efficacy and most benefit population through the baseline characteristics and variety of clinical index. However, further analysis in the larger scale study is still looking forward.

Keywords: NSCLC, Anlotinib, third-line treatment

P3.01-088 MOLECULAR TESTING AND FIRST-LINE TREATMENT OF PATIENTS WITH NSCLC. FIRST RESULTS FROM THE GERMAN CRISP STUDY (AIO-TRK-0315)

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Background: Treatment of non-small cell lung cancer (NSCLC) is quickly evolving. New biomarkers and targeted agents have been approved at a rapid pace. It is of high interest to patients, physicians and reimbursement institutions to investigate molecular testing and subsequent treatment decisions in routine practice. **Method:** The prospective, national clinical research platform CRISP recruits patients in up to 150 cancer centres in all therapeutic sectors in Germany. Patients will be followed until death or for a maximum of 3 years. Raw data from 717 patients recruited by 78 centers by April 03rd was analysed regarding molecular testing and 1st-line treatment. **Result:** Data on histology was available for 635 patients, 71% non-squamous carcinoma (nsqc), 18% squamous carcinoma (sqc). Median age was 67 years and 61% of patients were male. 11% of patients were never smokers. In patients with nsqc (n=507) molecular test rates for EGFR, ALK, ROS-1 and PD-L1 were 69%, 65%, 51% and 26%, respectively. The overall PD-L1 test rate (nsqc & sqc) was 21% in 2016 and has been 27% so far in 2017. Of patients for whom test results were available at time of analysis 58% (n=87) were PD-L1 positive (nsqc 60%, n=76 and sqc 46%, n=11). An EGFR alteration was detected in 16% (n=57), an ALK alteration in 8% (n=25), and a ROS-1 alteration in 4% (n=9) of nsqc patients. Overall, 53% of patients received a carboplatin-based, 22% a cisplatin-based, and 7% a platin-free chemotherapy, while 14% received targeted and 4% other (experimental) therapies. Patients with EGFR alterations (n=57) were most frequently treated with 1st-line afatinib (33%), erlotinib (12%), or gefitinib (11%). Patients with ALK alterations (n=25) were most frequently treated with 1st-line crizotinib (48%). Patients with PD-L1 positive tumours were most frequently treated with platinum based doublet therapies (carboplatin combined with gemcitabine/taxane/pemetrexed or cisplatin combined with pemetrexed) or with pembrolizumab. The use of 1st-line pembrolizumab increased from 7% to 16% from 2016 to 2017. An update with data collected until October 2017 (>1,100 patients expected) will be presented. **Conclusion:** For the first time, CRISP presents real life data from all therapeutic sectors in Germany. Patients are frequently tested for molecular alterations and more than half of the patients with molecular alterations can start 1st-line treatment with a targeted therapy. Supported by AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer and Roche.

Keywords: Cohort Study, NSCLC, Biomarkers

P3.02-001 CLINICAL SIGNIFICANCE OF PLASMA EPSTEIN-BARR VIRUS DNA IN PULMONARY LYMPHOEPITHELIOMA-LIKE CARCINOMA (LELC) PATIENTS

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Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small-cell lung cancer (NSCLC) and an Epstein-Barr virus (EBV)-associated epithelial neoplasm. We investigated the clinical significance of plasma concentrations of EBV DNA in pulmonary LELC patients. **Method:** Two independent sets of plasma samples from a total of 429 patients with pulmonary LELC patients (287 initial and 142 confirmatory) were available for EBV DNA determination. Plasma samples from the patients were subjected to a real-time quantitative polymerase chain reaction (qPCR) before treatment and three months after radical resection. Cutoff points were determined for pretreatment plasma EBV DNA (low, < 4000 copies/mL; high, ≥ 4000 copies/mL) on the basis of a measure of heterogeneity with the log-rank test statistic with respect to overall survival. Kaplan-Meier method and Cox regression were used to evaluate the relationship between plasma EBV DNA concentrations and clinical outcome. Among advanced stage pulmonary LELC patients who underwent sequential blood draws, we evaluated the relationship between change in disease status and change in EBV DNA concentrations using nonparametric tests. **Result:** High EBV DNA concentration was associated with poor OS in the initial, confirmatory, and combined data sets (combined data set: hazard ratio (HR), 3.67; 95% CI, 2.72 to 4.38; P < 0.001). These findings persisted after multivariable adjustment. Compared with low EBV DNA concentration, high EBV DNA concentration was associated with poor OS in patients with any stage. High EBV DNA concentration was also associated with poor disease-free survival (DFS) in patients with stage I/II disease. Patients with persistently detectable plasma EBV DNA had significantly poor OS (P < 0.001) and DFS (P < 0.001) than patients with undetectable EBV DNA three months after radical resection. In patients who underwent sequential evaluation of EBV DNA, an association was identified between an increase in EBV DNA concentration and a poor response to treatment and disease progression of pulmonary LELC. **Conclusion:** High baseline EBV DNA concentration is an independent poor prognostic marker in pulmonary LELC patients. These results should be confirmed in larger prospective trials.

Keywords: lung cancer, lymphoepithelioma-like carcinoma, Epstein-Barr Virus DNA

P3.02-002 LIQUID AND SOLID REBIOPSIES IN EGFR-MUTATED NSCLC PATIENTS

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Background: Treatment of EGFR-mutated NSCLC patients with acquired resistance to EGFR tyrosine kinase inhibitors (TKI) relies on identification of the mechanism of resistance. **Method:** We performed a retrospective multicentric study in order to investigate use and results of liquid (circulating free DNA) and solid rebiopsies in routine practice. **Result:** We included 95 EGFR-mutated NSCLC patients with at least one rebiopsy after treatment with EGFR TKI (mostly 1st generation TKI). 87 solid rebiopsies and 71 liquid rebiopsies were performed. The number of liquid biopsies increased over time, from 1/y (6,6% of all rebiopsies in 2014) to 53/y (70,6% of all rebiopsies in 2016). The proportion of liquid biopsies increased with the number of rebiopsies per patient, from 35,5% for the first rebiopsy to 83,3% for the third rebiopsy. The rebiopsy identified a mechanism of acquired resistance in 48 patients (50,5%), including 43 patients with a T790M mutation (45,2%), 2 patients (2,1%) with MET amplification, 1 patient (1%) with small cell lung cancer transformation, 1 patient (1%) with a C797S mutation and 1 patient (1%) with a KRAS mutation. The initial EGFR mutation was found in 74 solid rebiopsies (85%) and 43 liquid rebiopsies (60%). The T790M mutation was found in 32 solid rebiopsies (36,8%) and 18 liquid rebiopsies (25,3%). Among 44 patients having both liquid and solid rebiopsies performed at the same time, an EGFR mutation was found by both techniques in 26 cases (59,1%) and the overall concordance was 88,6%. Analysis of cerebrospinal fluid was positive in 10 patients (100%) for the initial EGFR mutation and 1 patient (10%) for the T790M mutation. A T790M mutation was identified in 37,3% of all first rebiopsies. Repeated rebiopsies when the first biopsy was negative identified the T790M mutation in 29,6% of cases. **Conclusion:** In our series representative of daily practice, rebiopsies of EGFR-mutated NSCLC patients with acquired resistance to EGFR TKI identified a mechanism of resistance in half of the cases. Repeating rebiopsies increased the chance of detecting a T790M mutation.

Keywords: T790M, Rebiopsies, EGFR

P3.02-003 TISSUE AND SERUM LEVELS OF GALECTIN-3 IN NSCLC PATIENTS

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Background: Galectin-3 is a β-galactoside binding lectin, which is associated with cell proliferation, cell adhesion, apoptosis, angiogenesis and metastasis in several types of malignancies. However, the role of galectin-3 in the prognosis of lung cancer remains to be elucidated. In this study, we examined whether tissue expression and serum level of galectin-3 could serve as a prognostic marker in NSCLC. **Method:** Galectin-3 expression was analyzed by immunohistochemistry for 42 NSCLC patients who had undergone the radical surgery between 2014 and 2016. Serum galectin-3 level was assessed before surgery and 1 month after surgery by the enzyme-linked immunosorbent assay method. **Result:** Galectin-3 expression was observed in 14 patients (33.3%), and significantly associated with the incidence of recurrences (p<0.001) and the relapse-free survival time (p<0.001). Serum galectin-3 level was not reduced after radical resection, and there was no significant correlation between tissue expression and serum level of galectin-3. **Conclusion:** These data suggest that galectin-3 expression on tumor cells would serve as a prognostic marker in NSCLC, but serum galectin-3 level has no prognostic role on recurrence.

Keywords: Galectin-3, NSCLC

P3.02-004 ANALYSIS OF MET IN LIQUID BIOPSY AND TISSUE BIOPSY IN PATIENTS WITH ADVANCED NSCLC: INCIDENCE AND PATTERN.

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Background: MET pathway is dysregulated in several cancers, having three types of alterations: overexpression, amplification and mutation. MET amplification has been reported in 2-4% of NSCLC while MET exon 14 skipping mutation has been found in 3-4% of lung adenocarcinoma. Increased MET expression is associated with higher malignancy, and acts as a negative prognostic factor. To date, several MET inhibitors are in development. Hence, the importance of understanding MET biology, its incidence, patterns of appearance, and which type of genomic abnormality. Is MET a trunchal genomic abnormality or does it appear as a result of mechanism of resistance of tumor cells once exposed to therapeutic agents? In the past, MET inhibitors have failed to improve OS in clinical trials; lack of benefit from this approach was the fact that there was no standard method for detecting MET related anomalies that allowed an adequate patient (pt) selection. **Method:** A search for MET alterations was performed in a retrospective analysis from November 2014 until May 2017. A total of 142 liquid biopsies (LBx) from pts with advanced NSCLC using NGS were identified. Once pts with a MET genomic alteration were identified by LBx, we proceed to review their initial tumor biopsy (TBx) genetic analyses and assess for the presence of MET alterations. Data regarding histologic subtypes, therapy received in each case, and timing of LBx analysis were collected. **Result:** A total of 142 LBx were identified in our cohort of patients with advanced NSCLC from November 2014 until May 2017. These samples came from 127 pts; 20 pts (15.7%) had MET alterations identified by LBx. Characteristics of these 20 pts were: median age was 72 (range, 62-85); 15 pts (75%) were females; all patients had adenocarcinoma histology. Genomics alterations in LBx were distributed as: 5 amplifications and 15 mutations. Genetic analyses from the TBx of these 20 pts done at initial diagnosis were reviewed. There were 8 pts who had TBx and LBx done at the same time and at initial diagnosis; only 2 pts out of these 8 had MET alterations in both tests (amplifications). The other 6 pts (with both TBx and LBx done simultaneously) had MET alterations identified only by LBx despite other genetic abnormalities concordance found between TBx and LBx in 5/6 pts. In these pts, median number of alterations identified by LBx and TBx were 7 and 0.5, respectively. There were 12 pts who had LBx done after progression of disease. All these pts had MET alterations identified in LBx however, none of them had MET genomic abnormalities in their TBx at initial diagnosis. One pt who had MET exon 14 skipping mutation in LBx (at progression of disease) did not have TBx genetic analysis due to insufficient tumor tissue. **Conclusion:** In this pt sample, we were able to identify more sensitivity from LBx than TBx for detection of MET alteration at initial diagnosis when both tests were done simultaneously. Our pts had metastatic disease with lesions outside the lung parenchyma. This will increase the diagnostic yield of LBx. Also, tumor heterogeneity plays a major role for discrepancies between TBx and LBx. The median number of genomic alterations identified by LBx was also higher than the one reported by TBx. Interestingly, 12 pts with MET alterations at progression of disease did not have these anomalies at TBx (initial diagnosis). Many questions remain unanswered. A prospective clinical trial using NGS in both tissue and blood at initial diagnosis will help us to identify and understand the biology of MET. It seems that LBx could be a complimentary tool at initial assessment of pt with metastatic NSCLC.

Keywords: Genomics, MET alteration, lung cancer

P3.02-005 APPLICABILITY OF ION TORRENT COLON AND LUNG SEQUENCING PANEL ON CIRCULATING CELL-FREE DNA

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Background: Identifying tumor-specific mutations in plasma from cancer patients serves as a non-invasive supplement to taking biopsies. Targeted sequencing of the circulating cell-free DNA (cfDNA) is an efficient method, for screening for a number of relevant mutations. Different approaches of targeted sequencing have been optimised for clinical use on FFPE, e.g. the Ion Torrent Colon and Lung panel. The size of DNA extracted from FFPE tissue is comparable with that from cfDNA. We therefore investigated the performance of the clinically relevant Ion Torrent Colon and Lung panel on cfDNA. **Method:** We used the Horizon multiplex cfDNA standard with eight known mutations at concentrations of 5 % (5-6.3 %), 1 % (1-1.3 %) , 0.1 % (0.1-0.13 %) and no mutations (wild type), respectively, to test the reproducibility of the panel. We obtained plasma from healthy donors from the danish Blood Bank to set a baseline for the panel. Lastly, the panel was tested on 52 patient samples. Patient plasma samples are from a previously collected cohort of EGFR wild-type non-small cell lung cancer patients (: NCT02043002) All samples were sequenced using the Ion Torrent Oncomine Solid Tumor DNA kit (Colon and Lung panel) from Thermo Fisher. Sample preparation was performed using the Ion Torrent Chef and sequencing was performed on the Personal Genome Machine (PGM) system. Data was analyzed using the Torrent Suite software, and variants called by Ion Reporter. **Result:** No somatic mutations were identified in neither the Horizon multiplex wild type nor the cfDNA from healthy donors. The Horizon multiplex samples were sequenced three times in different runs, to test the reproducibility of the panel. For the 5 % sample all mutations were detected in all runs. For the 1 % sample the four mutations at 1.3 % where detected in all runs, while two out of three runs missed one mutation at 1 %. In both cases the mutation could be identified by visualization of the reads, but was not called. For the 0.1 % sample, no mutations were detected. After finishing the validation the panel was used for sequencing patient samples. Of the 52 samples, 47 were successfully sequenced (90 %), and COSMIC-verified mutations were identified in 32 samples. **Conclusion:** The panel reliably and reproducibly detects mutations down to 1.3 %. Mutations present in lower concentration can also be detected, but for reliable detection higher coverage is needed. Sequencing was successfully performed on a range of patient samples.

Keywords: sequencing, cfDNA, mutations

P3.02-006 MONITORING GENETIC ALTERATIONS IN PLASMA DURING ANTI-CANCER TREATMENT IN ADVANCED NSCLC (MAGIC1-VALIDATION COHORT: PRELIMINARY RESULTS)

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Background: No molecular markers are available so far to predict the efficacy of treatment and to monitor outcome in patients with EGFR-ALK-ROS1 wild-type advanced non-small cell lung cancer (wtNSCLC). Detection of genetic alterations in plasma may allow to follow biological effects of treatment without invasive procedures. Aim of this study (validation cohort) is to evaluate the detection rate and to monitor tumor-associated mutations in plasma during treatment in wtNSCLC. **Method:** Advanced wtNSCLCs referring to our Institution and undergoing anti-cancer systemic treatment are prospectively enrolled. Tissue genetic alterations are screened by Sequenom massarray platform (Diatech) or next-generation sequencing (NGS) (Illumina). Plasma samples are collected at baseline, after the first cycle of treatment, at first radiological restaging and at radiological progression. DNA is extracted and analyzed for genetic alterations previously detected in tissue by using droplet digital PCR (ddPCR,Biorad) or real-time PCR (Diatech). Semi-quantitative index of fractional abundancy of mutated allele is used. Primary end-point of MAGIC1 is to assess the sensitivity of technologies to detect genetic alterations in plasma (target: 60% within +/-15%). **Result:** Since January 2017 we have prospectively enrolled 56 patients treated with platinum-based chemotherapy (28), single-agent chemotherapy (9) or immunotherapy (18). 21 tissue samples have been analyzed (by Sequenom) in order to detect mutations in *EGFR, HER2, KRAS, NRAS, BRAF, ALK, MET, PI3K, DDR2*: ten *KRAS* mutation (including 3 G12D, 4 G12C, 2 G13D, 1 G12A mutations), one *BRAF* V600E and three EGFR exon 20 mutations were detected. At baseline, a concordance plasma/tissue was confirmed in 5/10 *KRAS*, 0/1 exon 20 *EGFR*, and 1/1 *BRAF* mutations. Longitudinal exploratory analysis was performed in 8 patients and 4/5 mutations found at baseline were not detected at subsequent evaluations in patients not experiencing systemic progression. The only patient with persistent KRAS mutation in serial plasma samples experienced radiological progression. In 1/5 patients negative at baseline, one sub-clonal KRAS mutation emerged at the third evaluation when progression was recorded. NGS tissue analysis is ongoing and ddPCR will be used to detect and monitor other genetic alterations such as *STK11/LKB1*, *TP53*, *AKT mutations*. The validation cohort will include 68 patients. MAGIC2 will include an expansion cohort to monitor genetic alterations in plasma during immunotherapy and assess timing of modifications in plasma according to clinical benefit. **Conclusion:** Preliminary data indicate the feasibility of detecting *KRAS* and *BRAF* mutations in plasma in clinical practice and potential usefulness in tracking biological changes in tumors.

Keywords: liquid biopsy, tumor burden, non-oncogene addicted NSCLC

P3.02-007 CIRCULATING MIRNAS AS PROGNOSTIC BIOMARKERS IN RESECTED EARLY-STAGES NON-SMALL-CELL LUNG CANCER

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Background: Non small cell lung cancer (NSCLC) is the primary cause of cancer-related death, and 5-years survival rate remains below 16% mainly because of disseminated disease, also in fully resected early stages. Biomarkers identifying patients with a higher risk of relapse could be very useful. Circulating microRNAs (miRNAs), represent promising markers in this setting. **Method:** A case series of 182 resected early stage (IA-IIIA) NSCLC, of which 99 adenocarcinoma (ADC) and 83 squamous cell carcinoma (SCC), was analyzed. Peripheral blood samples were collected from each patient before surgical resection and serum was obtained after centrifugation and stored at -80°C until miRNA extraction. A panel of 84 circulating miRNAs was analyzed by Real Time PCR. Data were normalized by means of an external spike in, cel-miR-39, and the mean of two most stable endogenous housekeeping chosen separately for ADC and SCC samples. miRNA expression was analyzed in relation to disease-free survival (DFS) through Cox regression model. Results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). **Result:** Of the 99 ADC, 45 (45.5%) had a relapse during the follow-up whereas among the 83 SCC patients, 50 relapses (60.2%) were observed. The minimum follow-up time was three years for both groups of patients. In the group of ADC patients, stage was significantly associated with DFS (HR stage II-IIIA vs stage I = 4.94 , 95% CI [2.71 - 9.02]). Multiple statistical analysis methods were used to analyze miRNA expression data. At univariate analysis, two miRNAs (miR-222-3p and miR-22-3p) were significantly associated with time to relapse (p = 0.033 and p = 0.041, respectively). The significance was not maintained after adjustment for multiple testing. In the group of SCC patients, stage of disease was significantly associated with DFS (HR stage II-IIIA vs stage I = 3.31, 95% CI [1.74 - 6.33]). Five miRNAs (let-7a-5p, miR-126-3p, miR-26a-5p, miR-130b-3p, miR-21-5p) were found significantly associated with DFS even after adjustment for multiple testing false discovery rate q-value <0.001. **Conclusion:** Pre-surgery circulating levels of let-7a-5p, miR-126-3p, miR-26a-5p, miR-130b-3p and miR-21-5p seem to be significantly correlated with prognosis in resected early stage SCC patients.

Keywords: Early-stage NSCLC, prognostic factor, miRNA

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-008 NON-INVASIVE DIAGNOSIS OF SOLITARY PULMONARY NODULES USING HIGH-THROUGHPUT TARGETED DNA METHYLATION SEQUENCING OF CIRCULATING TUMOR DNA

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Background: It remains a great challenge to differentiate solitary pulmonary nodules which might cause excessive medical care and unnecessary psychological burden. Disadvantages of previous image-based or invasive methods call for better diagnostic tools . **Method:** Based on several cohorts, we performed methylation profiling by high throughput bisulfite DNA sequencing in tissue samples to learn methylation patterns that differentiate cancerous from benign lesions by in-depth data mining. Then we filtered out methylation patterns exhibiting high background in cfDNA for plasma sample classification. Notably, given the usual low amount of ctDNA in plasma, we developed an ultra-sensitive library preparation method (AnchorIRIS™) to perform targeted bisulfite DNA sequencing from as low as 1 ng of cell free DNA (cfDNA) or 1 mL of plasma. **Result:** In the training set (n = 230) which includes 129 malignant specimens with different subtypes (invasive adenocarcinoma, MIA, AIS, squamous carcinoma, small cell and large cell lung cancer) as well as 101 benign specimens in different categories (hamartoma, granuloma/tuberculosis, inflammation and infections), we were able to achieve a preliminary sensitivity of 94.3% ± 4.3% for identification of maglignacies, with a preliminary specificity of 93.6% ± 4.9% against all benign specimens. From an independent validation set of 145 plasma samples, this assay obtained a preliminary sensitivity of 78.5% and a preliminary specificity of 83.3% for differentiating patients with malignant tumor (n = 79) from patients with benign lesions and asymptomatic normal individuals (n = 66). Specifically, our assay is demonstrated to be highly sensitive towards early-stage lung cancer detection, with a preliminary sensitivity of 71.1% in 38 patients with stage Ia lung cancer and 87.5% in 16 patients with stage Ib lung cancer. To further confirm the clinical application of this model, an additional validation study was carried out in an independent center. Our assay obtained an overall sensitivity of 89.2% for 37 malignant tissue samples, particularly with a sensitivity of 100% for adenocarcinoma, and an overall specificity of 85.7% for 21 benign tissue samples. For plasma samples, our assay achieved a sensitivity and a specificity of 80% and 66.7% respectively for 20 malignant and 3 benign samples. **Conclusion:** We have developed a highly sensitive blood based non-invasive diagnostic assay for differentiation of solitary pulmonary nodules, which can aid clinical decisions for patients with a CT scan positive for lung nodules. To the best of our knowledge, this is the first study to examine the diagnostic value of high throughput targeted DNA methylation sequencing for early stage lung cancer.

Keywords: methylation signatures, solitary pulmonary nodules, High throughput sequencing of circulating tumor DNA

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-009 MUTATION DETECTION IN CELL-FREE DNA FROM PATIENTS WITH LUNG ADENOCARCINOMA BY NEXT-GENERATION SEQUENCING

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Background: Cell-free DNA (cfDNA) is an alternative non-invasive source to assess gene mutations which are necessary for precision medicine in cancer patients. Next-generation sequencing (NGS) can list multiple gene mutations in single testing and require low input of DNA. We evaluated NGS application to detect cfDNA mutations in lung adenocarcinoma (LAC). **Method:** Retrospectively, cfDNA was isolated from 12 LAC patients in Hiroshima University Hospital (first group). Then another cfDNA was isolated from 30 LAC patients (second group). Ion PGM AmpliSeq system was applied using two panels, Cancer Hotspot (50 genes) for first group and Colon and Lung Cancer Research (22 genes) for second group. Variants were manually reviewed. EGFR mutation in cfDNA and tumor DNA (tDNA) were matched. EGFR mutations in tDNA, derived from either cytology or biopsy specimen, were previously analysed using PNA-clamp PCR. **Result:** Stage were 1 IIA, 1 IIIA and 10 IV in first group and 3 IA, 7 IB, 3 IIIA and 17 IV in second group. Mean coverage in first and second group were 863 and 2915, respectively. Mutation were found in TP53 (33/42), EGFR (8/42), STK11 (5/42), PTEN (3/42), ERBB4 (2/42), SMAD4 (2/42), MET (2/42), KDR (8/12), APC (4/12), RB1 (2/12), GNAQ (1/12), KIT (1/12), MLH1 (1/12), RET (2/12), VHL (1/12), KRAS (1/42). KRAS (A146V) mutated in one patient with no EGFR mutation detected in tDNA. In first group, EGFR mutations from tDNA were identified in 5 of 12 patients. Concordant EGFR mutations between cfDNA and tDNA were found in 1 of 5 patients (Exon 19 deletion, Allele Frequency, AF 9.1% (11/121)). In second group, EGFR mutations from tDNA were identified in 15 of 30 patients. Concordant EGFR mutations between cfDNA and tDNA were found in 7 of 15 patients. AF in EGFR exon 19 deletion were 0.1% (3/2424), 0.2% (6/2973), 8% (272/3394) and 24% (470/1960) and in exon 21 mutations were 2% (61/3884), 0.3% (5/1702) and 57% (1711/3025). The sensitivity and specificity in first and second group were 25%, 100% and 40%, 100%, respectively. In both group, patients whose EGFR mutations were detected in both tDNA and cfDNA were all in stage IV. **Conclusion:** NGS using cfDNA is less invasive method to detect various mutations simultaneously, especially in advance stage. EGFR mutation detection in cfDNA by NGS achieved a high specificity. Reducing target genes or deep sequencing may increase the sensitivity of detecting mutations.

Keywords: lung adenocarcinoma, cell-free DNA, next-generation sequencing

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-010 SIGNIFICANT INCREASE OF BLOOD EXTRACELLULAR VESICLES IN PULMONARY VEIN AS POTENTIAL PROGNOSTIC BIOMARKER FOR LUNG CANCER PATIENTS

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Background: Exracellular vesicles(EVs) are endosome-derived nano-size (30-1000 nm) vesicles released from many cell types including cancer cells. Previous researches have demonstrated that the level of EVs is increased in cancer patients than healthy controls. This study was conducted to evaluate the variation of EVs-count in the proximal tumor-drainage vessel and peripheral vessels during surgery for VX2 rabbit lung cancer model and primary lung cancer patients **Method:** A total of 6 rabbits were used in this study (3 in normal group, 31 in lung cancer group). Rabbit VX2 lung cancer model was made by real-time computed tomographic guided inoculation of VX2 cancer. Two weeks after injection, blood was collected from rabbit peripheral vessel and pulmonary vein (proximal tumor-drainage vein). A total of 3 healthy controls and 31 patients with primary lung cancer who had pT2aN0 (stage IB) and underwent lobectomy were selected. For each patient, 3 ml of blood was sampled from the radial artery (peripheral vessel) before surgery and from pulmonary vein of the primary tumor site (proximal tumor-drainage vein) during surgical procedure. Healthy controls blood were collected from peripheral vessels. EVs were isolated by serial centrifugation followed by ExoQuick™ and quantitative analysis was performed by NanoSight and western blotting. **Result:** EVs-count was not different in normal rabbit model according to blood sampling sites (peripheral vessel: 2.78 x 10^8 particles/ml, pulmonary vessel: 2.64 x 10^8; p = 0.104). However, in rabbit lung cancer model, EVs were increased by 623.5% in peripheral vessels (1.73 x 10^9 particles/ml; p = 0.003) and 787.9% in proximal tumor-drainage vein (2.08 x 10^9 particles/ml; p = 0.001) comparing to those of normal rabbits. Moreover, we confirmed that EVs-count in VX2 lung cancer model was increased by 120.0% (p = 0.05) on the proximal tumor-drainage vein than peripheral vessel. In human blood samples, peripheral blood derived EVs were increased by 181.6% in lung cancer patient in comparison with healthy controls (2.44 x 10^8 particles/ml in healthy control, 4.43 x 10^8 particles/ml in lung cancer patients; p = 0.04). And, EVs were significantly increased by 700.8%

in pulmonary vein of the primary tumor site (1.71 x 10^9 particles/ml; p = 0.0001) comparing to peripheral vessels in lung cancer patients **Conclusion:** The increase of EVs was more prominent in tumor-drainage veins than peripheral vessels in animal cancer models and lung cancer patients. We suggest that increase of EVs from tumor-drainage veins may provide more relevant prognostic information of the lung cancer patients comparing to those from peripheral vessel after surgery.

Keywords: Animal lung cancer model, Extracellular Vesicle, lung cancer

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P3.02-011 A PROSPECTIVE STUDY OF SERIAL CIRCULATING TUMOR DNA ASSESSMENT IN DETECTING RECURRENCE OF RESECTED EARLY-STAGE LUNG CANCER

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Background: In advanced non-small cell lung cancer (NSCLC), circulating tumor DNA (ctDNA) can be used to identify clinically actionable mutations when tissue is insufficient or unobtainable for genotyping. In early-stage NSCLC, the persistence of ctDNA after complete resection may suggest the presence of minimal residual disease and predict an increased risk of recurrence; however, data on the longitudinal use of ctDNA is very limited. The aim of this study is to assess the clinical feasibility of ctDNA assessment for the prediction of lung cancer recurrence following surgical resection. **Method:** Patients undergoing curative-intent surgery for NSCLC were prospectively enrolled. Peripheral blood samples were collected at pre-specified time points immediately prior to surgery and 2-3 weeks after surgery. Plasma cell-free DNA samples were analyzed with a novel 21-gene Digital Sequencing NGS panel (Guardant Health, Inc.) with a theoretical genomic sensitivity of > 90% for NSCLC. For each patient, the identities and quantities of somatic alterations identified in ctDNA were correlated to clinical outcomes. **Result:** Of the 55 pair-matched patients, 33 were evaluable at the time of abstract submission. The median age was 61 (18 men). The histologic type was adenocarcinoma in 19 (58%), squamous cell carcinoma in 14 (42%), and small cell lung cancer in 2 (6%). The pathologic stage was I in 20 (61%), II in 3 (9%), and IIIA in 10 (30%). Median clinical follow up was 13 months. Of the 4 patients with detectable post-operative ctDNA, 3 recurred within the follow-up period. Of the 8 total recurrences observed, the most common site was the brain (4) and lung (3). One of 4 adenocarcinoma recurrences, 1 of 2 squamous cell carcinoma recurrences, and 1 of 2 small cell recurrences were associated with detectable post-operative ctDNA. By stage, post-operative ctDNA was detected in 1 of 1 stage II and 3 of 7 stage IIIA patients. Recurrences not associated with detectable post-operative ctDNA were enriched in oligometastatic recurrence (4 of 5 unpredicted recurrences were in isolated lymph nodes or the brain). **Conclusion:** In this small pilot cohort, ctDNA detected at 2 weeks post resection was associated with recurrence (RR 9.38, p=0.038), while the absence of detectable ctDNA was not significantly associated with lack of recurrence (RR 0.65, p=0.12). Oligometastatic disease, especially in the brain, was a primary risk factor for ctDNA-negative recurrence. These findings establish proof of concept for the use of ctDNA diagnostics as a risk stratification tool in resected lung cancer.

Keywords: Circulating Tumor DNA, Recurrence detection, Early-stage lung cancer

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P3.02-012 LIQUID BASED CYTOLOGY (LBC) SPECIMENS WERE USEFUL FOR EGFR MUTATION TEST

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Background: Reliable EGFR mutation testing techniques are required to identify eligible patients for EGFR-TKI treatment. Nowadays, surgically resected tissues or biopsy specimens are mainly used for the molecular testing. However, the biopsy samples sometimes have a certain limitation and so the cytology specimens are chosen for EGFR testing instead. Plasma sample has also become an option in EGFR-TKI resistant cases in which often have difficulties to obtain the inadequate tumor yield. In this study, we evaluated the feasibilities of using cytology samples and plasma specimens the EGFR molecular testing. **Method:** 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 references. The feasibilities of both cytology and plasma specimen were evaluated comparing the results with the tissue samples. **Result:**

EGFR mutation rate of tissue, plasma and LBC			
	Tissue	**Plasma**	**LBC**
EGFR mutation +	18	9	14
EGFR mutation -	42	51	43
Invalid	0	0	3
Total	60	60	60
Positive rate (%)	30.0	15.0	23.3

One-hundred seven patients were registered to this study. 60 patients were enrolled to this study. EGFR mutation rates in tissue, cytology, and plasma were 30.0, 23.3 and 15.0 %, respectively. Concordance analysis was performed comparing cytology specimens and plasma specimens to the tissue samples. Overall concordance EGFR mutation status was 85.0 and 81.7%, respectively. A total 7 cytology specimens had discordances and 3 were invalid results. For plasma samples, discordants were found in11 samples but no invalids. **Conclusion:** Plasma was easy to obtain sample, but rate of detection was low. If a cancer cell is detected enough, LBC is useful for the examination for EGFR. Preservation of sample is easy, and re-useful for the examination, repeatedly.

Keywords: LBC, lung cancer, EGFR mutation

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P3.02-013 PROGNOSTIC ROLE OF CIRCULATING TUMOR DNA (CTDNA) AND IMMUNE CELL BIOMARKERS IN NON-SMALL CELL LUNG CANCER (NSCLC)

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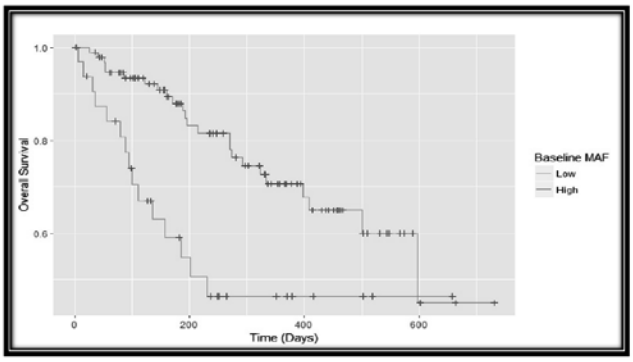
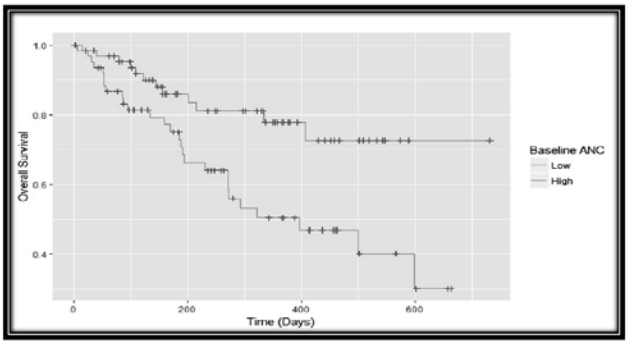
Background: Peripheral blood biomarkers can provide valuable information in a relatively non-invasive manner. In solid tumors, it has been suggested that ctDNA mutant allele frequency (MAF) and immune cell counts from peripheral blood complete blood count (CBC) at baseline may be associated with survival outcome. Here, we investigated the role of ctDNA MAF and immune cells as prognostic biomarkers that may predict overall survival in patients with NSCLC. **Method:** A retrospective cohort of 128 patients with ctDNA sample testing performed by ctDNA NGS test (Guardant360) were selected. ctDNA MAF of the dominant clone was collected. CBC's drawn within a 1-2 week window (baseline) of ctDNA were reported for absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), neutrophil lymphocyte ratio (NLR) and platelet count. Platelets and MAF were analyzed by quartiles (lower 75% vs highest 25%). Survival analyses and Cox regression analyses were performed on these variables. **Result:** A significant association was found for ANC (hazard ratio (HR) = 1.17, p<0.001), AMC (HR=1.98, p=0.037), MAF (HR=2.53, p=0.005), NLR>5(HR=2.98, p<0.001), and platelet counts (HR=2.49, p=0.006) with overall survival (OS), but not ALC. In multivariate analyses adjusting for clinical variables including age, sex, smoking status, histology, disease stage, number of prior lines of treatment, prior radiation, history of other cancers and ALK/EGFR mutation status, ANC remained as an independent predictor of OS(HR= 1.19, p<0.001).



MAF and overall survival- [HR = 2.53, 95% CI: [1.32, 4.85], P = 0.005]



ANC and overall survival- [HR = 1.17, 95% CI: [1.08, 1.26], P < 0.001]

Conclusion: Higher ANC, AMC, NLR, platelet counts and MAF were associated with poor overall survival. Further studies are required to validate our findings in patients with NSCLC.

Keywords: ctDNA, MAF, CBC

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P3.02-014 AMPLICON-BASED NEXT-GENERATION SEQUENCING (NGS) OF PLASMA CELL-FREE DNA (CFDNA) FOR DETECTION OF DRIVER AND RESISTANCE MUTATIONS IN NSCLC

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Background: While several studies have evaluated hybrid-capture NGS for cfDNA genotyping, amplicon-based NGS is an attractive alternative with the potential to be faster and less expensive. We performed a blinded evaluation of this approach for the characterization and monitoring of the molecular profile of advanced NSCLC during genotype-directed therapy. **Method:** Plasma samples from patients with advanced NSCLC and a known targetable genotype (*EGFR*, *BRAF*, *MET*, *HER2* mutations; *ALK*, *ROS1* rearrangements) were collected and analyzed, blinded to tumor genotype, with IRB approval. Up to 4 specimens were collected for each patient: baseline, initial 2 follow-ups, and progression. Plasma NGS was performed using enhanced tagged amplicon sequencing of hotspots and coding regions from 36 genes. A novel approach was used to detect *ALK*/*ROS1* fusions using amplicon sequencing in cfDNA. Diagnostic accuracy was compared to plasma ddPCR and tumor genotype (including NGS when available). **Result:** A total of 146 specimens from 49 patients were studied. Testing was completed for 115 specimens at the time of analysis. Matched plasma NGS and ddPCR were available across 95 samples and revealed high concordance of allelic fraction (AF). At baseline, sensitivity of plasma NGS for the detection of the driver was 100% (26/26) for *EGFR* (88.5% ddPCR sensitivity). Sensitivity for the detection of *ALK*/*ROS1* fusions was 89% (6/7 *ALK*, 2/2 *ROS1*). Rare instances of plasma NGS-positive/tissue NGS-negative discordance were seen across 13 cases with match tumor NGS (3/442 genes sequenced) and appear related to resistance heterogeneity, clonal hematopoiesis, and low tumor content of biopsy. Among patients with acquired T790M and available specimens at osimertinib resistance (n=21), 11 resistance mechanisms could be detected including tertiary *EGFR* mutations (e.g. C797S), mutations in *BRAF*, *PIK3CA*, or *KRAS*, and amplification of *MET*, *HER2*, or *FGFR1*. 4 were detected pre-osimertinib. **Conclusion:** This blinded analysis demonstrates for the first time the ability of amplicon-based plasma NGS to detect a full range of targetable genotypes in NSCLC. This approach has attractive sensitivity and specificity and deserves further study as an alternative to better-established hybrid capture approaches. Serial plasma NGS can detect competing resistance mutations in patients with TKIs resistance, highlighting the pitfalls of PCR-based plasma assays in patients with heterogeneous resistance and paving the way towards combination therapies.

Keywords: mechanisms of resistance, cell-free DNA, next generation sequencing

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P3.02-015 433MHZ MICROWAVE RADIATION INDUCES G2/M CHECKPOINT ARREST AND PROMOTES APOPTOSIS UNDER HYPERTHERMIA IN NON-SMALL CELL LUNG CANCER CELLS

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Background: Postoperative hyperthermia has been applied as an important adjuvant therapy to enhance the efficacy of traditional cancer treatment. To provide an update on the recent knowledge about the mechanisms of microwave (MW) hyperthermia on NSCLC cells using special MW device in vitro. **Method:** The various NSCLC cells (H460, PC-9 and H1975) were exposed to hyperthermia treatment using water bath or MW applicator. Cell survival was determined by CCK-8 assay. Cell apoptosis and cell cycle distributions were performed by Flow cytometry. Western blot assay was used to detect cell cycle arrest related molecular changes. Assessment of intracellular ROS changes in cells was performed using fluorescence probes DCFH-DA staining. **Result:** The MW hyperthermia can significantly inhibit cell growth in 3 cell lines, compared with water bath heating system. Flow cytometry results showed that the apoptotic cells increased significantly in MW hyperthermia treatment group, mean value of percent apoptosis treated by the MW hyperthermia was 12.45%, 40.00%, 37.70% in H460, PC-9, and H1975 cells respectively. The cell cycle distribution analysis showed that MW hyperthermia induced G2/M phase arrest. Western blot results suggested that MW thermal down-regulated the expressions of cyclinB1/cdc2, cdc 25c and p-cdc-25c, up-regulated expression of p21. Assessment of intracellular ROS change showed that MW hyperthermia induced production of ROS in NSCLC cells. **Conclusion:** Exposure of NSCLC cells to 433 MHz microwave hyperthermia induces ROS production and cell cycle arrest, which in turn induces cyclinB1/cdc 2 complex inactivation through inhibiting expressions of cdc 25c and increasing expression of p21, and finally promotes cell apoptosis. The heat treatment by water bath has not the same effect. This study suggests that microwave hyperthermia may be a potential therapeutic option for treating NSCLC in future.

Keywords: hyperthermia, microwave, anticancer

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P3.02-016 CORRELATION OF PROGRAMMED CELL DEATH LIGAND-1 MESSENGER RNA AND PROTEIN EXPRESSION IN NON-SMALL CELL LUNG CANCER

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Background: Monoclonal antibodies targeting the programmed cell death 1 (PD-1) receptor and its ligand (PD-L1) have been showing promising results in advanced non-small cell lung cancer (NSCLC). Here, we investigated PD-L1 messenger RNA (mRNA) expression by a novel RNA *in situ* hybridization technique and compared it with PD-L1 protein expression in NSCLC. **Method:** Primary NSCLC specimens of 687 patients (476 adenocarcinoma and 211 squamous cell carcinoma) were constructed into tissue microarrays. PD-L1 mRNA in situ hybridization was performed with RNAscope® assay and classified using two independent scoring systems (RNA scope score and RNA proportion score). We also performed immunohistochmisty (IHC) using the Dako 22C3 pharmDx assay for evaluating PD-L1 protein expression. **Result:** PD-L1 mRNA expression was detected in 11.9% by RNA scope score and 8.3% by RNA proportion score. PD-L1 protein expression showed a positivity of 25.2% for the 1% cut-off, and 9.9% for the 50% cut-off. The two RNA scoring systems showed a linear correlation to each other ($r = 0.83, p < 0.01$), as well as to PD-L1 IHC respectively ($p < 0.0001$). The cut-off value that best correlated with PD-L1 protein expression was "1" for both RNA scope score ($\kappa = 0.43$ for the 1% and 0.58 for the 50% IHC cut-off) and RNA proportion score($\kappa = 0.36$ for the 1% and 0.60 for the 50% IHC cut-off). Applying this criteria, discordant cases were found in 20% and 9% with 1% and 50% IHC cut-offs, respectively. **Conclusion:** PD-L1 mRNA expression, evaluated either as RNA scope score or as RNA proportion score, showed promising statistical results in predicting PD-L1 protein levels. We could thereby set out the RNA scoring system for PD-L1 in NSCLC. Discordant cases with positive mRNA levels and negative immunohistochemical results may indicate that PD-L1 mRNA *in situ* hybridization could be a more sensitive marker than immunohistochemistry. To verify the predictive role of PD-L1 mRNA expression in immunotherapy, however, therapeutic response to anti-PD-1/PD-L1 inhibitors should be investigated in future studies.

Keywords: RNA in situ hybridization, Programmed cell death ligand-1 (PD-L1), lung cancer

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P3.02-017 APOPTOSIS-RELATED PROTEIN IN NON SMALL CELL LUNG CANCER: CORRELATION OF CLINICOPATHOLOGIC, MOLECULAR CHARACTERISTICS AND PROGNOSIS

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Background: The role of apoptosis protein that regulates the biological behavior of non-small-cell lung carcinoma (NSCLC) is still controversial. We aimed to investigate the expression of apoptosis-related protein (survivin and bcl-2 family) and to identify their association with the clinicopathologic parameters and prognosis of patients with NSCLC. **Method:** Immunohistochemical (IHC) staining of pro-apoptotic (bax, bad, bim), anti-apoptotic proteins (bcl-2, survivin) and proliferation marker (Ki-67) was performed on tissue microarray sections from tumor tissues of 373 NSCLCs. Correlations between the expression of the above proteins and clinicopathologic, molecular features (*EGFR mutation, KRAS mutation, ALK* translocation and *MET* amplification) and prognostic significance were analyzed. **Result:** Analysis of the two main subtypes of NSCLC,

adenocarcinoma (ADC) and squamous cell carcinoma (SCC) individually showed that different markers were significant in the different subtypes. The expression of survivin, bax and Ki-67 was significantly different in ADC and SCC. In ADC, the increased expression of survivin was associated with the presence of vascular invasion, lymph node metastasis and tumor recurrences, but we did not find any correlation with survivin expression and clinicopathological parameters in SCC. The increased expression of bax was associated with the presence of lymphatic invasion and tumor recurrence in SCC, but no correlation with bax expression and clinicopathological parameters was observed in ADC. Kaplan–Meier survival analysis showed that survivin and Ki-67 were significant prognostic markers for ADC, whereas bax was a significant prognostic marker for SCC**.** Patients with high survivin and Ki-67 expression had significantly shorter disease-free survival as well as shorter overall survival than those with low survivin and Ki-67 expression. In SCC, patients with high bax expression had significantly shorter disease-free survival than those with low bax expression. Multivariate Cox analysis confirmed that survivin, Ki-67 and bax were independent prognostic factors in ADC and SCC, respectively. Among the six markers, only high bim expression was significantly related with the presence of *MET* amplification (p = 0.025), however, other five markers lack significant associations with *EGFR, KRAS, ALK, MET* gene status. **Conclusion:** Our results suggest that survivin and Ki-67 are independent negative prognostic factors in ADC and bax is an independent negative prognostic factor in SCC. Testing for these markers will help to determine the clinical relevance of NSCLC. Bim may possibly play a role in *MET*-amplified lung cancer.

Keywords: NSCLC, prognosis, apoptosis, survivin, bcl-2 family, immunohistochemistry,molecular type

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P3.02-018 PATIENTS HARBORING ALK REARRANGEMENT ADENOCARCINOMA AFTER ACQUIRED RESISTANCE TO CRIZOTINIB AND TRANSFORMATION TO SCLC: A CASE REPORT

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Background: Anaplastic lymphoma kinase(ALK) rearrangement responds to ALK tyrosine kinase inhibitors (TKIs) in lung cancer. Many cases ultimately acquired resistance to crizotinib. Resistance mechanisms have been described including ALK dominant or ALK non-dominant. A mechanism of transformation to small-cell lung cancer is rare. **Method:** A 54-year-old male diagnosed with adenocarcinoma, who shown EGFR wild and ALK rearrangement detected by RT-PCR and treatment with crizotinib. A re-biopsy showed a small cell lung cancer after disease progression. **Result:** The next generation sequencing (NGS) was carried out and it detected TP53 gene mutation and ALK rearrangement, no loss of retinoblastoma gene (RB). Regimen for small-cell lung cancer (SCLC) may be one of the treatment options. However, the heterogeneous tumor may be at diagnosed and the course of disease. **Conclusion:** Oncologists should realize the possibility of transformation to SCLC after patients acquire resistance to ALK-TKI therapy. A re-biopsy should be performed to enable histological and detect molecular analysis. And finding transformation to SCLC is important for choosing appropriate therapy due to the potential efficacy of standard SCLC treatments or combination of next generation AKL-TKIs.

Keywords: crizotinib, Resistance, small-cell lung cancer

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P3.02-019 CLINICAL VALIDATION OF A REAL TIME PCR ASSAY FOR THE DETECTION OF ROS1 FUSION IN CHINESE NON-SMALL CELL LUNG CANCER

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Background: ROS1 fusion has been approved to be the second effective target of Crizontinib in the treatment of non-small cell lung cancer (NSCLC). The traditional way of gene fusion detection is split FISH which is time consuming. A simple and fast real time PCR method (AmoyDx RT-PCR) has been developed for the detection of ROS1 fusion. **Method:** AmoyDx RT-PCR method was developed for detection of 14 types of ROS1 fusions (ADx-ROS1 kit) by combining reverse transcription and real-time PCR. An EGFR-ALK-ROS1 three gene aberration one-shot detection kit (ADx-EAR kit) was developed as well by combing DNA-based mutation detection (for EGFR gene) and mRNA-based fusion detection (for ROS1 and ALK genes). Two cohorts of FFPE NSCLC tissue samples, 1007 and 1137, were analyzed for ROS1 fusions by ADx-ROS1 and ADx-EAR, respectively. For positive samples, Sanger sequencing was used to confirm the fusions. **Result:** In the first cohort of 1007 tumors, 40 (3.97%) were detected to be ROS1 fusion positive and all of the fusions were confirmed by Sanger sequencing to be true fusion positive. In the second cohort of 1137 tumors, 29 (2.55%) were detected to be ROS1 fusion positive that were also confirmed to be true positive by Sanger sequencing. The positivity of ROS1 fusion was detected to be more in adenocarcinoma, female and never-smoker, although no statistical significance was find. Also, ROS1 was detected more in tumors without EGFR mutation and ALK fusion. **Conclusion:** RT-PCR based method is reliable for the detection of ROS1 fusion in FFPE samples of Chinese NSCLC.

Keywords: ros1, real time PCR

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P3.02-020 COMPARISON OF DIAGNOSTIC ABILITY FOR EGFR MUTATION OF THE SPECIMEN GROUPS: HISTOLOGY – CYTOLOGY – PLASMA

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Background: EGFR mutations in NSCLC therapy play a very important role. Currently, many types of specimens are used to perform EGFR mutations. At Pham Ngoc Thach Hospital with RealTime-PCR Technique on cobas@ z 480 machine has been done on a variety of clinical specimens. **Method:** Research with cross sectional descriptive statistics. - Period from November 2016 to May 2017: 6 months. Diagnose EGFR mutations in 3 groups: histology, cytology, plasma. - Control check with next-generation gene sequencing **Result:** - Total number research: 56 cases with 26 EGFR mutation (+) with next generation sequencing. - Histology specimens: EGFR (+): 44.64%; Sensitivity: 96.15%, Specificity: 96.67%; Number of cases to be resumed: 0 shifts; Not quantifiable. - Cytology specimens: EGFR (+): 42.86%; Sensitivity: 92.31%; Specificity: 96.67%; Number of cases to be resumed: 2 cases for the second time; Not quantifiable. - Plasma specimen: EGFR (+): 33.93%; Sensitivity: 73.31%; Specificity: 96.55%; Number of cases to be resumed: 12 cases for the second time, 7 cases for the third time; Average mean quantity: 15.66 ± 7.05 ng / µl. → Statement: * Use a variety of specimens to diagnose EGFR mutations. * Sensitivity and detection rates of histological and cytological specimens were higher than plasma samples. * The specificity of these three groups is comparable. * It is not possible to determine when to get the best blood sample for the plasma diagnosis of EGFR mutation. * Plasma samples have the advantage of being semi-quantifiable. So consider predictive factor evaluates the treatment. **Conclusion:** * Histology and cytology specimens are more sensitive and detectable than in diagnosis of EGFR mutation. Therefore, this is an important factor in the diagnosis. * Semi quantitative in plasma specimen to monitor treatment response & some cases to diagnose when no re-biopsy is available.

Keywords: EGFR mutations, Histology, Cytology, Plasma, Specimens

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P3.02-021 SECONDARY EGFR EXON 20 T790M MUTATION FOR THERAPY OF NON SMALL CELL LUNG CANCER AT PHAT NGOC THACH - HO CHI MINH CITY - VIETNAM

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Background: The EGFR Exon 20 T790M mutation is nowadays widely mentioned in studies on the treatment of non-small cell lung cancer. Especially the secondary mutation T790M or accquired T790M mutation. Aims: I.Investigation of EGFR Exon 20 T790M mutation appears secondary to treatment with targeted therapy or chemotherapy. II.Ability to diagnose EGFR Exon 20 T790M secondary mutation of clinical specimens: Histology - Cytology - Plasma. **Method:** * Retrospective study, statistics describing series of clinical cases. * Collect EGFR mutation data in 3 groups: histology, cytology and plasma. * Use RealTime PCR on cobas @ z480 to perform EGFR mutation diagnosis. * All patients have admitted to the hospital. Pham Ngoc Thach with diagnosis of advanced stage non-small cell lung cancer (IIIB and IV) with the following requirements: - They have been treated witht the target therapy or chemotherapy. Then, the disease progresses back to the standard RESIST 1.1. - There has been an initial diagnosis of EGFR mutations. - Diagnosed with mutations in EGFR with samples: histopathology, cytology and plasma. **Result:** * Primary EGFR Exon 20 T790M mutation: 7 cases: 4.07%, including 4 simple mutation (2.33%) and 3 combined mutations (1.74%) (Exon 20 T790M + Exon 20 G719X, Exon 20 T790M + Exon 19 Deletion; Exon 20 T790M + Exon 20 S768I). * Secondary EGFR Exon 20 T790M mutation: high rate: 97 cases (56.39%). Compared with other studies in the world, especially in Asia, the values are similar (P = 0.059 - 0.088> 0.05). We have been presented the statements: - The EGFR Exon 20 T790M mutation was significantly higher in the primary EGFR mutation group (97 cases vs 7 cases: P = 0.0047 <0.05). - Comparison of mutant EGFR Exon 20 T790M mutation with other studies in the world of the majority showed similar results (P = 0.051 - 0.081> 0.05). - Ability to detect EGFR Exon 20 T790M mutation among 3 groups specimens: Histology - Cytology - Plasma are similar. - With the RealTime PCR technique on plasma samples, it has been helpful in detecting this Exon 20 T790M EGFR mutation. **Conclusion:** Secondary EGFR Exon 20 T790M mutations are more likely to be present than in the primary group and predominate in the other secondary EGFR mutations. With the RealTime PCR technique on plasma samples, it has been very helpful in diagnosing this type of mutation.

P3.02-022 PROTEIN TYROSINE PHOSPHATASE INTERACTING PROTEIN 51 MIGHT IMPROVE EGFR-TKI SENSITIVITY IN NON-SMALL-CELL LUNG CANCER

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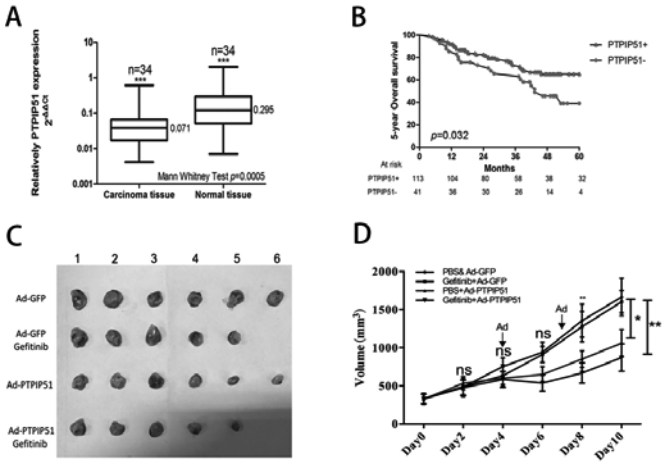
Background: Epidermal growth factor receptor (EGFR) -mutant tumors define a subset of Non-small-cell lung cancer (NSCLC), tumors that harbor EGFR mutation are highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib. However, acquired resistance develops in most NSCLC patients with EGFR mutations after 10-14 months of treatment. In this study we aimed to testify the tumor suppressing function of Protein tyrosine phosphatase interacting protein 51 (PTPIP51), an apoptosis related protein and its effect in improving EGFR-TKI sensitivity. **Method:** Tumor tissues and matched adjacent normal tissues of 154 patients undergoing surgery in the department of Thoracic Surgery II of Beijing Cancer Hospital during 2006–2011 were tested. Patient-derived xenograft mice (PDX model) carrying primary tumor was prepared and Gefitinib/adenovirus-PTPIP51 were used for treatment in vivo and vitro. **Result:** PTPIP51 was down-regulated in NSCLC on both RNA and protein level, and high PTPIP51 expression was revealed as a favorable predictor for better outcome of NSCLC patients(Figure A,B), and elevated PTPIP51 expression exhibited a higher objective regression rate(ORR) to EGFR-TKI therapy of patients with EGFR mutation. Sensitivity to EGFR-TKI of PC9 and A549 cell lines were both enhanced after transfection of PTPIP51. After treatment with adenovirus-PTPIP51+placebo, Gefitinib+placebo, and PTPIP51 plus Gefitinib, it suggested that PTPIP51 could significantly improve EGFR-TKI efficacy in PDX model with wild-type NSCLC tumors (Figure C,D), suggesting a potential correlation between PTPIP51 and EGFR signal pathways. Over-expression of PTPIP51 in NSCLC cell lines significantly inhibited the downstream signaling of EGFR, including PI3K/Akt, Ras/Raf/Erk and Jak/Stat3 pathways, and Gefitinib co-effected with PTPIP51 could induce apoptosis of NSCLC cell lines PC9 and A549. Meanwhile, PTPIP51 interacted with PTEN could induce ubiquitylation then degradation of EGFR via lysosome.



Conclusion: Our findings first highlighted PTPIP51 as a novel tumor suppressor gene in NSCLCs, and it might play a potential role in outcome prediction and improvement of EGFR-TKI sensitivity.

Keywords: PTPIP51, NSCLC, TKI

P3.02-023 SEMAPHORIN 7A REDUCES RESPONSE TO EGFR-TKI TREATMENT VIA APOPTOSIS IN HUMAN LUNG ADENOCARCINOMA

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Background: Most patients harboring epidermal growth factor receptor (EGFR) mutations experience relapse to EGFR-Tyrosin kinase inhibitors (TKI). So it is necessary to overcome the resistance to EGFR-TKI. We found that Semaphorin 7A (SEMA7A) is upregulated by EGFR signals. The role of SEMA7A in human lung adenocarcinoma is unknown, so we annlyzed the function of SEMA7A in human lung adenocarinoma. **Method:** We compared transcriptomes of NIH3T3 cell lines overexpressing wild type (WT) EGFR with Next, we investigated which pathways regulated the expression of SEMA7A in human lung adenocarcinoma cell line. Furthermore, we investigated the expression of SEMA7A by immunohistochemistry (IHC), and the correlation of SEMA7A and phosphorylation S6 (pS6) in 129 lung adenocarcinoma patients were analyzed. We also investigated the correlation of SEMA7A expression with the prognosis or drug response in 44 stage IV lung adenocarcinoma patients. Finally, we investigated the efficacy of EGFR-TKI in SEMA7A WT and KO (by CRISPR/CAS9) in vitro and in vivo. **Result:** The expression of SEMA7A was regulated by EGFR signals. Furthermore, the expression of SEMA7A was downregulated by mTOR signals in human lung adenocarinoma cells and clinical samples. High SEMA7A lung cancers tended to get EGFR-TKI resistance, in vivo, in vitro via apoptosis. In clinical samples, high SEMA7A expression tumor tended to get EGFR-TKI resistance. **Conclusion:** We revealed that the SEMA7A regulated the efficacy to EGFR-TKI via apoptosis.

Keywords: Semaphorin, EGFR-TKI, apoptosis

P3.02-024 ROLE OF FBXW7 IN THE MAINTENANCE OF QUIESCENT CANCER STEM CELLS RESISTANT TO GEFITINIB IN EGFR MUTATION-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Accumulating evidence indicates that quiescent cancer stem cells (CSCs) are involved in the resistance to gefitinib in non-small cell lung cancer (NSCLC) as non-mutational mechanism. We have previously reported that gefitinib-resistant persisters (GRPs) highly expressed stemness factors and had characteristic features of the CSCs phenotype. Recent studies demonstrate that FBXW7, a type of F-box protein, plays an important role in the maintenance of quiescent CSC by mediating the degradation of c-Myc protein by ubiquination. The aim of this study is to figure out the role of FBXW7 in the resistance to gefitinib in NSCLC with EGFR mutation. **Method:** NSCLC cell lines, PC9 and HCC827, harboring sensitive-EGFR mutation were exposed to high concentration of gefitinib in order to develop GRPs. We tried to knockdown FBXW7 gene expression, and evaluated their sensitivity to gefitinib and CD133-positive stem cell population in GRPs. We also introduced FUCCI plasmid via lentiviral infection in the cells and then investigated the cell cycle and G0-phase cells in GRPs. Furthermore, we established gefitinib-resistant tumor (GRT) model by injecting PC9 cells into NOG-mice followed by gefitinib administration after tumor growth, and evaluated mRNA and protein expression of quiescence-related markers including FBXW7 *in vivo*. **Result:** *In vitro*, GRPs showed high expression of stem cell marker CD133 and quiescence-related markers including FBXW7 and low expression of c-Myc at protein level. Cell cycle analysis revealed that majority of GRPs existed in G0/G1 phase. Silencing of FBXW7 gene reduced CD133-positive cell population in GRPs. Knockdown of FBXW7 also increased susceptibility of cells to gefitinib, reversed population of G0/G1-arrest cells to G2/S/M cells, and decreased cell number of GRPs. *In vivo*, GRTs after gefitinib treatment revealed high expression of FBXW7 and low expression of c-Myc. **Conclusion:** These findings suggest that FBXW7 may play a pivotal role in the maintenance of quiescent CSCs resistant to gefitinib in EGFR mutation-positive NSCLC.

Keywords: Role of FBXW7, Quiescent cancer stem cell, Gefitinib resistance

P3.02-025 65 CASES OF MOLECULAR PROFILING ANAYSIS IN SURGICAL RESECTED PULMONARY NEUROENDOCRINE CARCINOMA

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Background: Due to a low frequency of pulmonary neuroendocrine carcinoma, little is known for its molecular aberrations and prognosis. The aim of this study is to investigate the characteristics of surgical resected pulmonary neuroendocrine carcinoma and to analyze the prognostic factors. **Method:** We retrospectively reviewed the clinical data and genetic status from 65 patients with pulmonary neuroendocrine carcinoma[small-cell cancer (SCLC), n=26; large cell neuroendocrine carcinoma (PLCNC), n=34; carcinoid, n=5], and the survival rate was calculated by Kaplan-Meiermethod and log-rank test was used to compare the survival rates. Univariate and multivariate factors for survival were analyzed by COX proportional hazards regression model. **Result:** There was no significant difference with clinical characteristics in 65 cases of pulmonary neuroendocrine carcinoma (P>0.05); The genetic change was given priority to with PIK3CA gene mutations, SCLC and PLCNC and carcinoid the median overall survival time (26.7 months *vs* 30.4 months *vs* did not reach) (P=0.039) and staging was differences statistically significant by the single factor analysis in SCLC (P<0.05). **Conclusion:** Pulmonary neuroendocrine carcinoma genetic change was rare, and it is given priority to with PIK3CA gene mutations, common genomic aberrations are rare for PNC. Molecular profiles vary widely among different subtypes of PNC. Carcinoid offers better survival than PLCNC and SCLC, whereas no survival difference existed between PLCNC and SCLC.

Keywords: small-cell cancer, large-cell neuroendocrine carcinoma, carcinoid

P3.02-026 THE STUDY OF ROS1 REARRANGEMENT IN ADVANCED PRIMARY NON-SMALL CELL LUNG CANCER AND ASSOCIATED METASTATIC LESIONS

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Background: ROS1 rearrangement in non-small cell lung cancer(NSCLC) patients has recently been identified as a driver gene and benefited from crizotinib treatment. However, no data are available for ROS1 rearrangement NSCLC about relationship between primary and metastatic patients. The aim of this study is to examine the positive rate of ROS1 rearrangement in primary and metastatic NSCLC, and to investigate their relationships. **Method:** From January 2013 to May 2015, 384 cases of primary NSCLC consisting of 246 cases of matched metastatic tumors and 47 cases of normal lung specimens as the control group were collected in multicenter. The positive rate of ROS1 rearrangement among NSCLC population was figured out, thus the consistency of ROS1 rearrangement in advanced primary NSCLC and associated metastases and the relationship between ROS1 rearrangement and clinical data was analyzed. **Result:** The positive rate of ROS1 rearrangement on primary tumor was 2.60% (10/384). For those 246 paired cases, the positive rate on primary tumor was 2.85% (7/246), with that of metastases 1.63% (4/246). Among the 246 cases, there was one case whose metastases was positive, primary tumors negative and 4 case whose primary tumor were positive, metastases were negative. Positive rate of ROS1 rearrangement was higher in the primary lesions than metastases. It was of statistical significance between the two groups (χ^2=52.341, P<0.001). The positive rate of primary tumors could be predicted by metastases (κ=0.536, P<0.001). The sensitivity was 42.86% (3/7) and the specificity was 99.58% (238/239). **Conclusion:** The metastases of NSCLC can predict ROS1 rearrangement of the primary lesions. It can be used as alternative means for metastases to detect ROS1 rearrangement which are not readily available.

Keywords: metastatic lesions, ROS1 fusion gene, primary lesions

P3.02-027 LUNG ADENOCARCINOMA PATIENT WITH EGFR 19 EXON INSERT MUTATION: I740_K745INSIPVAIK AND ITS RESPONSE TO ICOTINIB: A CASE REPORT

C. Xu[1], W. Wang[2], W. Zhuang[3], Y. Chen[1], G. Chen[1], M. Fang[2], R. Chen[4], Y. Guan[4], X. Yi[4], T. Lv[5], Y. Song[5]

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Background: Screening for epidermal growth factor receptor (EGFR) mutation before choosing a therapeutic strategy for patients with advanced non-small-cell lung cancer (NSCLC) is universally accepted at present. One of the reasons that certain patients without activating EGFR mutation respond to EGFR-tyrosine kinase inhibitor (TKI) treatment is possibly due to false-negative EGFR mutation. However, none of the available methods can provide the entire information of EGFR mutation; while maintaining the best sensitivity and specificity. Uncommon mutations are often evasive due to the limitation of screening methods. **Method:** A 74-year-old smoking male diagnosed with adenocarcinoma, who detected EGFR gene by reverse transcription polymerase chain reaction (RT-PCR) and the next generation sequencing (NGS) **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 RT-PCR that found EGFR wild type, but it found EGFR p.I740_K745insIPVAIK and BRCA2 p.C315S by NGS. Albeit rare, this specific type of EGFR mutation deserves more attention because it was related to a good response to EGFR-TKI therapy. The patient received icotinib therapy, and icotinib therapy showed a good response. We report here, to our knowledge, the first case received icotinib in mainland China of EGFR exon 19 insert. **Conclusion:** To reduce the frequency of false negatives, hence not to lose any opportunities for a potential icotinib treatment, NGS for EGFR mutation examination according to the specimen quality and quantity (tumor load and DNA yield) is proposed.

Keywords: exon 19 insert, icotinib, uncommon mutation

P3.02-028 276 CASES OF EGFR/ALK GENE STATUS AND PREDOMINANT HISTOLOGIC SUBTYPE IN CHINESE SURGICALLY RESECTED LUNG ADENOCARCINOMA

Z. Huang[1], C. Xu[2], W. Wang[3], W. Zhuang[1], Z. Song[3], Y. Chen[2], G. Chen[2], M. Fang[3], T. Lv[4], Y. Song[4]

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Background: A new lung adenocarcinoma classification proposed by WHO (2015) classification of tumors of the lung has recently been published. The aim of this study is to investigate the mutations of EGFR gene and ALK fusion gene in Chinese surgically resected lung adenocarcinomas. **Method:** Reverse transcription polymerase chain reaction (RT-PCR) was used to detect the tissues in 276 patients of surgically resected lung adenocarcinomas with paraffin tissue EGFR gene mutation and ALK fusion gene. **Result:** The total mutation rate in 276 patients of surgically resected lung adenocarcinomas was 54.71% (151/276). EGFR gene mutation rate were found in 19del (28.99%, 80/276), L858R (23.19%, 64/276), 20-ins (0.72%, 2/276), L861Q (0.72%, 2/276), G719X (1.09%, 3/276), S768I (0.36%, 1/276) and T790M (0.72%, 2/276) in surgically resected lung adenocarcinomas, including one case of G719X plus S768I, 19del plus T790M, L858R plus T790M, respectively. The total fusion positive rate in 207 patients of surgically resected lung adenocarcinomas was 5.80% (12/207). There were statistically significant (P<0.001, P<0.001, P=0.023, P<0.001 and P=0.030) in each subtype of lung adenocarcinoma of EGFR gene mutation, including lepidic predominant adenocarcinoma, acinar predominant adenocarcinoma, papillary predominant adenocarcinoma, solid predominant adenocarcinoma and invasive mucous adenocarcinoma, and there were not statistically significant(P>0.05) among other types. There were not statistically significant(P>0.05) among each types of lung adenocarcinoma of ALK fusion gene. **Conclusion:** Histologic subtyping was found to be associated with EGFR mutations. The EGFR mutation frequency of lepidic predominant, acinar predominant and papillary predominant subtypes was found to be more pronounced than that of other subtypes.

Keywords: lung adenocarcinoma, EGFR gene, ALK gene

P3.02-029 218 CASES OF EGFR/ALK GENE STATUS ANAYSIS IN CHINESE LUNG SQUAMOUS CELL CARCINOMA

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Background: Due to the low frequency of EGFR mutation and ALK fusion gene in lung squamous cell carcinoma. Thus the efficacy of icotinib and crizotinib for these patients is not well known. The aim of this study is to investigate the mutations of EGFR gene and ALK fusion gene in lung squamous cell carcinoma. **Method:** The reverse transcription polymerase chain reaction (RT-PCR) method was used to detect the tissues in 218 patients of lung squamous cell carcinoma with paraffin tissue EGFR gene mutation and ALK fusion gene. **Result:** The total mutation rate in 218 patients of squamous cell carcinoma was 54.71% (151/276). EGFR gene mutation rate was 2.29% (5/218), which was both found in 19del and L858R, ALK fusion gene positive rate was 6.14% (7/114). **Conclusion:** There are a certain proportion of EGFR gene mutation and ALK fusion gene in lung squamous cell carcinoma, and the detection the EGFR gene mutation and ALK fusion gene can not be ignored in squamous cell carcinoma.

Keywords: EGFR gene, Squamous cell carcinoma, ALK gene

P3.02-030 INHIBITORY EFFECTS OF MITOCHONDRIAL TRAP1 ON GEFITINIB-RESISTANCE IN NON-SMALL LUNG CANCER CELLS

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Background: TNF receptor-associated protein 1 (TRAP1) has been reported to be upregulated in some tumors, and protected against apoptosis and oxidative stress. This study was designed to investigate overcoming gefitinib resistance in NSCLC through a mechanism-based approach using gamitrinib variant containing triphenylphosphonium (G-TPP), TRAP1 inhibitor. **Method:** We developed an in vitro model of acquired resistance to gefitinib by continuously treating HCC827 with escalating doses. The effects of G-TPP on apoptosis and ROS-dependent mitochondrial dysfunction in HCC827GR cells were examined by annexin V binding assay, MitoSoX, and immunoblot analysis. and we tested the effects of pretreated with NAC or DPI, free radical scavenger. In addition, TRAP1 and antioxidant MnSOD were respectively knocked down or overexpressed to determine its role in modulating ROS-mediated apotosis signals by G-TPP. **Result:** Downregulation of TRAP1 through siRNA or G-TPP enhanced ROS-mediated apoptosis whereas TRAP1 overexpression

attenuated ROS-mediated apoptosis induced by gefitinib. On the other hand, pretreatment with NAC or DPI prevents apoptosis induced by gefitinib and G-TPP. We next showed that the combination of gefitinib and G-TPP resulted in decreased expression of MnSOD in HCC827GR cells, not HCC827 cells. MnSOD siRNA and combined with gefitinib and G-TPP resulted in a greater apoptosis. In contrast, overexpression of MnSOD could confer protection against the apoptosis reduced by gefitinib and G-TPP. **Conclusion:** TRAP1 downregulation could overcome gefitinib resistance in NSCLC via ROS-mediated apoptotic pathway. Moreover, enhanced apoptosis by gefitinib and G-TPP in HCC827GR cells was due, at least in part, to the down-regulation of MnSOD.

Keywords: TRAP1, Gefitinib resistance, Lung cancer

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-031 DETECTION OF ACTIVATING EGFR MUTATIONS AND RESISTANT T790M MUTATION FROM CFDNA IN MALIGNANT PLEURAL EFFUSION(MPE-DNA)

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Background: Analysis of activating EGFR and resistant T790M mutations from plasma cfDNA is now recognized as one of the standard testing methods in clinical practice. (Mok et al CCR 2015, Oxnard et al JCO 2016) Sensitivity varies from 60 to 80% while specificity is above 90%. Malignant pleural effusion (MPE) is an alternative rich source of cfDNA and efficacy of mutation testing from this sample source remains unclear. **Method:** Objectives of this study is to study the feasibility of testing EGFR mutations using MPE-DNA and to compare the diagnostic utilities with plasma cfDNA in lung cancer patients with known EGFR mutation status established by tumor tissue. 10 ml of blood and 10 ml of pleural fluid were collected after consent. DNA was extracted and tested by digital PCR (Sanomics Inc. Hong Kong, China). **Result:** We enrolled 45 patients between November 2016 and May 2017. Patient demographics are summarized as follows: male (n=21) vs female (n=24); tissue EGFR wild type (n=13) vs mutation (n=24) vs unknown (n=8); treatment naïve (n=26) vs progression of TKI (n=19). Diagnostic utilities are summarized in table below. 9 plasma samples were positive for T790M compared to 14 samples of MPE-DNA being positive. (Detection rate: 0.20 vs 0.31, respectively) Total of 6 negative T790M plasma samples were tested positive in MPE-DNA, and vice versa, 2 samples. Concordance rate of T790M testing between plasma cfDNA and MPE-DNA is 0.82.

	EGFR mutation	
	Plasma cfDNA vs tumor	**MPE-DNA vs tumor**
Sensitivity	0.83	0.92
Specificity	0.92	0.92
Concordance	32/37=0.86	34/37= 0.92
Mean allele frequency of cfDNA only (range)	13.43% (0.10%-58.66%)	31.77% (1.21%-83.40%)

Conclusion: It is feasible to detect activating EGFR and resistant T790M mutations from MPE-DNA. Sensitivity of testing MPE-DNA is similar if not better than plasma cfDNA. Further investigation is warranted.

Keywords: EGFR, cell-free DNA, biomarker

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-032 SPATIAL HETEROGENEITY OF EGFR AND KRAS VARIANT ALLELE FREQUENCIES CORRELATES WITH HISTOLOGICAL PATTERNS OF LUNG ADENOCARCINOMAS

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Background: Analysis of spatially distinct regions revealed a considerable histological and molecular heterogeneity of lung adenocarcinomas (ADCs). The predominant histological growth pattern and driver gene alterations (e.g. in *EGFR* and *KRAS*) have been shown to be of high prognostic and therapeutic relevance. This project aimed to examine the spatial distributions of *EGFR* and *KRAS* mutation frequencies in the various histological growth patterns of ADCs. **Method:** Central tumor sections from 19 ADCs were subdivided into 467 tumor segments of 5x5 mm. The segments were evaluated separately in order to enable a systematic analysis of histological and molecular markers within and between patients. We determined the predominant histological growth patterns and the variant allele frequencies (VAFs) of *EGFR* and *KRAS* in each segment by digital PCR. We further quantified the absolute cell counts and proportions of tumor and non-neoplastic cells in all segments in order to examine the cellular fractions and allow a precise normalization of VAFs. **Result:** Histopathological classification revealed morphological intratumor heterogeneity with more than one histological growth pattern in 16 of the 19 cases. The 467 malignant segments exhibited a mean tumor cell fraction of 28% with an extensive variability within and between the individual cases. The predominant solid pattern revealed the significantly lowest fraction of tumor cells. Furthermore, *EGFR* and *KRAS* VAFs were measured by digital PCR and normalized to the cellular fractions of the respective segment. While driver gene mutations were detected in > 99% of malignant segments, we found a heterogeneous spatial distribution of normalized VAFs: Some cases showed ubiquitously low or high mutant allele frequencies, others revealed regions with focally elevated frequencies and driver gene amplifications. In addition, we found a significant correlation between mutated allele frequencies and histological patterns. Micropapillary and solid patterns harboured higher mutant allele frequencies compared to lepidic and papillary histologies. Correlation analysis did not show an association between the tumor size and the normalized VAF or driver gene amplification. **Conclusion:** Our findings indicate that driver gene mutations are present with high levels of inter- and intratumor heterogeneity throughout all ADC samples tested. Allele frequencies correlated with histological growth patterns, but not with tumor size.

Keywords: lung adenocarcinoma, Tumor heterogeneity, EGFR KRAS

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-033 PATHOLOGICAL AND MOLECULAR ALTERATIONS AFTER FIRST AND SECOND GENERATION EGFR-TKI THERAPY IN PATIENTS WITH EGFR-MUTATED LUNG ADENOCARCINOMAS

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Background: Molecular alterations, including *EGFR* T790M point mutation and *MET* gene amplification, are reported as resistance mechanisms to first and second-generation EGFR tyrosine kinase inhibitors (TKIs). However, pathological transformation after EGFR-TKI administration has not been adequately studied. We compared the pathological alterations before and after EGFR-TKI administration in patients with *EGFR*-mutated lung adenocarcinomas. **Method:** Between January 2016 and March 2017, 61 patients received first and second generation TKI therapy for *EGFR*-mutation–positive lung adenocarcinomas or adenosquamous carcinomas. Among them, 31 patients experienced recurrence, and 22 of these patients, for whom diagnosis was confirmed through re-biopsy, were included in this study. Pathological and molecular alterations in the re-biopsy specimens were analyzed for these patients. Based on the 2015 WHO classification, lepidic predominant lung adenocarcinomas were categorized as low grade, papillary or acinar lung adenocarcinoma as intermediate grade, and micropapillary or solid lung adenocarcinoma as high grade. **Result:** The *EGFR* T790M mutation was positive in 11 of the 22 patients. Seven patients were cytologically diagnosed by pleural and cerebrospinal fluid analysis, as well as by endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA). The remaining 15 patients underwent pathologically analysis. Twelve patients were found to have adenocarcinomas, two had large-cell neuroendocrine carcinomas (LCNECs), and one displayed epithelial-mesenchymal transition (EMT). Of the 12 adenocarcinomas analyzed, eight were the same tumor grade before and after TKI therapy, and four were higher grade than before TKI therapy.

Table 1 Pathological and molecular alterations after EGFR-TKI therapy

Case number	*EGFR* mutation	Baseline histology	TKI	T790M status	Pathological diagnosis
1	L858R	AC	Afatinib	Negative	LCNEC
2	L858R	AC	Afatinib	Negative	LCNEC
3	L858R	AC	Erlotinib	Negative	EMT
4	L858R	Lep	Gefitinib	Positive	AC
5	L858R	AC	Erlotinib	Positive	Solid
6	19 del	AC	Afatinib	Positive	Solid
7	L858R	AC	Afatinib	Negative	Solid
8	19 del	AC	Erlotinib	Positive	AC
9	19 del	AC	Afatinib	Negative	AC
10	19 del	AC	Afatinib	Negative	AC
11	L858R	AC	Afatinib	Positive	AC
12	19 insertion	AC	Erlotinib	Negative	AC
13	L858R	PAP	Erlotinib	Negative	AC
14	19 del	AC	Erlotinib	Positive	PAP
15	19 del	PAP	Erlotinib	Negative	AC

LCNEC: large-cell neuroendocrine carcinoma; EMT: epithelial-mesenchymal transition; Lep: lepidic; AC: acinar; PAP: papillary.

Conclusion: Neuroendocrine and epithelial-mesenchymal transformations have an

important role in EGFR-TKI resistance mechanisms, as previous reports have shown. Regarding the re-biopsy specimens, in one third of cases, the adenocarcinomas were of a higher tumor grade than the specimens analyzed before EGFR-TKI therapy.

Keywords: EGFR-TKI, lung adenocarcinoma, Pathological alteration

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-034 ACQUIRED RESISTANCE TO OSIMERTINIB BY CCDC6-RET FUSION IN A PATIENT WITH EGFR T790M MUTANT METASTATIC LUNG ADENOCARCINOMA

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Background: Resistance to third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is thought to be most commonly mediated by acquisition of a C797S mutation in EGFR. Identification of novel mechanisms of resistance to third generation EGFR TKIs is of critical importance for continued advancement of the field of targeted therapies for patients with EGFR mutant non-small cell lung cancer (NSCLC). **Method:** We report the case of a patient who developed resistance to osimertinib via acquisition of a CCDC6-RET fusion. **Result:** The patient was a 49yo woman with stage IV lung adenocarcinoma who was initially treated with afatinib for EGFR exon 19 deletion disease. She acquired a T790M mutation identified on peripheral blood circulating cell free DNA (cfDNA) assessment at the time of first progression 18 months after diagnosis. She was changed to osimertinib at that time, and nine months into therapy with osimertinib she was noted to have disease progression with acquisition of a CCDC6-RET fusion and no C797S EGFR mutation identified in peripheral blood cfDNA. The CCDC6-RET fusion was not seen on tumor tissue next generation sequencing from the time of initiation of osimertinib, and tumor tissue sequencing was not performed at the of progression on osimertinib. **Conclusion:** The CCDC6-RET fusion protein is known to be pathogenic in lung adenocarcinoma. The identification of this novel mechanism of acquired resistance to a third generation EGFR TKI contributes to the critical landscape of defining all the ways that NSCLC can acquire resistance to the latest targeted therapy agents.

Keywords: CCDC6-RET fusion, Osimertinib resistance

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-035 MUTATIONAL SIGNATURES AND THEIR ASSOCIATION WITH CLINICOPATHOLOGICAL FEATURES IN LUNG ADENOCARCINOMA OF SMOKERS

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Background: Lung adenocarcinoma (LADC) harboring druggable driver oncogene such as EGFR mutation and ALK fusion can be treated with molecular-targeted drugs. These oncogene aberrations are frequently observed in LADCs of never-smoker, while LADCs of smokers often lack such druggable oncogene aberrations. Therefore, understanding mutation profile of LADCs of smokers is required to improve precision lung cancer medicine. **Method:** We analyzed mutational signatures of somatic mutations in 373 LADCs (smoker 220 cases; 59%, never-smoker 153 cases; 31%) of Japanese using whole exome sequencing data. Four mutational signatures were identified by non-negative matrix factorization and logistic regression analysis. We are now analyzing significantly mutated gene (SMG)s by MutSigCV1.5 of LADCs of smokers and associations of each signature with clinicopathological factors including histological subtype and prognosis. **Result:** Indel mutations as well as well-characterized C>A mutations were defined as mutational event more prevalent in LADC of ever-smokers than in never-smokers (P=8.76E-15 and P=0.000417 respectively). A novel set of genes were identified as a main target for indel mutations (7.4%; 22 of 296 samples), and their mutations were significantly associated with smoking and with UIP co-occurrence in their lung (P=0.0068 and P=0.037, respectively). Indel mutations in 3'-UTRs of these genes caused specific reduction in mutant transcripts, while those in coding region caused truncation of polypeptide. **Conclusion:** A novel gene set including those in 3'-UTR, would contribute to LADC development in smokers and associated with usual interstitial pneumonia, by promoting undifferentiation of tumor cells.

Keywords: lung adenocarcinoma, smoking, Genome analysis

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-036 FEASIBILITY STUDY TO EVALUATE PATTERNS OF METASTASES AND EFFECT OF SURGERY ON LUNG CANCER XENOGRAFTS WITH DIFFERING SENSITIVITY TO EGFR TKI

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Background: Lung cancer cell lines with differing sensitivities to the epidermal growth factor receptor tyrosine kinase inhibitor, Erlotinib have different invasive and metastatic potential. Surgical intervention may play a role in altering the pattern of metastases and survival. Studying these patterns may help in designing trials to evaluate the efficacy of peri-operative EGFR inhibition. **Method:** Two lung cancer cell lines with known different sensitivity to Erlotinib were selected; A549 known to be resistant to Erlotinib (sensitive to Everolimus) and HCC 827, known to be sensitive to Erlotinib. 12 NOD SCID mice were injected with A549 and 17 NOD SCID with HCC 827 as xenografts in the thigh. FDG-18 PET scans were performed in all mice thrice, at 7-10 days, 4 weeks and at 6 weeks. 8 of the 12 mice with A549 cell line and 12 of the 17 with HCC 827 cell line underwent surgery for local tumour at 4-5 weeks from inoculation. The rest of the mice; 4 in A549 group and 5 in HCC 827 group served as controls. All mice were subjected to autopsy at death. **Result:** For the mice with the HCC 827 cell line: Local invasive potential was 90%. 40% of the mice in the control group and 33.3% of the mice in the operated group produced metastases. Survival was similar in operated and control groups (126 versus 127 days). For the mice with A549 cell line: Local invasion and metastases were seen in all mice. The survival in the group undergoing surgery was 129 days versus 107 days in the control group. **Conclusion:** Both the cell lines have good invasive potential, A549 cell line scored over HCC827 in producing metastases. All the metastases were noted only in the lungs. This study can serve as a background to evaluate the role of peri-operative inhibition with epidermal growth factor receptor tyrosine kinase inhibitors and/or mTor inhibitors.

Keywords: EGFR TKI, xenografts, surgical intervention

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-038 DIAGNOSIS OF LEPTOMENINGEAL DISEASE AND CLONAL HETEROGENEITY WITH DIGITAL DROPLET PCR (DDPCR) IN EGFR MUTATED NSCLC

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Background: Non-small cell lung cancer (NSCLC) spread to the central nervous system (CNS) is associated with universally poor outcomes. Diagnosis of leptomeningeal (LM) disease is particularly challenging, with radiological and cytological assessment of CSF often negative. Examination of cell-free DNA (cfDNA) is promising method for the assessment of tumour mutation status and disease monitoring. We examine its utility in the diagnosis and management of LM disease. **Method:** Patients with EGFR mutated NSCLC with symptoms suggestive of LM disease underwent cerebrospinal fluid (CSF) sampling and ddPCR assessment. Matched plasma and/or tumour biopsy samples were obtained. Clinical data was collected retrospectively. Genomic DNA was extracted from 1 mL of CSF and 4 mL of plasma using the Qiagen QIAamp Circulating Nucleic Acid kit and T790M and L858R mutations were assessed by using the QX200 ddPCR assays. Survival was calculated from diagnosis and diagnosis of LM disease. **Result:** Seven patients (pts) were included in the analysis. Most pts, 6/7 (86%) developed LM either during or after EGFR tyrosine kinase inhibitor (TKI) therapy. EGFR mutations were demonstrated in CSF in 6 (86%) pts, but only 2 (29%) demonstrated the same mutation profile in both CSF and plasma. Causes of discrepancy were between CSF and plasma/tissue were: two cases were CSF positive but had no extrathoracic disease to biopsy, 1 case was negative in the CSF for T790M but positive in plasma and on biopsy and one case was wild type in CSF but positive on plasma and biopsy for G719A+T790M mutation. Six pts (86%) received therapy after diagnosis of LM disease and OS from LM diagnosis ranged from 1.0 -15.8 months.

Sex/ Age	Therapy at diagnosis of CNS disease	Duration of response to prior TKI (months)	Therapy after diagnosis of CNS disease	OS from diagnosis (months)	OS from diagnosis of LM (months)
M/64	Nivolumab	Erlotinib: 12.4 Gefitinib: 2.5	AZD3759 WBRT Osimertinib	52.7*	15.8*
F/68	Osimertinib	Erlotinib: 18.2 Osimertinib: 7.2	Nil	28.6	1.7
F/50	Osimertinib	Erlotinib: 6.4 Osimertinib: 6.1	Erlotinib (1500mg weekly)	15.7	1.0
F/79	Nil	N/A	Erlotinib (1500mg weekly)	74.5*	9.5*

M/64	Erlotinib	Erlotinib: 10.5	Erlotinib (1500mg weekly)	15.0	9.1
F/63	Erlotinib	Erlotinib: 5.9	Osimertinib	7.8*	1.3*
M/60	Erlotinib	Erlotinib: 22.0	Erlotinib (1500mg weekly)	31.0*	7.4*

Sex/ Age	Baseline EGFR mutation	Tissue biopsy mutation profile	CSF EGFR mutation profile (ddPCR)	Plasma EGFR mutation profile (ddPCR)	CSF cytology
M/64	L858R	L858R	L858R + T790M	L858R + T790M	Positive - carcinoma
F/68	L858R	L858R + T790M	Sample 1: L858R Sample 2: L858R + T790M	N/A	Sample 1 - negative Sample 2 - positive
F/50	L858R	L858R + T790M	L858R	L858R + T790M + C797S	Positive - carcinoma
F/79	Exon 19 deletion	No site for biopsy	Exon 19 deletion	Wild type	Positive - carcinoma
M/64	L858R	No site for biopsy	L858R	Wild type	Not performed
F/63	G719A	G719A + T790M	WT	G719A	Not performed
M/60	Exon 19 deletion	No site for biopsy	Exon 19 deletion	Exon 19 deletion	Negative

Conclusion: ddPCR is able to detect cfDNA in CSF, where other diagnostic modalities may be negative, and demonstrates both initial and resistance mutations. Heterogeneous mutation status may guide therapy when LM disease remains sensitive to targeted therapy.

Keywords: Heterogeneity, cell-free DNA, Lemptomeningeal disease

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-039 ACQUIRED RESISTANCE TO EGFR-TKI IN THE UNCOMMON EGFR MUTATION, G719S

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Background: Acquired resistance (AR) to EGFR-TKI is a common event and several mechanisms including T790M, MET amplification, PTEN down regulation have been reported for the common EGFR mutations, Deletion 19 and L858R. An EGFR G719X mutation is an uncommon mutation and is known to show sensitivity to EGFR-TKIs in a series of clinical reports and in experiments using transformed cultured cells. However, there is neither established lung cancer cell line nor resistant cell line reported in the literature, which harbors the EGFR G719X mutation. Here we established a lung adenocarcinoma cell line (G719S-GR) from malignant pleural effusion of a patient whose tumor developed acquired resistance from initial gefitinib treatment. **Method:** G719S-GR cells were established and maintained in RPMI1640 medium supplemented with 10%FBS and 10μM ROCK inhibitor (Y-27632, Wako). The ROCK inhibitor was removed from the medium for the following experiments. Cell growth inhibition was examined with gefitinib, afatinib and osimertinib using CellTiter-Glo (Promega), and a comprehensive genomic analysis was performed using hybrid capture based NGS (NCC oncopanel, Agilent; MiSeq, Illumina) for G719S-GR and MLPA (Salsa, MRC-holland) for clinical samples. Western blot analyses were also performed to identify the mechanism of resistance to gefitinib. **Result:** Cell growth inhibition test revealed EGFR-TKI resistance in G719S-GR cells with LC50 of approximately 20μM for either gefitinib or afatinib, and 2μM for osimertinib, indicating the G719S-GR cells are also resistant to EGFR-TKIs in vitro. From the NGS analysis, G719S-GR cells are proven to harbor EGFR mutations (G719S and E709A) as well as amplification of EGFR, IL7R, MYC and FGFR1 locus. Homozygous deletion of CDKN2A and loss of PTEN, TSC1 were also detected. In order to estimate the mechanism of EGFR-TKI resistance, copy number analyses of several tumor suppressor genes were performed by MLPA using genomic DNA from G719S-GR and tumor biopsy sample (obtained before gefitinib treatment). Losses of CDKN2A, PTEN and TSC1 were confirmed in G719S-GR cells, whereas the loss of PTEN was not observed in gefitinib-naiive tumor sample. Finally, an AKT inhibitor, LY294002 could inhibit the AKT pathway, when it was combined with gefitinib. **Conclusion:** EGFR-TKI resistant mechanisms have not been investigated for uncommon mutations so far. The newly established G719S-GR cell line could be a useful tool for AR mechanism of the G719X mutation, and PTEN loss could be one of the AR mechanism. Further experiments are warranted.

Keywords: Acquired resistance, EGFR-TKI, PTEN

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-040 DRIVER GENE DETECTION IN CHINESE NSCLC PATIENTS USING CSMART AND PROGNOSIS ANALYSIS

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Background: Circulating single-molecule amplification and resequencing technology (cSMART) based on next-generation sequencing is highly sensitive, accurate and quantificational. The purpose of this study is to detect the status of 9 driver genes in Chinese NSCLC patients using cSMART and analyze the associations of gene status, clinical characteristics and prognosis. **Method:** The tissue or plasma samples of 85 patients diagnosed NSCLC from Hangzhou First People's Hospital were collected. *EGFR, KRAS, ALK, ROS1, PIK3CA, c-MET, RET, BRAF* and HER2 genes were combined detection using cSMART. The association between gene status and clinical characteristics was analyzed by chi-square test and Fisher's exact. Kaplan-Meier survival curves were plotted for overall survival (OS) and analyzed with the log-rank test. Cox proportional hazards regression was used for multivariate analysis. **Result:** Amongst 85 NSCLC patients, EGFR mutations were more frequent (57.6%), followed by KRAS mutation (18.8%), ALK mutation (10.6%), ALK fusion (9.4%), MET mutation (9.4%), PI3KCA mutation (8.2%), ROS1 fusion (3.5%), BRAF mutation (1.2%), RET fusion (1.2%) and HER2 mutation was not found. Furthermore, the abundances of gene mutation were relatively low. The EGFR mutation rate was higher in patients with adenocarcinoma histology than in those with squamouscarcinoma histology *(P=0.03)*. T790M mutation was more common in patients with a history of TKI treatment (P<0.01) and acquired T790M mutation was often accompanied by the original sensitive mutation (P<0.01). ALK fusion was more easily detected in tissue sample. All 8 MET gene exon14 skippings were found in adenocarcinoma histology and this gene alteration often happened after TKI treatment *(P=0.02)*. OS was significantly improved in the EGFR mutation group compared with the wild group (median 32m vs 19m) (P=0.05). No significant survival difference between KRAS mutation and wild group was found *(P>0.05)*. Among EGFR wild advanced NSCLC patients, the median OS of KRAS mutation group was 13 months while that of wild group was 26 months, but there was no significant difference *(P>0.05)*. Multivariant analyses showed gender, TKI treatment history and smoking history were independent prognostic factors in NSCLC*(P<0.05)*
Conclusion: EGFR mutation is the most common driver gene in Chinese NSCLC, especially in adenocarcinoma patients, which often occurs in exon 19,20 and 21 region. Then followed by KRAS mutation, it mostly occurs in exon 2. MET gene exon14 skipping is common in patients with adenocarcinoma or post-TKI treatment, which may be related to TKI resistance. Gender, smoking history and TKI treatment history could be independent prognostic factors in NSCLC.

Keywords: NSCLC, driver gene, cSMART

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-041 EGFR AMPLIFICATION MEDIATES RESISTANCE TO TAS121, A THIRD-GENERATION EGFR-TKI, IN EGFR T790M-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Third-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have shown promising efficacy in EGFR T790M-mutation-positive non-small cell lung cancer (NSCLC). However, acquired resistance to third-generation EGFR-TKIs has been reported in EGFR T790M-positive NSCLC. The mechanism of resistance to these third-generation EGFR-TKIs has not been fully elucidated. We report a case of metastatic NSCLC harboring an EGFR T790M mutation in which EGFR amplification mediated acquired resistance to TAS121, a novel third-generation EGFR-TKI. **Method:** A 68-year-old woman with metastatic lung adenocarcinoma, harboring an *EGFR* L858R mutation, received gefitinib in September 2013. Although the patient achieved a partial response, the tumor progressed and she was treated with 4 cycles of chemotherapy using cisplatin and pemetrexed followed by pemetrexed maintenance therapy. In April 2015, computed tomography (CT) showed disease progression (PD) with liver metastases, and re-biopsy of hepatic lesions was performed. Tumor genotyping with the PNA LNA PCR-Clamp method revealed an original mutation of *EGFR* L858R in exon 21 and a secondary mutation of *EGFR* T790M in exon 20. Tumor progression was noted after completion of one cycle of docetaxel, and she was enrolled into a phase 1 trial of TAS121 in June 2015. Although she showed a partial response to TAS121, PD was confirmed on CT, which indicated progression of liver metastases. She discontinued TAS121 and received supportive care. She died in October 2015, and an autopsy was performed. To determine the mechanism of resistance to TAS121, we performed next-generation sequencing (NGS) (NCC OncoPanel, Agilent) with post-TAS121 samples obtained from progressing liver lesions during TAS121 treatment. We also conducted fluorescence *in situ* hybridization (FISH) analysis for *EGFR* in pre-TAS121 liver lesions, post-TAS121 liver lesions, and autopsy samples from the lung and liver. The study protocol

was approved by the Ethical Review Committee of the National Cancer Center Hospital. **Result:** NGS with the post-TAS121 liver samples showed *EGFR* amplification in the tumor cells (log2 ratio 2.2). On FISH analysis, *EGFR* amplification was not detected in the pre-TAS121 liver lesions (the ratio of EGFR signals to CEP signals 1.7), but was detected in the post-TAS121 liver lesions (2.1) and those obtained at autopsy (3.0). *EGFR* amplification was not detected in the autopsy samples of the lung lesions (1.0), which remained stable during TAS121 treatment. **Conclusion:** Our case revealed that genomic instability of the *EGFR* domain contributed to the development of resistance to TAS121. Further molecular analysis is warranted to understand the role of *EGFR* amplification in acquired resistance to third-generation EGFR-TKIs.

Keywords: EGFR-TKI, TAS121, EGFR amplification

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-042 DS-1205B, A NOVEL, SELECTIVE, INHIBITOR OF AXL, DELAYS THE ONSET OF RESISTANCE AND OVERCOMES ACQUIRED RESISTANCE TO EGFR-TKIS

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Background: AXL is a receptor tyrosine kinase that plays an important role in signal transduction in normal and malignant cells. Abnormal expression and/or activation of AXL can provide a survival advantage for certain cancer cells, and AXL up-regulation is associated with poor prognosis in several cancers. Recently, it has been reported that up-regulation of AXL expression represents a mechanism of EGFR-TKI resistance in EGFR-mutant non-small cell lung cancer. **Method:** Kinase activity was measured by mobility shift assay. The inhibition of hGAS6-induced migration was measured in AXL-transfected NIH3T3 (NIH3T3-AXL) cells using a real-time cell analyzer (RTCA) DP instrument. The in vivo anti-tumor effects of DS-1205b mono- and combination-therapy with EGFR-TKI were evaluated in NIH3T3-AXL allograft and EGFR-mutant NSCLC (T790M-negative) HCC827 xenograft models. Protein expression was analyzed by Western blot or immunohistochemistry, and gene expression was analyzed by RT-PCR or RNA seq. **Result:** DS-1205b selectively inhibited AXL kinase activity with IC_{50} of 1.3 nM, and with NIH3T3-AXL cells, DS-1205b inhibited hGAS6-induced migration in vitro with EC_{50} of 2.7 nM. DS-1205b monotherapy exerted significant antitumor activity including tumor regression in an NIH3T3-AXL allograft model. In an HCC827 xenograft model, combination treatment with DS-1205b and osimertinib significantly delayed on the onset of tumor resistance compared to osimertinib alone in a manner proportional to DS-1205b dose. DS-1205b also showed a similar resistance delay effect in combination with erlotinib or gefitinib in the same xenograft model. AXL up-regulation was associated with the development of resistance to erlotinib or gefitinib treatment in another HCC827 xenograft study, and DS-1205b restored the antitumor activity of erlotinib in erlotinib-resistant tumors in a dose-dependent manner. Combination treatment of DS-1205b with osimertinib, erlotinib, or gefitinib delayed the onset of resistance in acquired-resistance models using HCC827, and among these three models, the delay of resistance onset with DS-1205b was observed to be greatest in the osimertinib model. AXL and some EMT-related genes were up-regulated in EGFR-TKI-resistant tumors, while cell cycle, migration, or angiogenesis factors were down-regulated by treatment of those tumors with combination of DS-1205b and EGFR-TKI. **Conclusion:** In an HCC827 xenograft model of EGFR-mutant NSCLC, inhibition of AXL activity by DS-1205b restored sensitivity to erlotinib, and addition of DS-1205b to osimertinib delayed the onset of resistance to osimertinib. These findings support further non-clinical and clinical studies targeting inhibition of AXL in EGFRm NSCLC. A phase I study in combination with osimertinib is ongoing, and its design is shown in a separate presentation.

Keywords: EGFR-TKI, DS-1205, Axl

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P3.02-043 CLINICAL AND GENETIC FEATURES IN LUNG ADENOCARCINOMA WITHOUT EGFR MUTATION AND ALK REARRANGEMENT IN TAIWAN

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Background: For the majority of advanced lung adenocarcinoma patients, absence of epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement usually means platinum based doublet chemotherapy would be the standard treatment. However, treatment result of chemotherapy is suboptimal. Several driver mutations, although not common, are potential therapeutic targets which may significantly influence patients' outcome. **Method:** Lung adenocarcinoma patients with neither EGFR mutation nor ALK fusion were recruited in this study. KRAS, NRAS and BRAF mutations were examined by mass spectrometry. Other 53 gene fusions and mutations were analyzed by Archer FusionPlex Solid Tumor Kit on Ion Torrent PGM next generation sequencer. **Result:** Forty patients were enrolled. Demographics showed a median age of 62.5 (39-88), male predominance (M/F, 24/16), and non-smoking history dominance (never/past/current, 19/9/12). The average pack-year of smoking was 22.1 (0-120). The specimens examined were from lung (20), bone (1), brain (3), pleura (1), pleural effusion (11), lymph node (2) and soft tissue (2), respectively. Collectively, we identified eight KRAS mutations (20%), one NRAS mutation (2.5%), one BRAF mutation (2.5%), one CD74-ROS-1 fusion (2.5%), two MET exon 14 splicing (5%), and all of them were mutually exclusive. There were three invasive mucinous adenocarcinomas, and two of them harbored KRAS mutation. The majority of patients had received chemotherapy and two had received immunotherapy. The patient with CD74-ROS-1 fusion, a female non-smoker, was enrolled in an entrectinib clinical trial (STARTRK2) and experienced a rapid and dramatic response. **Conclusion:** Survey for other driver mutations brings treatment options for lung adenocarcinoma patients without EGFR mutation and ALK rearrangement.

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P3.02-044 DIAGNOSIS AND MONITORING OF EGFR MUTATION STATUS WITH CFDNA IN ADVANCED NSCLC: A PROSPECTIVE SINGLE INSTITUTION STUDY IN ASIA

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Background: NSCLC patients in advanced stage with tumors that harbor EGFR sensitizing mutations are eligible for treatment with tyrosine kinase inhibitors (TKI) due to a high likelihood of response. The challenge with NSCLC is that often only small biopsy samples are available and when they are insufficient for molecular diagnostics, a repeat biopsy is not always possible and this results in delays in starting treatment. Molecular testing on circulating cell free DNA (cfDNA) from plasma is an alternative methodology that is readily applicable. We used the Roche **cobas®** EGFR Mutation Test V2 to diagnose (on tissue) and follow patients with EGFR sensitizing mutations to evaluate longitudinal changes in EGFR mutation status and SQI (Semi-quantitative Index) in plasma relative to standard of care for patients during TKI treatment. The sequential EGFR SQI values will be used to evaluate the relationship between molecular and clinical responses. **Method:** We included 60 patients (36 F/24 M) who had at least three follow up blood samples drawn post TKI treatment start. Ten ml of blood was collected in EDTA tubes from each subject at every visit. All patients had both tissue as well as baseline plasma EGFR results available. Serial follow up plasma samples were available on all patients. All subjects were treatment naïve, 80% (48/60) had no history of smoking and majority (45/60, 75%) presented with extra thoracic disease with clinical stages ranging between III-IV at diagnosis. **Result:** The L858R mutation was the most common EGFR mutation detected (58.3%) on the tissue followed by exon 19 deletion (35.0%). Two patients had dual mutations detected on tissue as well as in the baseline plasma. Plasma cfDNA analysis detected EGFR mutations in 78% of the baseline samples. Analysis of the serial plasma collected from patients who progressed while on 1st line TKI showed reappearance of the original EGFR sensitizing mutations with increasing SQI levels before emergence of a T790M mutation. T790M mutation was detected in 20.0% (12/60) of the patients on TKI treatment. **Conclusion:** This study clearly demonstrates that EGFR mutations can be reliably detected in plasma of NSCLC patients to confidently diagnose the presence of TKI resistance mutations using the Roche **cobas®** EGFR Mutation Test V2. Additionally, plasma SQI measurement can be used to monitor patients to detect the development of molecular TKI resistance. We will also show that serial measurement in the EGFR SQI can predict the relationship between molecular and clinical responses as well as tumor progression.

Keywords: Non-small cell lung carcinoma, circulating cell free DNA, EGFR mutation

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P3.02-045 PREVALENCE OF ALK GENE ABNORMALITIES IN ROUTINE DIAGNOSTICS OF POLISH NSCLC PATIENTS

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Background: In NSCLC patients, *ALK* gene rearrangement should be diagnosed using fluorescence *in situ* hybridisation (FISH) method. However, immunohistochemistry (IHC) is considered as screening method for expression of ALK abnormal protein. There are discrepancies regarding the specificity of both methods and result interpretation. **Method:** 1102 Polish NSCLC patients (85,7% of adenocarcinoma, 443 female, 659 male, median age: 65 years) were analysed for *EGFR* gene mutations using real-time PCR, after that for *ALK* abnormalities using IHC technique with D5F3 antibody, followed by FISH method using Vysis molecular probe. **Result:** *ALK* rearrangements detected by FISH method were confirmed in 49 (4.5% of all patients) out of 203 cases (18.4% of all patients) with ALK abnormal protein expression (specificity of IHC test – 85.4%). The median age of patients with *EGFR* gene mutations was 65 years, with *ALK* rearrangement 64 years

(p=0.1040) and without these changes - 65 years (p=0.4932). *ALK* rearrangement was significantly more frequently detected in women (28 cases, 6.3%) than in men (21 cases, 3.2%; p=0.0134) and in FFPE tissue (46 case, 5.9%) than in cell-blocks (3 cases, 0.95%; p=0.0003). Median percentage of nuclei with *ALK* rearrangement in *ALK*-positive patients was 25%. In *ALK*-positive cases, ALK rearrangement defined as coexistence of single red and split signals were observed in 27 cases (55.1%), only split signals were observed in 1 case (2%) and only single red signals were diagnosed in 21 patients (42.9%). In this group of patients, median percentage of single red signals per nuclei was 45%, split signals – 8%, and fused signals – 47%. The polysomy (≥4 gene copy number per nuclei) of *ALK* gene was observed in 43 (36% of all FISH diagnosed patients) cases. **Conclusion:** The IHC method as a screening method is characterized by relatively low specificity. Cell blocks are a rather difficult material for ALK abnormalities analyzes (probably high risk of false negative results). The interpretation of FISH results with predominant single red signals requires considerable attention.

Keywords: ALK gene abnormalities, NSCLC, Diagnostics

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-046 EGFR-GRB2-GEP100 COMPLEX PROMOTED ITS INVASIVE AND METASTATIC POTENTIAL VIA ARF6 PATHWAY IN LUNG ADENOCARCINOMA

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Background: Invasive and metastatic activities are the most challenging hallmark of cancer. We previously showed that GEP100-Arf6 pathway signals from stimulated ErbB family receptors was pivotal for epithelio-mesenchymal transition (EMT) and induced cancer invasive activity leading to nodal and distant metastasis. Here we have examined the enhancing effect of Grb2 on the binding of GEP100 with EGFR leading to Arf6 activation and EMT, and the significance of EGFR-Grb2-GEP100 binding complex on the invasive and metastatic potentials in lung cancer cells as well as in clinical settings. **Method:** A549 lung cancer cells with overexpressed HA-tagged Grb2 or HA alone were stimulated with EGF, and the lysates were applied for the immunoprecipitation assay against GEP100. Arf6 activities of these cells were examined using the pulldown assay with GST-tagged GGA protein. *In vitro* invasive activities of those cells were measured by Matrigel invasion assays. To clarify the mutual binding sites between Grb2 and GEP100, GST-tagged proteins including Plekstrin homology (PH) domain of GEP100 or SH2/SH3 domain of Grb2 inserted into pGEX vector were produced in bacteria with glutathione-beads purification. Furthermore, mutant Grb2-R86K which impairs the binding to pEGFR was transfected into A549 cells to examine the changes of the binding affinity between pEGFR and GEP100. Last, we performed immunohistochemistry against Grb2, GEP100, and phosphorylated receptor tyrosine kinases (pRTKs) comprising EGFR, Her2, c-Met, and VEGFR, which have been known to bind GEP100 leading to Arf6 activation, for 239 cases of primary lung adenocarcinoma specimens resected in our hospital. The expression of these molecules integrated with the clinicopathologic data and EMT status information were statistically analyzed. **Result:** Grb2 overexpression via Grb2-GEP100 interaction promoted EGFR-GEP100 binding leading to Arf6 activation and tumor invasive activity in A549 cells. PH domain of GEP100 and N-terminal SH3/SH2 domain of Grb2 were contributed to this binding. Mutant Grb2-R86K exogenous expression in A549 cells resulted in the decrease of the binding between pEGFR and GEP100. Among 155 cases of positive pRTKs, the combination of Grb2 and GEP100 positivity were significantly associated with activated EMT levels, node metastasis, and poor disease-free survival (p=0.048, p=0.08, and p=0.0075, respectively). **Conclusion:** EGFR-Grb2-GEP100 complex promoted its invasive and metastatic potential via Arf6 pathway in lung adenocarcinoma. The inhibition of the binding among these molecules may be useful to control lung cancer progression.

Keywords: EGFR, GEP100-Arf6 pathway, invasion and metastasis

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-047 TESTING EGFR AND ALK IN LARGE CELL NEUROENDOCRINE CARCINOMA OF THE LUNG. LOOKING FOR BIOLOGICAL FEATURES IN RARE TUMORS

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Background: Large-cell neurodendocrine carcinoma (LCNEC) of the lung is a high-grade carcinoma. It is a very rare tumor, approximately 3% of all lung malignancies. Despite LCNEC responds to cisplatin-based chemotherapy prognosis remains poor. We try to Identify positive cases for EGFR mutations and ALK rearrangement by using fluorescence in situ hybridization (FISH) as gold standard and its correlation with immunohistochemistry (IHC) in LCNEC aming to find new therapeutic options for those patients. **Method:** Patients with LCNEC in our Hospital between 1998 and 2017 were included; classification were originally performed according to the WHO2004 scheme and updated to the WHO2015 scheme. EGFR mutation was determined on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue with the cobas® EGFR Mutation Test v2. ALK FISH testing was performed using the Vysis ALK break-apart FISH kit (Abbott Molecular). At least 50 non-overlapping nuclei were scored by two FISH assays expert pathologists. A higher number of nuclei (100) was counted in cases with the results close to cut-off values.Tumours were interpreted as positive if a split pattern and/or single orange signal without a corresponding green signal were identified in at least 15% of tumour cells ALK IHQ test was performed retrospectively on freshly cut 4-lm thick FFPE tissue sections using anti-ALK (D5F3 clone) rabbit monoclonal antibody on a BenchMark XT autostainer with the Ultraview diaminobenzidine (DAB) detection kit. Staining was positive if tumour cells showed moderate or strong multifocal or diffuse expression. Positive cases showed granular cytoplasmic pattern. Cases were considered concordant if ALK FISH and ALK IHC results were identical. **Result:** 27 cases, all of them with enough samples for additional EGFR, ALK FISH and ALK IHC testing were identified. Although 4 cases were positive for ALK staining with IHC only one showed expression in more than 90% of tumor cells and it was also positive for ALK rearrangement with FISH. As reported in literature, we have observed some moderate stippling staining in alveolar and peritumoral macrophages with IHC . Only one was EGFR mutated in exon 20, harboring G719X mutation **Conclusion:** To our knowledge very few LCNEC carrying EGFR mutation or ALK rearrangement have been reported. It highlights the possibility of treating those patients with targeted therapy Although we have found good correlation between FISH and IHC, we dare to recommend still as gold standar test, FISH to assess ALK gene rearrangement.

Keywords: EGFR, ALK, Large-cell-neuroendocrine carcinoma

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-048 CLINICOPATHOLOGIC CHARACTERISTICS OF NON-SMALL CELL LUNG CARCINOMAS HABOURING MET EXON 14 SKIPPING MUTATIONS

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Background: Non–small cell lung carcinomas (NSCLC) harboring mutations involving MET exon 14 splice sites may respond to MET inhibitors. We investigated the clinicopathologic characteristics of patients with NSCLC with MET exon 14 skipping mutations. **Method:** We examined 192 patients with NSCLC with wild-type EGFR/KRAS/ALK by reverse transcritase-polymerase chain reaction combined with SYBR Green melting curve/fragment analyses to detect the presence of MET exon 14 mutation. Clinical characteristics of MET exon 14 mutated NSCLC were compared with those of NSCLC with EGFR or KRAS mutations. MET immunohistochemistry and fluorescent in situ hybridization will be performed afterwards. **Result:** MET exon 14 mutations were identified in 21 of 192 NSCLC with wild-type EGFR/KRAS/ALK (10.9%), accounting 6.6% of all NSCLC (n=319). Patients with MET exon 14–mutated NSCLC were significantly older (median age, 77 years) than patients without MET exon 14 mutation (median, 71.5 years), and 12 (57%) were men. MET exon 14-mutated NSCLC were staged as stage 0 (n=1), stage IA (n=12), stage IB (n=4), stage IIA (n=3), or stage IV (n=1). MET exon 14–mutated NSCLC were histologically adenocarcinomas (n=20), consisting of adenocarcinoma in situ (n=1), minimally invasive adenocarcinomas (n=2), invasive adenocarcinomas (n=17) including lepidic (n=7), papillary (n=7), acinar (n=5), or solid (n=1) predominant subtypes, and adenosquamous carcinoma (n=1). **Conclusion:** MET exon 14 mutations were identified in 6.6% of all NSCLC, which may represent a clinically unique molecular subtype and an important therapeutic target in NSCLC.

Keywords: MET exon 14 skipping mutation, Non-small cell lung carcinoma, RT-PCR

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-049 THE EVALUATION OF CIRCULATING MIRNA EXPRESSION IN PLASMA AS THE EPIGENETIC MARKER OF EGFR MUTATION STATUS IN NSCLC PATIENTS

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Background: The epidermal growth factor receptor (EGFR) mutation status is so far the only validated predictive biomarker of response to EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy in non-small cell lung cancer (NSCLC) patients. MicroRNA (miRNA) is the class of small non-coding RNA that regulates gene expression. Dysregulation of miRNA function has been implicated in lung carcinogenesis. Stable forms of miRNAs are present in blood (circulating miRNAs) and their expression pattern is disease-specific. This phenomenon implies their potential usefulness as molecular markers in NSCLC diagnosis and therapy. Nevertheless, there is no consensus regarding normalization of the circulating miRNA expression analysis. We aimed to evaluate the potential diagnostic usefulness of several circulating miRNAs, that according to different data normalization approaches might have discriminative

value for EGFR mutant-positive and negative NSCLC patients. **Method:** Total RNA was extracted from 100 µL of plasma, material with signs of hemolysis was excluded (as per visual inspection and factor ΔCq value (miR-23a-miR-451a)<5). The exogenous UniSP6 RNA spike-in was used as an internal control of extraction efficacy. Expression of 5 miRNA sequences (miR-504, miR-122, miR-195, miR-10b and miR-21) and UniSP6 in plasma of 60 non-squamous NSCLC patients (43 resectable and 17 advanced stage; 31 patients EGFR+ in paired tumor tissue and plasma specimen) was investigated using reverse transcriptase real-time PCR (RT-qPCR), Next, association between circulating miRNA expression and EGFR mutation status was analyzed according to different data normalization approaches (miR-16 and miR-191 as normalizers). **Result:** Among the 5 circulating miRNAs tested, only plasma miR-504 expression was significantly associated with EGFR mutation status in NSCLC patients regardless the normalizer used (p=0.0158 and p=0.002 for miR-16 and miR-191 normalization, respectively). This association was significantly stronger when only plasma samples from adenocarcinoma patients were analyzed (p=0.0004 and p=0.001 for miR-16 and miR-191 normalization, respectively). Moreover, the highest discriminatory power of circulating miR-504 was showed for patients with exon 19 deletions versus those with wild-type EGFR when the data was normalized according to mir-191 (AUC=0.807 p<0.0001). **Conclusion:** Our study demonstrated the feasibility and potential diagnostic value of mir-504 expression analysis in plasma for discrimination between EGFRm+ and EGFRm- NSCLC patients. However, the normalization strategy is of key importance, strongly impacting circulating miRNA analysis outcome. The study is to be continued.

Keywords: EGFR mutation status in NSCLC, Predictive biomarker, microRNA

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-050 MECHANISMS OF ACQUIRED RESISTANCE TO THE ALK INHIBITOR LORLATINIB IN ALK-REARRANGED NSCLC CELL LINES

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Background: Lorlatinib is a potent third-generation ALK tyrosine kinase inhibitor, which has demonstrated promising efficacy in ALK-rearranged NSCLC patients and excellent preclinical activity against ALK resistance mutations. However, as with all targeted treatments, resistance inevitably emerges. The molecular mechanisms underlying lorlatinib resistance remain largely undescribed, except for the L1198F mutation in ALK that was presented in a case study involving a single patient. Thus, the present study is performed to discover novel mechanisms of resistance to lorlatinib treatment. **Method:** H3122 (EML4-ALK v1) and H2228 (EML4-ALK v3) NSCLC cell lines were treated with increasing doses of lorlatinib or the first-generation ALK inhibitor crizotinib (10 nM - 1 µM). The resulting cell lines were investigated using MTS viability assays with ALK inhibitors to confirm resistance. Targeted next generation sequencing (NGS) using the Oncomine Focus Panel (Thermo Fisher) will be used to examine potential ALK-dependent resistance mutations and/or bypass mechanisms. This panel detects variants in 52 different genes – 35 genes are investigated for hotspot mutations, 19 genes for focal CNV gains, and 23 genes for fusions. The *ALK* gene is covered by both the hotspot, CNV, and fusion analyses, thus ensuring that all types of ALK-dependent resistance mechanisms will be discovered. **Result:** The two cell lines were treated with either lorlatinib or crizotinib in triplicates resulting in 12 resistant cell lines. Resistance occurred following approximately 4-6 months of drug treatment and was confirmed using MTS assays. The lorlatinib-resistant H3122 cell lines were insensitive to both crizotinib and lorlatinib treatment. This indicates that the mechanism of resistance is of a novel character, as the known L1198F ALK mutation is sensitive to crizotinib treatment. Hence, we are currently performing NGS analyses of all 12 resistant cell lines in order to discover potential resistance mechanisms. **Conclusion:** Using the comprehensive NGS Oncomine Focus Panel, we will be able to discover novel resistance mechanisms to the ALK-targeted drug lorlatinib, which will provide new knowledge of the nature of acquired resistance. This will help determining which mechanisms of resistance to look for in lorlatinib-resistant patients in future investigations, ultimately improving the treatment of this subset of patients.

Keywords: ALK-TKI, Acquired resistance, NSCLC

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P3.02-051 LOW CONSISTENCY BETWEEN FGFR1 GENE AMPLIFICATION AND PROTEIN EXPRESSION IN SQUAMOUS CELL LUNG CANCER (SQCLC)

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Background: FGFR type 1 (*FGFR1*) gene amplification has been identified as one of the key potentially actionable targets in SqCLC, given FGFR1 role in oncogenesis. Equivocal results from the pre-clinical and clinical studies point at the necessity of efficient and reliable predictive identification of potential candidates for therapy with FGFR1 inhibitors. Published data regarding correlation between FGFR1 protein expression and *FGRF1* gene amplification are discordant. Our previous analyses demonstrated relatively low intra-tumor heterogeneity of both markers in analyzed SqCLC cases. Therefore, we aimed at verifying their concordance, or lack thereof, in the larger series of SqCLC tumors. **Method:** 74 SqCLC tumors were analyzed (2 FFPE sections per tumor). *FGFR1* gene copy number was assessed by FISH method using probes specific for the 8p12 locus and the chromosome 8 centromere (CEN8). *FGFR1* amplification criteria: FGFR1/CEN8 ≥2.0 or the average number of FGFR1 signals per cell >6 or >10% of tumor cells containing ≥15 FGFR1 signals. FGFR1 protein expression was determined by immunohistochemistry (IHC). Expression was defined as staining intensity (graded from 0 to 3+) in >1% of the cancer cells. Correlation between FISH and IHC results was performed using the GraphPad Prism software using Spearman test. **Result:** 11/74 (14.86%) SqCLC tumors demonstrated *FGFR1* amplification. The average *FGFR1* gene copy number per cell ranged from 1.23 to 13.97 (mean±SD 3.61±2.08) while the mean FGFR1/CEN8 ratio was 1,27 (range: 0.53–4.35). The mean content of tumor cells with ≥15 *FGFR1* copies was 10.19%. In IHC(+) tumors (22/74, 29.73%) the percentage of stained cancer cells with intensity ≥2 was low - only 12/74 (16.22%) samples.The FISH and IHC results were consistent in 79.73% SqCLC tumors (n=59), 55/74 (74.32%) tumors were double-negative, while only 4/74 (5.41%) double-positive. 15/74 pts results were discordant: 7/74 (9.46%) IHC(-) FISH(+), while 8/74 (10.81%) pts IHC(+) FISH(-). There was no correlation between *FGFR1* amplification and FGFR1 protein overexpression (P=0.466; r=0.086) in the analyzed series of 74 SqCLC tumors. **Conclusion:** While we demonstrated relative SqCLC tumor homogeneity in terms of *FGFR1* amplification and expression for as many as 74% of tumors, most were double negative. In samples demonstrating any positivity, *FGFR1* amplification did not relate to protein expression. Therefore, further more detailed comparative evaluation of *FGFR1* gene expression or FGFR1 locus might be informative to better understand the determinants of response to FGFR inhibitors. Study funded by NCBiR: ‹Development of novel biomarkes and innovative FGFR kinases inhibitor as an anti-cancer therapy› (nr 266776, program: STRATEGMED2).

Keywords: FGFR1 expression, biomarker, Squamous cell lung cancer

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-052 STABILITY OF EGFR MUTATIONS IN WHOLE BLOOD AND PLASMA IN PATIENTS WITH NSCLC

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Background: The **cobas**® EGFR Mutation Test v2 (Roche Molecular Systems Inc.) has recently been IVD approved in the US for detection of epidermal growth factor receptor (EGFR) mutations in blood samples. Knowledge of the EGFR mutation status in non-small cell lung cancer (NSCLC) patients is essential to designing optimal, individualised treatment. However, implementing blood-based analyses to detect cancer-specific mutations demands standardized preanalytical conditions, but research in this field is rare and inadequate. The aim of this project was to investigate if the result of the EGFR mutation test was influenced by storage of blood and plasma samples under various preanalytical conditions. **Method:** Blood drawn in EDTA tubes from patients with advanced NSCLC was used to establish EGFR mutation stability. The mutation status and amount of mutated DNA was determined using the **cobas**® EGFR Mutation Test v2. **Result:** EGFR mutations are stable in whole blood stored at 32˚C for up to 8 hours. The EGFR mutations are also stable in plasma stored at: 32˚C for up to 24 hours; 2-8˚C for up to three days; and at -20˚C and at -80˚C for 31 days. Investigation of plasma stored for 13 months at -20˚C and at -80˚C is ongoing. **Conclusion:** Our results establish that DNA extracted from blood or plasma stored for an extended period or under different temperatures is suitable for use with the **cobas**® EGFR Mutation Test v2, verifying the robustness, accuracy, and suitability of the assay in the clinic. The results support shipping patient samples to a testing center for EGFR mutation testing using the **cobas**® EGFR Mutation Test v2, enabling more patients to benefit from targeted therapy based on EGFR mutation status.

Keywords: ctDNA, EGFR mutation, Preanalytics

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-053 OPTIMIZATION AND CHARACTERIZATION OF ASSAYS TO IDENTIFY MET EXON 14 SKIPPING IN FFPE EMBEDDED NSCLC SAMPLES

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Background: The hepatocyte growth factor (HGF)receptor (MET), is frequently altered in NSCLC. Despite having a significant number of diverse mutations/ alterations, randomized trials with MET inhibitors have proved disappointing, with no clinical benefit (1). More recently MET exon 14 skipping alterations have emerged as potential therapeutic targets as MET exon as they inhibit the degradation of Met, prolonging its oncogenic activity (2). Patients with Met exon 14 skipping have been found to sensitive to MET inhibitors such as crizotinib, and clinical trials of MET TKIs in METex14 mutated NSCLC are ongoing (1). **Method:** A one-step RT-PCR end-point PCR assay to examine for the detection of Met exon14 skipped mRNAs in FFPE was designed, optimized and tested on a cohort of NSCLC patients. Positive samples were confirmed by targeted next-generation sequencing of these samples. Finally RNA *in situ* hybridization (RISH) was optimised on a cMET exon 14 skipped cell line (NCI-H596) and subsequently performed on full-face sections using a specific BaseScope™ Assay (Techne). **Result:** Initial studies found that standard end-point PCR resulted in significant false-positives. However, a one-step RT-PCR methodology resolved this issue. Met exon 14 skipped samples were then examined in a cohort of pulmonary sarcomatoid carcinomas (PSCs). In agreement with another study of Caucasian patients (3), we identified Met Exon 14 skipped mutations in 2/20 (10%) of patients. Expression of Met exon 14 skipped was confirmed using targeted resequencing by NGS. RISH was also examined in the same samples. **Conclusion:** These results demonstrate the optimization of a methodology to robustly detect Met exon 14 mutated patients in FFPE material by a PCR based assay, with results comparable to those obtained in similar studies. This methodology can be utilised by any standard hospital diagnostic laboratory without the need for any specialized technology such NGS, RISH or FISH. A qPCR based version of this assay is currently being optimized and the results will be presented at the meeting. **References** Reungwetwattana, T. et al., (2017). Lung Cancer 103: 27–37
Pilotto, S. et al. (2017). Ann Transl Med 5(1):2 Saffroy, R. et al (2017). Oncotarget. 2017 Mar 21. doi: 10.18632/oncotarget.16403. [Epub ahead of print]

Keywords: RISH, FFPE, c-Met

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-054 PROGNOSTIC IMPLICATIONS OF ROS1 POSITIVITY IN NON-SMALL CELL LUNG CANCER (NSCLC): A SYSTEMATIC REVIEW OF PUBLISHED LITERATURE

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Background: Oncogenic ROS1 mutations are found to occur in 1-2% of NSCLCs, and efficacy of single-agent Crizotinib (a ROS1 tyrosine-kinase inhibitor) has been demonstrated in ROS1-positive NSCLC. However, our knowledge on the natural disease course in ROS1-positive compared to ROS1-wild type (WT) NSCLC is currently limited. Furthermore, since no randomized prospective trials are likely to be planned to assess treatment outcomes in ROS-1 positive patients, the question whether ROS1-positivity is a favorable or an unfavorable prognostic factor in advanced NSCLC, may remain unanswered. To address this important question, we undertook a systematic review of published literature on the natural history of ROS1-positive NSCLC. **Method:** Databases were mined for published studies on ROS1-positive NSCLC. Studies that included outcomes (either Progression-Free Survival (PFS) or Overall Survival (OS)) with either prior treatment or treatment naïve patients were selected for the analysis. For each study identified, investigators independently extracted and tabulated relevant findings. Data such as ROS1 status, type of diagnostic test, treatment received and response to treatment was extrapolated. To determine if ROS1 status was prognostic, efficacy outcomes (PFS and / or OS) for ROS1-positive patients were compared to the ROS1-WT patients. **Result:** Fifteen publications where survival data for ROS1-positive patients was compared to ROS1-negative patients or other oncogenic driver mutations were selected. Majority (12/15) of these studies were retrospective in nature. Most studies had small numbers of ROS1-positive patients (ranging from 4 to 33). Altogether 179 out of 8292 NSCLC patients were identified as ROS1-positive (2.1%) by various standard diagnostic methodologies. Lack of randomisation and variable study designs limited a formal statistical comparison. The reported benefit in terms of a superior median overall survival (mOS) in ROS1-positive patients was observed in 3 out of 15 studies, whereas 12 out of 15 studies either demonstrated no significant difference or worse clinical outcomes in ROS1-positive vs ROS1-WT patients. Notably, majority of the ROS1-positive patients in the 3 studies showing a superior overall survival received treatment with either Pemetrexed or Crizotinib or Afatinib (an EGFR inhibitor) depending on the absence or presence of concomitant oncogenic driver mutations (EGFR , ALK or KRAS). **Conclusion:** Cumulatively, based on current analyses the body of evidence suggests that ROS1 positivity is unlikely to be a favourable prognostic factor in NSCLC. Importantly, this data may be useful in relatively assessing the impact of emerging therapies such as Crizotinib in ROS1-positive NSCLC patients.

Keywords: ros1, prognostic marker, NSCLC

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-055 DETECTING ALK, ROS1 AND RET GENE TRANSLOCATIONS IN NON-SMALL CELL LUNG CANCER (NSCLC) WITH THE NANOSTRING PLATFORM

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Background: Identification of *ALK, ROS1* and *RET* fusions is critical for guiding target therapy of lung cancers. In this study, we evaluated the transcript-based nanoString assay for detection of ALK fusions compared to immunohistochemistry (IHC) and FISH methods, and the simultaneous detection of ROS1 and RET transcripts in formalin-fixed and paraffin embedded tissues (FFPE). **Method:** A total of 44 patients with NSCLC were selected for this non-consecutive case study. Samples included 24 cases of non-smokers or patients younger than 50 years with negative *EGFR/ ALK* results that are more likely to contain a *ROS1* or *RET* translocation. Eight cases with a discrepancy between ALK IHC and FISH results or equivocal IHC ALK results, as well as 12 cases previously confirmed positive for ALK by IHC were also included. The specimens were assessed for ALK, ROS1 and RET fusion transcripts by nanoString nCounter profiling. **Result:** While nanoString demonstrated 94.9% concordance with IHC and 84.2% concordance with FISH, it detected unknown ALK active transcripts in 3 of 7 cases that showed a discrepancy between IHC and FISH, or which were negative for ALK by IHC and FISH (see table 1). The three equivocal ALK IHC cases were scored negative by the 2 other methods. In addition to ALK, 3 cases of ROS1 and 2 cases of RET fusions were detected by nanoString. ALK, ROS1 and RET fusions were found mutually exclusive. Table 1. Discrepancy of ALK findings by IHC, FISH and nanoString, and crizotinib response

Case	IHC	FISH	FISH positive nuclei (%)	nanoString	Crizotinib response
1	Positive	Negative	3.9	Unknown ALK active fusion	Positive
2	Negative	Negative	3.3	Unknown ALK active fusion	Positive
3	Negative	Negative	8.6	Unknown ALK active fusion	Unknown
4	Negative	Borderline	17.3	Negative	Not treated
5	Negative	Borderline	15.1	Negative	Not treated
6	Negative	Borderline	19.7	Negative	Not treated
7	Negative	Positive	24	Inconclusive	Unknown

Conclusion: NanoString performed well in lung cancer FFPE tissue including cytology materials. The results are highly concordant with the current standard methods of ALK-1 IHC and FISH. As a single test, it detected ALK, ROS1 and RET fusions simultaneously. NanoString profiling can be an alternative for a one tube test for ALK, ROS1 and RET translocations in a selected NSCLC patient group.

Keywords: ALK, ROS1, RET, Lung Cancer, FISH, immunohistochemistry, nanoString

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-056 EGFR MUTATION PROFILE OF NSCLC PATIENTS TESTED AT THE LUNG CENTER OF THE PHILIPPINES

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Background: EGFR mutation testing has been established as a companion diagnostic for targeted therapy of Non-Small Cell Lung Carcinoma (NSCLC). The Lung Center of the Philippines (LCP) established a program with pharmaceutical companies (Roche and Astra-Zeneca) to conduct free EGFR testing for several NSCLC patients. This report aims to showcase the EGFR mutation profiles observed and their implication to targeted therapy among Filipino patients. **Method:** Tumor block specimens from patients clinically diagnosed with NSCLC at stages II to IV with at least 5% density of histopathologic tumor cells were extracted with DNA and subjected to EGFR mutation analysis using the Roche EGFR mutation detection kit and Cobas Quantitative Real Time PCR. The laboratory test was UKNEQAS certified to assure the quality and validity of results. **Result:** EGFR positive specimens were detected at 42.6% (260/611) in cohort A and 42.4% (42/99) in cohort B close to the values earlier reported by our laboratory (i.e., 47.5%). For A, 14 mutation types were detected. For B, only 7 were detected. The dominant mutations in both A and B were Exon 19 Deletion (i.e., 58.8% and 54.5% respectively) and Exon 21 L858R (i.e., 27.7% and 21.4% respectively). The Exon 20 T790M, a mutation that confers TKI resistance, was detected in both

cohorts associated with Exon 19 Deletion (i.e., 1.9% in A and 4.8% in B). The same mutation was also detected in A associated with Exon 21 L858R but at low rate (i.e., 0.8%). Gender-wise, there were twice as much females as males that were positive for the EGFR mutation. The average age were 60.1 for males and 59.8 for females. **Conclusion:** The EGFR mutation profile showed that more mutation types are detected with sample size increase; the dominant mutation occurs in Exon 19 Deletion with count twice as much as Exon 21 L858R. The Exon 20 T790M mutation was detected in conjunction with these two mutations at less than 5%.

Keywords: EGFR Exon 19 deletion, Exon 20 T790M, Filipino NSCLC patients

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-057 COMPARISON OF MOLECULAR TESTING MODALITIES FOR DETECTION OF ROS1 REARRANGEMENTS IN A COHORT OF POSITIVE PATIENT SAMPLES

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Background: Targeting oncogenic gene fusions with small molecules has proven to be a highly successful treatment strategy in lung cancer. For *ALK* and *ROS1* rearrangement/fusion positive cases, fusion directed therapy is now considered standard of care for advanced disease. Consequently, the accurate clinical detection of rearrangements/fusions is of critical clinical importance. Multiple distinct methodologies are employed in the clinical setting for rearrangement/fusion detection. In this study, we compare the performance of several of these methodologies on a large cohort of *ROS1* rearrangement/fusion-positive patient samples. **Method:** Eighteen *ROS1* rearrangement/fusion-positive clinical samples were assessed by at least two of the following molecular testing methodologies: break-apart fluorescence *in situ* hybridization (FISH), DNA-based hybrid capture library preparation followed by next-generation sequencing (NGS), and RNA-based anchored multiplex PCR library preparation followed by NGS. **Result:** None of the testing methodologies demonstrated 100% sensitivity in detection of *ROS1* rearrangements/fusions. FISH results were negative in 2/18 tested clinical samples. One of these demonstrated an atypical staining pattern, suggestive of a complex rearrangement. The other occurred in a case of *GOPC-ROS1* fusion in which the genes are in close proximity on chromosome 6. The DNA-based NGS assay was negative in 3/11 tested clinical samples. This assay suffered from poor bait coverage in intronic regions containing repetitive sequences, and false negatives were likely due to this deficiency. The RNA-based NGS assay did not identify *ROS1* fusions in 3/15 tested clinical samples. However, this assay is highly reliant on RNA quality, and missed calls were associated with metrics derived from the assay suggestive of degraded RNA (and thus the results would have been deemed uninformative). Additionally, we report cases in which the detected fusion at the transcript level (via RNA-based NGS) occurred between exons not predicted by proximal exons bordering the detected genomic breakpoint (via DNA-based NGS), likely due to exon removal via mRNA splicing. For these cases, the detected genomic DNA breakpoint may have resulted in a non-call due to the prediction of an out-of-frame fusion transcript. **Conclusion:** Rearrangement/fusion detection in the clinical setting is complex and all methodologies have inherent limitations that users must be aware of. Consequently, careful scrutiny of negative results must be performed, particularly in cases negative for other known oncogenic drivers (pan-negative cases). Ideally, orthogonal rearrangement/fusion testing methodologies should be employed for such cases.

Keywords: Rearrangement/fusion, ros1, next-generation sequencing

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-058 DETECTION OF ROS1 REARRANGEMENTS IN 508 RUSSIAN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Identification of specific oncogenic genetic drivers can improve survival in a subset of patients with NSCLC, eligible for modern targeted therapies. Detection of ROS1 rearrangements became standard of diagnostic, but some challenges are under discussion in this setting. We report the first results of large-scale testing in an all-Russian Network for Molecular Diagnostics in cancer patients supported by RUSSCO **Method**: Tumor samples from 508 Russian pts negative for EGFR mutations and ALK rearrangements were submitted for ROS1 testing from September 2016 to May 2017. Initial screening was performed using IHC assay exploiting D4D6 antibody (Cell Signaling Technologies) and OptiView DAB IHC detection kits with OptiView Amplification kit (Ventana Medical Systems). All cases scored as positive/equivocal by IHC were forwarded for FISH. **Result:** 456 cases were negative by IHC, 12 cases (2%) were positive by the both assays and 31 cases were scored as equivocal (6,1%) with negative FISH results in 29. Nine cases (2%) failed because of serious defects of preanalytic managing or lack of tumor tissue. Three cases were additionally reviewed and scored as heterogenic positive by IHC and heterogenic by FISH with close-to-border amount of rearranged cells. One case harbored concomitant L858R *EGFR* mutation confirmed by repeated PCR investigation. All these cases are under additional investigation for revealing of possible role of *ROS1* rearranged clone in oncogenesis. **Conclusion:** Identification of ROS1 rearrangements in NSCLC patients has some challenges possibly indicating more complicated role of this aberration in NSCLC.

Keywords: Non Small Lung Cancer, ROS1 translocation, heterogeneity

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-059 T790M AND C797S AS MECHANISMS OF ACQUIRED RESISTANCE TO DACOMITINIB IN CELL MODELS

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Background: The ARCHER 1050 trial demonstrated the superiority of dacomitinib to gefitinib in terms of PFS. Lung cancers inevitably acquire resistance to these TKIs after an initial dramatic response. We previously reported that L792F and C797S, in addition to the major T790M, can develop in afatinib-resistant cells (Mol Cancer Ther 2017; 16: 357-64). This study aimed to clarify the mechanisms of acquired resistance to dacomitinib. **Method:** EGFR Del19, L858R, and G719A were introduced into Ba/F3 cells using retroviral vector. Dacomitinib-resistant clones were established from these Ba/F3 cells by exposure to fixed concentrations of dacomitinib (20nM or 200nM) using N-ethyl-N-nitrosurea (ENU) mutagenesis. EGFR secondary mutations were analyzed by Sanger sequence. **Result:** ENU mutagenesis screening established 21 dacomitinib-resistant clones so far: 10 Del19 clones with 20nM, 9 Del19 clones with 200nM, and 2 L858R clones with 20nM. T790M and each original mutation were detected in all of these resistant clones by mutational analyses. **Conclusion:** These preliminary data demonstrate that dacomitinib can directly induce T790M secondary mutation without selecting de novo T790M clones. Osimertinib could be potentially effective for a subset of lung cancers which acquired resistance to dacomitinib. Updated additional data will be presented.

Keywords: EGFR, Dacomitinib, Acquired resistance

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-060 EGFR MUTATION STATUS BY THREE SEQUENCING PLATFORMS IN 704 NON-SMALL CELL LUNG CANCER (NSCLC) BRAZILIAN PATIENTS

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Background: EGFR status has utmost importance in treatment of NSCLC with the emergence of highly effective anti-EGFR tyrosine-kinase inhibitors (TKI). Current technologies for EGFR evaluation are based on sequencing platforms, such as Sanger, Pyrosequencing (Pyro) and Next Generation Sequencing (NGS), used in different timeframes during the last 6 years of our local practice. Indirect evidence demonstrates that Latin American patients have higher frequency of EGFR mutations. We aimed to describe EGFR mutation frequency in a Brazilian population and concordance of findings and differences between available sequencing techniques. **Method:** Between August/2010-July/2016 we performed a retrospective analysis of the reports of formalin-fixed paraffin-embedded 704 consecutive biopsy samples from TKI-naïve patients tested for EGFR at A.C.Camargo Cancer Center, São Paulo, Brazil. EGFR exons 18 to 21 were analyzed by Sanger, Pyro or NGS. All tests were performed locally. **Result:** EGFR mutation aggregated rate was 26.7% for the overall population. Table 1 shows patient's characteristics (when medical records were available) including differences between mutated and non-mutated patients. Table 2 demonstrates differences between mutation findings for each sequencing platform.

Table 1. Patient Characteristics. WT: Wild Type. Mut: Mutant.

	WT EGFR	Mut EGFR	P value
GENDER			
Male	223/516 (43.2%)	63/188 (33.5%)	
Female	293/516 (56.8%)	125/188 (66.5%)	<0.001
MEDIAN AGE AT DIAGNOSIS (YEARS)	64	64.8	0.72
HISTOLOGY			
Adenocarcinoma	367/418 (87.8%)	156/161 (96.9%)	

Table 1. Patient Characteristics. WT: Wild Type. Mut: Mutant.			
	WT EGFR	**Mut EGFR**	**P value**
Non-Adenocarcinoma NSCLC	51/418 (12.2%)	5/161 (3.1%)	0.01
SMOKING STATUS			
Nonsmoker	81/308 (26.3%)	52/128 (40.6%)	
Smoker/Former Smoker	227/308 (73.7%)	76/128 (59.4%)	< 0.001
MEDIAN SMOKING LOAD (PACK-YEARS)	40	17.5	< 0.001
METASTASIS AT DIAGNOSIS			
Yes	238/333 (71.5%)	105/137 (76.6%)	
No	95/333 (28.5%)	32/137 (23.4%)	0.25

Table 2 – Numbers and types of mutations detected according to the test methodology.				
	Sanger	**Pyro**	**NGS**	**Aggregated**
EGFR Mutant Patients	82/352 (23.3%)	27/101 (26.7%)	79/251 (31.5%)	188/704 (26.7%)
Total Number of EGFR Variants Detected*	93	28	84	205
Patients with Multiple EGFR Variants	8/82 (9.8%)	1/27 (3.7%)	5/79 (6.3%)	14/188 (7.4%)
Sensitivity Variants	69/93 (74.5%)	26/28 (92.9%)	71/84 (84.5%)	166/205 (81%)
Resistance Variants	3/93 (3.2%)	0	6/84 (7.1%)	9/205 (4.4%)
Variants of Uncertain Significance	21/93 (22.6%)	2/28 (7.1%)	7/84 (8.3%)	30/205 (14.6%)
Inconclusive test	60/352 (17%)	4/101 (4%)	5/251 (2%)	69/704 (9.8%)

Conclusion: Our findings demonstrate higher than expected EGFR mutation rate among for caucasian patients in a Brazilian population and a numerically higher and broader EGFR mutation detection rate with NGS.

Keywords: next generation sequencing, EGFR mutated Lung Cancer, Tumor biology

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-061 AN ALK FOLLOW-ON COMPANION DIAGNOSTIC USING CGP FOR CLINICAL CARE OF PATIENTS WITH NSCLC

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Background: Advanced NSCLC patients may benefit from treatment with *ALK* inhibitors if they harbor *ALK* rearrangements such as an EML4-ALK fusion. While the FDA has approved companion diagnostics (CDx) using IHC and FISH-based assays for *ALK*, molecular diagnostic testing in NSCLC is rapidly evolving towards comprehensive genomic profiling (CGP) to test for a growing number of established predictive biomarkers. Clinical validity of *ALK* testing using CGP however, has not yet been demonstrated in an FDA approved manner. We present here the first follow-on CDx *ALK* test using CGP as a part of our universal CDx platform. **Method:** Clinical validity was established against the FDA-approved IHC and FISH CDx, using 291 samples from the ALEX clinical trial (NCT02075840), including *ALK*-negative screen-failed patients. Clinical validity was established such that the CGP concordance versus an FDA-approved test was statistically non-inferior to the performance comparison between IHC and FISH. Concordance reported in Table 1 was calculated on samples that were in agreement between IHC and FISH. **Result:** Concordance in patients in consensus between IHC and FISH is shown in Table 1. Positive percent agreement of 92.9% and negative percent agreement of 100% was achieved. Statistical non-inferiority demonstrates a non-inferiority margin of 5.4%. Limit of detection studies demonstrated the ability to detect ALK rearrangements down to 1.8% tumor content. **Table 1.**

Companion diagnostic	ALK rearrangements
Indicated use	ALK inhibitors in NSCLC
Approved CDx comparator	Ventana ALK (D5F3) CDx Assay Vysis ALK Break-Apart FISH Probe Kit
Positive percent agreement	92.9% (78/84)
Negative percent agreement	100% (75/75)
Median unique sequence coverage	807X
Precision	100%
Limit of Detection	1.8% tumor content

Conclusion: We developed and validated a follow-on CDx for *ALK* as part of a universal CDx platform. The platform provides a single assay with well-defined performance characteristics, identifies patients with cancer who may be eligible to receive FDA-approved targeted therapeutics, conserves tissue by avoiding serial testing and can serve as clinical trial assay for studies requiring a molecular biomarker for eligibility. The data demonstrating clinical and analytical validity of *ALK* may accelerate the use of CGP for routine clinical care.

Keywords: molecular testing, NGS, companion diagnostic

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-062 AN EGFR FOLLOW-ON COMPANION DIAGNOSTIC FOR CLINICAL CARE OF PATIENTS WITH NSCLC

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Background: Late-stage NSCLC patients may benefit from treatment with *EGFR* tyrosine kinase inhibitors if they harbor certain activating mutations in *EGFR*. While the FDA has approved companion diagnostics (CDx) using PCR to detect *EGFR* mutations, molecular diagnostic testing is evolving towards comprehensive genomic profiling (CGP). However, clinical validity of *EGFR* testing using CGP has not yet been demonstrated in an FDA-approved manner. We present here the first follow-on CDx *EGFR* test using CGP as part of our universal CDx platform. **Method:** Clinical validity was established against FDA-approved PCR-based cobas® *EGFR* Mutation Test v2, using 406 procured samples containing *EGFR* L858R mutations and exon 19 deletions, and 354 samples from the AURA clinical trials for T790M mutations. For each sample, two tests of cobas were run, and clinical validity was established such the concordance between CGP and cobas were statistically non-inferior to the performance between two runs of cobas. Concordance (PPA and NPA) reported on Table 1 was calculated on samples that were in agreement between the two cobas runs. **Result:** Concordance is shown in Table 1. For L858R and exon 19 deletions, statistical non-inferiority demonstrated a non-inferiority margin of 1.9%. For T790M, our assay has higher sensitivity: of the 61 samples that were below 10% mutant allele fraction (MAF) as detected by NGS, 30 were missed by cobas. **Table 1.**

Companion diagnostic	EGFR exon 19 deletions and L858R	EGFR T790M
Indicated use	erlotinib, afatinib, or gefitinib in NSCLC	osimertinib in NSCLC
Approved CDx comparator	cobas® EGFR Mutation Test v2	cobas® EGFR Mutation Test v2
Positive Percent Agreement (PPA)	98.1% (106/108)	98.9% (87/88)
Negative Percent Agreement (NPA)	99.4% (153/154)	86.1% (93/108)
Median unique sequence coverage	L858R: 1165X Exon 19: 1028X	1126X
Precision	100%	100%
Limit of Detection	L858R: 1.9% MAF Exon 19 deletions: 3.4% MAF	1.8% MAF

Conclusion: We present a follow-on CDx for *EGFR* as part of the universal CDx platform. The platform provides a single assay with well-defined performance characteristics, identifies patients with cancer who may be eligible to receive FDA-approved targeted therapeutics, conserves tissue by avoiding serial testing and can serve as clinical trial assay for studies requiring a molecular biomarker for eligibility. The data demonstrating clinical and analytical validity of *EGFR* may accelerate the use of CGP for routine clinical care.

Keywords: molecular testing, NGS, companion diagnostic

P3.02-063 EGFR EXON 20 INSERTIONS IN LUNG ADENOCARCINOMAS: MOLECULAR AND CLINICOPATHOLOGIC CHARACTERISTICS AMONG HISPANICS (GEN01.2-CLICAP)

A. Cardona[1], O. Arrieta[2], G. Oblitas[3], L. Rojas[4], Z. Zatarain-Barron[2], L. Corrales[5], C. Martin[6], J. Rodriguez[1], P. Archila[1], A. Ruiz-Patiño[1], M.A. Pérez[7], L. González[3], L. Chirinos[8], H. Carranza[9], C. Vargas[9], R. Rosell[10]

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Background: In contrast to other primary *EGFR* mutations in lung adenocarcinomas, insertions in exon 20 of *EGFR* have been generally associated with resistance to EGFR tyrosine kinase inhibitors. Their molecular spectrum, clinicopathologic characteristics and prevalence are not well established among Hispanics. **Method:** Tumors harboring *EGFR* exon 20 insertions were identified through a comprehensive screening of 4.500 lung adenocarcinomas from diverse Latin American Countries. Cases were tested for common and uncommon EGFR mutations and *KRAS*. Almost all cases (n=52) underwent extended genotyping for other driver mutations in BRAF, NRAS, PIK3CA, Her2 and MEK1 by NGS (TruSight tumor™), EGFR amplification, ALK and PDL1 protein expression (D5F3CDx Assay and 22C3 Clone). Clinical outcomes were evaluated using Kaplan-Meier and Cox proportional models. **Result:** 60 patients were included; median age was 66-yo (r, 24-79), 63.3% were females, most patients had a micropapillary (38.3%) or lepidic (20.0%) adenocarcinomas, 61.7% were never smokers and 36.7% had brain metastasis at diagnosis. 14 patients (23.4%) had common EGFR mutations (del19/L858R) in addition to the exon 20 insertion, 5 (10.0%) had non-common EGFR mutations (G719X /L861Q/S768I) plus the exon 20 insertion, and two cases had additional mutations in PIK3CA and MEK1. Insertion sequences were highly variable, with the most common variant (V769_D770insASV) making up only 21.7% of cases. 30% of patients had amplification of the EGFR and 75% had a PDL1 expression level of less than 50%. Overall response rate (ORR) to the first line was 30%, progression free survival (PFS) was 8.3 months (95%CI 6.9-9.6) and OS was 17.4 months (95%CI 16.4-19.5). Prognosis was positively influenced by concomitant presence of common EGFR mutations (p=0.016) and by response to first line therapy (p=0.06). **Conclusion:** Patients with EGFR exon 20 insertions have similar clinical characteristics to those with common EGFR mutations but a poorer prognosis. The mean PDL1 expression in this population appears to be higher than in patients with common EGFR mutations, finding that promote the potential use of immunotherapy alone or in combination for this population.

Keywords: EGFR, exon 20 insertion, outcome

P3.02-064 EPIDERMAL GROWTH FACTOR RECEPTOR GENE MUTATION IN PLEURAL LAVAGE CYTOLOGY FINDINGS OF PRIMARY LUNG ADENOCARCINOMA CASES

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Background: In the present study, we examined the relationship between intraoperative pleural lavage cytology findings and presence of EGFR gene mutations. **Method:** We investigated 160 patients who underwent surgical treatment for primary lung adenocarcinoma at our hospital from January 2011 to December 2013 to determine the presence of EGFR gene mutations and pleural lavage cytology. **Result:** Fifty-two subjects (31.5%) were positive EGFR gene mutations, of whom 38 were found to possess the Exon 21 L858R mutation. Intraoperative pleural lavage cytology examinations were performed in 160 subjects and 12 had positive results, of whom 6 were positive for EGFR gene mutations, which was the Exon 21 L858R mutation in all. In a comparison between subjects possessing the Exon 21 L858R mutation and those negative for EGFR gene mutations, lavage cytology-positive (p=0.02) and vascular infiltration-negative (p=0.01) were characteristics of the Exon 21 L868R mutation-positive group. **Conclusion:** Subjects positive for the EGFR Exon 21 L858R mutation had a higher positive rate of intraoperative pleural lavage cytology than those not possessing EGFR mutations.

Keywords: lung cancer, pleural lavage cytology, EGFR mutation

P3.02-065 LUNG ADENOCARCINOMA PATIENT WITH EGFR KINASE DOMAIN DUPLICATION(KDD) AND ITS RESPONSE TO ICOTINIB: A CASE REPORT

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Background: 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. And the curative effect to icotinib is still unclear. **Method:** A 63-year-old female diagnosed with adenocarcinoma, who was shown to have gene detected by the next generation sequencing (NGS) and treatment with icotinib. **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 EGFR-KDD, PIK3CG p.R839C and NTRK2 p.P50Lfs*14. Our case is the first report EGFR-KDD in Chinese populations. The patient was treated surgically and received icotinib therapy. And the surgery and icotinib therapy showed a good response. **Conclusion:** For patients with this subtype, further research and experience are needed to summarize them. This case illustrates the value of in-depth molecular testing with NGS of EGFR wild type non-small cell lung cancer patients.

Keywords: icotinib, Kinase Domain Duplication, Epidermal growth factor receptor

P3.02-066 WILD-TYPE KRAS MEDIATES GROWTH INHIBITION AND RESISTANCE TO MEK INHIBITORS THROUGH DIMERIZATION WITH MUTANT KRAS IN LUNG ADENOCARCINOMA

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Background: Mutations in *KRAS* are the most frequent *RAS* alterations in human cancers and the prevalent driver event in lung adenocarcinoma (LUAD). There are no effective targeted therapies for KRAS-driven LUAD and chemotherapy remains the standard of care. Small-molecule inhibitors of the MAPK pathway, one of the prominent downstream KRAS mediators, show minimal clinical activity either as single agents or in combination with chemotherapy. Recently, wild-type KRAS ($KRAS^{WT}$) was shown to enhance tumor fitness in *KRAS* mutant AML and CRC cell lines while concomitantly increasing sensitivity to MEK inhibition. We hypothesized that dimerization between KRAS proteins could be a key regulator for lung adenocarcinoma biology and determinant of treatment response. **Method:** To study the role of wild-type *KRAS* in the context of KRAS-driven cancer cells, we used genetically inducible models of *KRAS* loss of heterozigosity (LOH). We developed an isogenic $KRAS^{MUT}$ inducible system that lacks endogenous *HRas/NRas* but harbors conditional CRE^{ERT2}-controlled $KRas^{lox}$ alleles. Furthermore, we reconstituted $KRAS^{WT}$ and dimerization-deficient $KRAS^{D154Q}$ in KRAS-driven murine and human LUAD cell lines lacking the wild-type *KRAS* allele and evaluated the *in vitro* and *in vivo* impact on tumor progression and response to MEK inhibition. **Result:** $KRAS^{WT}$ decreased *in vitro* and *in vivo* fitness of human and murine *KRAS* mutant LUAD tumor cells. However, this phenotype was reverted upon MEK inhibition, with *KRAS* LOH cells being more sensitive than $KRAS^{WT}$ expressing cells. Interestingly, both effects were dependent on wild-type/mutant KRAS dimerization and not observed with the dimerization-deficient $KRAS^{D154Q}$. We provide a mechanistic model of the ambivalent function of $KRAS^{WT}$, linking its tumor suppressor function with increased MEK inhibitor resistance through dimerization with mutant KRAS. **Conclusion:** • $KRAS^{WT}$ affects cellular fitness in KRAS-driven LUAD • $KRAS^{WT}$ impairs response to MEK inhibitors in KRAS-driven LUAD • $KRAS^{WT}$ inhibitory effect is dependent on dimerization with mutant KRAS • Impaired wild-type/mutant KRAS dimerization restores sensitivity to MEK inhibitors *in vivo*

Keywords: MEK inhibitors, KRAS lung adenocarcinoma, Dimerization

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-067 LUNG CANCER WITH CONCURRENT EGFR MUTATION AND ROS1 REARRANGEMENT: 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 50-year-old female diagnosed with adenocarcinoma with sarcomatoid differentiation, who was shown to have EGFR and ROS1 mutations by the next generation sequencing. **Result:** The patient was treated surgically and received three cycles of adjuvant postoperative chemotherapy. And the surgery and postoperative adjuvant chemotherapy showed a good response. **Conclusion:** For patients with this subtype, further research and experience are needed to summarize the biologic features and optimal modes of treatment, including targeted therapy in advanced lung cancer patients.

Keywords: non-small cell lung cancer, EGFR gene mutation, ROS1 fusion gene

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-068 95 CASES OF EGFR/ALK GENE STATUS ANAYSIS IN LUNG ADENOSQUAMOUS CARCINOMA

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Background: Adenosquamous carcinoma is a rare subtype of lung cancer, it is mixed glandular and squamous cell carcinoma with a more aggressive behavior and poor prognosis than the other histologic subtypes. The aim of this study is to investigate the characteristics of lung adenosquamous carcinoma and to analyze the prognostic factors. **Method:** The reverse transcription polymerase chain reaction (RT-PCR) method was used to detect the tissues in 95 patients of lung adenosquamous carcinoma with paraffin tissue EGFR gene mutation and ALK fusion gene. And the survival rate was calculated by Kaplan-Meiermethod and log-rank test was used to compare the survival rates. Univariate and multivariate factors for survival were analyzed by COX proportional hazards regression model. **Result:** 95 cases of lung adenosquamous carcinoma were males, more than 60 years old and smoking patients predominant; COX univariate analysis revealed that gender, age, smoking history, EGFR gene status, ALK fusion gene status, stage, subtype patterns and subtype type were prognostic factors for lung adenosquamous carcinoma. COX multivariate analysis found that stage, subtype patterns and subtype type were independent prognostic factors for lung adenosquamous carcinoma ($P<0.05$). **Conclusion:** Lung adenosquamous carcinoma mainly occurred in men patients over 60 years old with smoking. Stage, subtype patterns and subtype type are the crucial prognostic factors for lung adenosquamous carcinoma.

Keywords: adenosquamous carcinoma, EGFR gene, ALK gene

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-069 58 CASES OF EGFR/ALK GENE STATUS ANAYSIS IN PULMONARY SARCOMATOID CARCINOMA

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Background: Sarcomatoid carcinomas are a rare type of cancer found in the lung and other organs. The aim of this study is to investigate the characteristics of pulmonary sarcomatoid carcinoma (PSC) and to analyze the prognostic factors. **Method:** Fifty-eight patients with pulmonary sarcomatoid carcinoma were retrospectively reviewed on the clinical data and genetic state, and the survival rate was calculated by Kaplan-Meier method and log-rank test was used to compare the survival rates. Univariate and multivariate factors for survival were analyzed by COX proportional hazards regression model. **Result:** Fifty-eight cases of pulmonary sarcomatoid carcinoma were men, less than 65 years old and smoking patients predominant; COX univariate analysis revealed that gender, age, smoking history, EGFR gene status, ALK fusion gene status, stage, histologic subtype were prognostic factors for pulmonary sarcomatoid carcinoma. COX multivariate analysis found that ALK fusion gene status, histologic subtype were independent prognostic factors for pulmonary sarcomatoid carcinoma ($P<0.05$). **Conclusion:** There is no specificity in the clinical characteristics of PSC and its successful diagnosis depends on pathological analysis. ALK fusion status and histologic subtype are the crucial prognostic factors for pulmonary sarcomatoid carcinoma.

Keywords: Pulmonary sarcomatoid carcinoma, EGFR gene, ALK gene

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-070 INVESTIGATION OF WHETHER HIF-1A INHIBITORS CAN INCREASE EGFR-TKI EFFECT FOR NON-SMALL CELL LUNG CANCER CELL LINES

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Background: Hypoxia-inducible factor-1α (HIF-1α) plays a crucial role in cancer progression, metastasis and angiogenesis. Activation HIF–1α pathway is also associated with epithelial growth factor receptor (EGFR) pathways. This study was to investigate whether inhibitors of HIF–1α increase the cytotoxicity of EGFR-tyrosine kinase inhibitors (TKI) on non-small cell lung cancer (NSCLC) and its mechanism. **Method:** NSCLC lines, including A549, Hcc827, Hcc827R, H460, PC-9, H23, H1299, C339, H3255, and H1975 were used as in vitro experiments. Western blot was used to observe expression of HIF-1α. MTT assay was used to investigate effects of different drug concentrations. The combination of EGFR-TKI (gefitinib) and HIF-1α inhibitors was used in EGFR wild-type, and EGFR- mutant cell lines. The combination index (CI) was used to determine the effect of drug combination. The mean CI (mCI) values more than 1.05 or less than 0.95 were defined as antagonism or synergism, respectively. **Result:** Western blot showed that HIF-1α expression was relatively high in EGFR- mutant cell lines and relatively low in EGFR wild-type cell lines. Under normoxia, HIF-1α expression increased in Hcc827 and H460 cell lines. Under hypoxia, HIF-1α expression increased in Hcc827R and H1975 cell lines. MTT assay showed that gefitinib was found to be superior to HIF-1α inhibitors in cytotoxicity effect on EGFR-TKI-sensitive NSCLC lines (PC9, Hcc827, C339, H3255). HIF-1α inhibitor was relatively better than gefitinib in cytotoxicity effect on EGFR-TKI-insensitive NSCLC cell lines (A549, H23, H460, H1299, Hcc827R, H1975). Under normoxia or hypoxia, cytotoxicity effect of HIF-1α inhibitor on EGFR-TKI-insensitive NSCLC cell lines (Hcc827R, H1975, A549, H460) was relatively better than gefitinib. Of five cell lines, including A549, Hcc827, Hcc827R, H460 and PC-9, their CI values for Gefitinib/HIF-1α inhibitor were 1.00, 0.925, 1.32, 0.76 and 1.23, respectively under normoxia. Data showed that cytotoxicity effect of HIF-1α inhibitor antagonized with gefitinib in Hcc827R and PC-9 cell lines. However, cytotoxicity effect of HIF-1α inhibitor synergized with gefitinib in the Hcc827, and H460 cell line. Of four cell lines, including A549, Hcc827, Hcc827R, and H460, their CI values for Gefitinib/HIF-1α inhibitor were 1.23, 1.17, 1.02, and 1.08, respectively under hypoxia. In this study, increased expression of HIF-1α in Hcc827 and H460 under normoxia may be related to synergistic cytotoxicity effect of HIF-1α inhibitors and gefitinib. **Conclusion:** HIF-1α inhibitors demonstrated anti-NSCLC activity in vitro and a selectively synergistic effect with gefitinib in EGFR-TKI-insensitive NSCLC cell line (H460). Our study suggested a potential treatment approach using HIF-1α inhibitors plus gefitinib.

Keywords: Hypoxia-inducible factor-1α inhibitor, Epidermal growth factor receptor tyrosine kinase inhibitor, non-small cell lung cancer

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-071 STATINS MAY IMPROVE THE PROGNOSIS OF PATIENTS WITH LUNG ADENOCARCINOMA BY SUPPRESSING MUTANT P53-INDUCED EMT

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Background: Epithelial-mesenchymal transition (EMT) is known to be pivotal for driving metastasis and recurrence in lung cancer. Some reports have shown statins suppressed EMT by inactivating mutant *p53* functions in vitro. Although several clinical trials regarding conventional treatments with statins have been performed, the effect of statins on the prognosis is still controversial. The purpose of the present study is to clarify the impact of statins on EMT and the prognosis of patients with lung adenocarcinoma harboring *p53* mutation. **Method:** Firstly, we transfected wild type *p53* or mutant *p53* (R175H, R273H) to H1650 cells and administrated simvastatin. We evaluated morphological changes by microscopic measurement and analyzed EMT markers (E-cadherin, vimentin) through western blotting of whole cell lysate. We also analyzed their invasive ability through Matrigel invasion assay. Secondly, a total of 282 lung adenocarcinoma specimens were collected from patients who underwent surgery in our institute from January 2001 to December 2007. We analyzed EMT markers through immunostaining of tumor specimens and we determined *p53* mutation by single stranded conformational polymorphism followed by direct sequencing. The association between EMT, *p53* mutation status, and statin use as well as the patients' clinical information was statistically analyzed. Correlations were compared using Pearson›s chi-square test and overall survival were compared using the log-rank test. **Result:** When mutant *p53* (R175H, R273H) were transfected, H1650 cells showed EMT like morphological changes. E-cadherin expression was decreased and vimentin expression was increased in H1650

harboring mutant *p53* (H1650$^{mut.p53}$). Additionally, H1650$^{mut.p53}$ obtained more aggressive invasiveness compared to H1650 harboring wild type *p53*. However, simvastatin-treated H1650$^{mut.p53}$ lost EMT character changes and aggressive invasiveness. According to the medical records, about 20% of the patients took statins (simvastatin, pravastatin, and so on) as a treatment of hyperlipidemia or coronary artery disease. Consistent with the results of in vitro experiments, IHC showed that statin administration was correlated to fewer EMT only in the patients with mutant *p53*. Moreover, the statin-administrated group showed significantly better survival compared to the non-statin group (p=0.04), which was observed only in the patients with mutant *p53*. **Conclusion:** Statins suppressed EMT and improved the prognosis of patients with lung adenocarcinoma in a *p53* mutation-dependent manner.

Keywords: p53 mutation, statin, lung adenocarcinoma

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-072 MIR-33B INHIBITS LUNG ADENOCARCINOMA CELL EPITHELIAL-MESENCHYMAL TRANSITION THROUGH CERNA REGULATORY NETWORK

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Background: Lung cancer is a signifcant health problem worldwide and the mechanism of lung cancer cell metastasis has not been fully elucidated.Epithelial-mesenchymal transition (EMT) is not only an important biological mechanism for natural physiological process but also has been proved to be related to cancer metastasis. Further studies have pointed out that EMT plays a indispensable role in the entire process of metastasis.In recent years , many miRNAs have been demonstrated to target EMT-related proteins, such as E-cadherin and Vimentin to regulate the initiation and progression of EMT. The preliminary study of my research group has indicated that miR-33b plays an inhibitory role in the EMT of lung cancer and two genes ,ZEB1 and Twist1 ,are downstream target of miR-33b.Then snail1 which is EMT-related proteins like ZEB1 has also been founded that a potential correlation with miR-33b.A ceRNA hypothesis tells that If different transcripts have the same miRNA binding site, it can combine with miRNA competely and influence its inhibitory effect on the target, and then adjust the expression of each other.Snial1,ZEB1 and Twist1 three genes would bind to the same miRNA which is miR-33b,but the relations among this three genes and miR-33b still need to be clarified **Method:** Western blotting,RT-pcr,Immunofluorescence ,Immunohistochemistry and Luciferase assay were used to explore the relations among Snial1,ZEB1,Twist1 and miR-33b.The effects of miR-33b and Snail1 on lung adenocarcinoma cancer cell functions were investigated by using migration and invasion assays.Construct gene expression vectors and transfect the cells to research the regulative relations among Snial1,ZEB1,Twist1 and miR-33b.Tumor formation in nude mice to certify the relations between Snail1 and miR-33b in vitro. **Result:** miR-33b suppresses EMT and lung adenocarcinoma cell proliferation and migration in vitro.miR-33b directly targets SNAIL1.miR-33b regulates lung adenocarcinoma cells by down-regulating Snial1 expression.miR-33b inhibits tumor growth through the SNAIL1 in vivo. Snial1,ZEB1,Twist1 influence each other. **Conclusion:** Snial1,ZEB1 and Twist1 fuction as cerna for each other.MiR-33b inhibits lung adenocarcinoma cell epithelial-mesenchymal transition through ceRNA regulatory network

Keywords: miR-33b,ceRNA,SNIAL1

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P3.02-073 STROMAL HEDGEHOG PATHWAY ACTIVATION SUPPRESSES GROWTH AND METASTASIS OF LUNG ADENOCARCINOMA

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Background: Aberrant activation of the Hedgehog (Hh) signaling pathway, a crucial developmental pathway, drives the tumor growth of Gorlin-type cancers. However, recent data suggest that paracrine activation of the pathway is tumor suppressive rather than oncogenic in sporadic epithelial cancers. The role of the pathway in non-small lung cancer is poorly understood. Thus, we explored the role of stromal Hh pathway activation in growth of lung adenocarcinoma. **Method:** Human lung adenocarcinoma cell lines were used to probe SHH mRNA and protein expression. Co-culture of high SHH expressing cell lines with murine embryonic and lung fibroblasts were used to confirm and probe the role of paracrine SHH expression on the growth of lung cancer cells. The in vivo role of paracrine SHH was tested using autochthonous lung cancer models with conditional KRAS^{G12D}activation, p53 loss, and SHH loss compared to wild-type SHH. **Result:** In human lung adenocarcinoma patients, higher expression of *SHH* mRNA in lung adenocarcinoma correlated with poor overall and progression free survival. A scan of 35 human lung adenocarcinoma cell lines revealed heterogeneous expression of SHH and IHH with high expression found predominantly in mutant K-Ras lines. Co-culture of high SHH expressing tumor epithelial cells and Shh-Light2 reporter cell lines demonstrated that SHH activated the fibroblast reporter in a paracrine manner, rather than an autocrine effect on cancer cells. Treatment with the SMO inhibitor, KAAD-cyclopamine, also inhibited the growth of tumor epithelial cells in co-culture with NIH-3T3 fibroblast cells but the effect was decreased when co-cultured with lung fibroblasts. Genetic loss of SHH in an autochthonous mouse model, *LSL-Kras$^{G12D/+}$;Trp53$^{fl/fl}$; Shh$^{fl/fl}$* (KPS) did not affect overall survival compared to *LSL-Kras$^{G12D/+}$;Trp53$^{fl/fl}$* (KP) mice However, early inhibition of the Hh pathway by anti-SHH/IHH antibody, 5E1, on KP mice resulted in significantly worse survival rates with increased metastatic burden compared to IgG treatment. Analysis of KP tumors revealed unexpected high levels of *IHH* mRNA by in situ hybridization and qPCR that may account for the survival differences seen between genetic ablation and pharmaceutical inhibition of the Hh ligands. **Conclusion:** The Hh signaling pathway acts upon lung stromal cells in a paracrine fashion and induces distinct transcriptional programs in murine embryonic and lung fibrtoblasts. Inhibition of paracrine Hh pathway activity *in vivo* worsened mortality rate due to increase in tumor growth and metastases. Furthermore, mutant Kras lung adenocarcinomas express high levels of IHH that dominates the tumor suppressive effects in our mouse models.

Keywords: Cancer Stroma, metastasis, Hedgehog signaling pathway

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P3.02-074 PODOPLANIN-POSITIVE CAF IS ASSOCIATED WITH A HIGHER NUMBER OF SINGLE NUCLEOTIDE VARIANTS IN CANCER CELLS IN LUNG ADENOCARCINOMA

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Background: Podoplanin-positive cancer-associated fibroblasts (CAFs) play an essential role in tumor progression. However, it is still unclear whether specific genomic alterations of cancer cells are required to recruit podoplanin-positive CAFs. The aim of this study was to investigate the relationship between the mutation status of lung adenocarcinoma cells and the presence of podoplanin-positive CAFs. **Method:** Ninety-seven lung adenocarcinomas for which whole exome sequencing data were available were enrolled. First, we analyzed the clinicopathological features of the cases with podoplanin-positive CAFs, and then, we evaluated the relationship between genetic features of cancer cells (major driver mutations and the number of single nucleotide variants, or SNVs) and the presence of podoplanin-positive CAFs. **Result:** Patients with podoplanin-positive CAFs had a significantly lower 5-year recurrence-free proportion than those with podoplanin-negative CAFs (p = 0.027). We could not find any significant correlations between major genetic mutations (*EGFR*, *KRAS, TP53, MET, ERBB2, BRAF*, and *PIC3CA*) in cancer cells and the presence of podoplanin-positive CAFs. However, cases with podoplanin-positive CAFs had a significantly higher number of SNVs in cancer cells than the podoplanin-negative CAFs cases (median; 84 vs 37, respectively; p = 0.001). This was also detected in a non-smoker subgroup (median: 64 vs 32, respectively; p = 0.037). Multivariate analyses revealed that the number of SNVs in cancer cells was the only statistically significant independent predictor for the presence of podoplanin-positive CAFs (p = 0.044). **Conclusion:** In lung adenocarcinoma, the presence of podoplanin-positive CAFs was associated with higher numbers of SNVs in cancer cells, suggesting a relationship between accumulations of SNVs in cancer cells and the generation of a tumor- promoting microenvironment.

Keywords: lung adenocarcinoma, podoplanin, cancer associated fibroblasts,

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P3.02-075 MOLECULAR DISORDERS OF THE GENES OF INTRACELLULAR SIGNAL PATHWAYS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) is about 85% of all cases of lung cancer. The most common types of NSCLC are adenocarcinoma (AC) and squamous cell carcinoma (SCC). The pathogenesis of them is activated by two different tyrosine kinase cascades (RAS/RAF/MAPK and PI3K/AKT/mTOR). The genes controlling these pathways are *EGFR*, *KRAS*, *PIK3CA* and *PTEN*. Therefore, the study of disorders of these genes will help to more accurately reveal the development of a specific histological type of NSCLC. The aim of this study is to identify mutations of *EGFR*, *KRAS*, *PIK3CA* and *PTEN* genes in patients with NSCLC among the population of people living in Belarus. **Method:** The study was conducted on 106 patients (78 men, 28 women) with histologically confirmed non-small cell lung cancer (51 cases of AC, 55 cases of SCC). Analysis of mutations was performed by PCR followed

by sequencing DNA, which was extracted from the tumor and non-tumor lung tissues of patients. **Result:** Analysis of associations between mutations and specific histological type of NSCLC showed that classical *EGFR* mutations are only in patient with AC. The frequency of them is 23.5%: deletions in exon 19 (p.E746_A750del, p.L747_P753delinsS) are 13.7%, insertions in exon 20 (p.A763_Y764insFQEA) are 7.8% and missense mutation in exon 21 (p.L858R) are 2.0%. In addition, there are detected silent mutations that have no effect on the functioning of the protein. There were mutation in intron 18 (.2184+19G>A) and synonymous mutation in exon 21 (c.2508C>T). The frequencies of them in patients with AC are 7.8% and 3.9% respectively, in patients with SCC are 14.5% and 1.8% respectively. Analysis of mutations in exon 2 *KRAS* gene detected 3 types of mutations: p.G12D, p.G12C and p.G13C. The frequency of this mutations in patients with AC are 5.9%, in patients with SCC are 1.8%. No mutations of *PIK3CA* and *PTEN* genes were found. To correct the treatment of patients, it is important not only the histological type of cancer, but also the gender characteristics of the population. In the studied population, mutations of the *EGFR* gene were found mainly in women with AC compared to men (39.3% and 1.0%, respectively). Mutations of the *KRAS* gene are found only in men, and in patients with AC mutations occur 4 times more often than in patients with SCC (10.7% and 2.4%, respectively). **Conclusion:** Thus, the RAS/RAF/MAPK signal pathway plays an important role in the pathogenesis of adenocarcinoma.

Keywords: KRAS gene, EGFR gene, non-small cell lung cancer

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P3.02-076 GLUTAMINASE INHIBITOR CB-839 RADIOSENSITIZES KRAS-MUTANT LUNG CANCER CELLS IN A LKB1- AND KEAP1/NRF2-PATHWAY DEPENDENT MANNER

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Background: KRAS mutant non-small cell lung cancers (NSCLC) bearing co-mutations in LKB1 (KL tumors) have a distinct biology, molecular vulnerabilities, and therapeutic sensitivities. KL tumors are characterized by upregulation of the NRF2/KEAP1 pathway which may serve as a compensatory mechanism to maintain redox homeostasis in the face of oxidative stress. The NRF2/KEAP1 pathway plays a role in regulating glutathione synthesis from glutamate. We hypothesized that glutaminase inhibition would reduce intracellular glutamate, reduce the ability to tolerate oxidative stress, and enhance radiotherapy sensitivity in KL tumors with KEAP1/NRF2 pathway upregulation. **Method:** Expression of NRF2 and NRF2 related genes were analyzed by Western blotting in isogenic KRAS-mutant LKB1 deficient/proficient NSCLC cell lines. Intracellular reactive oxygen species (ROS) levels were monitored using 2'7'-dichlorofluorescein (DCFDA) and flow cytometry. Cell apoptosis analysis was determined using PE-conjugated annexin-V/7-AAD staining and carried out by flow cytometry. Cell growth was evaluated by Cell Titer Glo Assays. Ionizing radiation sensitivity was assessed by clonogenic cell survival assay (CSA). **Result:** LKB1 loss increased ROS accumulation and resulted in up-regulation of NRF2 and NRF2 target genes in isogenic KRAS-mutant cell lines. KL cells were significantly more resistant to ROS than cells with KRAS mutation alone, as determined by the treatment with the ROS donor H_2O_2. NRF knockdown abrogated this resistance to in KL cells. KL cells also were more resistant to radiotherapy. Re-expression of LKB1 or NRF2 pathway suppression (via KEAP1 expression or NRF2 knockdown) enhanced radiotherapy sensitivity as measured by CSA with a dose enhancement ratio (DER) 1.6 and 1.2, respectively, at a surviving fraction of 0.5. The glutaminase inhibitor CB839 enhanced the radio-sensitivity of KL cells with NRF2 pathway activation (via KEAP1 mutation). Re-expression of LKB1 or NRF2 pathway suppression abrogated the CB839-induced radiosensitization. **Conclusion:** Our results suggest that upregulation of the NRF2/KEAP1 pathway in NSCLC bearing co-mutations in KRAS and LKB1 is critical to maintain redox homeostasis and GLS inhibition can sensitize KL tumors to radiotherapy in an LKB1- and KEAP1/NRF2-dependent manner.

Keywords: Liver kinase B1 (LKB1), Kelch-Like ECH-Associated Protein 1 (KEAP1)/ Nuclear Factor Erythroid 2-Like 2 (NRF2) Pathway, Glutaminase (GLS) inhibitor

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P3.02-077 PLATIN SENSITIVITY AND ATM-DEFICIENCY IN NON-SMALL CELL LUNG CANCER

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Background: Platinum based antineoplastic therapies (platins) are a first line treatment for non-small cell lung cancer (NSCLC) that generate DNA breaks and stimulate DNA damage response pathways. An inability to repair damage generated by these agents leads to cytotoxicity and cell death. A key mediator of the DNA damage response is ataxia telangiectasia mutated (ATM), an activator of downstream targets involved in DNA repair, cell cycle arrest, and apoptosis. Our lab has demonstrated that cell lines lacking ATM show increased sensitivity to platins. We hypothesize that platin exposure will activate ATM and that cells deficient in ATM will be innately sensitive to platins. Here we assess the molecular action of ATM in response to platins to determine if ATM-deficiency is predictive of platin sensitivity. **Method:** ATM status was determined in five NSCLC cell lines using western blotting and RT-qPCR. Cell lines were treated with varying concentrations cisplatin, carboplatin and oxaliplatin for 18-hours and assessed for ATM phosphorylation by western blot. Additionally, downstream targets of ATM (KAP-1, p53, and gamma-H2AX) were investigated to determine ATM pathway activation. Knockdown cell lines were generated using shRNA to ATM before testing for IR and cisplatin sensitivity using clonogenic assay. ATR and ATM inhibitors were tested on knockdown cell lines to investigate pathway response differences after cisplatin and IR. **Result:** NSCLC cell lines NCI-H226, NCI-H460, and NCI-H522 were found to be ATM-proficient whereas cell lines NCI-H23 and NCI-H1373 were found to be ATM-deficient. ATM-proficient cell lines demonstrated an increased level of phosphorylated-ATM in response to treatments with cisplatin, carboplatin, and oxaliplatin. ATM knockdown cell lines were found to have increased sensitivity to IR, however analysis of cisplatin sensitivity was inconclusive with only 1 out of 4 showing increased sensitivity. ATR inhibition in combination with cisplatin caused a large increase in DNA damage response from ATM and DNA-PKcs suggesting an avenue for synthetic lethality. **Conclusion:** It is clear that platin exposure induced an ATM mediated signalling response and that cells lacking ATM showed deficiencies in the phosphorylation of key downstream targets. Cells deficient in ATM may therefore be more susceptible to platin therapy due to an impaired DNA repair response. However, the predictive capabilities of ATM loss for platin sensitivity is still unclear. This data suggests that individuals with low or non-functioning ATM may be candidates for precision low dose therapies that exploit this deficiency.

Keywords: platins, ATM, Cisplatin

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-078 ESTABLISHING MALIGNANT PLEURAL MESOTHELIOMA PRIMARY CELL LINES USING THE 3D SPHEROID METHOD PRODUCES A MODEL WITH BETTER TUMOUR ARCHITECTURE

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Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy with no effective treatment options. Poor prognosis and drug resistance are the main challenges of this deadly disease. There is also no simple distinctive diagnosis tool for identification of MPM. Better diagnostic markers may also provide better biological information for newer treatment option development. In this study we have established primary MPM cell lines and characterised them with current biomarkers. Our ultimately goal is to use these cell lines for better identification of diagnostic biomarkers. **Method:** MPM cell lines were either established from tissue specimens or pleural effusion from patients with pathologically confirmed MPM. Cells were cultured in standard (2D) and spheroid (3D) versions for characterisation. Cells prepared in 2D and 3D were stained with H&E and analysed 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). Scoring and comments were provided by pathologists experienced in MPM diagnosis (KL, SK). Established cell lines were also analysed for ploidy (flow cytometry) and interphase (fluorescent microscope) for chromosome number. PBMC from healthy donor was used as a control diploid. **Result:** We successfully established nine cell lines from MPM patient specimens. The original tumour histological sub-types were: three epithelioid, four biphasic, one desmoplastic and one not otherwise specified. Cells grown in 3D with H&E staining revealed better tumour architecture, cell-cell contacts and morphology when compared to cells grown in standard 2D culture. Mesothelioma positive markers were more distinctive and intense in biphasic cell lines grown 3D culture. Other sub-types showed similar staining when grown in both formats. Results from ploidy showed no distinctive difference between sub-types, however, 5 out of 9 cell lines established had tetraploid chromosome content. **Conclusion:** Cells grown in 3D provide more tumour architecture when compared with 2D cells. 3D cells also provide more intensity and greater percentage of positive MPM markers

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-079 A 3D SPHEROID CULTURE REPRESENTS AN IMPROVED IN VITRO MODEL OF MALIGNANT PLURAL MESOTHELIOMA (MPM)

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Background: Most biologists rely on cell culture in the two-dimensional (2D) format for studying tumour context which does not accurately reflect the *in vivo* state. 3D cell culture techniques provide cell-to-cell interactions that better mimic pathological conditions such as cancer. Malignant pleural mesothelioma (MPM) is a deadly cancer with no effective treatment and is highly drug resistance. Our study has addressed this problem by growing cells in 3D thus creating an environment that is more closely

mimics the realistic tumour state for molecular and cell effect studies. **Method:** MPM cell lines were grown in conventional 2D, our newly optimised 3D format, hanging drop and poly-HEMA methods. Cells were analysed their structure by light, scanning electron (SEM) and transmission electron (TEM) microscopy. Drug infiltration was confirmed by intravital-microscopy. Cell proliferationswith with different dose of drugs (Cisplatin and Gemcitabine) were analysed in 2D and 3D cells. Cells grown as truly spherical spheroids and their 2D counterparts were harvested for tumour suppressor analysis. 16 previously reported tumour suppressors (ANK1, MIB1, RGS22, TNIL, GMC, SVIL, ATG4D, HOXB4, SCLC25A13, CHST11, ATG4D, GTF2A1, KIAA1361, PDZD2, WDR1 and TMSB15B) and 3 oncogenes (YAP1, ABCG2 and YB1) were analysed. **Result:** The 3D spheroids represent an improved 'mini-tumour' model as indicated by the visualization of cell junctions under TEM. The 3D spheroids (11 MPM lines) formed using our method also provided perfect spherical shape and revealed healthy and surface morphology by SEM analysis. We showed in our model drugs was able to penetrate from outside to centre of the spheroids. However, in our hands, the hanging drop and the poly-HEMA versions did not always produce spherical 3D cells. Cells grown in our 3D model display greater drug resistance when compared with 2D cells. Most tumour suppressor biomarkers we analysed showed down-regulation of mRNA expression level compared with cells in 2D. These tumour suppressor genes were host genes of microRNAs (e.g. MIB1 for miR-1). Most of them are frequently down-regulated in MPM. Our 3D model also showed up-regulation of genes that contribute to drug resistance such as Hif1a, YAP1, ABCG2 and YB1. **Conclusion:** 3D cells grown with the newly optimised method provide a better mimic of more realistic MPM evidence by the more resistance of MPM cells to cisplatin and gemcitabine when compared to cells grown in 2D. MPM cells grown in 3D also down-regulated of tumour suppressors and up-regulation of drug resistance genes when compared to 2D cells.

Keywords: 3D cell model, mesothelioma, tumour suppressor genes

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-080 DNMT3A DEFINES A UNIQUE MOLECULAR CLASS OF CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: DNMT3A mutation is detected in approximately 18%-23% newly diagnosed AML patients, while the mutation is less frequently detected in cancer. The aim of this study is to investigate mutations and prognosis of non-small-cell lung cancer (NSCLC) harboring DNMT3A mutations. **Method:** A total of 1367 patients with NSCLC were recruited between July 2012 and December 2014. The status of DNMT3A mutation and other genes were detected by next generation sequencing. **Result:** DMNT3A gene mutation was detected in 1.1% (15/1367) NSCLC patients, including p.V636M (1 patient), p.Y735C (1 patient), p.Y660F (1 patient), p.R183W (1 patient), p.Q653H (1 patient), p.A741P (1 patient), p.Q226* (1 patient), p.D340Y (1 patient), p.A398T (1 patient), p.A187T (1 patient), p.A910V (1 patient), p.R729W (1 patient), p.S770L (1 patient), c.1755+1G>T (1 patient) and G510D plus F545V plus R582Q (1 patient), and median overall survival (OS) for these patients was 19.7 months. Among them, all patients were DNMT3A gene with co-occurring mutations. Briefly, patients with (n=11) or without (n=4) co-occurring EGFR mutations had a median OS of 19.1 months and 22.9 months respectively (P=0.82);patients with (n=13) or without (n=2) co-occurring TP53 mutations had a median OS of 16.0 months and 29.8 months respectively (P=0.98); patients with (n=5) or without (n=10) co-occurring HER2 mutations had a median OS of 44.3 months and 14.6 months respectively (P<0.01); patients with (n=2) or without (n=13) co-occurring SMARCA4 mutations had a median OS of 32.3 months and 19.7 months respectively (P=0.43); patients with (n=2) or without (n=13) co-occurring BRCA1 mutations had a median OS of 29.6 months and 19.7 months respectively (P=0.93). **Conclusion:** EGFR, TP53, HER2, SMARCA4 and BRCA1 gene accompanied may have less correlation with DNMT3A mutation in NSCLC patients. Chemotherapy drugs may displayed moderated efficacy in patients with DMNT3A mutation. Analysis of DNMT3A mutations shows promise as a way to refine individual patients with NSCLC, and provides a platform for further research to offer individualized therapy with the purpose of improving outcomes.

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-081 NUTRITIONAL STATUS ASSESSMENT IN TREATMENT NAÏVE PATIENTS WITH LUNG CANCER

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Background: Malnutrition is multifactorial and frequently co-exists in patients with cancer. Cancer-related anorexia, cachexia and side effects of anticancer therapy can lead to inadequate nutrient intake and subsequent malnutrition. Lung cancer is the leading cause of cancer and cancer-related mortality globally and most patients present in an advanced stage. Nutritional status has a direct effect on the performance status, tolerance to treatment and outcomes. **Method:** We performed a cross-sectional, observational study in the outpatient department of a tertiary referral cancer hospital involving nutritional assessment of treatment-naïve patients with lung cancer. Patients who consented were assessed by two nutritionists using the patient reported subjective global assessment(SGA) and mini nutritional assessment (MNA) tools. Data collected included history, physical and anthropometric measurements. Assuming a prevalence of 33%, the required sample size was calculated to be 400. **Result:** 400 patients were recruited between August 2015 and January 2016. The mean age of patients was 58 years and 72% were male. The mean body weight was 57 kilograms and the mean body mass index (BMI) was 21.9 kg/m2. The mean hemoglobin was 12.4 gm% and the mean albumin was 3.9 gm%. 50% of patients were smokers, and 34.7% of the smokers also chewed tobacco. 95% of the smokers were male; 21% consumed alcohol. 64.5% of patients had lost weight, and 60% had anorexia. Most patients presented in advanced stages, with 60.75% in stage IV and 24% in stage III. Nutritional status assessed by the Subjective Global Assessment (SGA) score showed that 24.5% were well nourished (SGA "A"), 64.5% were at risk of malnutrition (SGA "B") and 11% were malnourished (SGA "C"). Using the Mini Nutritional Assessment (MNA) score, 80.7% of patients were found to be malnourished or at risk of malnutrition with 19.3% patients considered to have normal nutritional status. No significant correlation was found between age, ECOG status, smoking, disease stage or weight loss and the nutritional status scores. There was moderate agreement between the SGA and MNA scores with a kappa coefficient of 0.44. **Conclusion:** Malnutrition is widely prevalent in patients with lung cancer. Formal nutritional assessment using universally acceptable tools like the SGA or MNA should be a part of the work up of the patient along with staging and diagnosis. Early identification can guide nutritional intervention in order to improve the performance status and enable patients to receive and tolerate cancer directed therapy.

Keywords: malnutrition, lung cancer

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-082 HIGH MOBILITY GROUP BOX 1 ANTAGONIST LIMITS METASTATIC SEEDING IN THE LUNGS VIA REDUCTION OF CELL-CEL ADHESION

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Background: Metastatic spread is the leading cause for cancer-related mortality, with lungs being a major site for metastatic seeding. Available therapies for patients with metastatic disease are extremely limited. Therefore, there is a desperate need for new strategies to prevent or limit metastatic dissemination. The metastatic cascade is highly complex and is affected by multiple factors related to tumor cells themselves and the microenvironment in the future site of metastasis. We hypothesized that modifying the lung microenvironment by blocking central ubiquitous signals may affect metastatic seeding in the lungs. Given the high basal levels of the Receptor for Advanced Glycation End products (RAGE) in the pulmonary tissue, and its pro-inflammatory properties, we investigated the consequences of interfering with its ligand, High Mobility Group Box 1 (HMGB1). **Method:** We performed a panel of cell based assays aimed at identifying the effect of Carbenoxolone on specific steps of tumor growth and metastases. We chose Lewis Lung Carcinoma (LLC) murine cell line because of its highly metastatic potential and the possibility to evaluate both primary and secondary growth in the relevant microenvironment of the lung. To understand which metastatic step is most affected by Carbenoxolone, we applied varying in vitro assays: proliferation, migration, invasion, anoikis, adhesion, cell anchorage and colony formation. To study both tumor progression and spread of metastasis, we performed four different in vivo models. In vivo models applied were two primary tumor models: subcutaneous and orthotopic, and two metastatic-relevant models: cell pulmonary colonization and tumor resection model for spontaneous cancer cell spread. **Result:**

Model	Relevant processes in cancer formation	Dosage	Duration	Results
Subcutaneous Lung Model	Proliferation	50 mg/kg every other day	17 days	No significant difference
Orthotropic Lung Model	Proliferation	10 mg/kg every day	17 days	No significant difference
Tail Vein Injection – Lung Tumor Cell colonization	Anoikis, Adhesion, Colonization	40 mg/kg every other day	25 days	significantly lower number of lesions on lungs (p=0.006)
Tumor Resection Lung Metastasis Model	Adhesion, Anoikis, Colonization, Intravasation, Migration	50 mg/kg every other day	38 days	significantly lower number of lesions on lungs (p=0.002)

Conclusion: Carbenoxolone hinders adhesion and colonization of cancer cells in the lungs by antagonizing HMGB1 and consequently the downregulation of the ICAM1 and lowering cell-cell adhesion. This ultimately results in reduced metastatic burden. Carbenoxolone decreases significantly lung metastases formation and can be used potentially as prophylactic therapy for metastatic diseases.

Keywords: Metastases, HMGB1, ICAM1

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-083 DKK1 PROMOTES MIGRATION AND INVASION OF NON-SMALL CELL LUNG CANCER VIA B-CATENIN SIGNALING PATHWAY

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Background: Non-small cell lung cancer(NSCLC) accounts for 80–85% of all lung cancers, the leading cause of cancer-related deaths worldwide .NSCLC progression and metastasis have been the primary causes for poor clinical outcomes of patients. Therefore, it is essential to explore the underlying molecular mechanisms of NSCLC migration and invasion; also, a diagnostic marker for NSCLC is an indispensable prerequisite. **Method:** DKK1 was knocked out by the lentivirus-mediated short hairpin RNA interference (shRNA) approach in H1299 and 95C NSCLC cell lines. Subsequently, the migration and invasion ability were assessed by wound healing and transwell assays. In addition, epithelial-mesenchymal transition (EMT) markers and β-catenin were examined by Western blot. The signaling pathway downstream of DKK1 was characterized using the Wnt signaling pathway inhibitor, IWP2, and GSK3β inhibitor, LiCl. Immunofluorescence analysis investigated the subcellular localization of β-catenin. **Result:** Knockdown of DKK1 caused reduced migration and invasion ability of H1299 and 95C cells. DKK1 silencing resulted in the downregulation of EMT-related proteins, such as Snail, ZEB1(zinc finger E-box binding homeobox 1), Besides, DKK1 silencing inhibitedβ-catenin and promoted the phosphorylation of β-catenin. Mechanism results indicated that the expression of β-catenin was reduced in H1299 or 95C cells after being treated with Wnt signaling inhibitor, IWP2. In addition, the inhibition of β-catenin phosphorylation by GSK3β inhibitor, LiCl, significantly enhanced the migration and invasion capacities in DKK1-KD cell lines. Furthermore, cell immunofluorescence revealed that nuclear β-catenin was reduced when DKK1 was knocked down. **Conclusion:** Taken together, these suggest that DKK1 induces the occurrence of EMT and promotes migration and invasion in NSCLC cells. Mechanically, β-catenin plays a vital role in DKK1-induced NSCLC cell migration and invasion, and DKK1 inhibits the phosphorylation of β-catenin, resulting in the increased nuclear localization of β-catenin.

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-084 FGF9-FGFR PATHWAY INDUCE NEUROENDOCRINE DIFFERENTIATION IN LUNG EPITHELIAL CELLS

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Background: Small cell lung cancer (SCLC), an aggressive and metastatic disease, accounts for about 15% of lung cancer. Neuroendocrine differentiation is essential molecular event in SCLC development. The mechanisms of neuroendocrine differentiation and SCLC development remain elusive. For the improvement of the prognosis of SCLC patients, clarification of the mechanisms of neuroendocrine differentiation is essential. **Method:** For *in vitro* experiments, a stable cell line with constitutive expression of FGF9 in MLE12 (a mouse lung alveolar type II cell line transformed by SV40 large T antigen) was established by retroviral infections (H69: SCLC cell line, MLE12: mouse lung epithelial cell line transformed by SV40). Using these cell lines, the effect of FGF9 on proliferation, colony formation capacity and downstream signaling was evaluated by MTS assay, softagar colony formation assay and Western blotting, respectively. For *in vivo* experiments, these cell lines were transplanted into the immunodeficient mice subcutaneously, and the size of tumor was measured. To evaluate the efficacy of FGFR inhibitors for FGF9-driven lung cancers, AZD4547, selective FGFR inhibitor, was orally administered. For pathological characterization of the tumors, immunohistochemicalstry staining was performed. For patients study, 31 SCLC samples were obtained and the expression of FGF9 was evaluated by immunohistochemistry. **Result:** FGF9 is highly expressed in human SCLC samples (80.6%).FGF9 has oncogenic ability *in vitro* and its effect may be exerted by the activation of MAPK pathway through FGFR1 and FGFR3 in MLE12 cells. Unexpectedly, pathological analysis revealed FGF9-driven tumors exhibited SCLC histology. FGF9 transforms lung alveolar type II cells to SCLC *in vitro* and *in vivo*. Selective FGFR inhibitor, AZD4547 suppressed tumor growth of FGF9-driven MLE12 tumors. **Conclusion:** These results suggest that FGF9 has roles of tumor initiation and progression in lung cancer, especially in SCLC. SCLC which highly expresses FGF9 might may be a target of FGFR inhibitors.

Keywords: FGF9, FGFR, SCLC

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-085 SPHINGOSINE KINASE 1 (SPHK1) PROMOTES PROLIFERATION AND SURVIVAL IN NON-SMALL CELL LUNG CANCER

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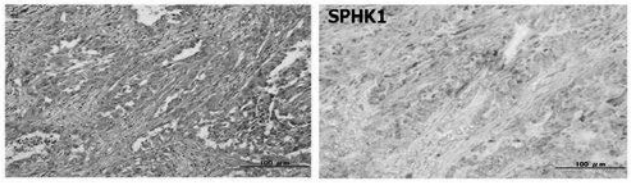
Background: Bioactive sphingolipids, such as sphingosine-1-phosphate (S1P) and ceramide, are signaling molecules involved in the activation of pathways that are directly relevant to carcinogenesis. Sphingosine kinase (SPHK) phosphorylates sphingosine to S1P, and is therefore an important regulator of the levels of ceramide, sphingosine, and S1P. Moreover, SPHK1 has been found to up-regulated in several tumor types, such as glioblastoma multiform, intestinal adenoma, acute erythroleukemia, prostate cancer, gastric cancer, and colon cancer. However, the relationship between bioactive sphingolipid pathway and lung cancer has not been clarified. **Method:** Paraffin-embedded non-small cell lung cancer (NSCLC) samples were obtained from 53 patients diagnosed between June 2009 and May 2014 at the Department of Thoracic surgery, Kanazawa Medical University. We characterized the SPHK1 expression in NSCLC by immunohistochemistry (IHC) and western blotting. **Result:** The SPHK1 expression was revealed at invasive area of NSCLC, and at fibroblast by IHC. The specific band of SPHK1 was detected approximately 52kDa by western blotting. We found that the SPHK1 expression in adenocarcinoma positively correlated with fibroblast expression and Ki-67 expression. On the other hand, the SPHK1 expression in squamous cell carcinoma was not significantly correlated with fibroblast score and Ki-67 expression. Low expression of the SPHK1 tended to prolong the relapse free survival (RFS) in lung adenocarcinoma patients (3-year RFS 100% vs 68.7%, p=0.38) .

Invasive Adenocarcinoma



Correlation among IHC scores

Variables		Correlation coefficient	p value
SPHK1	Fibroblast	0.302	0.06
	Vimentin	0.187	0.26
	E-Cadherin	0.080	0.63
	Ki-67	0.366	0.02
Fibroblast	Ki-67	0.350	0.03
Vimentin	E-Cadherin	-0.118	0.48

Conclusion: SPHK1 expression might regulate proliferation of cancer cell, as well as Ki-67. Furthermore, SPHK1 expression might activate fibroblast which is considered to induce epithelial mesenchymal transition.

Keywords: proliferation, non-small cell lung cancer, SPHK1

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-086 MGA SUPPRESSES THE MYC PATHWAY IN LUNG ADEOCARCINOMA

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Background: Recent exome-sequencing efforts have revealed that the *MGA* gene, which encodes a heterodimeric partner of the MYC-interacting protein MAX, is significantly mutated (~8%) in lung adenocarcinomas. Most *MGA* mutations are loss-of-function, suggesting that MGA may act as a tumor suppressor. *MGA* mutations are mutually exclusive to *MYC* gene amplification, suggesting the involvement of MGA in the MYC pathway. Here, we aimed to characterize both the cellular and molecular role of MGA in lung adenocarcinoma, with a focus on studying its role in modulating the MYC pathway. **Method:** Chromatin immunoprecipitation-sequencing (ChIP-seq) and RNA-sequencing (RNA-seq) analysis were used to identify MYC and MGA DNA binding sites and binding motifs. Inmunoprecipitation assays and mass spectrometry were used to elucidate MGA gene repression mechanism. Cell competition assay was performed to measure cell proliferation with and without MGA overexpression. Finally, electrophoretic mobility shift assays (EMSA) were used to functionally evaluate MGA DNA binding ability to E-boxes when missense mutations in the basic-Helix-Loop-Helix (bHLH) domain of *MGA* occur. **Result:** We found that ectopic expression of wild-type *MGA* represses the cellular growth of lung adenocarcinoma cell lines. Chromatin

immunoprecipitation-sequencing (ChIP-seq) and RNA-sequencing (RNA-seq) analyses revealed that MGA recognizes the same DNA binding motif as MYC, shares a large proportion of genomic DNA binding sites with MYC, and represses expression of MYC target genes. Immunoprecipitation assays in combination with mass spectrometry analysis reported that MGA interacts with several gene repressing proteins and complexes, such as the Polycomb repressive complex 1 (PRC1), histone deacetylases HDAC1/2, and the E2F6 transcriptional repressor, suggesting a potential mechanism by which MGA represses its target genes. In addition, we analyzed the mutation profile of *MGA* on a pan-cancer scale, revealing recurrent missense mutations in the basic-Helix-Loop-Helix (bHLH) domain of *MGA* in other cancer types such as colorectal and endometrial carcinomas. Electrophoretic mobility shift assays (EMSA) showed that these missense mutations impair the DNA binding ability of MGA, suggesting that these missense mutations, in addition to truncation mutations, disrupt the function of MGA in cancer cells. **Conclusion:** In summary, our results suggest that MGA plays a tumor suppressor role by binding to and repressing MYC target genes, thus expanding our current knowledge of genomic mechanisms for MYC pathway activation in cancer.

Keywords: tumor suppressor, transcription factor, MYC pathway

P3.02: BIOLOGY/PATHOLOGY -
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P3.02-087 LONG NONCODING RNA FOXF1-AS1 REGULATES EPITHELIAL-MESENCHYMAL TRANSITION IN NON-SMALL CELL LUNG CANCER CELLS

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Background: Lung cancer is still the leading cause of cancer related death in China and has become a severe public health problem. Two main subtypes of lung cancer are named as non-small cell lung cancer (NSCLC) and small cell lung cancer, which accounts for approximately 80-85% and 15-20% respectively. The high mortality is probably related to early metastasis, however the underlying mechanism remains unclear. The main critical changes of progression and metastasis are epithelial-to-mesenchymal transition (EMT). Long noncoding RNA (lncRNA) is consisted of more than 200 nucleotides in length. Recent evidence showed that lncRNAs trigger the initiation and progression of cancers. In this study, we aim to investigate whether lncRNA can regulate EMT in NSCLC. **Method:** Quantitive PCR was performed to investigate the different expression of lncRNA, FOXF1-AS1 in NSCLC and matched normal tissues. Full length FOXF1-AS1 cDNA was transfected into lung cancer cells by plasmid vectors to forced express the FOXF1-AS1. The morphology of cancer cells were observed after transfection with FOXF1-AS1. And transwell migration and invasion assay were performed using transwell chambers without (migration) or with (invasion) Matrigel. **Result:** We identified a panel of key factors dysregulated in lung cancer. Among them, the expression of FOXF1-AS1 was significantly downregulated in lung cancer.The loss expression FOXF1-AS1 in lung cancer tissues was further validated by real time qRT-PCR . When we stably overexpress FOXF1-AS1 in NSCLC, we observed the morphological changes of CALU1 and NCIH1975 cells from a fibroblastoid appearance elongated spindle shape to cobblestone shape after stable overexpression FOXF1-AS1.Then, CALU1-FOXF1-AS1 cell and H1975-FOXF1-AS1 cell that overexpressed FOXF1-AS1 or their negative control were allowed to migrate through a transwell membrane into complete media. Compared to the negative control, overexpression of FOXF1-AS1 induced the promotion of the motility of both two of the transfected cells. And FOXF1-AS1 overexpression also significantly promoted the invasion of the two transfected cells. And we also found that overexpression of FOXF1-AS1 decreased Vimentin and increased E-Cadherin in both CALU1 and NCIH1975 cells. **Conclusion:** FOXF1-AS1 regulates epithelial-mesenchymal transition in lung cancer cells.

Keywords: lncRNA, EMT, non-small cell lung cancer

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-088 ENHANCED GLYCOLYSIS IS CRITICAL FOR MAINTAINING INACTIVATION OF JNK AND STABILITY OF EGFR LEADING TO THE SURVIVAL OF EGFR-MUTANT LUNG CANCER CELLS

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Background: Metabolic reprogramming is required for cancer cells to meet the demands of enhanced cell proliferation. In this study, we investigated how altered cell metabolism is associated with oncogenic mutant EGFR in lung cancer. **Method:** Metabolomics and measurement of metabolites in glycolytic pathway and TCA cycle were done using lung cancer cells with mutant EGFR and wild-type EGFR. **Result:** EGFR-mutant lung cancer cells showed enhanced glycolysis with elevated glucose uptake and lactate production which resulted in high extracellular acidification rate compared to cancer cells with wild-type EGFR. EGFR-TKI treatment or knockdown of EGFR caused a significant decrease in the metabolites of glycolysis. They are much more sensitive to glucose deprivation, but not to glutamine deprivation. Glutamine is usually utilized to fuel the TCA cycle supporting tumor cell growth. However, glucose was the main source of TCA cycle to produce ATP in EGFR-mutant cells. This mutant EGFR-enhanced glycolysis was critical for EGFR stability. The failure to sustain ATP production in mitochondria by glucose deprivation or suppression of glycolysis induced ROS accumulation which resulted in JNK activation. Activated JNK mediated EGFR degradation causing apoptosis while SP600125, a JNK inhibitor, could rescue cells from apoptotic cell death. Importantly, almost same effects could be observed in EGFR-TKI-resistant cells by T790M. **Conclusion:** Together, our data showed that EGFR-mutant lung cancer cells require the enhanced glycolysis for maintaining inactivation of JNK and EGFR stability regardless of T790M. This could be an attractive target for treatment of EGFR-mutant lung cancer, especially with resistance to EGFR-TKI.

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-089 ESTABLISHMENT OF HIGHLY METASTATIC LUNG CANCER CELL SUBLINES IN LONG-TERM THREE-DIMENSIONAL LOW ATTACHMENT CULTURES

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Background: Previous studies demonstrated that lung cancer with floating cell clusters in histology is more likely to develop metastasis. We investigated whether cancer cells in long-term, three-dimensional low attachment cultures acquire high metastatic potential and examined the mechanisms underlying metastasis. **Method:** Two KRAS-mutated adenocarcinoma cell lines (A549 and H441) were cultured and selected on ultra-low attachment culture dishes, and the resulting cells were defined as FL (for floating) sublines. *In vitro* cell growth (in attachment or suspension cultures), migration, and invasion were assayed. Cancer cells were inoculated into NOD/SCID mice via an intracardiac injection, and metastasis was evaluated using luciferase-based imaging and histopathology. A whole genomic analysis was performed to identify key molecular alterations in FL sublines. **Result:** Upon detachment on low-binding dishes, parental cells initially formed rounded spheroids with limited growth activity. However, over time in cultures, cells gradually formed smaller spheroids that grew slowly, and, after 3-4 months, we obtained FL sublines that regained prominent growth potential in suspension cultures. On ordinary dishes, FL cells reattached and exhibited a more spindle-shaped morphology than parental cells. FL cells exhibited markedly increased growth potential under suspended conditions *in vitro* and stronger metastatic abilities *in vivo* (Fig.). A genomic analysis identified epithelial-mesenchymal transition (EMT) and c-Myc amplification in A549-FL and H441-FL cells, respectively, as candidate mechanisms for metastasis. The growth potential of FL cells was markedly inhibited by lentiviral ZEB1 knockdown in A549-FL cells and by the inhibition of c-Myc through lentiviral knockdown or the pharmacological inhibitor JQ1 in H441-FL cells. **Conclusion:** Long-term three-dimensional low attachment cultures may become a useful method for investigating the mechanisms underlying metastasis mediated by decreased cell-substratum adhesion.

Keywords: Metastasis model, epithelial-mesenchymal transition, Three-dimensional low attachment culture

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-090 HYPOXIA-INDUCED MODIFICATIONS OF THE SMALL NON-CODING RNA TRANSCRIPTOME DELINEATES RISK OF RECURRENCE IN EARLY-STAGE LUNG ADENOCARCINOMA

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Background: Hypoxia is central to neoplastic diseases. It has been associated with reduced survival in several tumor types, including NSCLC. A spectrum of poor outcome suggests a multifactorial modulation of the hypoxic response. Piwi-interacting RNAs (piRNAs) are small non-coding RNAs (sncRNAs) with a pivotal role in genomic stability and epigenetic regulation of gene expression. Changes in piRNA expression have been recently found to be deregulated during tumor progression, and responsive to tumor microenvironment conditions. Here, we investigate if hypoxia alters the piRNA transcriptome in human lungs, and assessed whether these alterations are indicative of outcome in patients with hypoxic lung tumours. **Method:** Tumors from lung and other six organs (TCGA) were classified according to their oxygenation state using signatures derived from established hypoxia-associated gene expression changes. By investigating >3000 piRNA transcriptomes, we generated a baseline of hypoxia-related changes which were further validated in a panel of cell lines exposed to hypoxia in vitro (16h at 1% O_2). In lung tumors (n=1,018), we identified the most robust hypoxia-related changes between hypoxic and non-hypoxic groups by including piRNAs that: 1) ≥ 10 RPKM median expression, 2) > 2-fold change in median expression, and 3) a significant p value following a Mann-Whitney U test. A piRNA-based score (*piSco*) was generated by grouping HR-piRNAs expression, weighted by coefficients from a Cox proportional hazard model. **Result:** Overall, piRNA expression is selectively deregulated by hypoxia. In vitro tumour models recapitulate HR-piRNAs expression patterns. Seventy-one HR-piRNAs were identified, showing statistically significant differences in expression between hypoxic and non-hypoxic tumours. Of these, 13 were exclusively deregulated in NSCLC tumors, showing a remarkable subtype specificity between adenocarcinomas and squamous cell carcinomas. We next investigated if the HR-

piRNA based score (piSco) was associated with NSCLC patient outcome. We found that *piSco* classify patients with hypoxic lung LUAD and LUSC as low or high risk of RFS. Remarkably, *piSco* was also able to classify Stage I LUAD patients into the same categories above (p = 0.0051). **Conclusion:** This study reveals the influence of the tumour microenvironment on DNA-level regulatory mechanisms with important implications for predicting recurrence in patients with hypoxic lung tumours. Our data encourage further exploration of HR-piRNAs as clinical tools for evaluating the likelihood of tumour recurrence, and as a mean to identify patients that would most benefit from adjuvant therapies and/or therapies designed to target hypoxic tumour cells.

Keywords: Hypoxia, Adenocarcinoma, non-coding RNAs

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-091 CONCURRENT ABERRATIONS IN G2/M-PHASE TRANSCRIPTIONAL PROGRAMS AND GENOMIC GATEKEEPERS HIGHLIGHT LUNG CANCER PREDISPOSITION IN COPD PATIENTS

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Background: Patients with chronic obstructive pulmonary disease (COPD) have a 7-fold increased risk of developing lung cancer. COPD is defined by clinical symptoms and reduced lung function measurements. It is characterized by chronic inflammation, small airway remodelling and loss as well as destruction of alveoli (emphysema). While this disease is an important lung cancer risk factor independent of smoking, the molecular progression from COPD to lung cancer tumourigenesis is relatively understudied. **Method:** In order to examine the molecular overlap between these two diseases, we first analyzed small airway epithelial gene expression profiles obtained from bronchial brushings from 127 COPD and 140 non-COPD ever-smoker patients. We performed weighted gene correlation network analysis (WGCNA) on these gene expression profiles to discover deregulated gene modules ('metagenes') associated with reduced lung function (Forced Expiratory Volume at 1 second, FEV_1)—a clinical measure of COPD severity most robustly negatively correlated with lung cancer risk. We then assessed the preservation of these modules in two non-small cell lung cancer (NSCLC) tumour/normal data sets (lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC), n= 887 tumors total). Airway and tumor patient cohorts were matched for age, gender, tumour stage, and smoking status. **Result:** We discovered 10 distinct small airway gene expression modules, two of which were significantly negatively correlated ($p < 0.05$) with patient FEV_1. One of these FEV_1 modules was the top overall module preserved in both NSCLC subtypes. This lung cancer-FEV_1 module contained 31 genes solely enriched for two related mitotic functions— G2/M phase transition (BH-p = 0.02) and mitotic roles of polo-like kinase (BH-p = 0.001, n=31). Of these, 28 genes were significantly overexpressed in both LUAD and LUSC, and mapped to a highly-clustered sub-network of 23 proteins with 465 known and *in silico*-predicted protein-protein interactions. When tumours enriched for this lung-cancer-FEV_1 gene signature were further examined, we observed a significant co-occurrence of DNA-level alterations in DNA damage associated checkpoints, specifically mutated *TP53*. **Conclusion:** Coordinated gene expression changes associated with COPD severity measures in small airways and preserved in NSCLC tumors are enriched for G2/M phase transition genes. These genes are further disrupted in tumors, where co-occurring mutations to gatekeeper genes are present. Progression of mitosis during abnormal aneuploidy in lung tissues of COPD patients may confer increased risk of oncogenic transformation in this population, and may underlie the molecular progression from COPD to lung cancer.

Keywords: Chronic obstructive pulmonary disease, initiation, Cell cycle

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-092 CD151-INTEGRIN-C-KIT AXIS PLAYS AN IMPORTANT ROLE IN THE PATHOGENESIS OF NON-SMALL CELL LUNG CANCER

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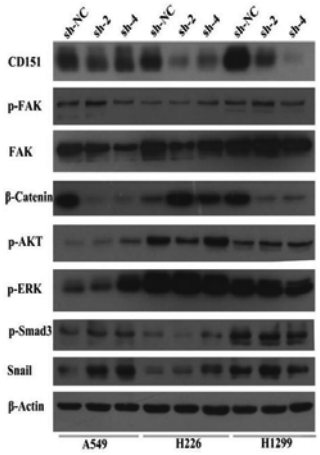
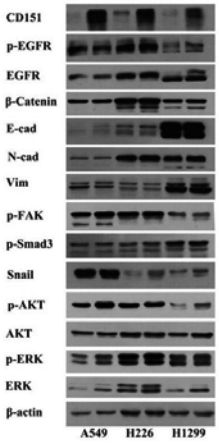
Background: CD151, a master regulator of laminin-binding integrins (α3β1,α6β1 and α6β1), assembles these integrins into complexes called tetraspanin-enriched microdomains. Hence, CD151 is well positioned to modulate integrin-dependent cell spreading, migration, signaling, and adhesion strengthening. Now, it has been shown to be involved in tumour progression. The molecular mechanism of CD151 in cancer is based on its ability to organize distribution and function of interacting proteins, ie, laminin-binding integrins (α3β1,α6β1 and α6β1), receptors for growth factors (HGFR, EGFR). Considering the fact that CD151-integrin complex can regulate receptors for growth factors (HGFR, EGFR), we hypothesized that CD151-integrin complex involving in the pathogenesis and acquired resistance to EGFR-TKIs in lung cancer. **Method:** o determine the expression of CD151 in NSCLC cell lines and tissues, quantitative real-time PCR (qRT-PCR), Immunohistochemistry (IHC) and Western blot were performed. Cell Counting Kit-8 assay was applied to evaluate the cell proliferation, and propyliodide organism (PI) staining was used to detect the cell cycle. Meanwhile we observed the alteration of cell proliferation and cell cycle after transient transfection with sh-CD151 and CD151 over-expressed into lung cancer cell lines. The Human Soluble Receptor Array Kit Non-Hematopoietic Panelprotein-kinase (R&D Systems, ARY012) and human RTKs phosphorylation antibody array. (RayBiotech Inc, Array-AAH-PRTK-G1), was performed according to manufacturer guidelines. **Result:**





The expression of CD151 was significantly increased in NSCLC cell lines and tissues. After transfected sh-CD151 or CD151 over-expressed vector into lung cancer cell lines, they showed significant growth-suppressing or promoting effect We utilized a human soluble receptor array and a human RTKs phosphorylation antibody array to investigate whether these and/or other oncogenic signaling pathways were activated downstream of CD151-integrin complex in NSCLC cells. Our results showed that CD151-integrin complex could regulated the growth and metastasis in NSCLC through c-kit signaling. **Conclusion:** CD151-integrin-c-kit axis plays an important role in the pathogenesis of non-small cell lung cancer

P3.02: BIOLOGY/PATHOLOGY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.02-093 KNOCKDOWN OF BRM CAUSES EPITHELIAL-MESENCHYMAL TRANSITION IN LUNG ADENOCARCINOMA CELL LINE H1975

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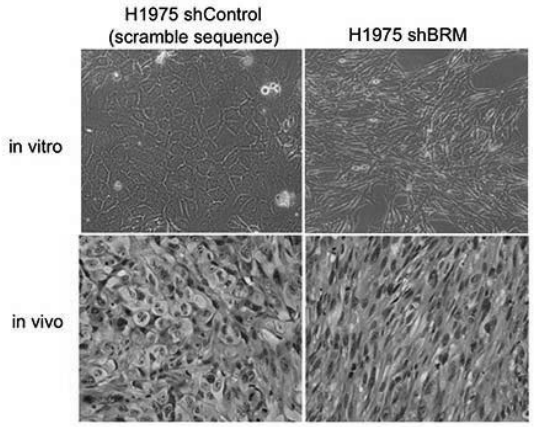
Background: Recent genomic studies have identified mutations in the multiple subunits of the chromatin remodeling complex in various cancers. Expression of BRG1/BRM, the core subunit of the SWI/SNF complex, is frequently altered in lung cancer, and our group has previous shown that loss of BRG1/BRM is associated with the EMT phenotype and poor prognosis in lung adenocarcinomas (Cancer Sci 2013). **Method:** In this study, we explored the effect of BRM knockdown (KD) with lentiviral sh-RNA in lung cancer cell line H1975. **Result:** BRM KD with lentiviral sh-RNA caused profound changes in H1975; original polygonal cells became spindled shaped, and when injected subcutaneously into SCID mouse, BRM-KD cells formed tumors composed of uniform spindle cells, mimicking sarcomatoid carcinomas. qRT-PCR and Western blot analyses confirmed downregulation of E-cadherin and upregulation of vimentin. Analysis of signaling molecules showed that EMT occurred independent of the EGFR, MET, or TGF-β/SMAD pathway. Among the master regulators of EMT, ZEB-1 was most remarkably upregulated, as compared to snail or slug, by BRM knockdown. **Conclusion:** Loss of BRM caused EMT, which was due to upregulation of ZEB1.



Keywords: lung adenocarcinoma, BRM, EMT

P3.02-094 IDENTIFICATION OF ONCOFETAL PIRNAS IN LUNG

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Background: PIWI-interacting RNAs (piRNAs) are a class of small non-coding RNAs (distinct from microRNAs) that recognize complementary DNA sequences in the nucleus. Their primary functions involve epigenetic control of gene transcription and maintenance of genomic stability through repression of mobile elements. Recent observations of cancer type specific aberrant expression have raised the possibility of a role for piRNAs in lung cancer. Here we characterize piRNA transcriptomes of fetal, adult and tumour lung tissue to identify fetal piRNA genes that are silenced in normal adult lung and re-activated in cancer. Our goal is to identify oncofetal piRNAs, which might represent ideal cancer therapeutic targets, as they are absent in normal adult lung tissue. **Method:** We determined piRNA expression profiles from small-RNA sequencing libraries using an in-house pipeline. All sequence reads were aligned to the hg38 build of the human genome. The expression levels of fetal lung samples (n=25) and two tumour/non-malignant paired cohorts (BCCA, n=118 and TCGA, n=91; derived from non-small cell lung cancer cases) were compared. piRNAs not expressed in non-malignant samples but with comparable expression in both fetal and tumour tissues were classified as oncofetal piRNAs. In order to identify the biological functions of the identified oncofetal piRNAs, we performed piRNA/DNA binding prediction using the miRanda algorithm adjusted for piRNA-specific features. **Result:** Our results provide a comprehensive characterization of piRNA expression in both normal and tumour lung tissues, as well as an unique piRNA expression profile of fetal lung tissues. A subset of the piRNA pool expressed in lung tissues are similarly expressed between fetal lung and lung tumours, but are absent in non-malignant tissue, implying that tumour initiation might involve the reactivation of developmental pathways. More importantly, target prediction analysis revealed that the identified oncofetal piRNAs are involved in key cellular processes, such as cell proliferation, migration and survival. **Conclusion:** Our study provides an unique and comprehensive characterization of the piRNA pool of lung tissues, as well as the identification of specific similarities in piRNA expression during both organ and tumour development. These similarities between fetal and tumour tissues might represent a promising avenue for the identification of strong biomarkers or optimal therapeutic targets with little toxicity for the treatment of lung cancer. Therefore, our study provides new and promising insights for lung tumour biology and may aid in the development of novel therapeutic approaches.

Keywords: PIWI-interacting RNAs, Oncofetal, lung cancer

P3.02-095 BASIC TRANSCRIPTION FACTOR 3 IS INVOLVED IN LUNG CANCER GROWTH AND PROGRESSION

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Background: Basic transcription factor 3 (BTF3) which is a general RNA polymerase II transcription factor plays a crucial role in the regulation of various biological processes. Evidence has demonstrated that BTF3 is aberrantly expressed and involved in the development and progression of gastric cancer and colorectal cancer. However, the role of BTF3 in lung cancer is not clear. The present study is to investigate the expression of BTF3 in non-small cell lung caner (NSCLC), its role in tumor growth as well as the underlying mechanisms. **Method:** BTF3 shRNA lentiviral vector was constructed and transfected in human NSCLC cells NCI-H1299 and A549. The cell proliferation, viability and apoptosis were evaluated by Celigo, MTT and AnnexinV-APC assays. The immunohistochemical stainings of BTF3 were performed on ten NSCLC tumors and matched adjacent lung tissues. Xenograft tumor model was established to evaluate the role of BTF3 in tumor formation in vivo. To further explore the underlying mechanism, a gene array was performed in BTF3 knockdowned A549 cells and pathway/network analyses was performed with Ingenuity Pathway Analysis (IPA). **Result:** Knockdown of BTF3 inhibited the proliferation and viability and increased apoptosis significantly in NSCLC cells. The BTF3 expression was much higher in NSCLC tumors compared to the adjacent lung tissues. A549 with BTF3 shRNA lentiviral transfection could not form subcutaneous tumors in immune-deficient mice in vivo. After BTF3 was inhibited in A549 cells, it was observed 489 upregulated and 148 downregulated genes (FC>1.5). IPA core analysis of these proteins revealed that acute phase response pathway was significantly enriched among other canonical pathways, and played a role in cell death, cell movement of myeloid cells and organismal death. We further utilized IPA upstream regulator analysis and found two transcriptional regulators XBP1 and NUPR1 that are predicted to be the key regulators of proteins changed in the BTF3 inhibited A549 cells. Western blot analysis verified that HK2, DUSP5 and KLF4 were significantly downregulated in BTF3 inhibited A549 cells. **Conclusion:** These results suggest, for the first time, that BTF3 is over-expressed in lung cancer and favors tumor growth, suggesting that BTF3 might play a role in the progression of lung cancer. The investigation of BTF3 in NSCLC survival and prognosis and further regulatory mechanisms are ongoing.

Keywords: growth, NSCLC, BTF3

P3.02-096 THE INTERACTION BETWEEN MAST CELLS AND LUNG CANCER CELLS THROUGH EXTRACELLULAR VESICLES

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Background: Exosomes are nano-sized extracellular vesicles that mediate cell-to-cell communication by transferring molecules. Mast cells are secretory cells that complete their differentiation and maturation in the micro-environment of tissues containing blood vessels, and were observed in the periphery of certain tumors. It has been hypothesized that tumor cells affect their environment by passing genetic codes such as miRNA through exosomes. In this study, we investigated the presence of exosomal content in the micro-environment of lung cancer cells as a communication mechanism that drives tumor development. **Method:** Human mast cells (HMC1) were exposed to Human lung cancer cells (H1299) in *in vitro* setting. Exosomes were isolated from mast cells alone, lung cancer cells alone and from a co-culture of mast cells and lung cancer cells. As a control, exosomes were produced from mast cells that were activated by membranes of lung cancer cells. Exosomes quantity and quality were analyzed including its miRNA composition. Samples were run on an HTG EdgeSeq Processor using the HTG EdgeSeq miRNA WT assay. Each assay contains 2102 probes for miRNA, including 13 housekeeper genes, 5 negative process controls, and 1 positive process control. The HTG EdgeSeq Parser was used to align the FASTQ files to the probe list to collate the data. CPM (counts per million) was normalized and differential expression was analyzed using DESeq2. **Result:** We exposed mast cells to membranes of lung cancer cells, in order to examine induction of mast cells. Out of 2066 miRNA analyzed only 3 were significantly upregulated: miR-31-5p, miR-100-5p and miR-125b-5p. Interestingly, the profile of the pathways activated by these 3 upregulated miRNAs shows the focal adhesion and adherens junctions as one of the top results. A comparison was made between miRNA expression of exosomes from mast cells vs. exosomes from lung cancer cells. Out of 2066 miRNA analyzed, a total of 112 miRNA were differently expressed. 79 miRNAs were downregulated, for example hsa-miR-6802-5p downregulated in HMC1 in comparison with H1299, and moreover hsa-miR-4700-5p. 33 miRNAs were significantly upregulated, for example miR-146b-5p/miR-146a-5p. Top upregulated miRNAs were tested using KEGG pathway and predicted to lead to the activation of the pathways like viral carcinogenesis, pathways in cancer and cell cycle. **Conclusion:** Mast cells and cancer cells do have common and discriminating exosomal content. Interestingly, mast cells have been induced by the presence of lung cancer cells' membranes, through a change in the canonical pathways of focal adhesion, by the upregulation of only 3 miRNAs.

Keywords: mast cells, exosomes, lung cancer

P3.02-097 CLINICOPATHOLOGICAL FEATURES AND GENETIC LANDSCAPE OF PULMONARY LARGE CELL CARCINOMA UNDER 2015 WHO CLASSIFICATION OF NSCLC

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Background: Pulmonary large cell carcinoma (LCC) was re-defined by 2015 WHO classification of non-small cell lung cancer (NSCLC) by excluding the tumors with adenocarcinoma, squamous and neuroendocrine features. The clinicopathological features and genetic landscape of pulmonary large cell carcinoma (LCC) with new classification were barely investigated. **Method:** Twenty-four LCC patients previously diagnosed under WHO 2004 criteria at Tianjin Medical University General Hospital were collected and re-classfied by 2015 WHO classification criteria. The specimen with more than 1% positivity of TTF-1/napsin A and 10% positivity of p40/p63/CK5/6 expression was excluded from LCCs under WHO 2015 criteria in this study. The specimens with CgA and Syn positivity, the feature of neuroendocrine tumor, were excluded too. The genetic analysis was performed by the next-generation sequencing (NGS) of 46 cancer-related genes on the newly re-classified LCCs. The correlation of clinicopathological and genetic data was further analyzed on these samples. **Result:** All 8 patients re-defined as LCCs under WHO 2015 criteria were male and 7 patients were smokers. None of significant difference was found between the LCCs patients and excluded patients under WHO 2015 criteria in terms of age, gender, smoking status, primary site and TNM staging. Although lower OS time was presented in LCCs under WHO 2015 criteria compared with the excluded ones, no significant difference was detected between these two groups (LCC under WHO 2015 criteria vs excluded specimens = 698.75±62.83 vs 1301.03 ±245.40 days, P=0.738). Ten of 46 candidate genes including EGFR, KRAS, TP53, KIT, PIK3CA, PTEN, IDH1, APC, ATM and BRAF were detected in all 24 specimens. Four of all 8 LCC patients under WHO 2015 criteria presented TP53 mutation and two showed concurrent TP53 and KRAS mutations. None of any somatic mutation was detected in the rest 4 of 8 LCCs. LCCs under 2015 criteria showed a lower heterogeneity and lower incidence of TP53

mutation compared to the with excluded specimens (TP53 mutation: LCCs *vs* excluded specimens=4/8 *vs* 15/16, p=0.015; Detected mutations: LCCs *vs* excluded specimens = 2/46 vs 10/46, p=0.030). **Conclusion:** LCCs re-classified by the new criteria remain the features of higher incidence in male and tobacco exposure. No significant difference change in terms of other clinical characteristics. The lower heterogeneity of somatic mutation in LCCs under WHO 2015 criteria might reflect the precision and uniformity of the new classification on the genetic level.

Keywords: next-generation sequencing, WHO Classification, Pulmonary Large Cell Carcinoma

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-001 IMMUNOTHERAPY TOXICITY: ARE GENERAL PRACTITIONER SATISFIED ABOUT INFORMATION TRANSMITTED? A RETROSPECTIVE SURVEY

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Background: Nivolumab is an immune check point inhibitor becoming a major tool in the treatment of Non-Small cell lung cancer (NSCLC). Its side effects are specific from its pharmacological class. General practitioners (=GP) may manage cancer patients and they would like to receive information about side effects of anticancer drugs. In our cancer center three oncologists prescribe nivolumab for NSLC. They use three different methods to inform the GP about Nivolumab expected side effects: a letter directly for the GP, an information sheet and/or a personal drug's card (OPDIVO® card) given to the patients. A survey has been conducted to assess GP satisfaction of information. **Method:** A complete list of all patients treated by nivolumab since its commercialization was obtained by medical prescription writing software (CHIMIO). Their GP have been identified with computer-based patient record (DX-Care). Through this same process, any information given about nivolumab side effects has been queried. A questionnaire has been drawn up, made up of 4 open questions and 1 closed question. All GP have been contacted by phone. **Result:** 121 patients have been identified. 5 patients were excluded because they died a few days after the first administration or because we could not find their GP. 103 GP were phoned over a one-month period and 86 GP responded to the survey. GP received 63 Nivolumab side effects letters and patients received 31 information sheets and 2 OPDIVO® cards. For 18 patients there was no evidence of information transmission. According to the survey, only 9 GP received information. For six of them in a letter, for two in an information sheet, and for one a patient showed its OPDIVO® card. They were satisfied with information. Most GP would like to be informed by secure messaging. **Conclusion:** No evidence of information was found in 21% of the electronic patient care. In the future, information must appear for all patients. Only 10% of GP could remember to have information, this may be partly explained by recall bias. As regards the desired method, they were different views. It was decided to harmonize oncologist practices. Nivolumab side effects are now systematically described in the letter for GP. All patients receive two information sheets with an OPDIVO® card. Patients are instructed to make an appointment with their GP to give one information sheet. In this way, we reinforce the communication between the hospital and the GP and thus hope to optimize patient's care

Keywords: Nivolumab, Communication, General practitioner

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-002 HISTONE DEACETYLASE INHIBITION ENHANCES THE ANTITUMOR ACTIVITY OF A MEK INHIBITOR IN LUNG CANCER CELLS HARBORING RAS MUTATIONS

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Background: Non-small-cell lung cancer (NSCLC) can be identified by precise molecular subsets based on genomic alterations that drive tumorigenesis and include mutations in EGFR, KRAS, and various ALK fusions. However, despite effective treatment for EGFR and ALK, promising therapeutics have not been developed for patients with KRAS mutations. Therefore, novel therapeutic strategies for KRAS mutated cancer based on molecular mechanisms are needed to improve their prognosis. It has been reported that one way the RAS-ERK pathway contributes to tumorigenesis is by affecting stability and localization of FOXO3a protein, an important regulator of cell death and the cell cycle. **Method:** We used NSCLC cells with RAS mutation to evaluate the effect of a MEK inhibitor in combination with a HDAC inhibitor through the expression and localization of FOXO proteins *in vitro* and *in vivo*. Protein expression was examined by Western blotting. **Result:** Combined treatment with a MEK inhibitor and a HDAC inhibitor showed synergistic effects on cell viability of RAS mutated lung cancer cells through activation of FOXOs, with a subsequent increase in BIM and cell cycle inhibitors. Moreover, in a mouse xenograft model, the combination of belinostat and trametinib significantly decreases tumor formation through FOXOs by increasing BIM and increase in cell cycle inhibitors p21 and p27. **Conclusion:** These findings demonstrate that FOXOs might be one of the critical pathways in RAS driven lung cancer cells, suggesting that the dual molecular targeted therapy for MEK and HDACs may be promising as novel therapeutic strategy in NSCLC with specific populations of RAS mutations.

Keywords: lung cancer with RAS mutation, MEK inhibitor

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P3.03-003 ABCB1 3435C≫T POLYMORPHISM INFLUENCES THE TOXICITY AND CLINICAL OUTCOME OF PATIENTS WITH TAXANE-BASED CHEMOTHERAPY

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Background: Taxane-based chemotherapy including paclitaxel, docetaxel, paclitaxel-albumin was wildly used in solid tumors. ABCB1 (P-glycoprotein, multidrug resistance 1) is a trans-membrane protein that acts as an energy-dependent drug efflux pump for chemotherapeutic drugs, including taxanes. In addition, ABCB1 has been suggested to have a role in the prediction of treatment response and toxicity of chemotherapy in breast cancer, gastric cancer et.al. In this retrospective study, we explore the influence of ABCB1 polymorphism on toxicity and taxane-based chemotherapy. **Method:** 118 patients (lung cancer 103, others 15) with taxane-based chemotherapy (paclitaxel 56 cases, docetaxel 55 cases, paclitaxel-albumin 7 cases) treatment were included in this study. Fluorescence in situ hybridization (FISH) was used for ABCB1 polymorphism detection. Statistical analysis was performed using SPSS 20.0. **Result:** The frequency of the ABCB1 3435 site homozygous mutation (TT genotype), heterozygous mutation (TC genotype) and wild type (CC genotype) was 11.0%(13/118) , 45.8%(54/118) and 43.2%(51/118) respectively. The occurrence of neurotoxicity was higher in patients had TT genotype (62.9%) compared with patients had TC (25.9%) and CC genotype (37.3%)(P=0.310). Especially in the docetaxol subgroup, the difference of chemotherapy-induced neurotoxicity was statistically significant (TT 75.0%, TC 9.5%, CC 11.5%, P=0.007). There was not significant difference between the three ABCB1 genotypes with regarding to other chemotherapy-induced toxicity, including diarrhea, constipation, leukocytes, neutrophils, anemia and thrombocytopenia. For non-small cell lung cancer (NSCLC) patients in this study, patient harboring ABCB1 3435 site CC genotype had longer median progression free survival (PFS) (5.1 months) than TC genotype (4.7 months) and TT genotype (2.6 months)(P=0.42). Especially in the paclitaxel subgroup (n=21), the median progression was significantly longer in patients with CC genotype when compared with TC and TT genotype (9.8 months vs. 4.5 months vs. 1.6 month, P=0.06). We failed to find the difference in either response rate or disease control rate between the different genotype, even in subgroup analysis. **Conclusion:** ABCB1 3435 site polymorphism is associated with neurotoxicity of taxane-based chemotherapy. It can also predict clinical outcomes for NSCLC.

Keywords: ABCB1, chemotherapy, toxicity

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P3.03-004 THE FREQUENCY AND CLINICAL IMPLICATION OF ALK, ROS1, RET AND NTRK1 GENE REARRANGEMENTS IN ADENOSQUAMOUS LUNG CARCINOMA PATIENTS

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Background: Adenosquamous lung carcinoma (ASC) is a hybrid tumor made of adenocarcinoma and squamous cell carcinoma in one tumor. It is a rare disease with poorer prognosis comparing with the other common variants of non-small cell lung cancer (NSCLC). There is a persisting need for identifying more effective targeted therapy methods. Our previous study had examined the EGFR mutation status in lung ASC, the results showed that its mutation rate is similar with that of lung adenocarcinoma. Because the rarity of lung ASC, little is known about its gene rearrangement status and its relationship with the clinical characteristics. **Method:** ALK, ROS1, RET and NTRK1 gene rearrangement in lung ASC were examined by next generation sequencing methods, and further confirmed by fluorescent in situ hybridization (FISH) and/or immunohistochemistry methods. Tissue microarrays (TMAs) containing formalin fixed paraffin embedded (FFPE) lung ASC cases were used in this study. **Result:** This study included 53 cases of lung ASC totally. ALK/EML4 gene rearrangement was detected in 3 cases (5.7%), ROS1 fusion gene was detected in 1 cases (1.9%), RET gene rearrangement was detected in 1 case (1.9%). One of the ALK/EML4 rearrangement case had a concurrent EGFR exon 21 L858R mutation. All the rearrangement results can be further confirmed by FISH and/or immunohistochemistry methods. No association were identified between ALK/EML4 rearrangement and patient age, tumor size, clinical stage, positive pleural invasion, lymphovascular invasion, smoking status, lymph node metastasis, therapy methods, recurrence free survival (RFS) time or overall survival duration. **Conclusion:** The gene rearrangement rate of lung ASC is similar with that of lung adenocarcinoma, which further support our suggestion that lung ASC is a peculiar subtype of lung adenocarcinoma with a poorer prognosis than lung adenocarcinoma.

Keywords: lung adenosquamous cell carcinoma, gene rearrangement, EGFR mutation

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P3.03-005 DIAGNOSIS AND TREATMENT ANALYSIS OF LUNG ENTERIC ADENOCARCINOMA: 6 CASE REPORT AND REVIEW OF THE LITERATURE

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Background: Primary lung enteric adenocarcinoma is a rare type of invasive lung carcinoma. This study mainly discusses the clinicopathological characteristics, diagnosis and treatment of primary lung enteric adenocarcinoma. **Method:** Retrospectively analysed clinical records of 6 cases admitted in hospital from Feb. 2013 to May 2016, and reviewed the literature of primary lung enteric adenocarcinoma. **Result:** Two patients were male and four patients were female with the age ranged from 25 to 78 years. Their symptoms consisted mainly of cough chest stuffy with 4 patients, neck mass with 1 case, dizziness nausea vomiting with 1 case; imagining scan showed mass of lung and or mediastinal, pathology form and the immunochemistry showed all positive for intestinal immune phenotypes and some positive for lung cancer immunophenotypic. But no tumor was found by gastrointestinal endoscopes; 1 case recurrence and metastasis after radical operation; 1 patient underdone palliative surgery, 1 patient with brain solitary metastasis onset received Cyber Knife and without system treatment, and 5 patients underwent chemotherapy. At the end of follow-up, 4 patients died, over survival time as long as 32 months. **Conclusion:** The primary lung enteric adenocarcinoma is easily confused with pulmonary metastases from colorectal cancer, confirmed diagnosis need to rule out intestinal lesion, the main early treatment is surgery, and systematic treatment programs need to be further studied.

Keywords: diagnosis, Lung enteric adenocarcinoma, Immunohistochemistry

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-006 EFFICIENCY OF ANLOTINIB AS 3RD LINE TREATMENT IN PATIENTS WITH DIFFERENT EGFR GENE STATUS, AN EXPLORATORY SUBGROUP ANALYSIS OF ALTER0303 TRIAL

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Background: Anlotinib hydrochloride is a novel TKI targeting the VEGFR, FGFR, PDGFR and c-Kit. ALTER0303 trial (NCT02388919), phase III study has demonstrated that Anlotinib significantly prolonged OS and PFS in advanced NSCLC patients as 3rd line treatment. Here we report the efficacy of anlotinib in patients with or without EGFR gene mutations from the ALTER0303 trial. **Method:** Eligible adult IIIB/IV NSCLC patients who progressed after at least 2 lines of prior therapies were randomized 2:1 to receive Anlotinib or placebo (12 mg QD from day 1 to 14 of a 21-day cycle) till progression. Patients harboring EGFR or ALK mutations must had received previous targeted therapies. Primary endpoint is OS. **Result:** Among patients with sensitive EGFR mutations, the PFS was 0.83 months for control arm and 5.57 months for anlotinib arm (p<0.0001, HR=0.15, 95%CI: 0.09-0.24). Accordingly, OS was found 4.43 months longer in anlotinib group (6.27 vs 10.70, p=0.0227, HR=0.59, 95%CI: 0.37-0.93). On the other hand, in the subgroup of patients with wild-type EGFR gene, remarkable advantages in PFS and OS were observed as well. Specifically, PFS in control arm was 1.57 months which is 3.80 months shorter than that in anlotinib group (1.57 vs 5.37, p<0.0001, HR=0.29, 95%CI: 0.22-0.39). As to OS, superiority of 2.40 months was found in anlotinib arm (6.47 vs 8.87, p=0.0282, HR=0.73, 95%CI: 0.55-0.97). In the patients treated with Anlotinib, the most common (≥ 3 grade) and significantly differ from placebo group AEs were hypertension (13.61%), dermal toxicity (3.74%) and hypertriglyceridemia (3.06%). These results indicate that either the patient with EGFR mutation or not, they can both benefit from Anlotinib treatment. **Conclusion:** In ALTER0303 trial, significant advances in OS and PFS were found in anlotinib treated patients from both subgroups (sensitive EGFR mutations and wild EGFR gene type), indicating that, independent of the EGFR gene status, anlotinb treatment led to a consistent improvement in OS and PFS for advanced NSCLC patients and may be an appropriate option for this difficult-to-treat population as 3rd line treatment.

Keywords: Third-line, non-small cell lung cancer, Anlotinib

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P3.03-007 LCMC2: EXPANDED PROFILING OF LUNG ADENOCARCINOMAS IDENTIFIES ROS1 AND RET REARRANGEMENTS AND TP53 MUTATIONS AS A NEGATIVE PROGNOSTIC FACTOR

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Background: The Lung Cancers Mutation Consortium (LCMC) is a multi-institutional effort where 16 sites identify oncogenic drivers and pool data to assess the impact of targeted therapies in patients with lung adenocarcinomas. We now report the results of the second patient cohort (LCMC2) with an expanded multiplex molecular panel to include *RET* and *ROS1* and tumor suppressors. **Method:** 904 patients with centrally confirmed stage IV lung adenocarcinomas who were candidates for therapy had at least one of 14 oncogenic drivers assessed in a CLIA-compliant laboratory using genotyping, FISH, massively parallel sequencing (NGS), and immunohistochemistry (IHC) analyses. **Result:** Among 423 patients tested for all 14 targets, we found a driver in 65%. Mutated *KRAS* was found in 31%, sensitizing *EGFR* in 14%, *MET* amplification in 5%, *ALK* rearrangements in 4%, *BRAF* V600E in 3%, and *HER2* in 3%. Rearrangements in *RET* and *ROS1* were each found in 2% (CI 1 to 3%). Using IHC, PTEN loss was found in 8% (CI 6 to 11%) and MET expression in 58% (CI 55 to 61%). Use of targeted therapies in patients with *EGFR, HER2,* or BRAF mutations, *ALK, ROS1,* or RET rearrangements, and *MET* amplification was associated with a gain in overall survival of 1.5 years relative to those with the same drivers not receiving targeted therapy and a gain of 1 year relative to those without an actionable driver. Current and former cigarette smokers derived a survival benefit from targeted therapies similar to never smokers (p=0.975). Among 154 patients who had all drivers assessed and NGS testing in addition, any *TP53* mutation was associated with poorer survival among those with *EGFR*, *ALK*, or *ROS1* (p=0.014). *STK11* was detected in 11%, all in patients with *KRAS* mutations. **Conclusion:** Using an expanded testing panel, LCMC2 demonstrates the survival benefit of matching targeted treatments to oncogenic drivers in patients with lung adenocarcinomas, identifies additional prognostic factors, and supports the performance of multiplex molecular testing on specimens from all individuals with lung adenocarcinomas irrespective of clinical characteristics. We detected either *MET* amplifications or *HER2* mutations in 7%, together more than the 4% with *ALK*. A targeted drug is available in the United States for 35% of patients with lung adenocarcinomas. The routine use of massively parallel sequencing (NGS) detects both targetable drivers and tumor suppressor genes that have significance for therapy selection and prognosis. Supported by Free to Breathe

Keywords: Targeted therapies, Oncogenic drivers, Multiple genotyping, Adenocarcinoma

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P3.03-008 ORGANOID CULTURES OF LUNG SQUAMOUS CELL CARCINOMA FOR DRUG SCREENING

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Background: The difficulty of establishing lung squamous cell carcinoma (LUSC) derived cell lines have posed significant challenges for identifying potential therapeutic targets and understanding the complexity of this disease. We have previously developed a LUSC patient-derived xenograft (PDX) platform in which over 50 models have been characterized on the genomic and transcriptomic level. We describe a method to culture and establish LUSC organoids from PDX models and demonstrate their utility for drug testing. **Method:** Surgically resected LUSC were implanted into the subcutaneous flank of NOD/SCID mice to establish PDXs. To generate organoids, PDX tissue was dissociated into single cells using Liberase and TypLE and plated in growth factor reduced matrigel dome with media overlay. Organoids were processed for histological and immunohistochemical marker characterization. Organoids and matched PDX were subjected to shallow next generation sequencing for mutation and copy number analysis. Drug screening was performed in 384 well plates and viability was determined by Celltiter Glo 3D assay. **Result:** Of the 17 LUSC PDX models attempted, organoid lines from 3 PDX models were propagated beyond 20 passages for over 100 days. The success rate of organoid establishment is 18%, which is higher than establishing LUSC cell lines. Organoids exhibited various doubling rates ranging from 38 to 48 hours. Organoid tumor cells faithfully recapitulated the immuno-phenotypes of the matched PDX, expressing p63 and CK5/6 and were EpCAM positive and H2K negative by flow cytometry analysis. Organoids implanted in NOD/

SCID mice formed tumors that reflected the histology of the matched PDX. Shallow sequencing revealed similar copy number status between the organoid and matched PDX. RNA sequencing analysis is pending and will be reported. Organoids were amenable for drug testing and exhibited varying sensitivities to the PI3K inhibitors BKM120 and BYL719 based on each model's PI3K pathway status. **Conclusion:** We describe a method of developing LUSC PDX-derived organoids that can be propagated long term and faithfully recapitulate the histological and molecular characteristics of the original tumor. Additionally, we demonstrate their utility for in vitro drug testing. Organoids may be useful for preclinical modeling and therapeutic evaluation of LUSC.

Keywords: Lung Squamous cell carcinoma, Organoid, PI3K inhibitor

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P3.03-009 CONCURRENT SOMATIC MUTATIONS IN DRIVER GENES WERE SIGNIFICANTLY CORRELATED WITH LYMPH NODE METASTASIS AND PATHOLOGICAL TYPES IN SOLID TUMORS

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Background: Development of targeted NGS technology resulted in more attention to be given in identifying cancer-related driver gene pathways, which precisely illustrate how different driver genes collaborate simultaneously to induce carcinogenesis and progression. **Method:** We profiled 165 solid tumor samples, including 9 cancer types and 4 sample types, by using amplicon-based next-generation sequencing panel covering 48 highly mutated tumorigenesis-related genes that were deep sequenced at an average coverage of 2000×. **Result:** Both tumor and sample types had significant effect on tumor genetic mutational profiles. Concurrent driver mutations were frequently detected in solid tumor, concentrating on both modes of action driver genes (activating or loss of function). Furthermore, in non-small cell lung cancer (NSCLC), concurrent driver mutations were also significantly correlated with the lymph node metastasis status and pathological types. Higher frequency of lymph node metastasis was observed in patients with NSCLC with concurrent mutations on at least two driver genes. In addition, patients with lung adenocarcinoma were more likely to harbor concurrent driver mutations than patients with lung squamous and large cell carcinoma. Multiple mutations in the epidermal growth factor receptor gene were more frequently detected in patients with refractory NSCLC compared to untreated naive ones. **Conclusion:** Therefore, concurrent multiple driver mutations, rather than a single genetic mutation, should be investigated extensively to probe novel genetic biomarkers with clinical benefits.

Keywords: NGS,concurrent somatic mutations,NSCLC

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P3.03-010 IDENTIFICATION OF MECHANISMS OF DRUG RESISTANCE IN RET-REARRANGED LUNG CANCER

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Background: Oncogenic fusions of the RET kinase gene, which was discovered by us in 1-2% of LADCs (Kohno et al, Nat Med, 2012), have been suggested as a therapeutic target for existing tyrosine kinase inhibitors (TKIs). Actually, several clinical trials investigating RET tyrosine kinase inhibitors (TKIs) for the therapy of RET-positive LAD showed promising clinical outcome. However, the cancer inevitably acquires resistance to TKI like other driver oncogene positive LAD. **Method:** To identify a mechanism of TKI resistance in RET-driven lung cancer, we generated resistant cells to several RET-TKIs using LC-2/Ad cells that are RET-rearranged lung cancer cell lines. In addition, we established cells stably expressing RET fusion cDNA and RET-rearranged cells edited by CRISPR/Cas9, and generated resistant cells using these cells. We performed targeted sequencing covering 50 genes on a pair of resistant and pre-treatment cells. To identify the bypath track, then we performed antibody array and investigated change of mRNA expressions. **Result:** No genetic alteration was found in resistant cells by targeted sequencing. Antibody array found the activation of other tyrosine kinase, including EGFR and other HER family. Actually, the addition of the growth factors activating the kinases reduced the inhibitory effect of the TKIs. In addition, the TKI to suppress signaling of the kinase in combination with RET TKI reduced the cell viability in resistant cells. **Conclusion:** The inhibition of bypath track in combination of RET signaling could be an effective therapy for RET-rearranged lung cancer. In the meeting we plan to report the progress.

Keywords: RET fusion, Resistance

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-011 A REPORT OF BRAF V600E POSITIVE LUNG ADENOCARCINOMA PATIENT WHO RESPOND WELL TO PEMETREXED

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Background: *BRAF* mutations is one of the important driver oncogene in non-small cell lung cancer (NSCLC), and are known to give the petients worse prognosis as same as *KRAS* mutations. However, we experienced that a patient with *BRAF* V600E positive lung adenocarcinoma was responsive to pemetrexed treatment. The patient has been followed for over 7 years without recurrence and metastasis. **Method:** Here, we introduce a pemetrexed well respond patient with *BRAF* mutation positive lung adenocarcinoma. Clinical presentation, radiological features, histopathologic findings and genetic findings of the patient are reported. **Result:** A 64 years-old never smoker female who complained bloody sputum visited our hospital. Chest X ray examination showed protrusion of the right first aortic arches. Transbronchial lung biopsy was performed and primary lung adenocarcinoma was diagnosed. Brain metastasis was suspected by magnetic resonance imaging. The patient was initially given combined chemotherapy with CDDP+VNR and Radiation therapy (60Gy). But after six months, tumor progression was found. Therapeutic agent was changed to 600mg single pemetrexed as outpatient chemotherapy for 14 months. Computed tomography showed reduction of tumor mass. Then, the patient has been still followed without any anti-cancer treatment. It passed for 7 years after diagnosis. The oncogenic driver mutations of the present patient were investigated in another study. Immunohistochemistry and DNA sequencing analysis showed the existence of *BRAF* mutation V600E in the present case. **Conclusion:** *BRAF* mutation in NSCLC was reported not associated with enhanced chemosensitivity. However, pemetrexed was effective to the present *BRAF* V600E positive lung adenocarcinoma patient.

Keywords: NSCLC BRAF pemetrexed

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P3.03-012 THE RELATIONSHIP BETWEEN EFFICACY OF WEE1 INHIBITOR AZD1775 AND MUTATIONAL STATUS OF TP53 IN KRAS-MUTANT NON-SMALL CELL LUNG CANCER

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Background: *KRAS* is frequently mutated in non-small cell lung cancer (NSCLC). However, direct targeting of KRAS has proven to be challenging, and inhibition of KRAS effectors has resulted in limited clinical efficacy. Wee1 kinase is an important regulator of the G2 checkpoint and is overexpressed in various cancers. Inhibition of Wee1 exerts anticancer effects as a monotherapy or in combination with DNA-damaging agents when cancer cells harbor *TP53* mutations. However, its role in *KRAS*-mutant NSCLC, especially as a single agent, has not been explored. **Method:** Here, we investigate the anticancer potential of Wee1 inhibitor AZD1775 as a monotherapy and uncover a possible cellular context underlying sensitivity to AZD1775. Eight *KRAS*-mutant NSCLC cell lines were treated with AZD1775 and cell viability, proliferation, and cell cycle were analyzed. Target modulation was assessed by Western blotting and immunohistochemistry. **Result:** Our data show that treatment with AZD1775 significantly inhibited cell survival, growth, and proliferation of *TP53*-mutant ($TP53^{MUT}$) compared to *TP53* wild-type ($TP53^{WT}$) in *KRAS*-mutant ($KRAS^{MUT}$) NSCLC cells. In $KRAS^{MUT}$/$TP53^{MUT}$ cells, AZD1775 treatment led to DNA damage, a decrease of survival signaling, and cell death by apoptosis. Interestingly, cell death through apoptosis was found to be heavily dependent on specific cellular genetic context, rather than inhibition of Wee1 kinase activity alone. In addition, AZD1775 treatment was well tolerated and displayed single-agent efficacy in a mouse xenograft model. **Conclusion:** This study provides rationale for inhibiting Wee1 using AZD1775 as a potential anticancer therapy against the $TP53^{MUT}$ subgroup of $KRAS^{MUT}$ NSCLC.

Keywords: NSCLC, KRAS, AZD1775

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P3.03-013 IDENTIFICATION OF PROTEASOMAL CATALYTIC SUBUNIT PSMA6 AS A THERAPEUTIC TARGET FOR LUNG CANCER THROUGH A POOLED SHRNA SCREEN

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Background: Recent advances in high-throughput genetic analysis revealed that single lung cancer cells harbour a number of genetic and epigenetic changes. Nevertheless, findings from cancer epidemiology and the experimental models of the multi-step lung carcinogenic process, which were developed by our group and others, suggested that only a handful of changes are 'drivers' whereas others are only 'passengers'. Thus, it is very important to identify those that truly contribute to the oncogenic properties of cancer cells by performing functional screening. To this end, we performed screening with a pooled shRNA library in search for genes that are critical for the survival and/or proliferation of lung cancer cells using a lung cancer cell line. **Method:** NCI-H460 cell line was used for semi-genome-wide dropout viability analysis using a pooled shRNA library that targeted 5,043 genes. Two *Cdk4/hTERT*-immortalised normal human bronchial epithelial cell lines, HBEC3 and HBEC4 were used as controls. Pathway analysis was done using NIH-DAVID. Microarray gene expression analysis was done using Illumina Human WG-6 v3.0 Expression BeadChip for 163 non-small cell lung cancer (NSCLC) cell lines and 59 normal control cell lines. DNA copy number analysis with array CGH was done for 108 NSCLC cell lines. Proteasome activity was measured using a 20S proteasome activity assay kit. 20 pairs of resected lung cancer and matched normal lung samples were used for immunohistochemistry of PSMA6. Cell growth was evaluated by WST-1 colorimetric proliferation assay. Cell cycle analysis was done using FACS for cells stained with propidium iodide. **Result:** shRNA screening targeting 5,043 genes in NCI-H460 identified 51 genes as candidates for therapeutic targets. Pathway analysis revealed that the 51 genes were enriched for the five pathways, including ribosome, proteasome, RNA polymerase, pyrimidine metabolism and spliceosome pathways. We focused on the proteasome pathway that involved six candidate genes because its activation has been demonstrated in diverse human malignancies, including lung cancer. Microarray expression and array CGH data showed that *PSMA6*, a proteasomal subunit of a 20S catalytic core complex, was highly expressed in lung cancer cell lines, with recurrent gene amplifications in some cases. Therefore, we further examined the roles of *PSMA6* in lung cancer. Silencing of *PSMA6* induced apoptosis or G2/M cell cycle arrest in cancer cell lines but not in an immortalised normal lung cell line. **Conclusion:** Our data suggested that *PSMA6* serves as an attractive target with a high therapeutic index for lung cancer.

Keywords: apoptosis, Proteasome Endopeptidase Complex, Spliceosomes,

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-014 TUMOR CAVITATION IN PATIENTS WITH PRIMARY LUNG CANCER FOLLOWING APATINIB TREATMENT

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Background: Apatinib is a specific tyrosine kinase inhibitor that targets VEGFR-2. Treatment of primary lung cancer patients with apatinib is a new promising paradigm. In addition to hypertension and hand-foot syndrome, tumor cavitation and increase in CEA value are frequently noted in these patients. However, there are limited literatures regarding whether they could be used as potential biomarkers for anti-angiogenic therapy. This study was to evaluate the frequency and clinical outcome of primary lung cancer patients who developed tumor cavitation or showed increase in CEA value following apatinib treatment. **Method:** This was a retrospective analysis of primary lung cancer patients treated with apatinib in the Affiliated Hospital of Qiingdao University between 2/1/2015 and 5/19/2017. Clinical data were retrieved from medical records, and chest imaging findings were documented. Survival data were analyzed with Kaplan-Meier estimates and compared with log-rank test. **Result:** A total of 38 primary lung cancer patients received oral apatinib as the third-line or beyond therapy at an initial dose of 250 mg (n=37) or 500 mg (n=1) per day. During treatment, tumor cavitation was developed in 20 of the 38 (52.6%) patients. No significant difference was observed between patients with and without cavity formation in age, gender, tumor histology, tumor stage, history of pulmonary surgery and apatinib typical adverse events. Cavity formation was accompanied with temporary increase in CEA value (65.0% *vs.* 5.6% in patients with and without cavitary lesions; P=0.0001). The progression-free survival (PFS) of patients with cavitary lesions was 11.25 (95% CI, 10.16-13.64) months, which was significantly longer compared with those without (6.11 [95% CI, 6.01-6.71] months; P<0.0001). Besides, patients with a temporary increase in CEA had a longer PFS than those without (10.64 [95% CI, 10.09-14.14] *vs.* 6.14 [95% CI, 6.07-8.13] months), but the difference was not significant (P=0.0703). **Conclusion:** Cavitation formation induced by apatinib is common in primary lung cancer patients, and is not correlated with age, gender, tumor histology, tumor stage, history of pulmonary surgery and common adverse events. Cavitation might have significant effects on the temporary increase in CEA value and PFS prognosis.

Keywords: tumor cavitation, Apatinib, primary lung cancer

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-015 ROS-1 REARRANGED NON SMALL CELL LUNG CANCER AND CRIZOTINIB: AN INDIAN EXPERIENCE

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Background: ROS1 is a receptor tyrosine kinase that belongs to insulin receptor family.It acts as a driver oncogene in 1 to 2% of NSCLC patients. ALK and ROS1 Kinase domain share 77% amino acid identity within the ATP-binding sites. Crizotinib binds with high affinity to both ALK and ROS1, Crizotinib is approved for patients with the ROS1 translocation including those who have received chemotherapy and those who are treatment naive. This is based on a phase 1 expansion study which enrolled 50 patients with ROS1 rearrangement. Over 80 percent of patients had received one or more prior chemotherapy treatment regimens. The objective response rate was 72 percent. The median duration of response was 17.6 months, and the median progression-free survival was 19.2 months.A retrospective series from Europe which included 32 patients reported 80% response rates and a PFS of 9.1 months.In this paper, we report our experience with ROS1 rearranged NSCLC from India. **Method:** Advanced NSCLC with the presence of ROS1 fusion (FISH) patients whose demographic data were retrieved from prospective lung cancer audit database Response by RECIST 1.1 criteria, side effects using CTCAE v 4.02 **Result:** Among 11 patients more than 1/4th of patients had PS of ≥2. Nearly 1/2 of patients had comorbidities and extrathoracic disease while none with brain or adrenal metastasis. Eight received platinum-based doublet chemotherapy, two oral EGFR TKI, and one upfront crizotinib. Four patients among those who received platinum doublet were subsequently exposed to crizotinib Among the 4 patients platinum-based doublet, 2 (PR)and 2 (SD).Out of 5 patients who received crizotinib, 3 patients experienced grade ½ fatigue and grade ½ vomiting. Grade ½ transaminitis, visual symptoms, grade ½ diarrhea, grade ½ neutropenia and asymptomatic bradycardia, grade ½ neutropenia and thrombocytopenia were seen in 1 patient each. Out of 8 patients who received chemotherapy 3 patients had grade ½ anemia, grade ½ vomiting. There was one mortality in non-crizotinib group.Out of 5 patients who received crizotinib, 4 patients had PR (80%).With a median follow-up of 9 months, median PFS and OS were 5.4 months and 8.5 months respectively for the entire cohort.Median PFS and OS was not reached for those who received crizotinib compared to median PFS of 2.5 months and median OS of 4.2 months(<0.01).Estimated 1 year OS was 80% for those who received crizotinib and 18% for who did not. **Conclusion:** In conclusion, Crizotinib is effective with acceptable side effect profile in patients with ROS1 rearranged NSCLC in our population

Keywords: ROS, indian nsclc, crizotinib

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-016 MORPHOMETRIC GENOTYPING IDENTIFIES LUNG CANCER CELLS HARBORING TARGET MUTATIONS; CELL-CT® PLATFORM DETECTS GENE ABNORMALITIES

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Background: The advent of genotype-directed therapy in personalized medicine requires the identification of driver-mutations that are often under-diagnosed due to limitations in tissue biopsy and high false negative rates associated with genomic tests. Studies have demonstrated that the mutation status of cancer cells correlates with changes in cellular morphology. 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 study reports the development of cell classifiers for lung cancer cell lines that harbor known mutations, helping pave the way to driver-mutation targeted therapy. **Method:** Non-invasive sputum specimens from patients without lung cancer ("normal cells") and the following cell lines were analyzed using the Cell-CT® platform: *Small Cell Lung Cancer cell line* NCI-H69 *Adenocarcinoma cell lines* A549 (EGFR wild-type, -c.1_471del471, KRAS- p.G12S) NCI-H1650 (EGFR- p.E746_A750del, CDKN2A- c.1_471del471, TP53- c.673-2A>G) NCI-H1975 (EGFR-T790M, CDKN2A- p.E69*, PIK3CA- p.G118D, TP53- p.R273H) NCI-H2228 (EML4-ALK+, CDKN2A- c.1_471del471, RB1- p.E204fs*10, TP53- p.Q331* high PD-L1). **Result:** 15,000 normal cells from sputum and 500 malignant cells from each of the five cancer cell lines were analyzed using Cell-CT® platform, measuring 704 structural biomarkers to sub-classify the cancer cells by mutation status. Cell classifiers were operated to drive the highest specificity (avoidance of false positives) while maintaining sensitivity above 50%. The area under ROC (aROC), sensitivity and specificity for each classifier were:

Cell Classifiers	aROC	Sensitivity %	Specificity %
Small cell lung cancer (NCI-H69)	0.991	74.8	99.98
Adenocarcinoma, EGFR wild-type (A549)	0.950	58.8	99.94

Adenocarcinoma, EGFR – pE746_A750del (NCI-H1650)	0.993	59.6	99.99
Adenocarcinoma, EGFR -T790M (NCI-H1975)	0.972	66.0	99.99
Adenocarcinoma, ALK+ (NCI-H2228)	0.992	76.8	99.97

Conclusion: This study demonstrates the feasibility of processing non-invasive sputum specimens by the Cell-CT® platform to accurately identify driver mutations in cancer cells to promote mutation-directed targeted therapy for the treatment of lung cancer.

Keywords: personalized medicine, Cell-CT, Targeted therapy

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-017 BLOOD SAMPLES NGS FOR BASELINE MOLECULAR SIGNATURE OF ANOTINIB TREATED ADVANCED NSCLC PATIENTS IN ALTER0303 TRIAL

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Background: Anlotinib hydrochloride, an oral multi-target TKI targeting *VEGFR*, *FGFR*, *PDGFR* and *c-Kit*, have demonstrated noticeable effects for advanced NSCLC as 3rd line treatment in phase III trial (ALTER0303). Anlotinib significantly improved OS (9.63 vs. 6.30 months, p=0.0018, HR=0.68) and PFS (5.37 vs 1.40 months, p<0.0001, HR=0.26) comparing to placebo. Here, we applied ctDNA-based NGS to investigate the association between baseline molecular signature and clinical parameters. **Method:** Blood samples were collected from patients who enrolled in Anlotinib arm in ALTER0303 trial. Total of 92 samples were analyzed by capture-based targeted ultra-deep sequencing using a panel consisting of critical exons and introns of 168 NSCLC-related genes for the baseline genetic profiling. **Result:** At baseline, ctDNA was detected in 85% samples (78/92), driver mutation was found in 58% (53/92) samples. *POM121L12* and *CDKN2A* mutations showed a tendency of co-occurrence with *TP53,* and mutually exclusivity was found between KEAP1 and *TP53*. The correlation between baseline molecular signature and treatment efficacy measured by PFS or best response was also investigated. Maximum mutation allele frequency (MAF) at baseline was inversely correlated with PFS (P=0.006, HR=0.612, 95%CI: 0.402-0.932). Patients achieving SD or PR had a significantly lower MAF comparing to patients having PD as their best response (p=0.018). Tumor mutation burden (TMB) is positively correlated with age (p=0.016) and gender (p=0.01). POM121L12, TP53 and MYC statuses are correlated with metastases burden. Moreover, as an important drive gene, EGFR mutation and/or EGFR amplification was found in 36 patients at baseline. In 27 patients with sensitizing EGFR mutation (L858R or 19 del), no significant differences was found in PFS compare to those without this mutation (n=65) (5.53 vs 5.53 months, p=0.495, HR=1.16, 95%CI: 0.73-1.85). As well, no significant difference was found in PFS between the patients with (n=17) or without EGFR T790M mutation (5.53 vs 5.53 months, p=0.253, HR=1.35, 95%CI: 0.75-2.41). Interestingly, in patients with EGFR amplification (n=10), the PFS is significantly shorter than those with normal *EGFR* copy number (2.12 vs 5.57 months, p=0.002, HR=2.70, 95%CI: 0.99-7.36). However, a tendency of PFS benefit is still observed in patients with EGFR amplification treated by Anlotinib comparing placebo arm in ALTER0303 (1.40 months). **Conclusion:** According to available data, no correlation was found between PFS and EGFR sensitizing mutations or T790M in anlotinib treatment. The negative correlation of EGFR amplification and PFS is still need verification to eliminate the bias caused by the disparity and limitation of samples. A larger scale analysis is ongoing.

Keywords: Anlotinib, NGS, ctDNA

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-018 TUMOR CAVITATION IN LUNG METASTASES IN PATIENTS WITH SOLID TUMOR TREATED WITH APATINIB

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Background: Apatinib, a specific tyrosine kinase inhibitor targeting VEGFR-2, shows anti-angiogenesis effects in multiple solid tumors including lung cancer. Correlation between cavitation formation and outcome of some anti-angiogenic drugs is evaluated in patients with pulmonary cancer. However, the onset of cavitation in lung metastases in solid tumor patients following apatinib treatment has not been mentioned yet. **Method:** The clinical data of solid tumor patients with lung metastasis treated with apatinib in the Affiliated Hospital of Qiingdao University between 4/1/2015 and 6/17/2017 were collected from medical records, and chest imaging findings were documented. Survival data were analyzed with Kaplan-Meier estimates and compared with log-rank test. **Result:** Sixty-four eligible patients were identified (Table). The main primary tumor sites were stomach (n=23, 35.9%), colorectum (n=14, 21.9%) and liver (n=10, 15.6%). 93.8% patients received 250 mg/day of apatinib orally. Tumor cavitation formation in lung metastases occurred in 20 (31.3%) patients. None of these patients had preexisting cavity, which demonstrated that all cavitary lesions were developed during apatinib administration. There was no significant difference in age, gender, primary tumor site, histology and stage of lung metastases, history of pulmonary surgery and typical adverse events of apatinib between patients developed cavity or not. Compared with those without cavitary lesions, patients with cavitary showed higher rate of temporary increase in CEA (85.0% *vs.* 34.1%, P=0.0002) and longer progression-free survival (PFS; 15.44 [95% CI, 12.12-20.65] months *vs.* 6.71 [95% CI, 6.11-8.13] months, P<0.0001). However, patients with temporary increase in CEA showed longer but not significant PFS (11.15 [95% CI, 6.71-15.44] *vs.* 8.13 [95% CI, 6.31-15.57] months; P=0.3047).

Table Baseline characteristics

Characteristics		Cavitation (n=20)	No Cavitation (n=44)
Age, years	mean±SD	58.65±10.35	61.27±13.86
Gender, n (%)	Male	13 (65.0)	33 (75.0)
	Female	7 (35.0)	11 (25.0)
Primary tumor site, n (%)	Stomach	4 (20.0)	19 (43.2)
	Colorectum	5 (25.0)	9 (20.5)
	Liver	6 (30.0)	4 (9.1)
	Other	5 (25.0)	12 (27.3)
Histology of lung metastases, n (%)	Adenocarcinoma	16 (80.0)	38 (86.4)
	Squamous cell ca	2 (10.0)	2 (4.6)
	Other	2 (10.0)	4 (9.1)
Stage of lung metastases, n (%)	IIIA	0 (0.0)	2 (4.6)
	IIIB	3 (15.0)	13 (29.6)
	IVA	10 (50.0)	20 (45.5)
	IVB	7 (35.0)	9 (20.5)
History of pulmonary surgery, n (%)		8 (40.0)	8 (18.2)
Treatment lines, n (%)	2	4 (22.2)	5 (11.6)
	3	12 (66.7)	33 (76.7)
	4	1 (5.6)	2 (4.7)
	5	1 (5.6)	3 (7.0)

Conclusion: Cavitation development in lung metastases is accompanied with temporary elevation of CEA in patients treated with apatinib, and might be used as a potential biomarker for survival free of progression.

Keywords: Apatinib, Lung metastasis, tumor cavitation

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-019 ACTIVITY OF PARP INHIBITOR IN NSCLC WITH GERMLINE AND SOMATIC MUTATION AND IN SILICO CHEMOTHERAPY LETHALITY

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Background: Challenges in Precision and Personalized Medicine with interpatient variation needs individualized protocols. PARP Inhibition may be one modality of treatment of NSCLC, as coadjutant to chemotherapy. **Method:** A 66 years old male

has been diagnosed with lung adenocarcinoma since 02-06-2016, c T4 c N1 c M1a (pleura and pericardium), had been exposed to carboplatin and pemetrexed for 6 cycles (January to March 2016) with disease progression, and peripheral neuropathy. He didn't have EGFR mutation, ALK translocation, MET/RET or ROS-1 FISH alterations. He had been treated with radiation therapy from September to November 2016 with 60 Gy, IMRT, and after he received Nivolumab, from November 2016 to Abril 2017 with radiological progression. He had been tested by RCGG in May 2017 looking for circulating tumor cells in vitro (the culture contains all substances measured to apoptotic ability using oncogene apoptosis kit; the result is confirmed by cultures of the tumor or circulating tumor cells), Idengen (inherited hot-spot mutations), and Guardiant 360 by liquid biopsy (circulating DNA sequencing somatic mutations). **Result:** With the Idengene test, he has had PALB2 inherited mutation germline with possible pathogenic significance, BRCA1 and BRCA2 with unknown pathogenic significance. Also, he had NBN, PTCH2, and PTEN as possible pathogenic significance. With the Guardiant 360 test, he had BRCA1, C24Y, NF1, R416Q somatic mutations. With the RGCC test, the specific tumor appears to have resisting populations because of the MDR1 overexpression that can be reversed using inhibitors of ABCG2 pumps. Also, the neoplastic cells have the greatest sensitivity in the alkylating agent (cisplatin, mitomycin), in the tubulin dimmer polymerization inhibitors (Vinorelbine). Inhibitor of Akt/mTOR pathway can be used, as Everolimus, temsirolimus. He has partial sensibility to nucleus spindle stabilizer I (paclitaxel, docetaxel), II (vincristine, vinblastine), and nucleoside analogues (methotrexate, gemcitabine, pemetrexed). Therefore he has been exposed to oral Olaparib 300 mg BID, intravenous Gemcitabine 600 mg/m2, and oral vinorelbine 60mg/m2 weekly both., with good tolerability, and improvement of Performance Status. **Conclusion:** PARP Inhibitor can be a target therapy in personalized medicine, guided by PALB2 / BRCA 1 / 2 mutations in codons inherited and / or somatic mutations, in addition to gemcitabine and vinorelbine in lung adenocarcinoma resistant to platinum/pemetrexed. The addition of Olaparib was possible in this patient, and feasible with a good tolerability, maybe impacting the outcome. More studies related to PARP inhibitor and NSCLC need to be developed.

Keywords: PARP INHIBITOR, SOMATIC / GERMLINE MUTATION, NSCLC

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-020 UNIQUE 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 might have the different prevalence of molecular alteration. This study aimed to explore the unique molecular profile of lung adenocarcinoma in Thai population. **Method:** We studied 120 lung adenocarcinoma patients' molecular profile by FFPE DNA extraction and using Next Generation Sequencing (NGS) on 45 genes lung cancer panel (Ion Torrent system). **Result:** We found 64% (77/120) of EGFR mutation, 13%(16/120) of BRAF V600E,32% (38/120) of KRAS mutation, 11% (13/120) of MET exon14 splice site, 7.5% (9/120) of AKT mutation (E17K), 2.5% (3/120) of ROS1 mutation, 0.8% (1/120) of PIK3CA mutation (H1047R), and 0.8% (1/120) of PTEN mutation by NGS method using the allele fraction cutoff at 2%. We also found 46 patients (38.3%) who had more than one mutation in each person. The validations by the other technique are on-going and will be presented at the WCLC 2017. **Conclusion:** Adenocarcinoma of the lung in Thai population had the unique molecular profile with high prevalence of BRAF V600E and MET exon 14 splice site comparing to the other populations. High prevalence of KRAS and dual different gene mutations in each patient are needed to be confirmed by the other technique because it could be from the artifact of formalin fixation for G12D, G12S, G13D, and G13S of KRAS mutation.

Keywords: Lung Adenocarcinoma /Molecular Alteration/Next Generation Sequencing

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-021 IN VITRO PHARMACOGENOMIC PLATFORM WITH A HIGH-PURITY PATIENT-DERIVED CELL MODEL

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Background: We have developed a high-purity patient-derived cell (HP-PDC) method for primary culture of malignant effusions from non-small cell lung cancer (NSCLC) patients with oncogenic driver mutations. We updated the results of HP-PDC with mutation test and drug response. **Method:** HP-PDCs were established by a multistep isolation protocol. Malignant effusions were cultured and examined with a light microscope to identify spheroid-forming cells. Immunofluorescence (IF) and flow cytometry were used to evaluate the purity of tumor cell in PDCs. EGFR, ALK or ROS mutation of PDCs was analyzed with direct or PCR-based sequencing and RT-PCR. The sensitivity of target agent to HP-PDCs were tested using a cell viability assay. **Result: C**onsecutive series of 79 malignant effusion samples was collected from 61 patients with advanced NSCLC. Spheroid-forming cells were detected in 41 samples which were cultured in AR5 media to establish PDCs. IF analysis revealed that TTF-1 was upregulated in 17 PDCs (21.5%), which also showed EpCAM-positive cell population in flow cytometry with high purity of over 70%. Time spent for establishment of HP-PDCs ranged from 26 days to 132 days. There were 9 PDCs (53%) which harbored active EGFR mutations. Three PDCs with ALK fusion and four with ROS1 fusion were established. Twelve PDC cases were from patients who experienced disease progression while on treatment with EGFR- (9) and ALK- (3) tyrosine kinase inhibitors. Four PDCs with ROS1 fusion were obtained before anti-cancer treatment. Three of PDCs with EGFR mutations were established from patients, who progressed on both gefitinib and the 3rd generation EGFR inhibitors. All of them showed *in vitro* resistance to both gefitinib and 3rd generation EGFR inhibitors. PDC from a patient with ROS1 fusion was sensitive to ROS1 inhibitors (entrectinib, crizotinib and ceritinib) *in vitro* test. The patient has been treated with entrectinib and showed partial response. **Conclusion:** HP-PDCs provide useful *in vitro* platforms of preclinical studies which predicts responses to targeted therapies in a short period of time and may provide an excellent platform for personalized therapies in NSCLC patients.

Keywords: Patient-derived cancer cell, lung cancer, Target therapy

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-022 LUNG CANCER IN YOUNG PATIENTS: HIGHER RATE OF DRIVER MUTATIONS AND BRAIN INVOLVEMENT BUT BETTER SURVIVAL

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Background: Young patients with Non-small cell lung cancer (NSCLC) represent a distinct subset of patients. There are few reports describing younger patient's characteristics and survival. Therefore, we conducted a retrospective study, in which we gathered clinical features of NSCLC patients under the age of 50 and matched patients who were older than 60 years at diagnosis. **Method:** Retrospective data of NSCLC patients was collected in a single tertiary hospital between January 2010 and December 2015. Patients were divided into 2 age groups according to the age at diagnosis: younger than 50 years (N=62) and older than 60 years (N=124). Their clinico-pathological characteristics, disease course and survival rate were analyzed. **Result:** The median age was 44 and 68 years of the younger and older cohort respectively. There were more never smokers (36% *vs.* 24%, p=0.08) and more brain metastasis (40% *vs.* 25%, p=0.04) in the younger group. Interestingly enough, upper lobes were more involved in the older vs. the younger cohort (p<0.001). A similar percentage of patients underwent NGS testing in both groups, but driver mutations were more common in the younger cohort: Epidermal Growth Factor Receptor (EGFR) mutations (32% *vs.* 25%, *NS*), Anaplastic Lymphoma Kinase (ALK) rearrangement (22% *vs.* 3%, p=0.002). Accordingly, the clinical impact of molecular testing on treatment decision was greater in the young vs. the older group (61% *vs.* 31%, p=0.002). Median survival was longer in the younger cohort, although not significantly different (34 *vs.* 21 months, p=0.1). **Conclusion:** Young patients with NSCLC have more driver mutations, more brain metastases and a trend of better survival. Therefore, this group of patients should undergo intensive mutation investigation and brain MRI on initial assessment.

Keywords: young patients, Brain metastasis, Driver mutation

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-023 NINTEDANIB SELECTIVELY INHIBITS THE ACTIVATION AND TUMOR-PROMOTING EFFECTS OF FIBROBLASTS FROM LUNG ADENOCARCINOMA PATIENTS

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Background: There is growing awareness that tumor-associated fibroblasts (TAFs) play critical roles in both tumor progression and response to therapies in solid tumors including non-small cell lung cancer (NSCLC). Nintedanib (NTD) is a multi-kinase inhibitor of VEGF, FGF and PDGF receptors that has been recently approved to treat advanced lung adenocarcinoma (ADC) patients in combination with docetaxel. The main goal of this study was to assess how TAFs contribute to the selective therapeutic effects of NTD in lung ADC. **Method:** Because TAFs are largely activated in vivo, patient derived lung TAFs from ADC and squamous cell carcinoma (SCC) patients as well as paired control fibroblasts from non-malignant pulmonary tissue were activated with TGF- β1 in the presence of increasing concentrations of NTD. Conditioned medium was also collected and used to stimulate the growth and invasion of several cancer cell lines. A panel of activation markers indicative of fibrosis were analyzed in TAFs, including alpha-smooth muscle actin, collagen-I/III and P4HA2.

Result: Nintedanib dose-dependently inhibited the TGF-β1-induced expression of all activation markers in both ADC-TAFs and control fibroblasts derived from uninvolved lung parenchyma, whereas such inhibiton was very modest in SCC-TAFs, suggesting that TAF activation is regulated by different mechanisms in ADC and SCC. Remarkably, nintedanib abrogated the stimulation of growth and invasion in a panel of carcinoma cell lines induced by the conditioned medium from activated TAFs in ADC but not SCC. These results reveal that the pro-tumorigenic effects of ADC-TAFs in vitro are markedly reduced in the presence of NTD. **Conclusion:** These results reveal that nintedanib is an effective inhibitor of fibrosis and its associated tumor-promoting effects in ADC, and that the poor antifibrotic response of SCC-TAFs to nintedanib may contribute to the differential clinical benefit observed in both subtypes. Our findings also support that preclinical models based on carcinoma-TAF interactions may help defining the mechanisms of the poor antifibrotic response of SCC-TAFs to nintedanib and testing new combined therapies to further expand the therapeutic effects of this drug in solid tumors.

Keywords: nintedanib, fibroblasts

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-024 REAL-LIFE EXPERIENCE AND CLINICAL CHARACTERIZATION OF BRAF V600E MUTATION IN AUSTRIAN NSCLC PATIENTS

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Background: Targeted therapy is becoming increasingly important and has improved the overall survival for patients with NSCLC. *BRAF*^{V600E} mutations (Val600Glu) are observed in 1-2% of lung cancer and play a major role in targeted therapy by providing an opportunity for affected patients as possible allocable target. In Austria an effective therapy is available with Dabrafenib and Trametinib. The aim of this retrospective analysis was to support ongoing research on the frequency of this promising genetic alteration by determining the prevalence of *BRAF*^{V600E} mutations among Austrian NSCLC patients. We also examined clinical characteristics of these patients. **Method:** Patient characteristics including age, sex, race, smoking history and localization of biopsy were collected. Tumor tissue from bronchoscopy, CT- and ultrasound guided biopsies as well as surgical specimen with histological type of adenocarcinoma and NSCLC NOS (Not Otherwise Specified) excluding large cell carcinoma and neuroendocrine carcinoma was reflex tested independent of the tumor stage and clinical characteristics (like sex, smoking history, demography) for *BRAF* mutations. The *BRAF* mutation detection was performed since February 2017 with the *BRAF/NRAS* Mutation Test Kit from Roche on a COBAS® z 4800 Analyzer. **Result:** *BRAF* alterations were found in 11 of 118 tested patients (9.3%), of which 7 patients (5.9 %) showed a *BRAF*^{V600E} positive mutation. Out of these patients with *BRAF*^{V600E} positive mutation, 4 were women and 3 men. 3 patients were Never-Smoker, 2 were former smokers and 2 smokers. Biopsies in 5 patients were taken from the primary tumor, in 1 patient from the lymph nodes and in 1 patient the analysis was performed by drainage of pleura effusions. Median age was 69 years. All patients were Caucasian. **Conclusion:** The prevalence of BRAF^{V600E} mutation in this real-world data, assessed in a cohort of 118 people, was higher than BRAF^{V600E} mutation rates previously reported by other published data, and thus underline the importance of reflex testing for this druggable target independent of clinical characteristics.

Keywords: NSCLC BRAF, BRAF

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-025 TUMOR BIOMARKERS FOR THE ROUTINE CARE OF ADVANCED NON-SMALL-CELL LUNG CANCER: A DECADE OF EXPERIENCE IN IMPLEMENTING PREDICTIVE GENOMIC EVENTS

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Background: Although a growing list of mandatory genomic/immune-based biomarkers are now routinely integrated into the management of advanced non-small-cell lung cancer (NSCLC), few reports have detailed the evolution of NSCLC predictive biomarker assessment in routine clinical practice. **Method:** We retrospectively probed 1,000+ NSCLC-patient pairs analyzed for predictive biomarkers from 2004 to 2017 at our institution and evaluated patterns of testing as well as correlation with clinical-pathologic characteristics. **Result:** The majority of 1,009 patient-tumor pairs had advanced adenocarcinoma with most specimens obtained from lung, mediastinal/hilar nodes, and pleura and with a similar distribution between surgical, small biopsy, and cytology specimens. All were tested for *EGFR* mutations, 895 for *ALK* rearrangement, 841 for *KRAS* mutation, 537 for *ROS1* rearrangement, and 179 using comprehensive genomic profiling. Implementation of near-universal genomic biomarker testing for *EGFR, ALK, ROS1* and PD-L1 occurred within the first year following evidence of activity/approval of a paired therapy. The failure rate after use of the best specimen for the most common tests was ≤5.5%. A quarter of tumors had a driver oncogene (*EGFR/ALK/ROS1/BRAF*-V600E) with an approved oral therapy, with the highest prevalence in patients with ≤15 pack-years tobacco use. **Conclusion:** Tumor biomarker testing in routine clinical NSCLC specimens at our institution evolves rapidly following approval of new therapies linked to diagnostic assays. Our practice's decade-plus experience indicates that it will be feasible for the thoracic oncology community to continue to expand the use of predictive genomic and immune biomarkers using currently available clinical specimens.

Keywords: NSCLC, EGFR, ALK

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-026 CELL-CT® DIFFERENTIAL DETECTION OF DYSPLASTIC BRONCHIAL EPITHELIAL CELLS FROM PATIENT EXPLANTS

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Background: Chemoprevention could have a great impact on lung cancer prevention. While Iloprost treatment has shown a significant reduction of dysplasia in former smokers, the identification of patients who would benefit from the drug is seriously hampered due to the need to use invasive diagnostic procedures in patients who are typically asymptomatic. Published clinical data shows that non-invasive sputum analysis using the Cell-CT platform detects early stage lung cancer with high sensitivity (92%) and specificity (95%). This abstract reports the development of cell classifiers that distinguish cultured human lung dysplastic explants from malignant and normal sputum cells. This study represents a first important step toward developing a non-invasive diagnostic test for detecting patients with moderate to severe bronchial dysplasia who may then be treated with chemopreventive drugs such as Iloprost. **Method:** To achieve diagnostic classifications, sputum from patients without lung cancer ("normal cells"), small cell lung cancer and five adenocarcinoma cell lines, and cultured bronchial explants from three patients with moderate to severe dysplasia were analyzed using the Cell-CT. **Result:** 15,000 normal cells from sputum, 500 malignant cells from each of the five lung cancer cell lines and 264 cells from patient dysplastic explants were analyzed using Cell-CT platform, measuring 704 structural biomarkers to sub-classify the cancer cells by abnormality and dysplastic status. Cell classifiers were operated to drive the highest specificity (avoidance of false positives). The area under ROC (aROC), sensitivity and specificity for each classifier were:

Cell Classifiers	aROC	Sensitivity %	Specificity %
Lung Cancer cell lines	0.999	93%	99.99
Cells from patient dysplastic explants	0.995	86%	99.99

Conclusion: These results show strong discrimination by the Cell-CT in classifying normal cells from sputum versus cells from lung dysplastic explants and lung cancer cell lines grown in culture. These data suggest that a non-invasive test using sputum liquid biopsy analyzed on the Cell-CT platform could enable the detection of dysplasia in patients who would benefit from chemoprevention drug therapy.

Keywords: chemoprevention, Cell-CT Platform, Dysplasia

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-027 LKB1 LOSS IS ASSOCIATED WITH RESISTANCE TO ANTI-ANGIOGENIC THERAPY IN NON-SMALL CELL LUNG CANCER MOUSE MODELS

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Background: LKB1 is a protein kinase that is mutated and down-regulated in 20-30% of non-small cell lung cancer (NSCLC). LKB1 mutations co-occur with KRAS alterations in 7%-10% of NSCLC, resulting in an aggressive phenotype with short survival. Because LKB1 activates AMPK, the master sensor of cellular energy, many of the best known functions of LKB1 are attributed to its ability to control metabolic alterations in the cells. However LKB1 also plays an important role in regulating angiogenesis, likely as a strategy to overcome energetic depletion of tumor microenvironment. Bevacizumab, the human anti-VEGF antibody, improves the PFS and OS of NSCLC patients combined with chemotherapy, but often the benefit is transient and therapeutic resistance occurs. Our laboratory has previously identified

alterations in cell metabolism and in vasculature of LKB1-deficient tumors when compared to LKB1 wild type in NSCLC. **Method:** LKB1 KO murine NSCLC cell lines were generated using CRISPR/Cas9 system in a $KRAS^{G12D}$ mutant background (LKR10 & LKR13). Syngeneic NSCLC models were established via s.c. injection of LKB1 intact and KO murine cells in immunocompetent mice. After tumors reached 150 mm^3 mice were randomly assigned to treatment groups consisting of vehicle, mouse anti-VEGF and nintedanib. Tumor volumes were measured and compared using student's t test and samples were collected for vasculature analysis. Survival curves will be calculated using log rank test. Hypoxia experiments were preformed and apoptosis was measured using annexin V and 7ADD staining. **Result:** Treatment with anti-VEGF or nintedanib significantly inhibited tumor progression in LKB1 wt $KRAS^{G12D}$ mutant mouse model ($p<0.001$) but did not show any therapeutic effect in the LKB1 KO $KRAS^{G12D}$ group. Furthermore in the LKB1 wt group, the median survival of anti-VEGF and nintedanib treated mice was 111 days and 84 days respectively and 37 days in the vehicle group. No improvement in survival was detected in the LKB1 KO group after treatment with anti-VEGF. *In vitro* studies showed that LKB1 loss is associated with a decrease in oxygen consumption and enhanced glycolysis. Furthermore LKB1 KO NSCLC cells showed a decrease in apoptosis under hypoxic and low nutrient conditions compared to LKR13 LKB1 wt cells. **Conclusion:** NSCLC LKB1-deficient tumors showed resistance to anti-angiogenic therapy and this effect is driven by the regulation of metabolic adaptations that allow cells to survive under hypoxic and low nutrient conditions.

Keywords: LKB1, Anti-angiogenic therapy, Resistance

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-028 WINTHER – A STUDY OF CANCER THERAPY BASED ON TUMOR AND NORMAL-MATCHED BIOPSIES – THE SHEBA MEDICAL CENTER LUNG CANCER EXPERIENCE

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Background: Patient-tailored therapy based on tumor genomics is limited to 30-40% of the patients whose tumor harbor actionable DNA mutations or amplifications. **Method:** WINTHER is an international open label non-randomized clinical trial developed by the WIN consortium. Matched tumor and normal tissue biopsies are collected and analyzed by NGS (Foundation Medicine) or by functional genomics utilizing a prediction model of efficacy developed at Ben Gurion University. **Result:** 56 patients were biopsied. 29 (52%) had lung cancer. Successful biopsies yielding sufficient material for full genomic analyses were achieved in 29 subjects (53%). Lung biopsy success rates were 71% and 61% respectively for normal and tumor specimens. To date, 11 lung cancer patients were treated with chemotherapy (1) or biologic agents (11). Targeted genomic alterations included EGFR (3), RET (2), KRAS (2), ALK (1), ErbB2 (1), ErbB3 (1), BRAF (1). Clinical benefit rate (CBR) was 55% (6/11) with 1 subject achieving compete response, 2 partial response and 3 stable disease. Response durations were 7, 14 and 18 months. **Conclusion:** Tumor genomic analysis based on the comparison of matched tumor and normal biopsies is acceptable and feasible. The experience of the multidisciplinary team is an important contributor to the program's success.

Keywords: clinical trial, genetic testing, biopsy

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-029 ROS1 ALTERATIONS IN LUNG ADENOCARCINOMA: THE PROGNOSTIC ROLE OF REARRANGEMENT AND COPY NUMBER VARIATION

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Background: ROS1 rearrangements define a distinct molecular subset of lung adenocarcinoma and patients (pts) experience significant improvements with oncogene-directed therapies. Break-apart/Split Fluorescence in situ hybridization (FISH) is a commonly used detection method for rearranged genes as well as the copy number variation (CNV). Based upon FISH, we aimed to thoroughly evaluate the prognostic role of ROS1 alterations in lung adenocarcinoma. **Method:** Between 1997 and 2016, 634 pts with complete FISH test data were enrolled and followed for outcome research. According to ratios of separated signals, ROS1 rearrangement status were dichotomized into positive and negative. Due to combinative patterns of the signals, positive ones were divided into typical (separation), atypical (single 3' signal) and rare patterns (single 5' signal), and CNV were divided into normal, amplification and deletion. **Result:** ROS1 rearrangement was present in 24 (3.8%) pts, including 17 (2.7%) typical or atypical patterns and 7 (1.1%) rare patterns. ROS1 rearranged pts confer sensitivity to treatment with ALK/ROS1/MET inhibitor crizotinib as the overall response rate (ORR: CR+PR) is 37.5% and the overall disease control rate (DCR: CR+PR+SD) is 75.0%; for 1st line therapy, these rates are 50.0% and 83.3%, respectively. However, the ORR and DCR were dramatically decreased in 2nd or 3rd line therapy as 25.0% and 25.0%. Overall survival rates differ among three kinds of rearranged patterns; rare pattern pts tend to have the worst prognosis. Multivariate Cox regression analysis indicated that ROS1 rearrangement (hazard ratio [HR], 0.49) was significantly associated with improved overall survival (OS) while disease free survival (DFS) was equivocal (HR=0.66; p=0.22), and CNV was not an independent prognostic factor for both OS and DFS. ROS1-negative pts had worse fatigue and lung cancer symptoms than positive ones, while CNV did not predict recent QOL. Younger age (<60 years), female gender, non-smoker and advanced stage (IIIb-IV) were significant indicators for ROS1 rearrangement. **Conclusion:** ROS1 rearrangement confers favor OS and QOL in lung adenocarcinoma pts and crizotinib induced preferable clinical remission, while CNV showed no exact implications, which might only act as an minor aspect of genetic heterogeneity in tumor cells. Therefore, our results highlight the importance of screening for ROS1 rearrangement in pts with lung adenocarcinoma, which should help to prolong pts' survival time and maintain or improve QOL.

Keywords: ros1, lung adenocarcinoma, Prognosis

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-030 TP53 ALTERATION, A POTENTIAL PRIMARY CAUSE OF EARLY PROGRESSION IN EGFR-MUTATED NSCLC PATIENTS TREATED WITH FIRST-LINE TKIS

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Background: EGFR-TKIs are recommended first-line treatment for patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC). Most patients develop resistance after an average of approximately 12 months. Among various mechanisms, about half are acquired with T790M in EGFR exon 20. Little is known about the mechanisms in patients progressed within 6 months after first-line treatment of EGFR-TKIs. Therefore, we prospectively designed this study to investigate the possible mechanisms of resistance in this group of patients. **Method:** NSCLC patients with sensitive EGFR mutations who treated with first-line EGFR-TKI in Zhejiang Cancer Hospital from Jun 2014 to Jan 2017 were screened prospectively. Tissue samples pre-TKI and after disease progression (RECIST1.1) were collected. Blood samples were collected after disease progression. The study was approved by hospital research ethics committees. Of the total 50 patients enrolled for the study, 21 patients were included and further divided into two groups: patients suffered disease progression within six months after taking EGFR-TKI were classified as Group A (rapid progress group, n=13); patients took EGFR-TKI more than two years were classified as Group B (long term survival group, n=8). Patients with a PFS between 6 months to two years were excluded. We performed NGS of ~416 cancer related genes from the primary cancer samples collected before TKI treatment. Differences of gene alterations between two groups were analyzed. **Result:** The median age was 55 years old (range: 34-75 years). There were 47.6% female and 53.8% non-smokers. All patients in Group A carried *TP53* mutation before treatment, none was found in Group B. The average cancer-related genetic mutations is 6.46 (range 3-16, 6 in Group A, 5.6 in Group B, $P>0.05$). There was enrichment for co-alterations in *TP53* (100%), *RB1* (38%), *NKX2-1* (31%), *BIM* (30.8%) in pre-treated tissues from Group A. *ERCC2* (38%), *JAK3* (38%), *BRCA2* (25%) were enriched in pre-treated tissues from Group B. Mutation rate of EGFR T790M after resistance was lower in Group A (2/13,15.4%) than in Group B (2/5, 40%). Three patients (3/8) are still benefit from first-line EGFR-TKI without disease progression in Group B. The median PFS was 3 months for Group A (range 1-5 months) and 26.5 months for Group B (range 24-52 months). **Conclusion:** This data highlights a model of genetic collectives as potential mechanisms of rapid progression in first-line EGFR-TKIs treatment. *TP53* mutation reduced responsiveness to TKIs and worsen prognosis in EGFR-mutated NSCLC patients, contributing to rapid disease progression. EGFR T790M mutation seems uncommon in rapid progression patients.

Keywords: NSCLC, TP53, EGFR

P3.03: CHEMOTHERAPY/TARGETED THERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.03-031 RESPONSE TO CRIZOTINIB CAN OCCUR IN C-MET OVEREXPRESSION NSCLC INDEPENDENT OF MET EXON14 ALTERATIONS AFTER FIRST-LINE EGFR-TKI RESISTANCE

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Background: Although non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations are responsive to EGFR-tyrosine kinase inhibitors (EGFR-TKIs), drug resistances are always inevitable. Concurrent multiple mutations and bypass mechanisms both can contribute to development of resistance to EGFR-TKIs. Preclinical and clinical evidences suggest a role for MET activation as a secondary driver of resistance to targeted therapy. Activation of the MET pathway can occur through a diverse set of mechanisms including MET amplification, MET exon 14 alterations, MET overexpression. As partial overlap of these biomarkers occurs, whether one is purely a surrogate for the other, or if both can represent true oncogenic driver states continues to be explored. Cases of MET inhibitor sensitive NSCLC harboring exon 14 alterations without co-incident amplification have already been described. But concurrent EGFR-mutation and MET overexpression in one

case is rare. Whether MET overexpression can be served as a driver alteration in NSCLC and its cut-off value need to be explored. **Method:** A NSCLC patient with EGFR mutation who took first line EGFR-TKI therapy was described in this report. The chest enhanced CT examination, whole-body PET/CT, coarse needle biopsy on right clavicle and bronchoscopy were taken to assess the disease condition before treatment. ARMS, IHC, FISH, ddPCR and NGS were used to detect gene alterations including gene mutation, overexpression and amplification, in cancer tissue samples obtained before TKI and after disease progression. **Result:** In this case, we described a 56-year-old male NSCLC patient with EGFR Ex21 L858R mutation who underwent refractory after first line EGFR-TKI therapy and was confirmed having concurrent c-MET overexpression (ICH: +++, 95%) before treatment. Disease progression was occurred after taking first-line EGFR-TKI for 4 months. Patient was then further confirmed having c-MET overexpression (ICH: +++, 90%) but without EGFR T790M mutation, c-MET amplification and MET exon 14 alterations in progressed cancer samples. Crizotinib was added to the treatment from Aug 8, 2016 after disease progression. And the recent chest enhanced CT examination on May 5, 2017 confirmed complete response (CR) to crizotinib in this patient. **Conclusion:** Our case report uncovered the underling mechanism of c-MET overexpression in EGFR-TKI resistance, and crizotinib may assist to overcome this resistance to EGFR-TKI. In this case, MET overexpression and EGFR mutation were concurrent before treatment. Thus, whether simultaneously applied EGFR-TKI and MET inhibitor in first-line treatment could result a better outcome was needed to be further demonstrated. The ideal cut-off value of MET overexpression is also waiting for determination.

Keywords: EGFR, NSCLC, MET

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-001 EVALUATE THE UTILITY OF THE PROLUNG CHINA TEST IN THE DIAGNOSIS OF LUNG CANCER

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Background: This Study will assess the stability of the ProLung China Test classification algorithm when used as an adjunct to CT scan. Also, we will assess whether there are any potential safety concerns of the ProLung China Test when used to evaluate patients with a positive CT scan for lung cancer. **Method:** This study is a multicentre, prospective, open, self-control study which aims to evaluate the utility of the ProLung China Test in diagnosis of lung cancer (ClinicalTrials.gov ID: NCT02726633). The subject whose age is between 18 and 80 years old and CT result shows a 4 ~ 50 mm nodule within 30 days is our object. In these objects, we will exclude those people who has TB, pulmonary edema, chronic lung infection, abnormal anatomy, skin disease effecting bioconductance and other tumors.The expected sensitivity and specificity of Prolung China Test are 70 % and 61%, and non-inferiority margin is 10 %. Based on these statistical information, four clinical trial centers, in the study, will enroll at least 452 samples with 20 % dropout rate. These samples must contain at least 182 effective malignant sample and 194 benign samples. **Result:** According to the inclusion and exclusion criteria, excision biopsy or follow-up examination will perform on enrolled subjects. Before these examination, a Prolung China test will be operated on these subjects. The subject in follow-up will be followed at least 24 months. The pathology result and follow-up result will be the gold standard in this study. The diagnosis result and adverse event will be recorded during the experiment. **Conclusion:** To demonstrate safety and efficacy of the ProLung China Test in the risk stratification of patients with pulmonary lesions identified by CT that are suspicious for lung cancer.

Keywords: pulmonary nodule, bioconductance, Prospective study

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-002 A RANDOMIZED PHASE II STUDY OF CARBOPLATIN PLUS NAB-PACLITAXEL WITH OR WITHOUT NINTEDANIB FOR NSCLC WITH IPF (J-SONIC): TRIAL IN PROGRESS

K. Otsubo[1], J. Kishimoto[2], H. Kenmotsu[3], Y. Minegishi[4], E. Ichihara[5], A. Shiraki[6], T. Kato[7], S. Atagi[8], H. Horinouchi[9], M. Ando[10], Y. Kondoh[11], M. Kusumoto[12], K. Ichikado[13], N. Yamamoto[14], Y. Nakanishi[1], I. Okamoto[1]

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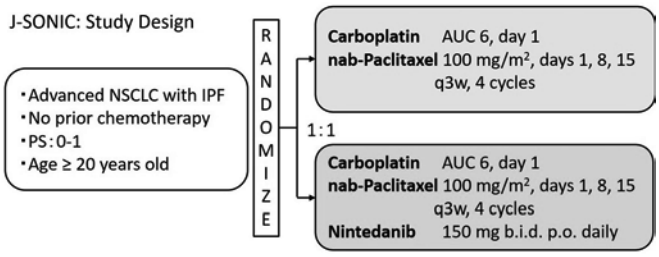
Background: Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease characterized by worsening dyspnea and progressive loss of lung function. Acute exacerbation of IPF is associated with high morbidity and mortality. Several studies have provided evidence of an association between lung cancer and IPF, with a prevalence of lung cancer in IPF patients ranging from 9.8% to 38%. Although the efficacy of nintedanib for IPF has been demonstrated, it has remained unknown whether this agent also reduces the risk of chemotherapy-induced acute exacerbation of IPF. Patients with interstitial pneumonia have been excluded from most prospective clinical trials for NSCLC because of the risk of acute exacerbation, with only two prospective single-arm phase II studies having been reported. In addition, it has been difficult to perform a randomized prospective clinical trial for patients with advanced NSCLC and IPF because of their rarity. The optimal chemotherapy regimen for advanced NSCLC with IPF has thus remained unclear. **Method:** Chemotherapy-naïve patients with advanced NSCLC associated with IPF (enrollment target of $n = 170$) are randomized at a 1:1 ratio to receive four cycles of carboplatin (AUC 6 on day 1) plus nab-paclitaxel (100 mg/m^2 on days 1, 8, and 15) administered every 3 weeks either without (arm A) or with (arm B) nintedanib (150 mg b.i.d., daily), to be followed in arm B by single-agent administration of nintedanib (150 mg b.i.d., daily). The primary end point of the study is time to acute exacerbation of IPF.



Result: Section not applicable **Conclusion:** J-SONIC is the first randomized controlled study for treatment of NSCLC associated with IPF. The goal of the study is to demonstrate that nintedanib in combination with carboplatin plus nab-paclitaxel prolongs time to acute exacerbation of IPF compared with carboplatin plus nab-paclitaxel alone. Study enrollment began in May 2017 and is to continue for 3 years.

Keywords: non-small cell lung cancer, idiopathic pulmonary fibrosis (IPF), nintedanib

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-003 PHASE II TRIAL OF ATEZOLIZUMAB BEFORE AND AFTER DEFINITIVE CHEMORADIATION FOR PATIENTS WITH UNRESECTABLE STAGE III NSCLC

H. Ross[1], D. Kozono[2], J. Urbanic[3], T. Williams[4], C. Dufrane[5], I. Bara[6], M. Gandhi[6], K. Schulze[7], J.M. Brockman[6], X. Wang[8], E. Vokes[9], T. Stinchcombe[10]

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Background: More than 40,000 US patients per year present with stage III NSCLC. These patients are of particular interest in that most are not resectable and while they can be treated with curative intent with excellent initial responses, only approximately 25% will be cured by conventional chemoradiotherapy. This, together with the generally better health of this cohort compared to patients with metastatic NSCLC, makes these patients ideal candidates for studies of immunotherapy to increase cure rates. The combination of checkpoint inhibition to counter tumor related immunosuppression along with standard chemoradiotherapy that depletes T-regulatory cells should create immunologic "space" to facilitate clonal expansion of effector T-cells in an environment that fosters improved tumor immunogenicity by blocking PD-L1. Responses to immunotherapy seem to be higher in patients for whom significant cytoreduction can be achieved, such as with radiation of all known disease. Further, both chemotherapy and radiation may expose otherwise hidden antigens that can present additional targets to the reconstituting immune system. **Method:** This phase II single arm Alliance Foundation study (NCT03102242) will evaluate safety and efficacy of atezolizumab before and after definitive chemoradiotherapy. 63 patients with stage III NSCLC, PS 0-1, no active autoimmune disease, adequate cardiopulmonary function and no underlying organ dysfunction will be enrolled at 15 Alliance sites in the US. Treatment consists of 4 cycles of neoadjuvant atezolizumab 1200 mg IV q 21 days before chemoradiotherapy with restaging after cycles 2 and 4. Nonprogressing patients undergo weekly carboplatin and paclitaxel concurrent with 60 Gy thoracic radiotherapy followed by 2 cycles of carboplatin and paclitaxel consolidation followed by completion of one year of atezolizumab. The primary endpoint of this pilot study is disease control (CR+PR+SD) after neoadjuvant atezolizumab. Secondary endpoints include ORR, PFS and OS, safety and QoL assessed by the EORTC QLQ-30. Translational endpoints seek to define the role of PD-L1 biomarker testing in selecting the population most likely to respond to neoadjuvant and adjuvant immunotherapy together with standard chemoradiotherapy and to study the association of biomarkers, including immunologic signatures, with response and survival. Tumor tissue will be assessed at study entry and, where possible, at progression. Plasma and immune cells will be assessed at baseline, post neoadjuvant atezolizumab, post chemoradiotherapy, during adjuvant atezolizumab and at study completion or progression. Analyses may include multipanel immunohistochemistry, gene expression profiling, whole exome and T cell receptor sequencing, cytokine/chemokine analysis, flow cytometry immunophenotyping, and T

cell function. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Neoadjuvant clinical trial, Immunotherapy, Stage III NSCLC

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-004 TREATMENT RATIONALE AND STUDY DESIGN FOR THE TAKUMI TRIAL

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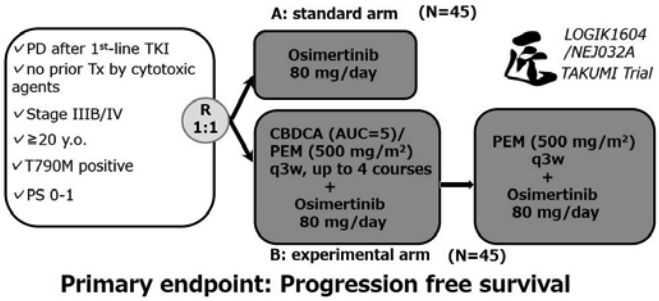
Background: 50%-60% of patients after the first-generation EGFR-TKI, gefitinib and erlotinib showed acquired resistance of T790M mutation and osimertinib is a standard regimen for this population. However, the median PFS by osimertinib alone is 8-10M and a better strategy is needed. One promising option is a combination of osimertinib and chemotherapy, and previous trials have suggested the promising efficacy by the combined treatment of EGFR-TKI with pemetrexed. We here present the treatment rationale and study design of TAKUMI trial, a multicenter randomized phase study of of osimertinib (Tagrisso) alone versus osimertinib plus carboplatin/pemetrexed for patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours harbour a T790M mutatlon within the epidermal growth factor receptor gene. **Method:**



schema of this study **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Osimertinib, T790M, chemotherapy

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-005 PD-L1 AND OTHER IMMUNO-MARKERS INFLUENCED BY OSIMERTINIB TREATMENT IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS (ATHENE STUDY)

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Background: This study will investigate whether PD-L1 and other immuno-markers will be influenced by osimertinib treatment in advanced EGFR T790M positive advanced NSCLC patients,who have progressed on an EGFR-TKI. **Method:** This study is an ASTRIS companion study. Major eligibility criteria include locally advanced (stage IIIB) or metastatic (stage IV) EGFR sensitive mutation NSCLC, not amenable to curative surgery or radiotherapy, with confirmation of the presence of the T790M mutation, prior therapy with an EGFR-TKI, PS 0-2, and the patients are willing to provide tumor specimens before osimertinib treatment and at the time of disease progression. The FFPE tissue samples will be collected at the time of baseline and disease progression. PD-L1 and CD8+ T cell will be detected by IHC (Ventana SP263). Immune-related gene will be detected by ThermoFisher Oncomine™ Immune Response Panel (398genes). The plasma samples will be collected at the time of baseline and disease progression, and tumor mutational burden will be detected by QIAGEN Mix-561-Match Panel (561 genes). A sample size of 62 will provide a power of 80% to detect the change at an alpha level of 0.05 based on Wilcoxon rank sum test. Assuming re-biopsy will be obtained from 40% patients at disease progression, the total number of patients will be 155. Estimated date of first subject enrollment will be before March 2017, and last subject last visit will be at June 2018. (NCT03029858) **Result:** The clinical trial is open for enrollment. **Conclusion:** The study points are not reached now.

Keywords: PD-L1, immuno-markers, osimertinib, lung cancer

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-006 SYSTEMS-2: RANDOMISED PHASE II TRIAL OF STANDARD VERSUS DOSE ESCALATED RADIOTHERAPY FOR PAIN IN MALIGNANT PLEURAL MESOTHELIOMA

M. Ashton[1], N. O'Rourke[1], N. Macleod[1], S. Smith[1], R. Valentine[1], B. Laird[2], S. Sheridan[3], L. Alexander[4], A. Chalmers[5]

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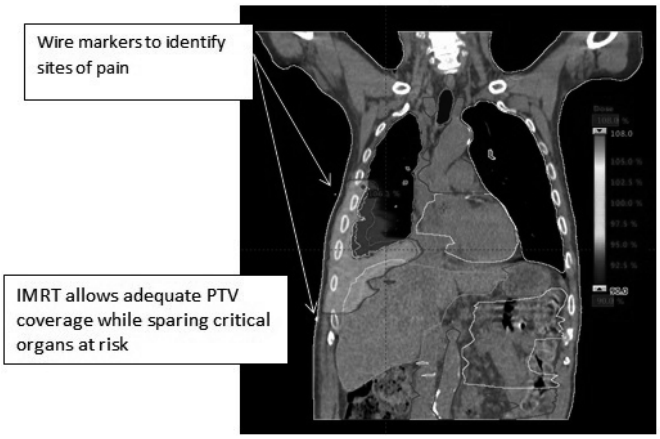
Background: Pain is common in malignant pleural mesothelioma (MPM) and tends to be poorly responsive to analgesia. Radiotherapy has traditionally been used for pain control, without robust supportive evidence. 'SYSTEMS' was the first prospective study to use validated endpoints to assess pain response to a standard dose of palliative radiotherapy (20Gy/5#). This multicentre, phase II trial demonstrated clinically meaningful improvements in pain in one third of patients at week 5, with minimal toxicity. The SYSTEMS-2 study is comparing pain control at week 5 in the standard arm (20Gy/5#) with that in the dose escalated arm (36Gy/6#). **Method:** Recruitment target is 112 patients across 15-20 UK hospitals. Eligible patients have: • MPM diagnosis • ECOG PS 0-2 • Pain score ≥ 4/10 after analgesia optimisation • CT scan with contrast within 8 weeks of starting radiotherapy • Radiotherapy plan compatible with dose escalated arm prior to randomisation. Wire markers are used to indicate sites of pain at radiotherapy planning and doses to organs at risk (OAR) are minimised through advanced planning techniques (e.g. intensity modulated radiotherapy- IMRT). (Figure 1) The primary outcome is pain control at the radiotherapy site at week 5. A clinically significant response is defined as a drop of ≥ 2 points in a validated numerical rating scale. Radiological response will be assessed at week 9.

Figure 1.



Result: SYSTEMS-2 opened to recruitment in August 2016. More than 30 patients have been screened across a total of 5 UK sites and 15 patients have been randomised. A further 19 sites are currently in set-up. PTV coverage and OAR doses have been consistently achieved, despite large treatment volumes and nearby radiosensitive structures. Radiological responses have been seen across both cohorts. **Conclusion:** This study will provide robust and accurate symptom response data for palliative radiotherapy in MPM and help to establish the optimal dose and fractionation.

Keywords: Radiotherapy, Pain, Mesothelioma

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

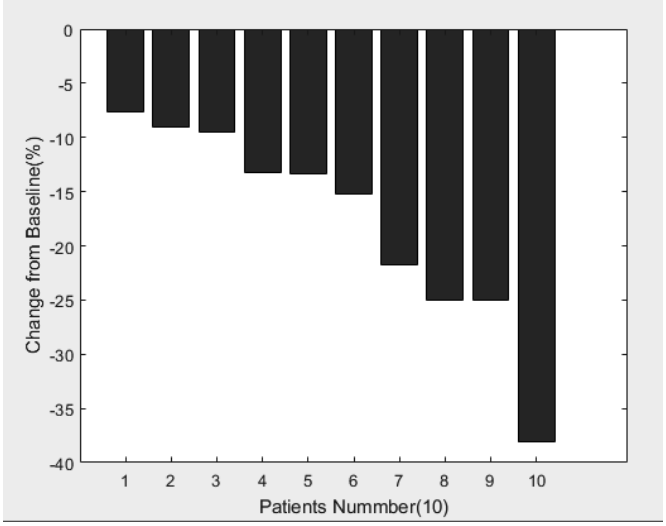
P3.04-007 A PROSPECTIVE STUDY OF APATINIB IN ADVANCED SMALL CELL LUNG CANCER PATIENTS FAILED FROM TWO OR MORE LINES OF CHEMOTHERAPY

Y. Liu, X. Hu, J. Jiang, S. Zhou, P. Liu, J. Li, Y. Wang, X. Hao, Y. Shi

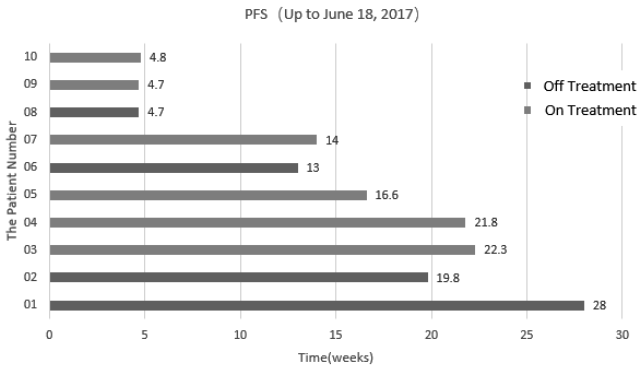
Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing/CN

Background: Small cell lung cancer (SCLC) is an aggressive and invasive variant of lung tumors,and its treatment strategy is poor. Apatinib is an oral TKI against VEGFR-2. We determined the efficacy of Apatinib as third- or later-line treatment in advanced SCLC. **Method:** The study was expected to enroll 30 patients diagnosed with advanced SCLC. Patients received oral Apatinib 500mg QD and make an efficacy evaluation after first cycle, then every two cycles once again. The primary endpoint was progression-free-survival (PFS). **Result:** From November 10, 2016 to June 18, 2017, 10 patients were enrolled. 1 patient showed PR when make efficacy evaluation the first time, 8 patients were evaluated SD and 1 patient showed PD due to liver metastasis. Although only one patient showed PR, all the patients' target lesions were

reduced, as figure 1.



Up to June 18, 4 patients out of the group due to PD, the PFS is 28 weeks, 19.8 weeks, 13 weeks and 4.7 weeks respectively. Another 6 patients are still investigated, as figure 2, the blue bars are their PFS .



Conclusion: Apatinib in advanced SCLC is worth expecting.To further investigate the role of Apatinib in SCLC patients, large sample and additional clinical trials are needed.

Keywords: Small cell lung cancer(SCLC), Apatinib, Prospective study

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-008 A PHASE 1B/2 STUDY OF ATEZOLIZUMAB WITH OR WITHOUT DARATUMUMAB IN ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Daratumumab (DARA), a human CD38 monoclonal antibody, is approved for the treatment of patients with relapsed/refractory multiple myeloma (RRMM). DARA produces deep clinical responses in RRMM and induces T-cell expansion through the reduction of immune suppressive cell populations, such as CD38$^+$ myeloid-derived suppressor cells and regulatory T and B cells. Atezolizumab (atezo) is a humanized programmed death-ligand 1 (PD-L1) monoclonal antibody that blocks the interaction between PD-L1 and the programmed death-1 and B7.1 receptors, reinvigorating anticancer immune responses. Atezo was recently approved for patients with metastatic NSCLC that progressed on or during platinum therapy based on data showing improved overall survival (OS) in the atezo vs docetaxel treatment arm in two clinical trials. The combination of DARA and atezo may improve clinical responses in NSCLC by enhancing anti-tumor T-cell responses facilitated by checkpoint inhibition. This study will assess the anti-tumor activity and safety profile of DARA plus atezo vs atezo alone in patients (pts) with previously treated advanced or metastatic NSCLC. **Method:** This is an ongoing phase 1b/2 randomized, open-label, multicenter study of DARA (16 mg/kg intravenous [IV] weekly for 3 cycles [Days 1, 8, and 15] and then Day 1 of each 21-day cycle thereafter) in combination with atezo (1200 mg IV; Day 2 of Cycle 1 and Day 1 of each 21-day cycle thereafter) versus atezo alone (1200 mg IV; Day 1 of Cycle 1 of each 21-day cycle). Eligible pts (≥18 years) must have advanced or metastatic NSCLC and have received 2 or more cycles of standard platinum-based therapy with disease progression or intolerance to therapy. Eastern Cooperative Oncology Group performance status of ≤1 and known PD-L1 tumor status are required. Pts previously treated with anti-CD38 therapy, including DARA, CD137 agonists, or immune checkpoint inhibitors are excluded. The primary endpoint is overall response rate. Secondary outcomes include safety, duration of response, clinical benefit rate (≥16 weeks duration), progression-free survival, OS, and pharmacokinetics and immunogenicity of DARA and atezo when given in combination. Approximately 96 pts will be enrolled; 6 pts will receive combination therapy in a safety run-in cohort for evaluation of dose-limiting toxicity followed by 90 pts randomly (1:1) assigned to the 2 treatment arms. ClinicalTrials.gov number, NCT03023423. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: NSCLC, daratumumab, atezolizumab

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-009 STEREOTACTIC BODY RADIOTHERAPY TO ALL SITES OF OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) COMBINED WITH DURVALUMAB AND TREMELIMUMAB

M. Bassetti[1], J. Lang[2], Z. Morris[3], B. Morris[4], J. Eickhoff[5], A. Traynor[3], T. Campbell[6], K. Matkowskyj[7], A. Baschnagel[3], T. Leal[6]

[1]Human Oncology, University of Wisconsin, Madison, Madison/US, [2]Hematology/Oncology, University of Wisconsin, Madison, Madison/WI/US, [3]Human Oncology, University of Wisconsin, Madison, Madison/WI/US, [4]School of Medicine, University of Wisconsin, Madison, Madison/US, [5]Biostatistics and Medical Informatics, University of Wisconsin, Madison, Madison/WI/US, [6]Medicine/Oncology, University of Wisconsin Carbone Cancer Center, Madison/WI/US, [7]Pathology, University of Wisconsin, Madison, Madison/US

Background: PD-1/PD-L1 axis inhibition and comprehensive stereotactic body radiation (SBRT) treatment to all gross disease have both been independently associated with improved outcomes for patients with oligometastatic NSCLC in randomized trials. Interest has increased in the use of dual immune checkpoint inhibition in NSCLC, which adds targeting of CTLA-4 to PD-1/PD-L1 inhibition, as this has showed improved outcomes in melanoma, though with increased side effects. Recent appreciation for the immunostimulatory effects of SBRT and possible synergy with checkpoint inhibition therapies has prompted interest in combining these treatments, however the toxicity of this combination is unknown. This is the first trial evaluating the sequential combination of comprehensive SBRT and dual immune checkpoint inhibition. **Method:** This phase I trial will assess the safety and preliminary outcomes for a 21 patient cohort undergoing SBRT to all sites of oligometastatic (EGFR/ALK wildtype) NSCLC followed by combined duvalumab and tremelimumab immune checkpoint inhibition. Patients with 1-6 extracranial sites of disease will undergo SBRT from 30-50 Gy in 5 fractions. One week after radiation they will receive 4 cycles of combination Durvalumab 1500mg/Tremelimumab 75mg every 4 weeks followed by Durvalumab 1500mg monotherapy q 4 weeks. The primary endpoint of this study is safety. Secondary endpoints include overall survival (OS) and (PFS). Correlative studies of PD-L1 expression on post SBRT biopsy and circulating tumor cells are incorporated into the protocol. **Result:** Section not applicable **Conclusion:** The study is currently undergoing IRB review and FDA IND approval. This study will open to accrual in August 2017.

Keywords: Trememlimumab, durvalumab, SBRT

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-010 VALIDATION OF A CTDNA METHYLATION ASSAY TO DIFFERENTIATE BENIGN AND MALIGNANT PULMONARY NODULES: A CHINESE NATIONWIDE MULTI-CENTER STUDY

W. Liang[1], J. He[1], X. Zhi[2], F. Yu[3], C. Cheng[4], Z. Wang[5], K. Cai[6], G. Jiang[7], C. Chen[7], Q. Luo[8], L. Chen[9], J. Hu[10], L. Liu[11], X. Li[12], Q. Wu[13], S. Xu[14], J. Liu[15], Y. Yang[16], H. Tian[17], X. Cai[18], J. Fan[18], O.B.O. Chinese Clincal Trial Consortium (Cctc)[19]

[1]The First Affiliated Hospital of Guangzhou Medical University, National Clinical Research Center for Respiratory Disease, China State Key Laboratory of Respiratory Disease, Guangzhou/CN, [2]Xuanwu Hospital Capital Medical University, Beijing/CN, [3]The Second Xiangya Hospital of Central South University, Changsha/CN, [4]The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou/CN, [5]Shenzhen People's Hospital, Shenzhen/CN, [6]Nanfang Hospital, Guangzhou/CN, [7]Shanghai Pulmonary Hospital, Shanghai/CN, [8]Shanghai Chest Hospital, Shanghai/CN, [9]Jiangsu Province Hospital, Nanjing/CN, [10]The First Affiliated Hospital, Zhejiang University, Hangzhou/CN, [11]West China Hospital, Sichuan University, Chengdu/CN, [12]Tangdu Hospital, Xian/CN, [13]The First Affiliated Hospital of Chongqing Medical University, Chongqing/CN, [14]Harbin Medical University Cancer Hospital, Harbin/CN, [15]Fourth Hospital of Hebei Medical University, Shijiazhuang/CN, [16]Beijing Cancer Hospital, Beijing/CN, [17]Qilu Hospital of Shandong University, Jinan/CN, [18]Anchordx Medical Co., Ltd., Guangzhou/CN, [19]Cctc, Guangzhou/CN

Background: Current state-of-the-art lung cancer early screening utilizes low-dose CT scan to identify lung nodules smaller than 3 cm in diameter. However, it's still a clinical challenge to differentiate between malignant and benign nodules. In previous studies, we had taken the approach of methylation profiling by high- throughput bisulfite DNA sequencing to learn methylation patterns that differentiate malignant vs. benign lesions from tissue samples by in-depth data mining, and then used pattern matching to classify plasma samples. We were able to achieve a preliminary sensitivity of 94.3% for identification of malignancies, with a preliminary specificity of 93.6% against all benign specimens in the training set (129 malignant specimens and 101 benign specimens). From an independent validation set of 145 plasma samples (79 malignant specimens and 66 benign specimens from asymptomatic normal individuals and patients), this assay obtained a preliminary sensitivity of 78.5% and a preliminary

specificity of 83.3% for differentiating patients with malignant tumor. Specifically, the assay is demonstrated to be highly sensitive towards early-stage lung cancer detection, with a preliminary sensitivity of 71.1% in 38 patients with stage Ia lung cancer and 87.5% in 16 patients with stage Ib lung cancer. In this multi-center clinical study, we aim to validate the accuracy of ctDNA methylation test for diagnosing early-stage lung cancer by comparing the pre-operational ctDNA methylation test results with the surgical pathology results. (NCT03181490,CCTC-1701) **Method:** Patients who are diagnosed with solitary pulmonary nodules (<=3cm) by LDCT/CT scans and have decided to undergo surgery will be recruited in this study. All blood samples are collected before surgery. We take the approach of targeted methylation profiling by high-throughput bisulfite DNA sequencing of plasma samples to identify lung cancer specific methylation signatures. By comparing the results of the methylation test and the histopathological diagnostic results, we calculate the specificity and sensitivity of the methylation test on differentiating patients with malignant lesions from benign diseases. The laboratory technicians and analysts who perform the methylation tests are blinded to this study. Sample size determination: expected specificity and sensitivity is 80% based on pre-clinical study, permissible error is ±5%, α=0.05, β=0.10. According to the study design, patients with benign nodules make up ~20% of all patients. Therefore, the estimated sample size for each of the benign and malignant group is estimated to be at least 246. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: high throughput sequencing of ctDNA methylation, solitary pulmonary nodules suspected to be lung cancer, multicenter validation study

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-011 A PROSPECTIVE STUDY TO OPTIMIZE THE EXTENT OF PULMONARY RESECTION ACCORDING TO DECISION-MAKING ALGORITHM IN CSTAGE IA NSCLC

H.K. Kim[1], H.Y. Lee[2], Y. Choi[3], H. Kim[4], K. Lee[4], S. Shin[1], J.H. Cho[1], Y.S. Choi[1], J. Kim[1], J.I. Zo[1], Y.M. Shim[1]

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Background: Recent advances in imaging technology and the widespread use of low-dose computed tomography screening have greatly increased the chance of detecting small-sized non-small cell lung cancer (NSCLC) with indolent features (radiologically ground-glass opacity and histopathologically lepidic pattern adenocarcinoma). This change in the disease pattern of NSCLC has led to a resurgence of interest in sublobar resection. The purpose of this study is to determine the outcome of patients with clinical stage IA NSCLC treated by 3 types of surgical resection (wide wedge resection, segmentectomy, or lobectomy) according to the institutional decision-making algorithm. **Method:** In this study, we are planning to prospectively enroll 1,000 patients with clinical stage IA NSCLC undergoing curative-intent surgical resection. Our decision-making algorithm regarding the optimal extent of pulmonary resection has been developed based on our institutional consensus building meetings. We are planning to prospectively measure radiologic features such as tumor diameter and consolidation/tumor (CT) ratio. For ≤ 2cm tumors with CT ratio of ≤ 0.25, wide wedge resection needs to be performed. For ≤ 2cm tumors with CT ratio of 0.25 to 0.5 or 2-3cm tumors with CT ratio of ≤ 0.5, segmentectomy should be chosen. When CT ratio is larger than 0.5, lobectomy is required regardless of tumor size. When either parenchymal or bronchial resection margin is found to be insufficient during surgery, segmentectomy or lobectomy should be done even when a lesser resection was planned. Resection margins greater than the maximal tumor diameter (lesions less than 2cm) or at least 2cm gross margins (lesions larger than 2cm) should be achieved. Hilar and mediastinal lymph node dissection or at least systematic lymph node sampling is strongly recommended for any kind of pulmonary resection. **Result:** The primary objective is to determine disease-free survival following sublobar resection and lobectomy. The secondary objectives are (1) to determine overall survival following surgery, (2) to determine rates of loco-regional and systemic recurrence following surgery, (3) to compare postoperative pulmonary function between 3 different resection types, (4) to explore the relationship between radiologic parameters and pathologic subtypes, and (5) to determine the predictors of unexpected nodal involvement. **Conclusion:** This study is registered with ClinicalTrials.gov, number NCT03066297 ("OREX-IA" study) and we started recruiting patients in February, 2017 and will also be planning to follow up patients for at least 5 years to analyze their survival and recurrences.

Keywords: Optimal extent of pulmonary resection, Institutional decision-making algorithm, Clinical stage IA non-small cell lung cancer

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-012 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 inhibition 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 explored 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:** Trial Design: This is a multicenter, open-label, Phase 1 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. 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, or afatinib, have at least one measurable lesion per RECIST v1.1, do not have spinal cord compression or clinically active brain metastases, 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 osimertinib. Escalation of DS-1205c dosing between subjects is determined from 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. In Dose Expansion, subjects receive DS-1205c at the recommended dose for expansion determined in Dose Escalation, in combination with osimertinib. Primary objectives are to determine the safety, tolerability, and recommended dose for expansion 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). **Clinicaltrials.gov identifier:** NCT03255083 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Axl, EGFR mutation, drug resistance

P3.04: CLINICAL DESIGN, STATISTICS AND CLINICAL TRIALS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.04-013 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 the treatment of EGFR-mutant NSCLC has significantly improved with the use of EGFR tyrosine kinase inhibitors, there remain limited treatment options for many patients who develop resistance to these agents. The HER3/ERBB3 oncogene is overexpressed in many cancers, including NSCLC, and higher expression is correlated with poorer outcomes. U3-1402 is a novel 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 of ~8:1. **Method:** Trial Design: This is a multicenter, open-label Phase 1 study of U3-1402 in metastatic or unresectable non-squamous 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 erlotinib, gefitinib, afatinib, or osimertinib, have at least one measurable lesion per RECIST v1.1, have adequate bone marrow and organ function, do not have LVEF < 45% by either ECHO or MUGA scan, do not have mean QTc prolongation to > 470 ms for females and >450 ms for males, and do not have spinal cord compression or clinically active brain metastases. This study includes two parts: Dose Escalation and Dose Expansion. In Dose Escalation, subjects receive U3-1402 via intravenous infusion in 21-day cycles. In Dose Escalation, escalation of U3-1402 dosing between subjects 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. In Dose Expansion, subjects receive U3-1402 at the recommended dose for expansion determined in Dose Escalation. Primary objective is to determine the safety, tolerability, and recommended dose for expansion of U3-1402. Secondary objectives are to assess the pharmacokinetic parameters of U3-1402, total anti-HER3 antibody, and MAAA-1181a (drug payload), and to assess antitumor activity of U3-1402 (RECIST v1.1). **Clinicaltrials.gov identifier: NCT03260491 Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: EGFR mutation, antibody drug conjugate, HER3

P3.05-001 BREATH ANALYSIS FOR EARLY DETECTION OF LUNG CANCER: THE LUCID STUDY

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Background: There is an urgent need for methods to detect lung cancer earlier. If detected early, over half of lung cancer patients could be cured with existing treatments. Therefore, our greatest opportunity lies in increasing rates of early diagnosis through improved cancer screening. Exhaled breath contains over 1,000 Volatile Organic Compounds (VOCs), which are the products of metabolic activity, hence they directly reflect the current state of cells and represent a valuable source of information about the health of an individual. As the earliest stages of tumour development are characterized by profound changes in cellular metabolic activity, VOCs are potential non-invasive biomarkers for early detection of lung cancer. The LuCID study aims to collect breath samples and evaluate VOCs in exhaled breath as non-invasive biomarkers for early detection of lung cancer. **Method:** 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 for 7 minutes to collect alveolar- and bronchial-enriched breath fractions on stable sorbent tubes for later analysis by Gas Chromatography-Mass Spectrometry and Field Asymmetric Ion Mobility Spectrometry (FAIMS, Owlstone Medical Ltd). A classification algorithm will be constructed from chemical spectral data, and undergo internal and external blinded validation to provide a ROC-curve detailing diagnostic accuracy. The LuCID study has an adaptive trial design, recruiting up to 2,600 patients depending on interim results. **Result:** The LuCID study has recruited 980 patients to date from 20 centres (mean age 67.5, SD 12.0). Of patients with completed follow-up (n=802), 33% have histologically confirmed lung cancer (of those with lung cancer: 40% early stage 1a-2b, 60% advanced stage 3a-4). Non Small Cell Lung Cancer (NSCLC) comprised 87% of these cancers, and Small Cell Lung Cancer 9%. NSCLC were further categorized as adenocarcinoma (50%), squamous cell carcinoma (38%), with the remaining 12% belonging to other categories. **Conclusion:** The LuCID study is evaluating the analysis of exhaled VOC biomarkers as a new diagnostic modality for early detection of lung cancer. Successful completion of the LuCID study will pave the way for the development of a non-invasive, easy-to-implement test that could markedly improve screening and early detection rates, reducing lung cancer morbidity and mortality.

Keywords: Screening, breath analysis, Biomarkers

P3.05-002 THE EFFECT OF NODULE SIZE ON THE SENSITIVITY OF THE LUCED® TEST FOR LUNG CANCER

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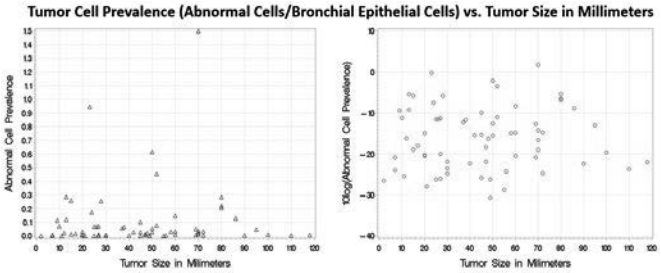
Visiongate, Phoenix/AZ/US

Background: The LuCED® test is based on analysis of sputum by the Cell-CT® platform that computes 3D images of cells with isometric resolution, allowing orientation-independent measurements of 704 3D structural biomarkers to generate a probabilistic score to identify abnormal cells. that was consistent by tumor histology and stage. Early stage tumors are generally smaller in size. One view is that smaller tumors might exfoliate fewer abnormal cells into sputum, making early stage tumor detection less likely. Here, we test the hypothesis that tumor size is a primary determinant of LuCED sensitivity. **Method:** Sputum samples from 74 biopsy confirmed non-small cell lung cancer cases were studied. The tumor size (mm) was characterized as the maximum tumor dimension supplied by the clinic. The numbers of bronchial epithelial cells and abnormal cells in sputum were measured and confirmed by cytological review. Tumor cell prevalence was characterized as (abnormal cells)/(bronchial epithelial cells) and plotted versus tumor size to assess any trend towards lower abnormal cell prevalence with decreasing tumor size. **Result:** The figures show the abnormal cell prevalence and the log of prevalence versus tumor size.



Conclusion: No trend was observed that might support the hypothesis that lower abnormal cell prevalence would occur with smaller tumor size. Moreover, variance in abnormal cell prevalence for any tumor size is large, suggesting that factors other than tumor size are more important in determining prevalence. There is no evidence to suggest that the LuCED test sensitivity decreases for smaller tumors, and this further suggests that early stage cancer, where tumors might be smaller, can still be detected. Published data shows that the LuCED test is 92% sensitive to stage 1 lung cancer.

Keywords: Cell-CT, Early Detection, early stage lung cancer

P3.05-003 SERUM THIOREDOXIN REDUCTASE 1 AS A DIAGNOSTIC BIOMARKER FOR NON-SMALL CELL LUNG CANCER

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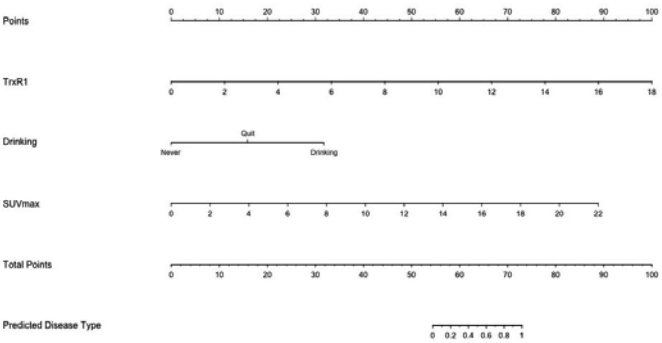
Background: Non-invasive diagnostic biomarkers for patients with suspicious non-small cell lung cancer (NSCLC) may provide needed guidance on invasive diagnostic and therapeutic decisions. Thioredoxin reductase 1 (TrxR1) is a pivotal intracellular redox sensor and antioxidant enzyme, and plays an important part in tumor growth, progression, metastasis, and chemotherapy resistance. The goal of this study is to test the feasibility of developing plasma TrxR1 as a novel diagnostic biomarker for NSCLC. **Method:** The plasma TrxR1 activity was determined spectrophotometrically by monitoring the NADPH-dependent production of 2-nitro-5-thiobenzoate at 412nm and at 37°C. A random forests method was adopted to identify and measure the important diagnostic variables for NSCLC. A nomogram that allowed more accurate prediction of probability for NSCLC was developed. **Result:** In this study, the plasma levels of TrxR1 were measured in 102 treatment-naïve NSCLC patients and 11 individuals with benign tumor-like pulmonary diseases. The random forest analysis identified that TrxR1, PET SUVmax, smoking and drinking history were potentially significant variables for NSCLC diagnosis and differentiation. After cross validation, the nomogram for the cohort was accurate and discriminating, with an area under the receiver operating characteristic (ROC) curve of 0.70.



Conclusion: Our data suggest that plasma TrxR1 activity is a useful non-invasive diagnostic marker for NSCLC. We developed a user-friendly nomogram that uses information commonly available to the clinician to easily and accurately calculate the likelihood of NSCLC.

Keywords: diagnositic, lung cancer, biomarker

P3.05-004 THE IMPACT OF EGFR MUTATIONS ON INCIDENCE AND SURVIVAL OF NSCLC PATIENTS WITH BRAIN METASTASIS: A SINGLE CENTER RETROSPECTIVE STUDY

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide. Despite advances in systemic therapy and improvements in survival for advanced non-small cell lung carcinoma (NSCLC), brain metastasis (BM) remained an important etiology of morbidity and mortality. This study was designed to analyze the association between the epidermal growth factor receptor (EGFR) mutation status and the incidence of brain metastases (BM) and associated survival. **Method:** We retrospectively investigated the medical records of 491 patients diagnosed with NSCLC stage I to stage III from 2004 to 2015, who were tested for EGFR mutations. The time from the diagnosis of advanced NSCLC to the development of BM and the overall median survival after BM development were evaluated and compared by EGFR mutation status. **Result:** Seventy-eight of 491 patients developed BM. From 280 patients had EGFR mutations, 49 patients developed BM and 29 of 211 patients harboring wild-type EGFR developed BM. Comparing with wild-type EGFR group, the incidence of subsequent BM was statistically higher in patients with EGFR mutations [49 (17.5%) vs. 29 (13.7%), p=0.023]. Patients with EGFR mutations also demonstrated the trend with longer overall survival (OS) after BM diagnosis than patients with wild-type EGFR (17.8 v.s. 12.2 months, HR:0.79 , 95% CI: 0.45-1.40, p = 0.416) (Figure 1).

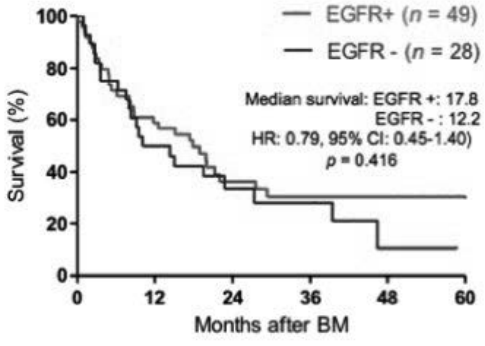

Figure 1: Kaplan-Meier curves for overall survival in patients with different EGFR mutation status after the diagnosis of brain metastasis

Conclusion: Our data suggested that EGFR mutation is a predictive risk factor for the development of brain metastasis. Though there is no statistical significance, NSCLC patients with EGFR mutation and brain metastasis tend to have longer survival than those with EGFR wild type.

Keywords: EGFR mutation, Brain metastasis, survival

P3.05: EARLY STAGE NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.05-005 HYPERMETHYLATION OF THE RASSF1A AND SOX1 GENES IN TUMOR DNA PREDICTS UNFAVORABLE OVERALL SURVIVAL IN SURGICALLY RESECTED NSCLC PATIENTS

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Background: The possibility of detection of tumor suppressor genes methylation in tumor DNA of NSCLC patients and the lack of methylation in healthy individuals makes this epigenetic alternation a potential diagnostic and prognostic marker of lung neoplastic processes. The aims of our study was to evaluate the promoter methylation of 7 genes in tumor DNA of NSCLC patients, matching nonmalignant lung tissue and blood samples to test weather these changes are lung cancer specific. We also wanted to investigate usefulness of this test for predicting the lung cancer course. **Method:** Genes methylation status was evaluated in DNA isolated from tumor, matching nonmalignant lung tissue and peripheral blood samples from 65 NSCLC patients treated with curative resectional surgery. Hypermethylation status was quantified at multiple CpG sites within each promoter in multiple genes - CDH13, MGMT, ESR1, SOX1, RASSF1A, HOXA9, and DAPK by pyrosequencing. Percent methylation for each CpG as well as average methylation across CpG's was calculated for each promoter using PyroMark software (Qiagen). **Result:** Aberrant methylation in SOX1 and RASSF1A genes in tumor tissues were associated with inferior survival in surgically resected NSCLC patients. This effect was independent of TNM stage, which was also a predictor of survival. Methylation in tumors was significantly higher than in normal lung for SOX1, DAPK, RASSF1A, HOXA9 and CDH13. 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. **Conclusion:** Hypermethylation of SOX1 and RASSF1A genes in NSCLC correlates with poor prognosis of patients. It may serve as novel epigenetic-based diagnostic biomarkers with further clinical impact for risk stratification of NSCLC patients. Our results also show that elevated methylation levels observed in genes SOX1, RASSF1A, HOXA9, CDH13 and DAPK in NSCLC were cancer-specific. We confirm that hypermethylation of these genes plays a role in NSCLC pathogenesis. However, the lack of reflection of these methylation changes in patients blood indicate their poorly suitability for a screening test.

Keywords: methylation; non-small cell lung cancer; RASSF1A; SOX1; 5-year survival rate

P3.05: EARLY STAGE NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.05-006 INTEGRATED GENOMIC ANALYSIS TO ASSESS THE MOLECULAR SIGNATURE OF JAPANESE PATIENTS WITH NON-SMALL CELL LUNG CANCER

M. Isaka[1], M. Serizawa[2], T. Nagashima[3], S. Ohnami[4], K. Ohshima[5], K. Urakami[4], H. Kojima[1], S. Takahashi[1], A. Ono[6], T. Sugino[7], T. Takahashi[8], Y. Ohde[9], M. Kusuhara[10], K. Yamaguchi[11]

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Background: Increasing molecular evidences have led to the development of molecular-targeted cancer therapies for non-small cell lung cancer (NSCLC). Especially, clinical implementation of EGFR- and ALK-targeted therapies has improved clinical outcomes in lung adenocarcinoma (LUAD). However, not all patients with LUAD benefit from these therapies. Moreover, molecular-targeted therapies for lung squamous cell carcinoma (LUSC) have not progressed much, because definitive drug targets have not been identified. To further expand the range of molecular-targeted therapeutics for NSCLC, this study explored novel therapeutic targets by integrated genomic characterization. **Method:** Surgically resected primary tumor specimens obtained between January 2014 and June 2016 from 372 patients with NSCLC (LUAD, 296; LUSC, 76) were subjected to whole-exome sequencing (WES) and gene-expression profiling (GEP). Corresponding peripheral blood samples were collected as controls to identify tumor-specific genetic alterations in WES. Written informed consent was obtained from all patients. WES was performed on an Ion Proton system. An Agilent SurePrint G3 Human Gene Expression 8×60K v2 Microarray was used to detect tumor-specific gene expression. Oncogenic fusions were detected by a targeted RNA-sequencing. Copy number alterations were detected by integrating copy numbers resulting from WES and GEP. Promising oncogenic genetic alterations were selected with OncodriveFML and Cancer Genome Interpreter. **Result:** Patient characteristics (LUAD; LUSC) were as follows: median age (70; 73), men (52%; 87%), smokers (59%; 99%), ratio of stage I/II/III/IV (70/16/13/1%; 57/32/12/0%). The median tumor mutational burden (TMB) in LUAD and LUSC was 1.59 mutations (mt)/Mb (0.06–65.6) and 5.63 mt/Mb (0.32–26.2), respectively. Eleven and two patients showed a hypermutator phenotype (TMB ≥ 20 mt/Mb) in LUAD and LUSC, respectively. In LUAD, hypermutator had significantly more truncating somatic mutations in DNA repair genes than others (73% vs. 5%, $p < 0.0001$). Oncogenic fusions of *EML4-ALK*, *KIF5B-RET* and *EZR-ROS1*, and *FGFR3-TACC3* were observed in 2.7%, 0.3%, and 0.3% of LUAD, and 2.6% of LUSC, respectively. Promising oncogenic mutations were detected in *EGFR*, *KRAS*, *SMARCA4*, *RBM10*, *BAP1* and *PBRM1* in LUAD; in *KEAP1*, *PIK3CA*, *NFE2L2*, *KMT2D*, *NF1*, *ATM*, *RASA1* and *PTEN* in LUSC; and in *TP53* and *CDKN2A* in both tumor types. Promising amplified genes include *FRS2*, *MDM2*, *CDK4*, *MET*, *AURKA*, *CCNE1* and *ERBB2* in LUAD; in *SOX2*and *CDK6* in LUSC; and in *EGFR* and *TERT* in both tumor types. **Conclusion:** Theses promising oncogenic genetic alterations of the patients with NSCLC revealed in this study could contribute to the development of novel molecular-targeted therapies.

Keywords: whole-exome sequencing and gene-expression profiling, hypermutator, non-small cell lung cancer

P3.05: EARLY STAGE NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.05-007 POTENTIAL OF CYFRA 21-1 AND CEA TO PREDICT ADJUVANT CHEMOTHERAPY BENEFIT IN EARLY-STAGE SQUAMOUS CELL LUNG CANCER

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Background: Tumor markers (TMs), cytokeratin 19 fragment (CYFRA 21-1) and carcinoembryonic antigen (CEA), which have demonstrated prognostic value in early-stage non-small cell lung cancer (NSCLC), may also predict which patients are suitable candidates for adjuvant chemotherapy (adCHT). **Method:** Presurgical serum samples collected during an observational study of patients with stage I-II NSCLC were analyzed for CYFRA 21-1 and CEA via electrochemiluminescence immunoassay (Elecsys®; Roche Diagnostics). Recurrence-free survival (RFS) was analyzed using Kaplan Meier methods and a Cox proportional hazards model. A TM-based risk score was generated with RFS as the endpoint and the log10 of CYFRA 21-1 and CEA values as independent risk predictors. RFS was compared for patients who received adCHT versus surgery alone, with patients stratified as high versus low risk based on pathological disease stage (I vs II), the TM-based risk score, and clinical characteristics (age, gender, smoking status, disease stage, Eastern Cooperative Oncology Group performance status). **Result:** 227 patients were included (stage I: 69%; male: 67%; median age: 65 years; adenocarcinoma [ADC]: 47%, squamous-cell carcinoma [SCC]: 40%, mixed histology: 13%); 70 received adCHT (84% with a platinum-based regimen). Median follow-up was 58.8 months. Median RFS for all

patients was 76.3 months (81.0 and 68.6 months for ADC and SCC, respectively). All high-risk patients, defined by TMs or clinical characteristics (but not stage alone), had a worse prognosis, irrespective of treatment received. A similar pattern was seen in patients with SCC, whereas stage and clinical characteristics (but not TMs) were prognostic in patients with ADC. All high-risk patients (defined by any method) derived an RFS benefit from adCHT versus surgery alone (stage HR 2.7, p = 0.002; TMs HR 2.1, p = 0.018; clinical characteristics HR 3.2, p = 0.001). However, in all low-risk patients, RFS was similar regardless of whether they received adCHT or not. High-risk SCC patients also derived an RFS benefit from adCHT versus surgery alone (stage HR 4.9, p = 0.004; TMs HR 9.4, p = 0.002; clinical characteristics HR 9.0, p = 0.003), whereas those with low-risk SCC did not. In patients with ADC, none of the methods used were able to predict which patients might benefit from adCHT. **Conclusion:** Baseline CYFRA 211 and CEA levels may provide further information beyond clinical characteristics that could help clinicians to decide which patients with early-stage SCC should receive adCHT. Further evaluation of these biomarkers is warranted.

Keywords: CEA, CYFRA 21-1, ADJUVANT

P3.05: EARLY STAGE NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.05-008 POTENTIAL OF CYFRA 21-1 AND HE4 TO DETECT RECURRENCE IN PATIENTS WITH EARLY-STAGE LUNG ADENOCARCINOMA

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Background: The Tumor markers (TMs) cytokeratin 19 fragment (CYFRA 21-1) and human epididymis protein 4 (HE4) have each been shown to be useful in diagnosis, prognosis and monitoring of NSCLC, but their combination has not been investigated. The objective of this analysis was to evaluate the ability of CYFRA 21-1 and HE4 to predict relapse in patients with adenocarcinoma (ADC). **Method:** In an observational study of adult patients with stage I-IIIA ADC, serum samples were prospectively collected prior to surgery and during follow-up at 3, 6, 12, 18 and 24 months and then every 6-12 months up to 5 years post-R0 resection. Patients could receive an adjuvant therapy of either radiotherapy or chemotherapy (not both) according to their clinical situation and local best practice. In a *post hoc* analysis, CYFRA 21-1 and HE4 levels from these samples were measured via electrochemiluminescence immunoassay (Elecsys®; Roche Diagnostics). All cases of disease recurrence were verified by imaging. The diagnostic performance of CYFRA 21-1, HE4 and their combination was assessed by the Receiver Operating Characteristic (ROC) and corresponding area under the curve (AUC). The combination of both TMs was based on the weighted sum of the logarithmized (base 10) markers. Weights were derived from a logistic regression model which included the log10 of CYFRA 21-1 and HE4 as independent variables and relapse (yes/no) as a dependent variable. **Result:** 117 patients were included in the *post hoc* analysis (stage I/II/IIIA: 64%/21%/15%; male: 55%; median age: 63 years), providing a total of 623 TM measurements. All patients had received surgery for ADC; 34 patients (29%) also received adjuvant chemotherapy and 16 patients (14%) received radiation. Blood samples were collected for a median follow-up of 37 months. At this timepoint, 31 patients (26%) had experienced disease recurrence. Median recurrence-free survival was 80.2 months. Both CYFRA 211 and HE4 were able to detect recurrence (AUC and corresponding 95% confidence interval [CI]): 76.6% [66.9–86.3%] and 73.7% [64.1–83.4%], respectively), but this increased with the combination (AUC 79.0%, 95% CI 69.4–88.6%). At a sensitivity of 80%, the respective specificities (95% CI) for CYFRA 211, HE4 and the combination were 56.0% (51.9–60.1%), 49.1% (45.0–53.2%), and 70.1% (66.2–73.7%). **Conclusion:** Serial measurements of serum CYFRA 211 and HE4 levels could provide a valuable alternative method for follow-up monitoring and recurrence detection in patients with early-stage ADC, which would trigger imaging if elevated.

Keywords: recurrence, HE4, CYFRA 211

P3.05: EARLY STAGE NSCLC -
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P3.05-009 HSA_CIRC_0044013: A POTENTIAL NOVEL DIAGNOSTIC BIOMARKER OF LUNG ADENOCARCINOMA

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Background: Circular RNAs (circRNAs) are a special class of endogenous RNAs exhibiting stable structure and high tissue- and developmental-specific expression. Recent studies have found that aberrant expression of circular RNAs plays important roles in carcinogenesis and tumor progression. However, their value in the diagnosis of lung adenocarcinoma remains unknown. In this study, we focused on hsa_circ_0044013, which was found to be upregulated in lung adenocarcinoma tissues in our previous microarray analysis. The purpose of this study was to clarify the possible role of hsa_circ_0044013 and to define its diagnostic value in lung adenocarcinoma. **Method:** Expression levels of hsa_circ_0044013 in 30 paired lung adenocarcinoma tissues and adjacent non-tumor tissues were measured by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). We also measured expression levels of hsa_circ_0044013 in three NSCLC cell lines by qRT-PCR. Then, we detected expression levels of hsa_circ_0044013 in the plasma samples from 70 lung adenocarcinoma patients and 70 healthy individuals. Differences in expression levels of hsa_circ_0044013 were analyzed using the paired t-test. Then, the association between the expression level of hsa_circ_0044013 and the clinicopathological features of patients with lung adenocarcinoma was further analyzed. A receiver operating characteristic (ROC) curve was generated to evaluate the diagnostic value. **Result:** Hsa_circ_0044013 was significantly upregulated in lung adenocarcinoma tissues compared with adjacent non-tumor tissues (P = 0.0143). Its expression levels in two detected lung adenocarcinoma cell lines (A549, SPCA1) were upregulated than those in HBE and H1703. Moreover, Hsa_circ_0044013 was detected to be upregulated in plasma samples from lung adenocarcinoma patients (P = 0.0046). Its expression levels were significantly correlated with tumor diameter and TNM stage. The areas under the ROC curve (AUC) of hsa_circ_0044013 in plasma were up to 0.753. The sensitivity and specificity of the combination were 0.592 and 0.959. **Conclusion:** These results suggested that hsa_circ_0044013 may be a novel non-invasive biomarker for the diagnosis of lung adenocarcinoma.

Keywords: lung adenocarcinoma, biomarker, hsa_circ_0044013

P3.05: EARLY STAGE NSCLC -
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P3.05-010 NOTCH 1 AND NOTCH 3 EXPRESSIONS FOR EARLY STAGE OF NON-SMALL CELL LUNG CANCER

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Background: Notch gene Encode 300kDa single-pass transmembrane receptors. It can variously serve as an oncogene or a tumor suppressor and a repressor or inducer of terminal differentiation. It also regulate cell division, differentiation and survival of stem and/or progenital cells in wide range tissues. We examined Notch 1 and 3 to study the correlation of Notch expression and prognosis for non-small cell lung cancer. **Method:** Paraffin-embedded tissue microarrays were constructed. We analyzed Notch 1 and 3 by immunohistochemical stain on surgical tumor specimens. **Result:** One hundred fifty-nine of 185 resected tissues for lung cancer (median age 62 years) were available for immunohistochemical stain. The types of tumor histology were adenocarcinoma;54, squamous cell carcinoma:79, others;26. 121 patients were taken lobectomy and 38 were done pneumonectomy. Notch 1 and 3 receptors were detected in 119 (74.8%) and 130 (81.7%) of total 159 (M:F=114:45) tumor tissues, respectively. Notch 1 receptors showed higher expressions on squamous cell carcinoma than non-squamous cell carcinoma (58.8% vs. 37.8%, p=0.03). However, it was not correlated with sex, smoking status or advanced stages. Five year-relapse free survival (RFS) and overall survival (OS) were 57.4 % and 59.3 % in 159 patients, respectively. Patients with any expression of Notch1 or 3 have correlated with neither RFS nor OS. 5 year OS for patients who showed Notch 3 expression were 62 % and the others were 47.8%, however, it was not statistically significant (p= 0.165). Both of their expressions were detected in 106 of 159 (66.7%) tumor tissues. Sixteen (10 %) had negative expressions in both of them. The patients with both positive expressions had the tendency of longer OS than all negative patients. Their 5 year OS were 60.8 % vs. 38.2% (p=0.068) and 5 year RFS were 56.5% vs. 49.7 % (p=0.35). **Conclusion:** Notch 1 showed higher expression on squamous cell carcinoma. Neither Notch 1 nor 3 have correlated with RFS or OS, but patients with both expressions had the tendency of longer overall survival.

Keywords: NSCLC, NOTCH, earsly stage

P3.05: EARLY STAGE NSCLCF -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.05-012 CLINICOPATHOLOGICAL DETERMINANTS OF CIRCULATING TUMOR DNA DETECTION IN EARLY-STAGE NON-SMALL CELL LUNG CANCER

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Background: Circulating tumor DNA (ctDNA)-based liquid biopsies have recently demonstrated substantial promise in the diagnosis and monitoring of advanced non-small cell lung cancer (NSCLC); however, data regarding utility in early-stage (operable) disease are very limited. The aim of this study is to define the clinical feasibility of ctDNA assessment in operable NSCLC. **Method:** We prospectively recruited 80 patients with clinical stage I-IIIa NSCLC undergoing cruative intent tumor resection. Pre-surgical plasma cell-free DNA (cfDNA) and matched tumor genomic DNA were collected and analyzed with a novel 21-gene Digital Sequencing NGS panel (Guardant Health, Inc.) with a theoretical genomic sensitivity of > 90% for NSCLC. Genomic results, including cfDNA yields, technical sequencing information, and identity and quantity of somatic variants, were correlated with

various clinicopathological characteristics, including age, sex, smoking history, clinical and pathologic stage, histological tumor type, and preoperative treatment status. **Result:** [Cohort enrollment and sample collection is complete. Sequencing and analysis have been completed for the first 20 patients. The remaining patients will be completed within 1-2 months. Results from the complete cohort will be updated as directed by the Core Program Committee and will include the data elements described in the methods above. A preliminary review of the data is included below.] Of the 18 patients with somatic variants detected in tumor tissue (18/20, 90%), pre-operative ctDNA was detected in 12 (67%). Pre-operative ctDNA detection was high in squamous cell carcinoma (8/8), small cell lung cancer (1/1) and mixed histology (1/1) relative to adenocarcinoma (2/10, 20%). Clinical stage did not influence detection of small cell or squamous cell carcinoma; however, no ctDNA was detected in stage I or II adenocarcinoma samples (0/5). Detailed data from the complete cohort will be submitted as a late-breaking abstract. **Conclusion:** [Conclusion to be updated pending full cohort data.] ctDNA demonstrates sufficient pre-operative clinical sensitivity to be a feasible recurrence monitoring tool but appears to be influenced by tumor type.

Keywords: Circulating Tumor DNA, non-small cell lung cancer, Surgery

P3.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.06-001 TOBACCO USE, AWARENESS AND ORAL HEALTH AMONG KANCHIPURAM SILK WEAVERS, TAMIL NADU, INDIA

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Background: India is one of the world's largest producers of textile and garments. Kanchipuram is a city in Indian state of Tamil Nadu known for saree, which is traditionally made by weavers from kanchipuram popularly known as kanjivaram sari. The silk weavers are considered as the master weaver of Gods. The silk is also known for its quality and craftsmanship, which has helped earn its name globally. The people living around Kanchipuram take weaving as their main profession. Weaving being a sedentary work, tobacco has been used by this community as an entertainment factor to ward off boredom. Till date, there are no studies that have been conducted on the oral health status of silk weavers. Hence this study was contemplated with an aim to assess the tobacco use and its awareness among silk weavers. **Method:** A cross-sectional descriptive study was conducted to assess the tobacco use, its awareness and oral examination among 400 silk weavers at kanchipuram, India. Silk weavers aged 18 to 75 years who were involved in this occupation for more than 5years were included. Data was collected using a survey proforma which comprised of a questionnaire and WHO Oral Health Surveys – Basic Methods Proforma(1997). **Result:** .Results showed that among 400 study population, 57% had no formal education. Of those who had tobacco habit - 26% smoked beedi, 10.9% smoked cigarette, 65% chewed raw tobacco, 18% chewed Hans and 28% had a combination of smoking and smokeless tobacco usage. 34% of oral precancerous lesions were observed. The reason for practicing these habits were as a measure to combat boredom, relieving stress and body pain after work, and the lack of awareness of the hazards of the materials used. **Conclusion:** From the results of this study it may be concluded that the silk weavers were characterized by a lack of awareness about oral health, high prevalence of tobacco use and limited access to health services. Prevalence of oral mucosal lesions in the study population was due to tobacco usage and alcohol consumption and lack of awareness regarding the deleterious effects of the products used.

P3.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.06-002 TOBACCO USE, AWARENESS AND ORAL HEALTH STATUS AMONG SEAFARERS IN VOC PORT, TUTICORIN, TAMILNADU, INDIA

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Background: A sailor, seaman, mariner, or seafarer is a person who navigates waterborne vessels or assists as a crewmember in their operation and maintenance. Seafarers hold a variety of professions and ranks, each of which carries unique responsibilities which are integral to the successful operation of an ocean-going vessel. Seafarers are also frequently exposed to difficult working conditions and particular occupational risks. Seafaring is an exploratory profession with little research has been done to identify conditions that may lead to assess seafarer general health as well as oral health. Past research showed a prevalent use of tobacco and drug abuse among this population. **Method:** A cross-sectional descriptive study was conducted to assess the tobacco use, cancer awareness and oral health status among seafarers in VOC port, Tamilnadu, India. Data was collected using a pretested Questionnaire, which included Demographic data, tobacco habits, its frequency, form and oral examination was done The data collected was analysed using SPSS version15. **Result:** Total of 360 subjects participated in the survey. Adverse habits show the overall 72.3% prevalence among the study population. The percentage of oral mucosal lesions observed were as follows: 29% leukoplakia, 35% ulceration and 3% malignant tumor. 27% of the study populations had other abnormal conditions like candidiasis and OSMF. Prevalence of oral mucosal lesions in the study population was due to tobacco usage and alcohol consumption. **Conclusion:** Findings of the present study suggest that oral health condition of seafarer community was relatively poor, with high oral lesions and poor periodontal health. This epidemiological survey has provided baseline information to underpin the implementation of oral health programmes.

P3.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.06-003 WHAT DO THE CHILDREN THINK ABOUT SMOKING AND HOW ARE THEY HELPED IN PREVENTION?

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Background: Despite a lot of reports on the harmful effects of smoking on health, according to DOXA (Italian Institute of Health survey, 2016), most of people smoke the first cigarette between age 15 and age 17 (56.8%). The aim of this study was to evaluate the attitudes and knowledge of school-age children about cigarette smoking **Method:** Within the national primary prevention campaign "Questa non me la fumo" supported and promoted by WALCE we asked to teachers to administer a dedicated questionnaire to pupils. 724 questionnaires were analyzed between September 2016 and May 2017: 365 from 9 years-old primary-school pupils and 359 from 10 years-old Primary-school pupils (357 male: 49.3%). **Result:** 66% of pupils believes that a program of intervention might be useful as prevention action; however, the perception about smoke is that harms only those who smoke, improves sports performances and can help to lose weight in 28%, 1.8% and 5.1 % of cases, respectively. Among the smoking disadvantages, pupils describe bad breath (74.3%) and yellow teeth (70.1%), without reporting hair and muscle damage. 82.2% of students declare "I will never smoke", but 7.8% of them "the curiosity to try". Considering the living environment, it resulted that 44% of parents, 20% of grandparents, 21% of teachers, and 8% of peers smoke; however, most parents talk of smoking damage to their children (72%). Answers to "In your opinion, is it possible to quit smoking?" are encouraging: 76.2% responded "Yes" while "No" in 23.8% of cases. According to age, the reason "to be cool" why starting smoking was reported in 48.2% and 55%, in the fourth and firth grade of Primary school, respectively. Other reasons frequently reported were: "to imitate adults" and "to try". When asked, "What do you think is more dangerous for you?", "smoking a cigarette" was the most frequent (78%) among heterogeneous responses such as to travel by hitchhiking or skydiving . **Conclusion:** These results highlight the awareness of children about the deleterious effect of smoke on health, but areas of greatest vulnerability emerged, such as poor knowledge about the smoking effects on some parts of the body or the consequences of passive smoking. Notably, children live with adults (family and school educators) but also with peers who smoke and this is worrying if we consider that the main reason for adolescent to start smoking attitude is emulation. These data emphasize the need to implement specific prevention programs also in primary school.

Keywords: smoking prevention, children, Survey

P3.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.06-004 ROLE MODELS "A TOOL FOR EFFECTIVE TOBACCO CONTROL CAMPAIGN"

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Background: Each day, nearly 6,000 children under 18 years of age start smoking; of these, nearly 2,000 will become regular smokers. In Nigeria, 25.9% students in Lagos Nigeria currently live in homes where others smoke in their presence, 43.1% are around others who smoke in places outside their home, 14.6% of the students currently use any tobacco product. Approximately one half of student's exposed to cigarette smoking will also die prematurely from second hand or tobacco use; this is mostly after several years or more of excess disease and disability. **Method:** Experience has showed that adolescent and youths all over the world especially Nigeria are attracted to media of any form. Three (3) Role Models loved by adolescents were used to give a tobacco control sensitization talk and showed support towards implementation of the Nigeria Tobacco Control Bill for ten minutes each on a video that was televise in the targeted schools. **Result:** These methods creatively increased the awareness level of young people in Nigeria on the harmful effect of tobacco smoking and promote the campaign against tobacco smoking. The video reached about 12,200 students with over 721 success stories; the method reduced the rate of youth smoking among students in targeted schools by 27%. **Conclusion:** Evidence has showed that some of these role models are used as a campaign tool by the tobacco industry in Nigeria and other countries. It is therefore systemic and appropriate to use the same method to reduce the current upsurge in youth smoking and cancer related disease in Nigeria and Africa.

Keywords: Tobacco Control, youth, Role model

P3.06-005 INFORMATIONAL NEEDS ON SMOKING CESSATION OF CANCER PATIENTS

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Background: Newly diagnosed cancer patients are motivated to quit smoking and are more receptive to discussions on how to best accomplish this goal, but require support. However, little is known about the informational needs of cancer patients that would assist with their smoking cessation efforts. The purpose of this study is to determine the smoking cessation informational needs of cancer patients. **Method:** Patients at Princess Margaret Cancer Centre who are current smokers (smoking or quit within the last 6 months) completed a cross-sectional survey during their outpatient clinic appointments. The survey captured demographic data, details about smoking history and behaviors, and informational needs including: general information and support (8-items), health and disease (14-items), relationships (5-items), testimonials from patients who had quit (7-items) and smoking cessation interventions (3-items). Each item asked for information priority (not important, somewhat important or very important) and how much information is desired (none, a little bit or detailed). Data are summarized using descriptive statistics and Chi-square test was used to explore relationships between socio-demographic variables and smoking behaviour variables (perception of health, motivation to quit and readiness to quit). **Result:** 44 current smokers were recruited. The mean age was 43 (23-76 years), 28 (64%) were male and 35 (80%) were Caucasian. 21 (48%) had college/university level education and 11 (25%) had completed high-school. 18 (41%) were married and 30 (68%) were working. 23 (52%) lived with a support person. 29 (66%) of patients currently use a tobacco product and 15 (34%) had quit within the last 6 months. 23 (52%) were motivated/very motivated to quit smoking and 12 (27%) were somewhat motivated. Only 7 (16%) reported a lack of cessation services as a reason for continued smoking and 26 (59%) reported smoking will have a negative impact on their health. Only employment status was found to be related to readiness to quit p=.028. The three most important information needs were: "Information about strategies to help you stay quit" (n=24, 54.5%),"Information about why patients continue to smoke even with the known health risks" (n= 23, 52.3%) and "Information about strategies to help you quit" (n= 22, 50%). The preferred modality for this information was pamphlets followed by one-on-one teaching. **Conclusion:** Patients are most interested in obtaining information about strategies to help them quit and to stay quit and exploring their motivations to quite may be critical to success. Pamphlets are the preferred modality for this information.

Keywords: Smoking Cessation, Information needs, Patient Education

P3.06-006 THE GOVERNMENT WILLINGNESS TO LEGISLATE TOBACCO CONTROL AND CHANGES ON INDIVIDUAL BEHAVIOR IN BRAZIL

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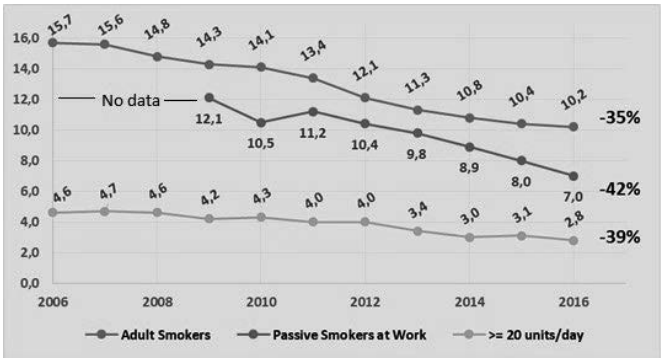
Background: The government willingness to legislate tobacco control, as part of the Complex Tobacco Landscape developed by the Initiative on the Study and Implementation of Systems (ISIS), is directly related to tobacco taxes and antismoking legislation to make changes on individual behavior. According to the NCI (2007)[1], "The willingness of government to take actions against tobacco interests depends on the balance of forces created by the protobacco and antitobacco constituencies and the government's perceptions of health risks associated with tobacco use". In 2011, the Brazilian government established a new taxation system and a minimum price policy for cigarettes. In 1996, Brazil started promoting smoke-free places, banning the advertising, promotion and sponsorship that were finally regulated in 2014 by a federal decree. [1]National Cancer Institute. Greater Than the Sum: Systems Thinking in Tobacco Control. Tobacco Control Monograph No. 18. Bethesda, MD: U.S. Department of Health and Human Services, April 2007 **Method:** Quantitative secondary data analysis confronting the prevalence rates found in Risk and Protective Factors Surveillance for Chronic Diseases Telephone Survey (VIGITEL). **Result:** The total adult prevalence rate decreased from 15.7% in 2006 to 10.2% in 2016 for both sexes; the prevalence of passive smokers at work decreased from 12.1% in 2009 to 7% in 2016 and daily smokers of 20 units or more also reduced from 4.6% in 2006 to 2.8% in 2016.



Conclusion: The present study shows a decline in prevalence as a positive result coming from smoke-free places, banning the advertising, promotion and sponsorship, and higher prices of cigarettes in Brazil between the years 2006 and 2016. In 2015, there were around 100,000 deaths of men and 55,000 deaths of women attributable to cigarettes. In 1990, an estimated 204,000 deaths were attributable to smoking. In absolute numbers, 55,000 lives have been saved[2]. [2] Department of Surveillance and Health-Ministry of Health

Keywords: Tobacco related death, Tobacco Control, Cigarette consumption

P3.06-007 LEVEL OF AWARENESS OF VARIOUS ASPECTS OF LUNG CANCER AMONG COLLEGE STUDENTS IN INDIA: IMPACT OF CANCER AWARENESS PROGRAMES

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Background: Lung cancer is one of the most common causes of cancer mortality among men in India and incidence is increasing, but actually, they are largely preventable diseases. In India, advanced stage at the time of presentation is responsible for high mortality and morbidity and early detection is the only way to reduce it. The purpose of this study is to know the level of awareness of various aspects of lung cancer among college students and impact of awareness programmes in its prevention and early detection. **Method:** This assessment was part of Pink Chain Campaign—a campaign on cancer awareness. During the cancer awareness events in 2013–2016 at various colleges in different parts in India, pre-test related to lung cancer was followed by awareness programme. Post-test using the same questionnaire was conducted at the end of interactive session, at 6 months and 1 year. **Result:** A total of 1644 out of 1970 students participated in the study (overall response rate was 88.5 %). Mean age of the study population was 18.2 years (range 16-21 years). There was a significant increase in the level of knowledge regarding lung cancer at 6 months, and this was sustained at 1 year. Among students who were just asked yes or no question, 542 students (33 %) were smokers and 711 students (43.2 %) were alcoholics. Internet and Newspapers were sources for knowledge in 70–80 % of students, whereas approximately 40 % of students were educated by TV and Magazines regarding various aspects of lung cancer. Post awareness at 6 months and 1 year, Pink Chain Campaign was the major source of knowledge related to lung cancer in more than 90 % of students by continuous and timely update on subject. Post awareness at 6 months and 1 year, there was a significant change in alcohol and smoking habits. Major reasons for not going for check-up were ignorance (83.1 %), fear (30.1 %) and lethargic attitude (29.3 %) initially, but over time, lack of time, lethargic attitude and hesitation became important factors after knowing various aspects of lung cancer. **Conclusion:** Knowledge of lung cancer due to smoking was known to most of the students. Overall awareness of risk factors, sign and symptoms, screening modalities of lung cancer has improved in a year along with practices related to smoking and alcohol, but there was not much improvement in people undergoing regular check-ups. To inculcate safe practices in the lifestyle of people, awareness programmes Such as the Pink Chain Campaign should be conducted more widely and frequently.

P3.06-008 LUNG CANCER PATHWAYS: A FIVE-YEAR PROGRAM TO REDUCE IMPACT THROUGH EPIDEMIOLOGICAL MODELLING AND INVESTMENT IN PRIORITIZED INTERVENTIONS

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Background: *Pathways* is a five-year program of targeted research to identify and implement those interventions that will have the greatest impact in reducing lung cancer incidence and mortality, and improving quality of life. It includes a sharply-focused research program to identify relevant interventions and health actions, a

consultative phase with national and international experts to prioritise 'best value' interventions, whilst considering the broader political and economic issues around implementation and policy change. A final decision and investment stage will direct funding and research activities to implement the 'best value' interventions in lung cancer prevention, screening, early intervention, treatment and supportive care. **Method:** A microsimulation model ('Policy1') has been designed using a powerful, flexible platform that can be programmed with information about multiple aspects of lung cancer to formulate an evidence base for determining the 'best value' interventions by comparing the impact and costs of interventions. These aspects include the 'natural history' of the disease, prevention actions (including tobacco control and lifestyle interventions), individual risk factors and screening behaviours, and cancer treatment type and uptake in various population subgroups. Policy1 is informed by work programs in statistical projections of lung cancer mortality (based on available mortality data and Australian smoking survey data), systematic reviews, big data and epidemiological analysis, and implementation science, to address health behaviour change and contextual factors. A Scientific Advisory Committee (SAC) of key stakeholders provides content expertise and strategic advice about pursuing detailed analyses selected interventions. **Result:** The statistical projections program indicates that lung cancer mortality rates for males will continue to decline and plateau after 2035, while for females, the mortality rate is expected to decrease steadily after 2014. Data from over sixty years of Australian tobacco smoking surveys has been used to estimate smoking prevalence, tobacco consumption, quit rates and duration of smoking. Seven scoping reviews have been completed in the areas of preventative strategies, early diagnosis, treatment regimens and clinical practice guidelines, health services interventions, psychosocial and palliative care. Key questions have been formulated and presented to the SAC to guide selection of 'best value' interventions for detailed exploration. **Conclusion:** *Pathways* presents an innovative approach to addressing those interventions that are likely have the greatest impact on improving lung cancer outcomes. The program will make a significant contribution to reducing the burden of illness in the Australian population by engaging with key stakeholders, guiding future research priorities, and translating research evidence into action.

Keywords: Epidemiology, interventions, outcomes

P3.06: EPIDEMIOLOGY/PRIMARY PREVENTION/TOBACCO CONTROL AND CESSATION - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.06-009 HOW DOES SCREENING FOR THE EARLY DETECTION OF LUNG CANCER FACILITATE SMOKING CESSATION? A QUALITATIVE STUDY OF SCREENED SMOKERS

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Background: There is little evidence that lung cancer screening prompts smoking cessation in screened populations overall. However, a more complex relationship is emerging where abnormal screening results appear to promote abstinence and those smokers who attend screening seem more motivated to stop smoking than those who do not. There is a need to understand how screening programmes can best facilitate reductions in smoking prevalence in screening populations. We aimed to investigate in the context of lung cancer screening i) facilitators to smoking cessation and continued abstinence and ii) attitudes to cessation support. **Method:** A qualitative sub-study to the Early Cancer detection test Lung cancer Scotland (ECLS) trial was conducted. We examined responses to ECLS questionnaires completed pre- and post-screening to sample smokers who had made a successful attempt to stop smoking, an unsuccessful attempt to stop or no attempt to stop since screening. Participants with positive and negative screening test results were sampled. Thirty-one in-depth semi-structured face-to-face interviews were conducted to investigate wider experiences of smoking in the screening context. Audio recordings were transcribed verbatim and thematically analysed. We present here a subset of data relating to the specific aims above. **Result:** Participants reported receiving a 'fright' from positive test results and reassurance from negative results, both facilitating smoking cessation. Test results were seen as objective health feedback which could not be ignored. Recipients of positive test results were further motivated to remain abstinent by the prospect of future study-related CT scans. There was evidence that some had participated in screening with the intention of stopping smoking. Screening factors often acted in combination with other facilitators, including increasing smoking stigma, and life-stage changes such as becoming a grandparent. Attitudes to cessation support combined with a screening programme were mixed. Some felt they would be deterred from attending screening if they thought they would be targeted with cessation messages. Others were open to the idea of cessation support but doubted whether it could offer cessation strategies they had not already tried. **Conclusion:** Smoking cessation support targeted at lung cancer screening groups should take into account ways that test results can facilitate cessation attempts, and the contributing social and life stage factors of older smokers. Some smokers eligible for screening may be deterred by the prospect of associated cessation interventions. Others who want to quit may have exhausted available cessation strategies and may be seeking something novel to help them quit.

Keywords: Smoking Cessation, Tobacco Control, lung cancer screening

P3.07: IMMUNOLOGY AND IMMUNOTHERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.07-001 OVERCOMING RESISTANCE TO ANTI-PD IMMUNOTHERAPY IN A SYNGENEIC MOUSE LUNG CANCER MODEL USING ADENOVIRUS-MEDIATED GENE THERAPY

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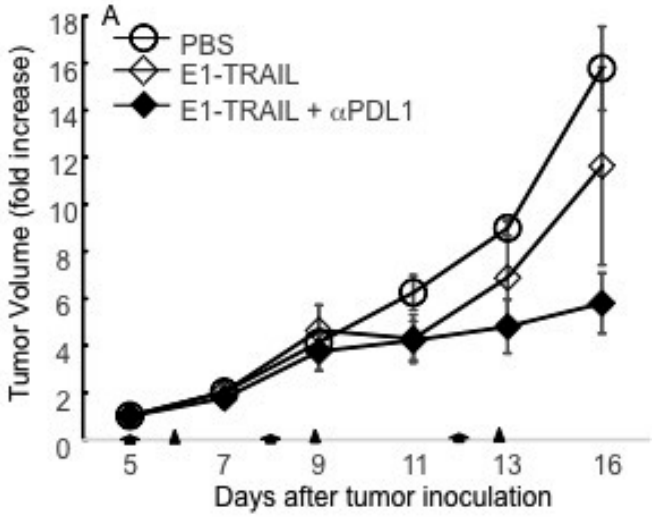
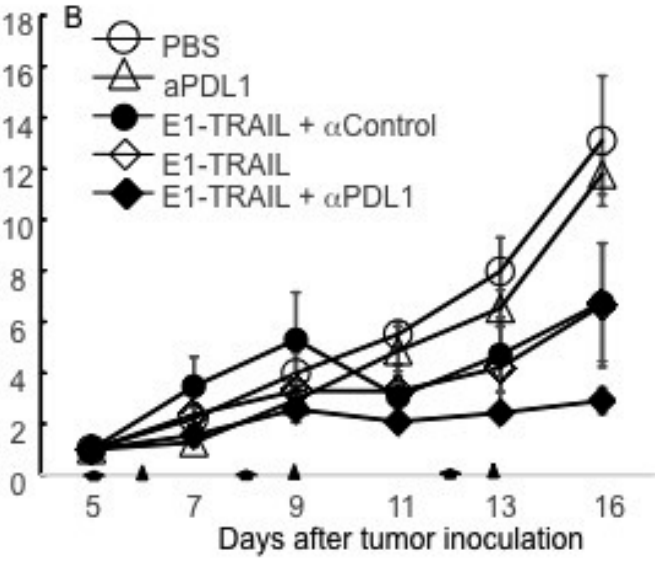
Background: Anti-PD immunotherapy has provided a new therapeutic opportunity for lung cancer. However, overall objective response rates are relatively low in all NSCLC patients who receive anti-PD therapy. We hypothesized that the barrier to the success of anti-PD therapy in most NSCLC patients can be overcome by stimulating the inflammatory response at cancer sites through adenovirus-mediated gene therapy. **Method:** We determined combination effects of anti-PD immunotherapy and oncolytic adenoviral vector-mediated tumor necrosis factor-α-related apoptosis-inducing ligand (TRAIL) gene therapy (Ad/E1-TRAIL) or adenoviral-mediated TP53 (Ad/CMV-TP53) gene therapy in syngeneic mice bearing subcutaneous tumors derived from M109 lung cancer cells. **Result:** Both anti–PD-1 and anti–PD-L1 antibodies failed to elicit obvious therapeutic effects in the M109 tumors. Intratumoral administration of Ad/E1-TRAIL or Ad/CMV-TP53 alone suppressed tumor growth in animals preexposed to an adenovector and bearing subcutaneous tumors derived from M109 cells. However, combining either anti–PD-1 or anti–PD-L1 antibody with these two adenoviral vectors elicited the strongest anticancer activity in mice preexposed to adenoviral vectors.





Conclusion: Our results showed that the mouse lung adenocarcinoma M109 cell line is resistant to anti–PD-1 and anti–PD-L1 antibody treatment, and this resistance can be overcome by adenovirus-mediated gene therapy.

Keywords: de novo resistance, Immunotherapy, Virotherapy

P3.07-002 BLOCKING OF ADAM17 MITIGATES KRAS-INDUCED LUNG ADENOCARCINOMA POSSIBLY VIA INHIBITION OF IL-6 TRANS-SIGNALING

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Background: Lung adenocarcinoma (LAC) accounts for approximately 40% of all lung cancers, the leading cause of cancer death worldwide. Oncogenic *Kras* mutations are a common feature of LAC, although the identity of signaling networks which engage *Kras* to promote LAC remains ill-defined. Moreover, LAC is characterised by dysregulated inflammatory responses, which contribute to tumor promotion and progression. In that regard, we have identified a requirement for interleukin-6 (IL-6) in the molecular pathogenesis of *Kras*-driven LAC. Specifically, this was dependent on the soluble IL-6 receptor (sIL-6R), which is produced by proteolytic cleavage of the membrane-bound IL-6R by a disintegrin and metalloproteinase 17 (ADAM17), also known as the TNFα-converting enzyme (TACE). Although clinical studies indicate that ADAM17 (mRNA and protein) is upregulated in lung cancer and correlate with poor prognosis, the role of ADAM17 in promoting *Kras*-driven LAC remains unknown. Here, we sought to investigate the role of ADAM17 in the pathogenesis of *Kras*-induced LAC. **Method:** We coupled the *Kras*^{G12D} LAC mouse model with *Adam17*$^{ex/ex}$ mice, which are homozygous for a hypomorphic *Adam17* allele resulting in a dramatic reduction in ADAM17 protein expression. Oncogenic *Kras*^{G12D} was activated using intranasal inhalation of Adenovirus Cre recombinase. Mice were culled 6 weeks following inhalation and LAC was evaluated using histopathology (H & E staining). Moreover, immunohistochemical analyses were carried out to assess markers for LAC (TTF-1), proliferation (PCNA) and inflammation (CD45). Serum sIL-6R levels were measured using ELISA. Quantitative PCR was also performed to assess the expression of IL-6 target genes. **Result:** Following *Kras* activation, Adam17$^{ex/ex}$ mice showed significant reduction in the area of lung parenchyma affected by tumor lesions. This was associated with reduced TTF-1 levels and cellular proliferation. Furthermore, reduced ADAM17 expression mitigates the inflammatory response associated with LAC. Serum levels of sIL-6R were significantly reduced in *Adam17*$^{ex/ex}$ mice, with significant down-regulation in IL-6 target genes. **Conclusion:** In conclusion, our data suggests that blocking of ADAM17 may represent an attractive therapeutic target for tackling LAC.

Keywords: ADAM17, IL-6 Trans-signaling, lung adenocarcinoma

P3.07-003 ANALYSIS OF DENDRITIC CELL DERIVED EXOSOMES THAT SUPPRESSED TUMOR GROWTH

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Background: Because dendritic cells (DCs) play a key role in immune reactions to activate T cells against cancer cells by cancer antigen presentation at cellular membrane, DCs have been used in clinical trials as cellular mediators for therapeutic vaccination. It has reported that the exosomes released from vaccinated DCs are responsible for the persistence of antigen presentation. Cancer cells derived exosomes play an immunosuppressive. We considered that whether DCs-derived exosomes could induce suppress cancer cells and more effective response of immune system against cancer with control for the cancer cells-derived exosomes. Because dendritic cells (DCs) play a key role in immune reactions to activate T cells against cancer cells by cancer antigen presentation at cellular membrane, DCs have been used in clinical trials as cellular mediators for therapeutic vaccination. It has reported that the exosomes released from vaccinated DCs are responsible for the persistence of antigen presentation. Cancer cells derived exosomes play an immunosuppressive. We considered that whether DCs-derived exosomes could induce suppress cancer cells and more effective response of immune system against cancer with control for the cancer cells-derived exosomes. **Method:** DCs were generated from bone marrow cells in C57BL/6J by stimulation with GM-CSF and IL-4 mice for 6 days. Murine lung cancer cell line (3LL) was cultured in RPMI1640 medium containing 10%FCS. 3LL cells-derived exosomes and DCs-derived ones were isolated by ultracentrifugation methods and exosomes purification kit (Qiagen). 3LL cells were injected to C57BL/6J mice by intraperitoneal administration. DCs, DCs-exosomes or 3LL-exosmes were weekly administrated to cancer bearing mice. Tumor growth inhibition by exosomes was evaluated measurement of luciferase activity by in vivo image analyzing system. **Result:** DCs and DCs-derived exosomes inhibited lung cancer cell growth, on the other hand, lung cancer derived-exosomes increased in compared with DCs, DCs-exosomes and non-treated. **Conclusion:** For cancer immunotherapy, DC-exosomes and cancer-exosomes play important roles in cancer immune reactions. Further examination, we are going on analyze immunosuppressive molecules possessing cancer cell-derived exosomes, and immune activation molecules in DCs-exosomes.

Keywords: dendritic cells, Immunotherapy, Exosome

P3.07-004 GSDMD IS REQUIRED FOR EFFECTOR CD8+ T CELL RESPONSES TO LUNG CANCER CELL

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Background: Cytotoxic T lymphocytes (CTLs) play a critical role in protection against intracellular pathogens and tumor. To induce target cell death, CTL mainly use two major contact-dependent cytotoxic pathways that are dependent on Fas ligand (FasL) and lytic granules. CTLs eliminate malignantly transformed cells principally by releasing the contents of cytotoxic granules into the immune synapse formed with their target cell. The granule serine proteases, known as granzymes (Gzms), induce apoptosis after they are delivered into the target cell cytoplasm by the pore-forming granule protein perforin. Therefore, we hypothesized that other pore-forming protein, especially those can form pores from within mammalian cells, may be implicated in the target cell killing process of CTL. Since GSDMD is a recently discovered pore-forming protein whose N-terminal domain can insert the inner leaflet of the cell membrane and form extensive pores, we speculate that GSDMD may participate in the CTL attack. GSDMD is a recently discovered pyroptosis executioner in monocyte, whose N-terminal domain can insert the inner leaflet of the cell membrane and form extensive pores. Although the role of GSDMD in the pyroptosis has been clear, the function of GSDMD in other biological system remains elusive. In the present study, we investigated the role of GSDMD during CTL responses to NSCLC cancer cells. **Method:** 3LL and H1299 cells were cultured in RPMI-1640 (HyClone, USA) supplemented with 10% fetal bovine serum, Ovalbumin-expressing 3LL cells (3LL-OVA) were generated by transfection with a lentiviral plasmids harbouring cytosolic chicken ovalbumin. C57BL/6 mice and TCR-transgenic OT-1 mice. Mouse CD8$^+$ T cell isolation and stimulation, Human CD8$^+$ T cell isolation and stimulation, Real-time PCR analysis, Western blot analysis, Immunofluorescence cell staining, Immunohistochemistry, Lentiviral vectors transduction, In vitro cytotoxicity assays, Bioinformatics analysis, **Result:** We showed that GSDMD expression was consistently correlated with CD8$^+$ T cell markers in TCGA cohorts. The expression of GSDMD protein could be detected in the tumor infiltrating lymphocyte. GSDMD cleavage increased both in the OT-1 CTLs and the human activated CD8$^+$ T cells. Moreover, Colocalization of GSDMD with granzymeB was observed in proximity of immune synapse. GSDMD deficiency reduced the cytolytic capacity of human CD8$^+$ T cells. **Conclusion:** These results identified a previously unknown role of GSDMD in CTL and demonstrated that GSDMD is required for an optimal CTL response to lung cancer cell.

Keywords: Immune response, NSCLC, Gasdermin family, GSDMD, CTL

P3.07-005 ACTIVATION OF TOLL-LIKE RECEPTOR-2 PROMOTES PROLIFERATION IN HUMAN LUNG ADENOCARCINOMA CELLS

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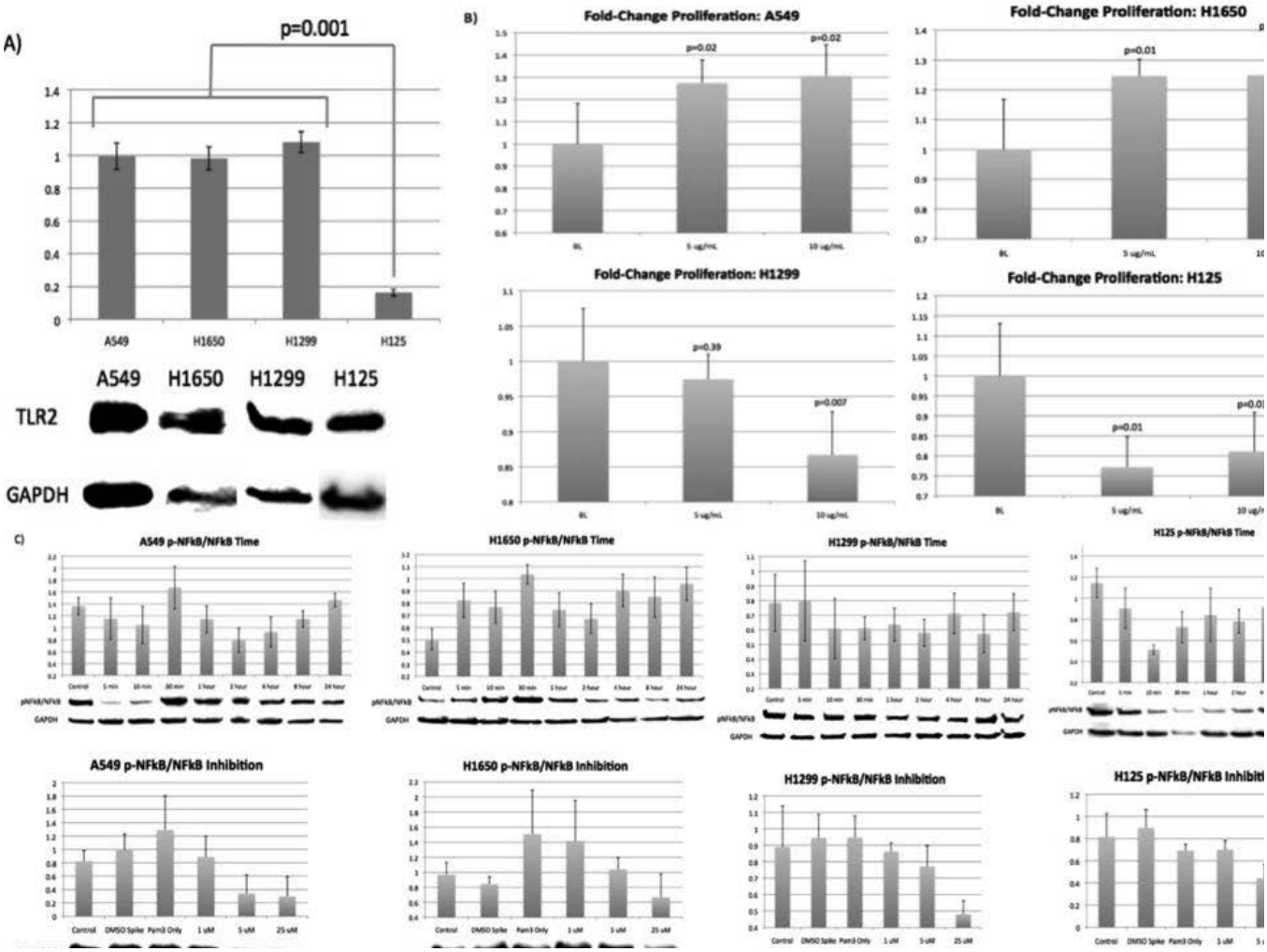
Background: Toll-like receptors (TLR) have been implicated in tumor progression by affecting the immune response in the tumor microenvironment. The role of these receptors in the growth and proliferation of human lung cancer cells is not known. We analyzed human lung cancer cells for the presence of TLR-2, their proliferation response to a TLR-2 agonist and the role of NFkB in TLR-2 activation. **Method:** Human non-small cell lung cancer (NSCLC) cell lines A549 and 1650 (adenocarcinoma), H1299 metastatic NSCLC and H125 adenosquamous were cultured using standard techniques. Standard Western blotting techniques determined baseline TLR-2 protein levels. Cells were treated with Pam3CSK4, a specific agonist of TLR-2, at doses of 0ug/ml, 5ug/ml, and 10ug/ml for 72 hours, and then the MTS assay was used for proliferation assessment. All cell lines were treated with 10 ug/ml Pam3CSK4 for 48 hours and Western blot analysis determined the level of increase in NFkB phosphorylation. Cells were treated with NFkB inhibitor, Bay11-7082, at doses of 1 uM, 5 uM and 25 uM with concomitant treatment of 10 ug/ml Pam3CSK4 over 5 hours. NFkB inhibition was evaluated by Western blot analysis. **Result:** Protein analysis demonstrated consistently detectable levels of TLR-2 in each cell line (Fig 1a). Proliferation was significantly promoted after Pam3CSK4 treatment in human lung adenocarcinoma cell lines ($p=.03$), but not in the other cell lines ($p<0.05$) (Fig 1b). NFkB phosphorylation was increased with TLR2-agonist treatment in adenocarcinoma, decreased in non-adenocarcinoma cells and decreased with specific inhibition of NFkB subunit p65 (Fig1c).



Conclusion: TLR-2 is consistently present and detectable on human lung adenocarcinoma cells. TLR-2 activation results in increased proliferation in human lung adenocarcinoma cells and this effect appears to be specific to adenocarcinoma cells. These effects are dependent on the NFkB signaling pathway. These findings may suggest TLR-2 to be a possible therapeutic target in human lung cancer.

Keywords: lung adenocarcinoma, Tumor immunology, Toll-like receptor

P3.07: IMMUNOLOGY AND IMMUNOTHERAPY - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.07-006 PEMETREXED EXERTS INTRATUMOR IMMUNOMODULATORY EFFECTS AND ENHANCES EFFICACY OF IMMUNE CHECKPOINT BLOCKADE IN MC38 SYNGENEIC MOUSE TUMOR MODEL

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Background: Pemetrexed is a well-known folate pathway inhibitor that is used in the treatment of non-small cell lung cancer (NSCLC) and mesothelioma. Folate pathway is also known to play a critical role during T cell activation. However, the role of pemetrexed in modulating antitumor T cell-mediated immune response is largely unknown. Recent clinical data for cohorts C and G in the KEYNOTE-021 trial revealed compelling activity of pemetrexed-based chemotherapy in combination with PD-1 antibody (pembrolizumab) in NSCLC patients suggesting a potential positive interaction between these two therapeutic modalities. The objective of the present study was to understand the effects of pemetrexed on tumor immune microenvironment and evaluate its efficacy in combination with PD-1 pathway inhibition. **Method:** C57BL/6 mice bearing syngeneic MC38 tumors were treated with pemetrexed with or without platinum agents (cisplatin, carboplatin). Immune cell subsets and immune-related gene expression changes in MC38 tumor tissue were assessed by flow cytometry and Quantigene Plex assay, respectively. Pemetrexed-related effects on energy metabolism were evaluated by Agilent Seahorse XF analysis. Anti-mouse PD-L1 antibody 178G7 was used to evaluate effects of pemetrexed in combination with anti-PD-L1 on MC38 tumor growth. **Result:** Treatment with pemetrexed resulted in an increased frequency of intratumoral leukocytes and T cells accompanied by upregulation of immune-related genes indicative of enhanced antigen presentation and T cell infiltration and/or activation. Immune gene expression signature induced by pemetrexed was largely unaffected by cisplatin or carboplatin. The results of Seahorse XF analysis suggested changes in the bioenergetics of T cells exposed to pemetrexed. Combination of pemetrexed and anti-PD-L1 significantly delayed MC38 tumor growth whereas single agent treatments were largely ineffective. **Conclusion:** Pemetrexed exerts positive effects on the intratumor T cell-mediated immune response independently of platinum agents, and enhances effects of PD-L1 antibody in MC38 syngeneic mouse tumor model.

Keywords: pemetrexed, immunotherapy, PD-1

P3.07-007 BLOCKADE OF THE COMPLEMENT C5A/C5AR1 AXIS IMPAIRS LUNG CANCER BONE METASTASIS

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Background: The complement system, a central part of innate immunity, is implicated in the maintenance of a favorable microenvironment for lung cancer progression. In particular, several studies have demonstrated a tumor-promoting role for the immune regulator C5a, but its direct impact on growth and dissemination of lung cancer cells is poorly understood. In this study we aimed to investigate the contribution of the C5a/C5aR1(CD88) axis to the malignant phenotype of NSCLC cells, particularly to skeletal colonization, a preferential lung metastasis site. **Method:** The association between C5aR1 expression and clinical outcome was assessed at both the mRNA and protein levels by *in silico* and immunohistochemistry analyses, respectively. The mRNA levels of C5aR1 were also determined in a panel of 45 cell lines representing the main lung cancer subtypes. The expression of the receptor was validated by flow cytometry. The functional significance of C5aR1 expression in NSCLC cells was evaluated using lentiviral gene silencing and drug inhibition in *in vivo* models of lung cancer bone metastasis. *In vitro* functional assays for signaling, migration, invasion, metalloprotease activity and osteoclastogenesis were also performed. **Result:** High levels of C5aR1 in primary human NSCLC tumors were significantly associated with shorter recurrence-free survival and overall survival both at the mRNA and protein levels. Many lung cancer cell lines expressed C5aR1 mRNA. C5aR1 was also detected by flow cytometry on the cell surface of representative lung cancer cell lines. Moreover, addition of C5a to cultured cells led to phosphorylation of p42/44 MAPK and translocation of NF-kB to the nucleus, demonstrating the functionality of the receptor. Silencing of C5aR1 in A549 and H460 lung cancer cells did not affect proliferation, but led to a substantial reduction in skeletal metastatic burden and osteolysis in *in vivo* models. C5aR1 pharmacological blockade also reduced the osseous metastatic activity of lung cancer cells *in vivo*. Moreover, metalloproteolytic, migratory and invasive tumor cell activities were modulated *in vitro* by C5aR1 stimulation or gene silencing. This effect was associated with decreased osteoclastogenic activity *in vitro*, which was rescued by exogenous addition of the chemokine CXCL16. **Conclusion:** Disruption of C5aR1 signaling in lung cancer cells abrogates osseous colonization through a CXCL16-mediated mechanism. This study reinforces the role played by the C5a/C5aR1 axis in lung cancer progression, and supports its potential use as a novel therapeutic target.

Keywords: bone metastasis, Complement system, C5a

P3.07-008 DEVELOPMENT OF IMMUNOMONITORING ASSAYS FOR DENDRITIC CELL-BASED LUNG CANCER IMMUNOTHERAPY

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Background: Allogeneic cancer cell lines might serve as a universal source of tumor antigens in the development of dendritic cell-based cancer vaccines. We showed that selected antigenic profile of lung cancer cell lines overlaps with antigenic profile of primary non/small cell lung cancer (NSCLC) tumors. However, it is unclear if T cells responses to all of these antigens can be detected in blood of NSCLC patients. **Method:** Peripheral blood mononuclear cells (PBMCs) of NSCL patients were stimulated and re-stimulated by commercially available mixes of antigenic peptides derived from these antigens over the course of 10 days. Tumor antigen-specific $CD8^+$ and $CD4^+$ T cells were characterized by IFN-γ production, granzyme B, perforin, an d CD137 or CD154 expression by flow cytometry. In addition, the expression of inhibitory molecules TIM3, CTLA-4, PD-1 and LAG-3 were evaluated on $CD8^+$ and $CD4^+$ T cells from PBMC of NSCLC patients. We further analysed 6 populations of myeloid-derived suppressor cells (MDCS) by a multicolor flow cytometry and their possible functional suppression by qPCR analysis of ARG1 and iNOS expression in PBMC and downregulation of CD3zξ in T cells from patient's PBMCs compared to T cells from PBMCs of healthy donors. **Result:** We were able to detect tumor antigen-specific IFN-γ, Granzyme B and Perforin producing $CD8^+$ and $CD4^+$ T cells as well as expression of inhibitory molecules TIM3, CTLA-4, PD-1 and LAG-3. We were also able to detect populations of MDSCs in blood of NSCLC patients as well as healthy donors. **Conclusion:** This data will allow us to develop a protocol for immunomonitoring studies of the effectivity of dendritic cell-based lung cancer immunotherapy in ongoing phase I lung cancer clinical trial (NCT02470468).

Keywords: immunomonitoring, DC-based vaccine, Tumor antigens

P3.07-009 PI3K/MTOR PATHWAY ALTERTIONS MAY MEDIATE PD-1/PD-L1 BLOCKADE RESISTANCE IN NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors have changed the clinical practice for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) as the first line or second line therapies. Although PD-1/PD-L1 blockade has been demonstrated as a promising anti-tumor therapy with significant clinical benefits, the fact of acquired resistance after a response to PD-1/PD-L1 blockade has become a common concern. The mechanism underlying acquired resistance to immune checkpoint inhibitors have remained unclear. **Method:** FFPE samples from 127 Chinese NSCLC patients were collected, including 103 (81.1%) adenocarcinoma, 21 (16.5%) squamous cell carcinoma, 2 (1.6%) adenosquamous carcinoma and 1 (0.8%) large cell carcinoma. Comprehensive genomic profiling (CGP) assay with 450 genes whole exon region were performed for 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. We considered high TMB as over 80% of the 500 patient TMB distrbutions from our inhouse cancer database across solid tumor types. **Result:** 32 patients with higher TMB values were collected from 127 Chinese NSCLC patients. Interestingly, we identified the frequency of PI3K/mTOR pathway genes (*AKT1, FBXW7, PIK3CA, PTEN, TSC1/2, STK11* and *mTOR*) was significantly higher in patients with high TMB value (28.1% vs 10.5%, p=0.033). Moreover, PI3K/mTOR pathway alterations existed in 3 patients who initially responded to PD-1/PD-L1 blockade and then were resistant to immune checkpoint inhibitors. Two patients with *PIK3CA* K111N and *FBXW7* R465H have started to receive mTOR inhibitor everolimus mono therapy after 6 cycle nivolumab or pembrollizumab treatments. So far both showed stable disease or minor shrinkage on tumor. More investments are under way. **Conclusion:** In our study, PI3K/mTOR pathway alterations occurred more frequently in the NSCLC patients with higher TMB values. Several PD-1/PD-L1 blockade resistance patients harbored PI3K/mTOR mutations showed responses. The activation of PI3K/mTOR pathway might mediate the acquired resistance to immune checkpoint inhibitors. This finding suggested that mTOR inhibitors might be a potential strategy for those who harbored mutations in PI3K/mTOR pathway after the resistance of PD-1/PD-L1 blockade therapies.

Keywords: PD-1 blockade, Resistance

P3.07-010 IMMUNOTHERAPIES EVALUATION IN AN EX-VIVO CULTURE MODEL OF NSCLC

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Background: NSCLC induces pro-tumorigenic immunosuppressive changes to evade the immune system. Response of tumors to therapy, including immunetherapy, depends on active interactions of epithelial tumor cells and the microenvironment. Ex vivo organ culture (EVOC) models directly established from fresh NSCLC tumor tissues can be used as a complete model that resembles real tumors and their microenvironment. Little is known about the impact of drugs such as chemotherapy, radiotherapy or targeted agents on the expression and activity of the PD1-PDL1 signaling molecules in human cancers. Combining such treatments with immunotherapy seems a promising approach that is actively investigated. **Method:** An EVOC model of NSCLC was established to study the impact of anti-PD-(L)1 agents in NSCLC. Anti-PD-(L)1 were tested alone or in combination with chemotherapy or with radiotherapy. Response to treatment was evaluated by LDH release, expression of linage-specific genes, and H&E staining. **Result:** Our results demonstrate the applicability of EVOC as a model of immunotherapy in lung cancer. Specifically, tumor and stromal cells are maintained over a time window of several days and cell death is seen in response to cytotoxic and immunotherapy drugs. PDL1 is induced in response to inflammation signals (e.g. IFNγ) and reduced in response to steroids. Variability in PDL-1 expression is seen between EVOCs from different patients. Anti-PD-1 (pembrolizumab and nivolumab), anti-PD-L1 (durvalumab), anti-CTLA4 (ipilimumab) and combinations of these drugs with chemotherapy agents were tested, in some specimens significant responses were seen. **Conclusion:** EVOC of NSCLC is a valid model of cancer, allowing evaluation of the efficacy of immunotherapies alone or in combination with other drugs. This model is promising as a tool for optimizing immunotherapy treatments for NSCLC.

Keywords: EX-VIVO, Immunotherapy, model

P3.07-011 INVESTIGATION OF AUTOLOGOUS TUMOR-KILLING EFFECT OF EFFUSION-ASSOCIATED LYMPHOCYTES IN MALIGNANT PLEURAL EFFUSION OF LUNG CANCER

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Background: Many lung cancer patients developed malignant pleural effusion during the course of the disease. Previous studies revealed that the effusion associated lymphocytes (EAL) were in dysfunctional state which appeared to be immunosuppressed and unable to kill tumor cells. This study will evaluate the combined effects of IL-2, IL-12, αCD3 antibody (ab), and PD-1 ab on antitumor activity of lymphocytes. The underlying mechanism and relevant immune biomarkers will also be investigated. **Method:** We choose the malignant pleural effusion from lung cancer patients to analyze the association among lymphocytes, cancer cells, and cytokines in order to realize the lymphocyte immunity in the malignant pleural effusion of lung cancer patients. Flow cytometry was used to determined lymphocyte subpopulation. The Proliferation assay was performed to evaluate the effect of medication on lymphocytes. ELISA was used to evaluate cytokine level. Cell-mediated cytotoxicity assay was performed to evaluate the tumor-killing effect of EAL. **Result:** EAL were isolated from 21 malignant pleural effusions. Lymphocyte subpopulation was determied by flow cytometry, and total lymphocytes were composed of 8.9% exhausted T cells (CD3+/CD8+/ PD-1+), and 27.8% PD1+ NK cells. IL-2+αCD3 ab+pembrolizumab has demonstrated the trend toward to enhance the proliferation of EAL. IL-2+αCD3 ab or IL-2+IL-12+αCD3 ab or IL-2+IL-12+αCD3 ab+pembrolizumab demonstrated the trend for EAL to produce more IFN-γ. IL-2+αCD3 ab or IL-2+IL-12+αCD3 ab demonstred the trend for EAL to produce more IL-10. IL-2+αCD3+pembrolizumab did not demonstrated the trend for EAL to produce more IL-10. The addition of IL-2+αCD3 ab or IL-2+pembrolizumab showed the trend toward increased EAL cytolytic activity against autologous tumors (effector:target cells= 30:1). The addition of IL-2+αCD3 ab did not show the trend toward increased EAL cytolytic activity against autologous tumors in different conditions (effector:target cells= 10:1). The addition of IL-2+αCD3 ab or IL-12+αCD3 ab or IL-2+IL-12+αCD3 ab showed the trend toward increased EAL cytolytic activity against autologous tumors (effector:target cells= 3:1). **Conclusion:** The depressed cellular function of EAL may be potentially reversed with multiple signal stimulation, including IL-2 plus αCD3 ab, IL-2 plus pembrolizumab, IL-12 plus αCD3 ab or IL-2 plus IL-12 and αCD3 ab. Further studies are warranted in order to confirm the synergistic cytotoxicity effect of cytokines plus PD-1 inhibitors.

Keywords: lung cancer, programmed cell death protein-1, Effusion-associated lymphocyte

P3.07-012 NIVOLUMAB VERSUS DOCETAXEL IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED NON-SMALL CELL LUNG CANCER AND LIVER METASTASES

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Background: Patients with non-small cell lung cancer (NSCLC) who have metastasis to the liver have poor prognosis. The phase 3 trials CheckMate 017 and 057 demonstrated improved overall survival (OS) and a favorable safety profile with nivolumab, an anti-programmed death-1 antibody, versus docetaxel in patients with previously treated advanced squamous and non-squamous NSCLC, respectively. A prior subgroup analysis from these trials evaluated and demonstrated efficacy and safety with nivolumab in patients with asymptomatic central nervous system metastases (Goldman J. ASCO 2016). Here we report subgroup analyses from these trials of patients with baseline liver metastases. **Method:** In both trials, patients were randomized 1:1 to nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks until progression or discontinuation. The primary endpoint of each study was OS. Patients from CheckMate 017 and 057 with baseline liver metastases reported as either target or non-target lesions were identified and pooled across studies by treatment. **Result:** Baseline characteristics were generally similar between patients with liver metastases randomized to nivolumab (n=99) and docetaxel (n=94). In the nivolumab group, 26% of patients had squamous and 74% had non-squamous NSCLC; in the docetaxel group, 36% had squamous and 64% had non-squamous NSCLC. The minimum follow-up was 24.2 months (Feb 2016 database locks). Nivolumab resulted in improved OS compared with docetaxel in patients with liver metastases (hazard ratio [HR]=0.68; 95% confidence interval [CI]: 0.50, 0.91), similar to findings from the ITT group (HR=0.72; 95% CI: 0.62, 0.84). Median OS in patients with liver metastases was 6.83 months with nivolumab versus 5.93 months with docetaxel, both of which were lower than those observed in the overall pooled intent-to-treat (ITT) population (11.14 months vs 8.11 months). Two-year OS rates were 18% with nivolumab versus 6% with docetaxel in patients with liver metastases. Rates of grade 3–4 treatment-related adverse events in patients with liver metastases were lower with nivolumab compared with docetaxel (7% vs 53%), and similar to those in the ITT population (10% vs 55%). **Conclusion:** The lower median OS observed in this subgroup of patients with previously treated advanced NSCLC and baseline liver metastases corroborates previous findings that metastasis to the liver is an unfavorable prognostic factor. However, nivolumab demonstrated sustained OS benefit versus docetaxel in these patients, similar to the ITT population. The safety profile of nivolumab was favorable versus docetaxel in this subgroup, with no new safety concerns identified.

Keywords: Nivolumab, non-small cell lung cancer

P3.07-013 COST-EFFECTIVENESS OF IMMUNE CHECKPOINT INHIBITORS IN THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer related death worldwide. Late diagnosis and poor prognosis of advanced cancer are considered to be the main causes for the high mortality rates in NSCLC. Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD1) demonstrated substantial improvements in overall survival (OS) compared with chemotherapy in previously treated patients with advanced NSCLC. However, the annual therapy costs are high (>EUR100,000 in Germany). The objectives of this study are to assess the cost-effectiveness of nivolumab and pembrolizumab in previously treated patients with advanced NSCLC from the perspective of the German statutory health insurance. **Method:** We developed a microsimulation model (discrete event simulation) to simulate the results of clinical trials and to extrapolate outcomes beyond the study duration. Clinical input parameters were gathered from published trial data (CheckMate017, CheckMate057, KEYNOTE-010). Kaplan-Meyer curves of progression free survival and OS were digitally reconstructed and survival analyses were conducted to inform model survival parameters. Utilities and cost data were extracted from published literature and German price databases. Cost-effectiveness analysis was performed for various PD-L1 expression levels. In each scenario, a Monte Carlo simulation with 10,000 iterations was performed to capture parameter uncertainty. **Result:** Additional cost per quality adjusted life year (QALY) gained of nivolumab vs. docetaxel in squamous-cell NSCLC, nivolumab vs. docetaxel in nonsquamous-cell NSCLC and pembrolizumab vs. docetaxel were EUR132,248 (EUR113,483 - EUR156,045), EUR197,187 (EUR171,718 - EUR228,407) and EUR208,652 (EUR182,492 - EUR237,161) respectively (table 1). Treating only patients with PD-L1-positive tumors substantially reduced additional costs per QALY gained for nivolumab in nonsquamous-cell NSCLC and for pembrolizumab but the incremental cost-effectiveness ratio still considerably exceeded EUR100,000 per QALY.

Table 1: Incremental cost-effectivenss ratio* (ICER) of PD1-inhibitors nivolumab and pembrolizumab in previously treated patients with advanced NSCLC**

	nivolumab vs docetaxel nonsquamous-cell NSCLC**	nivolumab vs docetaxel squamous-cell NSCLC**	pembrolizumab vs. docetaxel NSCLC**
additional cost per life year gained			
all patients	EUR112,304 (EUR104,241 - EUR121,369)	EUR79,979 (EUR74,644 - EUR89,082)	EUR114,507 (EUR106,711 - EUR123,480)
PD-L1 expression level ≥ 5%	EUR90,742 (EUR82,871 - EUR99,976)	EUR80,250 (EUR72,290 - EUR93,435)	-
PD-L1expression level ≥ 10%	EUR85,854 (EUR77,730 - EUR94,779)	EUR93,932 (EUR83,802 - EUR107,220)	-
PD-L1 proportion score ≥ 50%	-	-	EUR107,011 (EUR96,842 - EUR120,704)
additional cost per quality adjusted life year (QALY) gained			
all patients	EUR197,187 (EUR171,718 - EUR228,407)	EUR132,248 (EUR113,483 - EUR156,045)	EUR208,652 (EUR182,492 - EUR237,161)
PD-L1 expression level ≥ 5%	EUR159,974 (EUR134,207 - EUR196,740)	EUR131,321 (EUR104,742 - EUR166,697)	-
PD-L1expression level ≥ 10%	EUR156,086 (EUR127,886 - EUR194,042)	EUR136,073 (EUR110,322 - EUR176,364)	-
PD-L1 proportion score ≥ 50%	-	-	EUR188,944 (EUR161,336 - EUR227,125)

* discount rate 3%; 2.5% and 97.5% quantiles of Monte Carlo simulation in brackets; ** NSCLC: non-small cell lung cancer

Conclusion: PD1-inhibitors nivolumab and pembrolizumab are likely not cost-effective in previously treated patients with advanced NSCLC, even in patients with substantial PD-L1 expression, at current price levels in Germany.

Keywords: advanced NSCLC, Cost-effectiveness, Immune checkpoint inhibitors

P3.08-001 CONCURRENT CHEMORADIOTHERAPY WITH WEEKLY CARBOPLATIN-PACLITAXEL MAY BE FEASIBLE OPTION IN INOPERABLE STAGE III NSCLC

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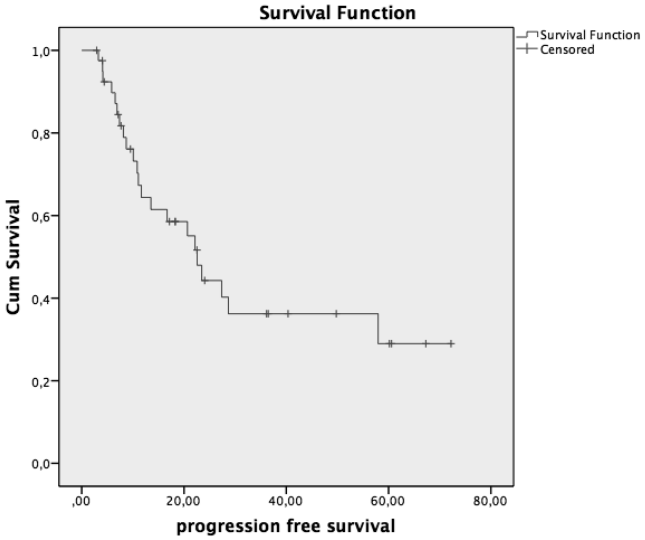
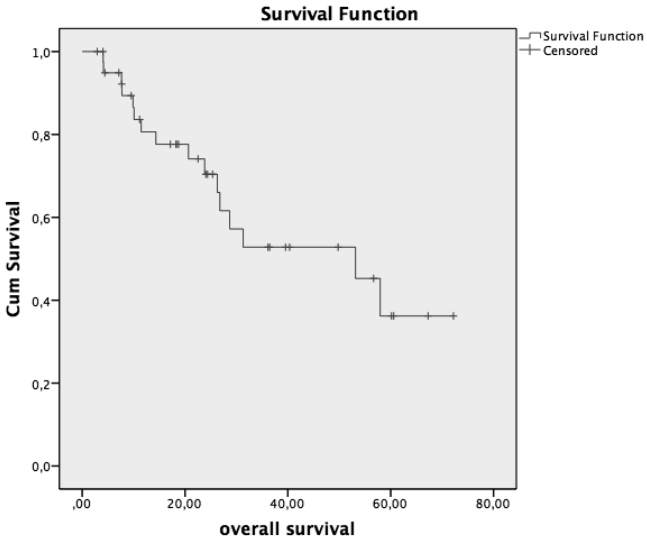
Background: Concurrent chemoradiotherapy (CCRT) is standard treatment modality for patients with unresectable stage III NSCLC disease. TIn this study, we aimed to investigate the efficacy and toxicity of CCRT with carboplatin (AUC 2) and paclitaxel (80 mg/m2) during radiotherapy. **Method:** Medical records of 41 patients with inoperable stage III NSCLC treated with concurrent chemoradiotherapy with carboplatin-paclitaxel were retrospectively analyzed. Carboplatin (AUC 2) and Paclitaxel (80 mg/m2) from peripheral route were administered weekly during radiotherapy **Result:** 41 consecutive unresectable stage IIIA-B NSCLC patients treated with CCRT were included into this study. Median age was 62 years old (range 40–77), and 37 (90.2%) of the patients were men. ECOG performance score was 0 in 23 patients (56.1%). Adenocarcinoma, the most common histology, was diagnosed in 18 patients (43.9%). There were 11 (26,8%) stage IIIA patients and 26 (63.4%) stage IIIB patients. Median follow-up time was 22.5 months. Median PFS and OS were 22.5 and 53.5 months. Hematological and non-hematological grade 3–4 toxicities were seen in 8 (19,5%) and 5 (12.2%) patients, respectively.





Conclusion: This study showed that carboplatin-paclitaxel provides results similar to that in the literature survival parameters and it may be an option with lower toxicities for CCRT in patients with unresectable stage III NSCLC.

Keywords: lung cancer, carboplatin-paclitaxel, Chemoradiotherapy

P3.08-002 LYMPHOVASCULAR INVASION IS NOT A POSTOPERATIVE PROGNOSTIC FACTOR FOR LARGE-SIZED LUNG CANCER

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Background: Numerous studies about small-sized lung cancer have been published recently. On the other hand, few studies have considered large-sized tumors. In this study we analyzed the prognostic factors for tumors that measured 5 cm or more. **Method:** Of the 547 patients who underwent resection of the lung due to primary lung cancer in our institution between 2002 and 2011, 90 had tumors that measured 5 cm or more. Among these 90 patients, 43 were adenocarcinomas, 32 were squamous cell carcinomas, 68 were male, and 14/26/1 cases were pathological N1/2/3, respectively. The average age was 70.1±8.9 years, and the average tumor diameter was 6.7±1.9 cm. Age at operation, gender, tumor location, operative method, tumor size, nodal status, lymphatic permeation, vascular invasion, pleural invasion (pl), preoperative pulmonary function status, serum carcinoembryonic antigen level, smoking status, and Charlson comorbidity index were analyzed using a Cox proportional hazards model to identify the postoperative prognostic factors. **Result:** In a univariate analysis, tumor size of 7 cm or more (p = 0.03), pathological N status of N2 or more (N0 vs. N2/3: p = 0.03), pl3 (pl0 vs. pl3: p=0.02), and < 80 (p=0.04) were found to be associated with a poor postoperative overall survival (OS). Lymphatic permeation (p = 0.66), and vascular invasion (p=0.10) were not significantly associated with OS. A multivariate analysis was performed using the 4 factors that were associated with a poor OS in the univariate analysis. As a result, tumor size of 7 cm or more (p < 0.01), pathological N status of N2 or more (N0 vs. N2/3: p < 0.01), and pl3 (pl0 vs. pl3: p=0.01) were independently associated with a poor OS. **Conclusion:** For large-sized lung cancer, tumor size, nodal status and pleural invasion were related to OS, whereas lymphovascular invasion was not.

Keywords: lymphovascular invasion, Large-sized lung cancer, Surgery

P3.08-003 MULTIMODAL TREATMENT IN THE INITIALLY INOPERABLE STAGE III N2 NON-SMALL CELL LUNG CANCER PATIENTS

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Background: A multimodal treatment is frequently performed in many initially inoperable stage III N2 non-small cell lung cancer. However, selection of the best treatment for these patients is controversial issue. This study was conducted to explore the benefit of neoadjuvant chemotherapy and adjuvant therapy in these patients. **Method:** Between Jan. 2008 and Dec. 2015, patients with stage III N2 NSCLC enrolled. All of them were treated with induction chemotherapy and surgical resection. Some of them who had high risk factors for disease recurrence underwent adjuvant treatment including chemothearpy, radiothearpy or concurrent chemoradiotherapy.We reviewed medical record including clinicopathologic characteristics and the survival outcome. **Result:** The median age was 65 (range 43-77), and male was more common (M:F, 3.8:1). Median follow-up period was 23.6 months (Range: 3.0-23.6 months). 32 patients (59.%) presented with squamous cell cancer (SqCC), and 20 patients (37.0%) were presented as adenocarcinoma. Docetaxel/cisplatin in 52 patients (96.3%) and gemcitabine/cisplatin in 2 patients (3.7%) were selected as neoadjuvant chemotherapy regimen. The overall clinical response rate to induction chemotherapy was 70.4%. After surgical resection, 27 patients (50.0%) underwent adjuvant chemotherapy alone and 20 patients (37.0%) underwent adjuvant radiotherapy with or without chemotherapy. Median OS was 56.4 months (range 33.5-79.3 months) and median PFS was 24.4 months (ranage 26.6-43.0 months). In multivariable analysis, the adjuvant treatment group showed better survival than the no adjuvant treatment group. Among them, median OS was not reached in adjuvant radiotherapy with or without chemotherapy group and 53.9 months in the adjuvnat chemotherapy alone group (p=0.016). **Conclusion:** Neoadjuvant chemotherapy is active in patients with stage III N2 NSCLC and adjuvant multimodal therapy including chemotherapy or radiotherapy demonstrated favorable survival outcomes. Based on our data, active multimodal neoadjuvant and postadjuvant treatment should be considered for the initially unoperable stage III N2 NSCLC patients.

Keywords: non-small cell lung cancer, Adjuvant treatment, neoadjuvant chemotherapy

P3.08-004 PHASE I/II TRIAL OF NAB-PACLITAXEL OR PACLITAXEL PLUS CARBOPLATIN WITH CONCURRENT RADIATION FOR INOPERABLE STAGE IIIA/B NSCLC

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Background: To determine the overall survival of Nab-Paclitaxel (Nab) or Paclitaxel (P) plus Carboplatin (C) with concurrent radiation therapy (RT) followed by consolidative chemotherapy (CT) with Nab-C or PC for patients (pts) with Stage IIIA/B Non-small cell lung cancer (NSCLC) when compared to historical controls and to assess for the safety of each regimen to guide further investigation **Method:** This phase I/II trial randomized 98 pts (6 pts phase I; 92 pts phase II). 75 pts were eligible for analysis on the phase II portion. For the phase I portion, weekly 50mg/m^2 of Nab and C AUC 2 was administered with concurrent thoracic RT (60-66 Gy) followed by CT comprising 100mg/m^2 Nab on days 1,8,15 (of a 21 day cycle) and C AUC 6 on day 1 for 2 cycles. For the randomized phase II portion, patients received either arm A) weekly 50mg/m^2 P and C AUC 2 or arm B) weekly 40mg/m^2 of Nab and C AUC 2 with concurrent RT followed by consolidative 200mg/m^2 P and C AUC 6 every three weeks for 2 cycles or 100mg/m^2 Nab on days 1,8,15 (of a 21 day cycle) and C AUC 6 on day 1 for 2 cycles. The primary end point was 2-year overall survival of 50% or greater. **Result:** Median follow up was 14.3 months. 2 patients experienced dose-limiting toxicities on the phase I portion as defined per protocol (grade 3 febrile neutropenia and grade 4 thrombocytopenia) leading to a dose reduction of concurrent Nab from 50mg/m^2 to 40mg/m^2 for the phase II portion. On the Phase II portion, Grade 3+ esophagitis was 3 and 2 pts, Grade 3+ pneumonitis was 3 and 5 pts and Grade 4+ hematological adverse events was 3 and 8 pts on A and B arms respectively. The 1- and 2-year overall survival rates for arm A and B were 80.6% (95%CI 63.4-90.3) and 69.2% (51.2-81.7); and 72.5% (48.4-86.8) and 56.5% (33.7-74.1) respectively. The 1- and 2-year progression free survival were 57.5% (38.7-72.5) and 46.1% (29.2-61.5); and 45.5% (24.7-64.3) and 20.7% (6.5-40.3) for arm A and B respectively. **Conclusion:** For pts with locally advanced Stage IIIA/B NSCLC, both arms A and B provided 2-year overall survival rates greater than 50%. The addition of Nab to chemoradiation was overall well tolerated, prompting potential interest going forward. Further analyses of quality of life measurements are currently underway. This project was supported by Celgene. Clinical Trial information: NCT01757288

Keywords: non-small cell lung cancer, Concurrent Chemoradiation, nab-paclitaxel

P3.08: LOCALLY ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.08-005 HEREDITARY FAMILIAL OVERLAP SYNDROME WITH MULTIPLE SYNCHRONOUS LUNG TUMORS

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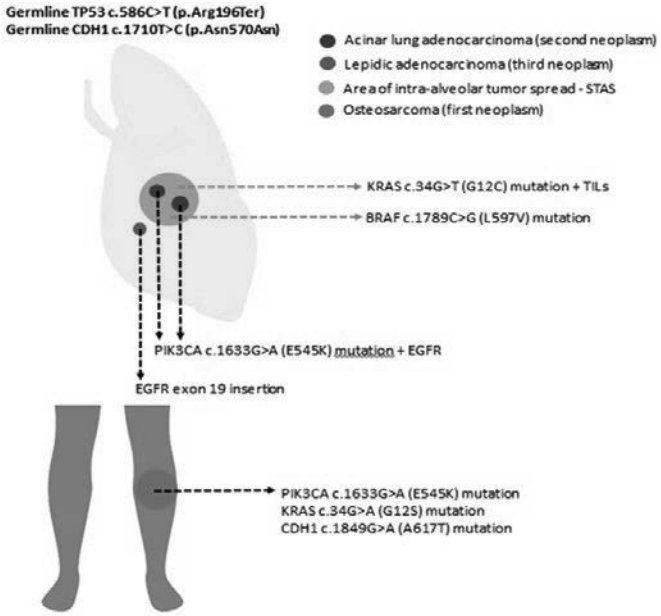
Background: Here we report the case of a young, never-smoker Hispanic woman with a hereditary familial overlap syndrome (*Li-Fraumeni* plus CDHI) who develop synchronous multiple primary lung adenocarcinomas related to Intra-alveolar Tumor Spread (STAS) several years after the diagnosis of a locally advanced lower limb osteosarcoma. **Method:** Comprehensive genomic profiling by next generation sequencing (NGS) was performed on 90 cancer-related genes over each lung lesion (including two nodules of acinar adenocarcina, one lepidic spread tumor and in STAS area). In the same way, the broad genomic analysis was performed in archival tissue from the previous bone tumor. **Result:** Lung tumors were found to harbor PI3KCA (invasive lesions) and a rare in-frame insertion of 6 amino acids in exon 19 of EGFR (lepidic tumor), STAS area showed KRAS and BRAF mutations in two different segments, and osteosarcoma tested positive for well known PIK3CA, KRAS and CDH1 alterations. **Conclusion:** This unique case raises practical questions as to the challenges of molecular testing and highlights the potential association of germline p53 and CDH1 mutations with concurrent somatic alterations that elucidate the basis of tumor heterogeneity.



Keywords: li-fraumeni, EGFR, next-generation sequencing

P3.08: LOCALLY ADVANCED NSCLC -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.08-006 TREATMENT RESPONSE AND SURVIVAL OUTCOMES ARE ASSOCIATED WITH HISTOLOGIC TYPE IN NON-SMALL CELL LUNG CANCER TREATED WITH TRIMODAL TREATMENT

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Background: Trimodal treatment incorporating neoadjuvant concurrent chemoradiotherapy (CCRT) and surgical resection is one of the treatment strategies for non-small cell lung cancer (NSCLC) patients with N2 disease. Although pathologic phenotypes as well as biological features might be different between adenocarcinoma (ADC) and squamous cell carcinoma (SqCC), histologic type has been rarely considered when selecting treatment strategy in patients with N2 disease. The aim of this study is to investigate if histologic type is associated with treatment response and survival outcomes in patients undergoing trimodal treatment for N2 disease. **Method:** A retrospective review of patients with N2 disease who underwent neoadjuvant CCRT followed by surgery at our institution was performed. Clinicopathologic features, response to CCRT, and survival outcomes were compared between ADC and SqCC. **Result:** From 2003 to 2013, 374 patients underwent curative-intent surgery after neoadjuvant CCRT for either ADC (n=233, 62.3%) or SqCC (n=141, 37.7%) with pathologically proven N2 disease. Sixty-nine patients (18.5%) had bulky and/or multi-stationed N2 diseases on pre-CCRT imaging tests. There were more male, more smokers, more advanced clinical T and N stages, and more bulky and/or multi-stationed N2 diseases in the SqCC group than in the ADC group. Conversely, the SqCC group had more radiologic responders, earlier pathologic T and N stages, more pathologic complete responders, and more frequent mediastinal downstaging than the ADC group. With a mean follow-up of 50.1 months, patients with SqCC showed significantly better 5-year recurrence-free survival than those with ADC (ADC, 22.8% vs. SqCC, 43%; p=0.001). However, there was no significant difference in the 5-year overall survival between the two groups (ADC, 57.5% vs. SqCC, 52.3%; p=0.366). This may be related to significantly better (p<0.001) post-recurrence survival in the ADC group (mean, 28 months) than in the SqCC group (mean, 14.5 months). In the ADC group, 164 patients developed recurrences and of those, 68 (41.5%) received targeted therapy. Patients who received targeted therapy for recurrences showed significant better 5-year overall survival than those who did not receive (61% vs. 45.6%, p=0.025). **Conclusion:** In this study, SqCC was associated with better treatment response and more favorable recurrence-free survival than ADC. Despite poor recurrence-free survival in ADC, its overall survival was improved by prolonged post-recurrence survival, which might be related to the use of targeted therapy for recurrence. Since treatment response and survival outcomes are different according to histologic type, individualized treatment strategy could be considered to improve outcomes of N2 disease.

Keywords: histologic type, Non-small cell lung cancer with N2 disease, Neoadjuvant concurrent chemoradiotherapy

P3.09-001 THE DOSIMETRIC ADVANTAGES OF INTENSITY MODULATED PROTON THERAPY (IMPT) FOR MESOTHELIOMA AFTER PLEURECTOMY/DECORTICATION

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Background: Radiotherapy (RT) after surgery for locoregionally advanced mesothelioma is particularly challenging. Recent surgical advances with pleurectomy and decortication techniques are clinically promising, however, applying comprehensive ipsilateral pleural irradiation is technically difficult with two RT-sensitive, intact lungs. With state-of-the-art IMPT, we have successfully treated a 77-year-old woman who has now been disease-free and alive for 7 months after RT (and 18 months since diagnosis), with minimal therapy-related toxicities so far. **Method:** A woman was diagnosed with locally advanced mesothelioma of the right hemithorax, epithelioid type. She underwent appropriate metastatic workup which was negative. She received 4 cycles of carboplatin and pemetrexed, and underwent thoracotomy with parietal and visceral pleurectomies, decortication, and mediastinal nodal dissection. She was found to have ypT3, N0 disease postoperatively, and elected to undergo proton therapy. A 4D-CT simulation scan was performed, and negligible respiratory motions were found. **Result:** A 3-field, active beam scanning, multi-field optimization IMPT plan was made and passed quality assurance. She received 50.4 Gy in 28 fractions, and completed IMPT without any treatment interruption; the acute toxicities included mild pain, cough, and dyspnea which were all grade 1. She also developed subacute, RT-related grade 1 dermatitis. She has not had clinically significant RT-induced pneumonitis. In preparation for her proton therapy-based treatment, multiple dosimetric iterations and comparisons were made, for the best intensity modulated radiotherapy (photon-based, IMRT) vs. IMPT plans (see Figure). With IMPT, the contralateral (left) lung, heart, and also esophagus received significant amount of RT reduction in an otherwise historically morbid adjuvant treatment which were only reserved for the medically fittest.

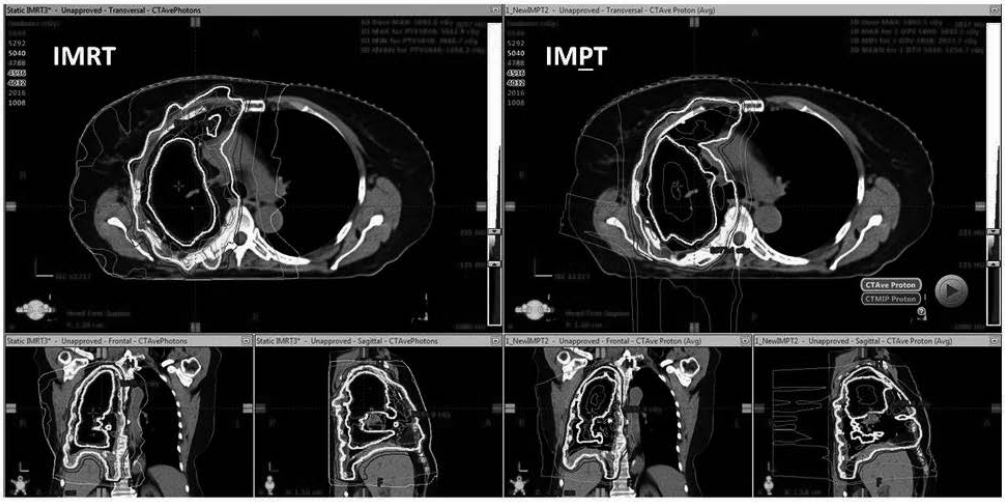

Figure. IMRT (Left column) vs. IMPT/Proton (Right) for Mesothelioma. The dosimetric advantages of proton therapy are apparent (see Table).

		Proton	Photon	Difference (%)
Lung_Total	Mean, Gy	19.8	23.22	-14.7
	V20Gy, %	40.1	43.4	-7.6
Lung_Left	**Mean, Gy**	**0.53**	**7.06**	**-92.5**
	V20Gy, %	0.4	1.7	-76.5
Heart	**Mean, Gy**	**9.35**	**20.62**	**-54.7**
Cord	Max, Gy	39.08	44.43	-12.0
Cord_prv	Max, Gy	48.16	49.29	-2.3
Esoph	**Mean, Gy**	**21.17**	**30.09**	**-29.6**
Bowel	D5%, Gy	18.09	32.64	-44.6
Liver	Mean, Gy	13.51	20.44	-33.9

Conclusion: Although promising, the clinical dosimetric levels of evidence are limited to this case report only. The paradigm of neoadjuvant platinum-based doublet therapy, pleurectomy/decortication, and adjuvant proton RT should be further explored and evaluated in the prospective settings in the future.

Keywords: Mesothelioma, Medical Physics, Intensity Modulated Proton Therapy (IMPT)

P3.09-002 CAN WE DO BETTER? FEASIBILITY DOSIMETRIC STUDY FOR UPFRONT RADICAL RADIOTHERAPY IN MESOTHELIOMA

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Background: Standard treatment for mesothelioma (surgery+/-chemotherapy+/-radiotherapy) does not provide satisfactory oncologic results in view of the lack of evidence for a preferred treatment option in such a rare disease with little published evidence. We aim to assess the feasibility of delivering radical doses of radiotherapy in mesothelioma patients. We would also like to evaluate the dosimetric parameters to establish organs at risk and optimal dose potentially delivered if radiotherapy is a sole agent. **Method:** Patients with Mesothelioma were chosen from the SYSTEMS-1 and SYSTEMS-2 trial cohort. Treatment volumes and organs at risk were performed on the Eclipse planning system. The treatment volumes outlined were CTV Pleural cavity and GTV bulky disease. Doses were prescribed as follows: PTV pleural cavity (CTV + 0.8 cm) 45Gy/ 25# and PTV Bulky disease (GTV+5mm) 55Gy/25#. Physics planning was carried on the Eclipse 13.6.23 treatment planning system, by using VMAT technique with either 2 or 3 arcs, 6MV beams at a dose rate of 600MU/min. We calculated overlap volumes between PTV and Organs at Risk (OAR's) in view of their proximity, prioritizing heart and liver dose constraints over PTV coverage. **Result:** 5 patients with confirmed epitheliod mesothelioma. Ages ranged from 55 - 72 years, 4/5 patients were male. A Cisplatin or Carboplatin-Pemetrexed doublet was given to all the patients prior to the CT Scan. The table below shows the dosimetry data gathered from the plans done.

Conclusion: Radical radiotherapy doses are achievable in mesothelioma by respecting organs at risk adequately, despite the challenging large volumes and complex disease anatomical pattern. VMAT is a promising technique allowing to potentially treat mesothelioma with radical doses of radiotherapy. Further trials are needed to assess the feasibility of radiotherapy as an upfront treatment for these patients.

	Objectives	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
TNM stage		**T4N2M0**	**T3N2M0**	**T4N3M0**	**T4N2M0**	**T4N2M0**
PTV Pleural cavity Volume (cc) D99% (% of the prescribed dose) **D95%** (% of the prescribed dose) **V105%** (%) **V95%** (%) Median Dose (Gy)	**Dose prescribed 45Gy/25# - - >95% - >95%**	**161 578.694.3 80.794.6 51**	**227 677 108 9697.6 53**	**146 582.896 58.596.1 47.9**	**370 158 9187.1 93.253.4**	**184 072 8979.7 89 48.9**
PTV Bulky disease Volume (cc) D99% (% of the prescribed dose) **D95%** (% of the prescribed dose) **V105%** (%) **V95%** (%)Median Dose (Gy)	**Dose prescribed 55Gy/25# - - >95% - >95%**	**290 57289.3 15.790 55**	**310 47989.6 15.281.2 54.6**	**492 45687.7 10.775.9 53.6**	**764 83 89 4.574 54.3**	**310 479 89.615 81 54.6**
Contralateral lung Volume(cc) Overlap with PTV (cc) Mean lung dose (Gy) V20Gy(%) V5Gy (%)	**- - ≤8-10 to 20 ≤4-10 to 35 ≤75**	**163 70.112.2 11.398.6**	**163 6 018.4 35.6100**	**124 70 1318.3 92.6**	**239 110.416.4 25.4 100**	**208 2 017.531.3 100**
Heart Volume(cc) Overlap with PTV (cc) Mean Heart Dose (Gy) V35Gy (%)	**- - <22-26 <35**	**776 44.433.5 33.6**	**619 94.925.5 30**	**790 15027.8 28.8**	**681 111.731.1 34.7**	**822 65.8 32.934.7**
Liver Volume(cc) Overlap with PTV (cc)Mean liver dose (Gy) V30Gy (%)	**- - 28-30 ≤40**	**165 7 23232.3 55.1**	**154 4 017.3 4.0**	**153 4 089.9 0.1**	**193 1 485 3257.2**	**133 3 23031.9 54.4**
Oesophagus Volume (cc) Overlap with PTV (cc) Max dose (Gy) V50Gy (%)	**- - ≤50-55 <40**	**285.3 55.68.3**	**33.5 0 53.45.9**	**30.5 155.613.4**	**193 48.7 60.926.6**	**43 7.7 56.313**
Spinal cord Volume(cc) Overlap with PTV (cc) Max dose (Gy)	**- - <50**	**70.3 0 45.7**	**80.4 0 52.7**	**55.5 0 50.7**	**87.6 1.9 54.5**	**75 0 49.6**
Contralateral Kidney Volume(cc) Overlap with PTV (cc) Max dose (Gy)	**- - <5**	**279 0 17.4**	**115 0 20**	**116 0 4.4**	**177 0 30.1**	**163 0 21.9**
Ipsilateral Kidney Volume(cc) Overlap with PTV (cc) V30Gy (%) **Mean Dose (Gy)**	**- - <50 ≤30**	**N/A N/A N/A N/A**	**118 0 29.617.4**	**89.8 0 02.1**	**134 2.8 23.318.9**	**239 20.5 44.629**
Small Bowel Volume(cc) Overlap with PTV (cc) Max dose (Gy)	**- - ≤45**	**183 0 18.3**	**348 0 27.9**	**307 0 10.7**	**672.5 0 33.2**	**309 0 23.4**
Stomach Volume (cc) Overlap with PTV (cc) Max Dose (Gy)	**- - ≤45**	**168 0.833.3**	**352 6.456.7**	**235 5.945.7**	**182.1 0 52.4**	**631 0 40.4**

P3.09-003 HEART RADIATION DOSE AS A RISK FACTOR FOR DYSPNEA WORSENING AFTER MULTIMODALITY TREATMENT FOR NSCLC AND MPM: AN EXPLORATORY ANALYSIS

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Background: The purpose of our study was to quantify the influence of heart dose on the early and late onset of dyspnea in a cohort of non-small cancer (NSCLC) and malignant pleural mesothelioma (MPM) patients having multimodality treatment including radiotherapy (RT). **Method:** In 121 patients with multimodality-treated NSCLC and MPM the maximal dyspnea score (CTCAE 4.0) before RT, at an early (≤6 months) and a late (7-12 months) time point were obtained. Included patients needed to be clinically and radiologically progression-free 9 months after the end of RT. The difference (Δ) between the maximal dyspnea at ≤6 months and at 7-12 months with the pre-RT dyspnea was calculated. **Result:** Forty-four percent (50/113) of the patients developed an early worsening of at least 1 point in their dyspnea score (Δdyspnea≥1) after the end of RT. Independent predictors of an early worsening were the mean heart dose (MHD) (for Δdyspnea≥1: OR=1.03, p=0.04) and the dyspnea score before RT (for Δdyspnea≥1: OR=0.40, p=0.0001; for Δdyspnea≥2: OR=0.35, p=0.05). At the later time point, only the dyspnea score before RT (OR: 0.40, p=0.001) was identified as predictor of Δdyspnea≥1. **Conclusion:** Our results, albeit exploratory, suggest that heart dose may play a role in the early worsening of the dyspnea in a heterogeneous cohort of patients having multimodality treatment including RT, whereas baseline dyspnea plays a major role for both early and later worsening.

Keywords: Mesothelioma, combined modality treatment, lung toxicity

P3.09-004 ROUTINE CLINICAL PARAMETERS CAN STRATIFY SURVIVAL CHARACTERISTICS IN MESOTHELIOMA PATIENTS UNDERGOING SURGERY

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Background: Malignant pleural mesothelioma (MPM) is a rare cancer with a heterogeneous prognosis. We have previously described and validated a prognostic model using a classification and regression tree (CART) model to analyse the interaction of multiple variables with survival in a broad MPM population.(1) We aimed to test the performance of our model on a population with MPM who had surgical intervention. **Method:** Cases from Australia and Japan with confirmed MPM who underwent surgery were analysed with clinical variables available at the time of referral recorded. The model uses combinations of different variables (Table 1) to stratify participants into different risk groups (1-4) and the survival characteristics were compared using the Log Rank test.

Risk Group	1	2		3	4			
		2a	2b		4a	4b	4c	4d
Variables:								
Weight loss	No	No	No	Yes/ missing	No	No	Yes/ missing	Yes/ missing
Haemoglobin g/L	>153	121-153	>153	-	121-153	<121	-	-
Albumin g/L	>43/missing	-	≤43	-	-	-	-	-
Histological Diagnosis	-	Epi/ND	-	-	Bi/Sarc	-	-	-
ECOG Performance Status	-	-	-	0-1/ missing	-	-	>2	0-1/ missing
Histological Diagnosis	-	-	-	Epi/Bi/ND	-	-	-	Sarc
n= per subgroup	18	61	2	140	13	53	0	2
Total n=	18	63		140	68			
Median Survival * (IQR, months)	82.5 (28.1-152.4)	42.3 (24.6-73.9)		35.2 (18.1-45.8)	22.0 (10.1-41.9)			
* Log Rank test p<0.0001								

Table 1. Risk group characteristics

Result: A total of 289 cases were included (205 from Australia and 84 from Japan) who had surgery between 1991-2016. Overall median survival was 34.6 (IQR 17.5-56.1) months; median age 63.0 (IQR 57.0-67.8) years, 240/289 (83.0%) were male. Epithelioid MPM was the most common subtype (80.9%), weight loss was present in 36.6%, dyspnoea in 54.4%, chest pain in 29.0% and 91.8% had an ECOG performance status of 0. EPP was the most common operation performed (56.7%), followed by pleurectomy/decortication in 30.4%. There were no clinically meaningful differences between the cohorts; 40 patients were alive at censure. Survival across the risk groups was significantly different (Log Rank test p<0.0001). The group with the longest survival (median 78.1, IQR 28.1-152.4 months) had no weight loss, Hb >153g/L and serum albumin >43g/L at the time of referral to specialist surgical centre. **Conclusion:** The combination and interaction of simple, clinical variables available early after diagnosis of MPM is able to stratify survival and discriminate higher and lower risk of death in high performance status patients

Keywords: Mesothelioma, Prediction, Prognosis

P3.09-005 THE RESULTS OF TRIMODALITY TREATMENT STRATEGY FOR MALIGNANT PLEURAL MESOTHELIOMA

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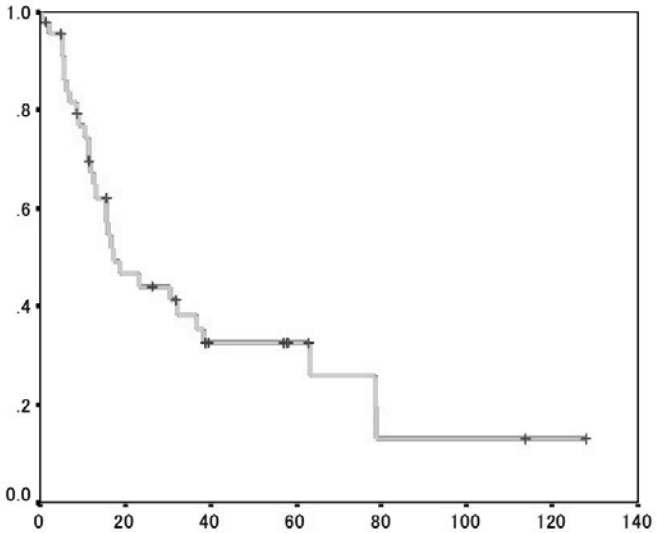
Background: Our standard treatment strategy for operable malignant pleural mesothelioma (MPM) is trimodality therapy with extrapleural pneumonectomy (EPP) followed by radiation and chemotherapy. Our experience to treat MPM is reported. **Method:** 45 consecutive EPP for MPM which were performed from June 2006 to February 2017 in our hospital were reviewed. We have instituted a trimodality therapy protocol consisting of EPP, adjuvant 45-50.4 Gy hemithoracic radiation, and adjuvant CDDP plus PEM chemotherapy. 36 patients have been treated with this protocol. However, 9 patients were given induction chemotherapy, and referred to us. They were scheduled to undergo EPP and adjuvant radiation. Overall survival was calculated using Kaplan-Meier method. **Result:** Median age at EPP was 61 years old (44-74). Female was 11, and male was 34. Right side was 25, and left side was 20. Epithelioid was 30, biphasic was 10, sarcomatoid was 2, and special variants was 3. Median EPP time was 7 hours 30 minutes (5 h 52 m-12 h 2 m). No blood transfusion during EPP was 17 cases (38%). Mortality was one patient (2.2%) who died due to acute aggravation of interstitial pneumonia. Atrial fibrillation was the most common morbidity, and developed in 16 patients (36%). IMIG pathological stage was stage IV in 3, stage III in 26, stage II in 8, and stage Ib in 8. Adjuvant 45-50.4 Gy radiation was completed for 38 patients (83%). 10 patients (22%) could not undergo chemotherapy. 31 patients (69%) underwent trimodality therapy. Postoperative median follow-up period was 5 years and 10 months. Five year survival, two year survival, and median survival of all 45 patients (graph) were 32%, 44%, and 17.4 months, and those of 30 epithelioid patients were 41%, 54%, and 30.4 months.



Conclusion: This trimodality treatment strategy with EPP, radiation, and chemotherapy for MPM is feasible, and the prognosis has been greatly improved.

Keywords: trimodality treatment, Mesothelioma, extrapleural pneumonectomy

P3.09-006 PREOPERATIVE SIX-MINUTE WALK DISTANCE AND DESATURATION IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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Background: Surgery for malignant pleural mesothelioma (MPM) is an invasive procedure associated with high morbidity. MPM often invades adjacent structures such as the chest wall, diaphragm, and mediastinum. Therefore, pulmonary functions and levels of physical fitness are reduced in advanced MPM. The aim of this study was to characterize preoperative exercise capacity and relate it to pulmonary functions, oxygenation, and postoperative outcomes in patients with MPM. **Method:** A retrospective study was conducted on 18 patients with MPM who were scheduled

to undergo extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D) followed by postoperative rehabilitation at Nagoya University Hospital from July 2012 to April 2016 (Institutional Review Board approval No. 2015-0413). To estimate preoperative exercise capacity, 6-min walk test (6MWT) and oxygen saturation of a peripheral artery (SpO_2) during the 6MWT were assessed. Grades III and IV of the Clavien-Dindo classification were defined as major postoperative complications. **Result:** The age was 65.8 ± 6.4 years. Preoperative 6-min walk distance (6MWD) was 465.9±96.7 m. Minimum SpO_2 ranged from 86% to 97%. The 6MWD significantly correlated with inspiratory capacity (r=0.507, *P*<0.05) and % of predicted value of diffusing capacity of the lung for carbon monoxide ($\%DL_{CO}$) (r=0.470, *P*<0.05). The minimum SpO_2 during 6MWT significantly correlated with % of predicted values of vital capacity (r=0.619, *P*<0.01) and total lung capacity (r=0.493, *P*<0.05) and postoperative days of extubation (r=-0.495, *P*<0.05). The preoperative partial pressure of oxygen in arterial blood significantly correlated with $\%DL_{CO}$ (r=0.505, *P*<0.05). There was a total of 13 major postoperative complications (8 respiratory failure, 2 pneumonia, 1 empyema, 1 atrial fibrillation, and 1 prolonged air leak) in 6 patients. There was no in-hospital death or death within 30 days after surgery. The incidence of major complications was significantly associated with longer stays in intensive care unit (3.3±1.8 vs. 1.7±1.0 days, *P*<0.05) and hospital (54.2±31.2 vs. 12.3±3.2 days, *P*<0.05) but not with preoperative physical status or pulmonary functions. Stays in hospital after EPP (n=7) were significantly longer than those after P/D (n=11) (median 28 vs. 12 days, *P*=0.01) but there was no significant difference in incidence of major complications between the EPP and P/D groups. **Conclusion:** Our results indicate that the 6MWT is a convenient and useful field test to assess preoperative physical status in patients with MPM. Future studies with a larger cohort are required to elucidate risk factors for postoperative morbidity and mortality.

Keywords: malignant pleural mesothelioma, Rehabilitation, 6-min walk test

P3.09: MESOTHELIOMA -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.09-007 THORACIC ASYMMETRY AND ITS IMPACT ON SURVIVAL AFTER RADIATION AND SURGERY FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: Staging for malignant pleural mesothelioma (MPM) remains a challenge due to poor prognostic utility. Other clinical factors may improve and refine the staging system. We investigate the impact thoracic asymmetry at time of initial presentation prior to therapy on survival in MPM patients treated with multimodal therapy. **Method:** We reviewed 93 consecutive treatment naïve MPM patients treated with Surgery for Mesothelioma after Radiation Therapy (SMART protocol) from Sep 2008 to Jul 2015. The right and left axial thoracic areas (defined as the product of the ant-post and med-lat extent of hemithoraces at the level of carina) were used to calculate the asymmetric thoracic ratio (ATR, where 1 is more symmetric, Figure 1). Significant factors were determined using univariate (log rank), multivariate (Cox proportional hazards) as well as recursive partition analysis (RPA). Continuous variables were discretized into binary categories split by its median value. **Result:** After a median follow-up of 15.6 months, 63 (68%) patients recurred, 56 (60%) died. The median ATR was 0.85, ranging from 0.52 to 1.00. On univariate analysis, histology (p=0.003 and 0.0002), gross tumour volume (GTV, p=0.004 and 0.001), and ATR (p=0.00001 and 0.0000002) all significantly impacted both overall and disease free survival, respectively, while mediastinal nodal involvement (p=0.03) was significantly associated with DFS only. On multivariate analysis, histology (p=0.01 and 0.005) and GTV (p=0.02 and 0.016) significantly impacted both overall and disease free survival, respectively. ATR significantly impacted disease free survival (p=0.02, HR=0.06 95% CI 0.02-0.20) and was suggestive of a trend for overall survival (p=0.07). On RPA, ATR<0.848 was significantly (p<0.001) associated with poorer DFS. **Conclusion:** A low asymmetric ratio (ATR<0.848) is significantly associated with poorer outcomes, specifically disease free survival, and is independent of histology and tumor volume. Further study is needed to validate this parameter.

Keywords: Mesothelioma, asymmetric thoracic ratio

P3.09: MESOTHELIOMA -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.09-008 ROLE OF SURGERY IN THE MULTIMODALITY TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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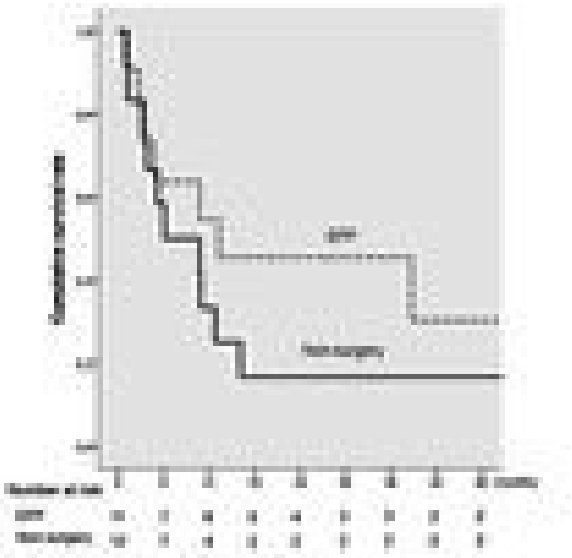
Background: The treatment of malignant pleural mesothelioma is challenging and multimodality treatment including surgery is recommended, although there are debates about the role of surgery. We analyzed the outcomes of surgery in MPM in the context of multimodality treatment focusing on extrapleural pneumonectomy (EPP). **Method:** Total 29 patients had pathologically proven malignant pleural mesothelioma from April 1998 to July 2015 were retrospectively reviewed. The overall survival rates of surgery group (any type of curative surgical treatment) and medical group (medical treatment only) were compared. Prognoses of EPP subgroup and medical group were also compared **Result:** Among 29 patients, 16 patients underwent surgery for curative intent, 12 patients underwent definitive chemotherapy, and one patient refused treatment. Epithelioid type (n=11, 68.8%) was the most common pathologic type in surgery group. Only 4 (33.3%) patients of medical group were epithelioid type. Half of surgery group patients were clinical stage I/II and there was no clinical stage I/II in medical group. Pulmonary functions of both group were not significantly different. In surgery group, 11 patients underwent EPP and one patient underwent pleurectomy/decortication. Four patients misdiagnosed as lung cancer preoperatively underwent lobectomy with chest wall resection. There were no postoperative 30-day nor in-hospital mortality. The median follow-up duration was 10.6 (1.0-78) months. The median survival time (MST) was 10.6 months, and the 3-year overall survival rate (3yr-OS) was 25 %. There was no statistical difference in overall survival between surgery and medical group (MST = 10.6 vs. 8.4 months, 3yr-OS = 31.1 % vs 16.7%, p=0.47) EPP subgroup (MST = 13.3 months, 3yr-OS = 45.5 %) also showed statistically similar survival with medical group (p=0.23). (Fig 1)



Conclusion: Multimodality treatment incorporating surgery was not superior compared with medical treatment in MPM. EPP with multimodality treatment also failed to show meaningful superior prognosis compared with non-surgical treatment in MPM.

Keywords: Mesothelioma, Surgery, extrapleural pneumonectomy

P3.09: MESOTHELIOMA -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.09-009 FOURTEEN CASES STUDY OF 5 YEAR SURVIVORS OF MALIGNANT PLEURAL MESOTHELIOMA FOLLOWING EXTRAPLEURAL PNEUMONECTOMY

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Background: We performed extrapleural pneumonectomy (EPP) as curative intent surgery for malignant pleural mesothelioma (MPM) from 2004 to 2012. We investigated that factors associated with long term survival in our current cases. **Method:** We retrospectively reviewed some factors concerning the patients underwent EPP from April 2004 to march 2017 and past more than 5 years after operation. We analyzed age, sex, epidemiology, side, clinical stage, measurements of pleural thickness, the value of SUV max of PET-CT, pathological stage, length from EPP to recurrence and end results. **Result:** A total of 54 patients were enrolled to this study. Six patients who had exploratory thoracotomy and three patients who had not macroscopic complete resection were excluded. Overall, 14 patients (31%) survived at least 5 years (Group S), and 31 patients (68%) survived less than 5 years (Group N). All patients had EPP. In Group S, 10 males (71%) and 4 females (29%); age when they had operation ranged from 37 to 69 years with a median age of 57.5 years. All of them, histological subtypes were epithelial type. By the comparison between Group S and Group N, there were significant differences among the value of SUV max of PET-CT validation of pre and post neoadjvant chemotherapy(<3.0 vs ≧3.0, p=0.03), length from EPP to radiotherapy (<60 days vs ≧60 days, p=0.02), length from EPP to recurrence (<1 year vs ≧1 year, p=0.0001). **Conclusion:** More than 30% patients survived at least 5 years in this study. One patient survived more than 10 years. Another patient survived more than 8 years without recurrence. This case suggest that cancer of the patient possibly cured radically. In the future, we need comparison the prognosis, complication, quality of life (QOL) between the patients who underwent EPP and the patients who underwent pleurectomy/decortications (P/D).

Keywords: malignant pleural mesothelioma

P3.09-010 18 YEARS SINGLE CENTER EXPERIENCE OF SURGICAL RESECTION OF MALIGNANT PLEURAL MESOTHELIOMA AFTER INDUCTION CHEMOTHERAPY

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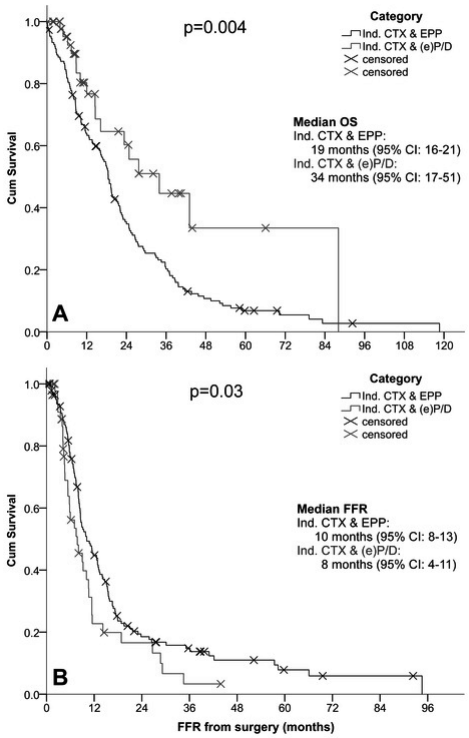
Background: Surgical resection of malignant pleural mesothelioma is discussed controversially. Using our data from nearly 2 decades of single center experience, and focusing on the shift from extrapleural pneumonectomy (EPP) to (extended) pleurectomy/decortication ((e)P/D) we compared the peri- and longterm outcomes of EPP and (e)P/D after induction chemotherapy. **Method:** In a retrospective analysis (September 1999 - June 2016) of our prospective database of mesothelioma patients 196 patients received mentioned multimodalty therapy: 149 treated with EPP, 34 with eP/D and 13 with P/D. Major morbidity was defined as bleeding necessitating reoperation, patch failure, chylothorax, empyema, bronchopleural fistula (BPF), pulmonary embolism and acute respiratory distress syndrome (ARDS). **Result:** Both groups did not differ significantly in pT stage, hisotype, but in age and lymph node stadium. Overall 30-day and 90-day mortality were 4% and 8%, respectively. However, patients treated with (e)P/D the 30- and 90-day mortality was 0. Major morbidity was not significantly different between both groups with 37% (EPP) and 23% ((e)P/D), respectively. Patient's characteristics, freedom from recurrence (FFR) and overall survival (OS) are demonstrated in figure 1.



Conclusion: Multimodality treatment with radical surgery is perfromed safely, (e)P/D known as the less invasive procedure than EPP, shows a longer OS whilst having a shorter FFR.

Keywords: (e)P/D, Mesothelioma, EPP

P3.10-001 PROGNOSTIC FACTORS OF SURVIVAL IN MALIGNANT PLEURAL EFFUSION

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Background: The aim of this study was to identify predictors of overall survival (OS) after pleural palliative procedures in patients with malignant pleural effusion (MPE). **Method:** Data was collected from our database between August 2013 and December of 2016 of patients with MPE. All patients were followed-up at least 30 days after the pleural procedure. Collected data included basic demographics, American Society of Anesthesiologists (ASA) physical status classification, performance status according to the Eastern Cooperative Oncology Group (ECOG) score, number of metastatic sites, hematological parameters, including white blood cells (WBC), number of neutrophils and lymphocytes, neutrophil/lymphocyte ratio (NLR), red blood cells (RBC) and platelets/lymphocyte ratio, in addition to body mass index (BMI) on the day before surgery. The influence of the primary tumor site was also assessed. During the period after the palliative procedure, we evaluated the volume of drained liquid, the type of palliative procedure performed, recurrence of pleural effusion, the presence of neoplastic cells in the pleural fluid, in addition to the biochemical profile including pleural fluid pH, levels of adenosine deaminase (ADA), total protein, albumin, glucose, lactate dehydrogenase (DHL) and the proportion of lymphocytes in pleural fluid. We also evaluated the presence of pleural thickening and pulmonary infiltrate through chest computed tomography. To analyze OS, patients were divided into two groups. Group I included OS greater than 30 days and Group II included OS shorter than 30 days. Prognostic factors for survival were identified by univariate analysis, using Fisher's exact and Student's T-Test. Subsequently, the significant variables were entered into a multivariate logistic regression analysis ($p < 0.05$). **Result:** A total of 208 patients were included in the analysis, 36,5% were male and the median age was 62 years. Median follow-up time for overall surviving was 127 days. The primary tumors were lung 39,9%, breast 29,3%, gastrointestinal 13%, gynecological 8,7% and others 9,1%. Factors affecting OS in univariate analysis were: procedure, ECOG, pulmonary infiltrate, albumin, protein, neutrophil, hematocrit and hemoglobin in peripheral blood. At the multivariate analysis, albumin (p=0.03), ECOG 3 e 4, hematocrit and pulmonary infiltrate with p<0.001 were identified as independents predictors of OS. **Conclusion:** Patients with MPE who presented pulmonary infiltrate, albumin < 2,5, hematocrit < 35, ECOG 3 and 4 were significantly associated with shorter survival. The identification of those prognostic factors may assist the choice of the optimal palliative support.

Keywords: survival, malignant pleural effusion, lung cancer

P3.10-002 IMPLEMENTING AN INNOVATIVE DISTRESS/SUPPORTIVE CARE SCREENING TOOL IN A LUNG CANCER CLINIC

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Background: The Institute of Medicine (IOM) 2013 report recommends that supportive oncology care start at cancer diagnosis; the Commission on Cancer (CoC) Standard 3.2 requires distress screening and indicated action. The Coleman Supportive Oncology Collaborative "Patient Screening Questions for Supportive Care" tool was used to investigate the relationships between demographic/diagnostic data and screening scores. **Method:** Lung cancer patients at the University of Illinois Cancer Center were screened using the following Coleman Foundation tool shown below:

Patient Screening Questions for Supportive Care

All patients are asked to complete this questionnaire as part of their standard of care. Please take a few minutes to answer the following questions to help us better address your needs.

Over the last 14 days, how often have you been bothered by the following problems?[1]

Please mark one box per row	Not at all	Several Days	More than half the days	Nearly every day
Feeling nervous, anxious or on edge	❑	❑	❑	❑
Not being able to stop or control worrying	❑	❑	❑	❑
Little interest or pleasure in doing things	❑	❑	❑	❑
Feeling down, depressed, or hopeless	❑	❑	❑	❑

Indicate if any of the following has been a concern for you in the past 7 days, please check Yes or No for each.

YES	NO	Practical Concerns[2]
❑	❑	Child care issues
❑	❑	Issues paying for food or housing
❑	❑	Issues with transportation to/from treatment
❑	❑	Work / school issues
❑	❑	Insurance coverage issues or no health insurance
❑	❑	Paying for medication or medical care

YES	NO	Family/Caregiver Concerns[2]
❑	❑	Concerns about my children
❑	❑	Concerns about my partner
❑	❑	Concerns about caregivers
❑	❑	Ability to have children
❑	❑	Concerns about other family members

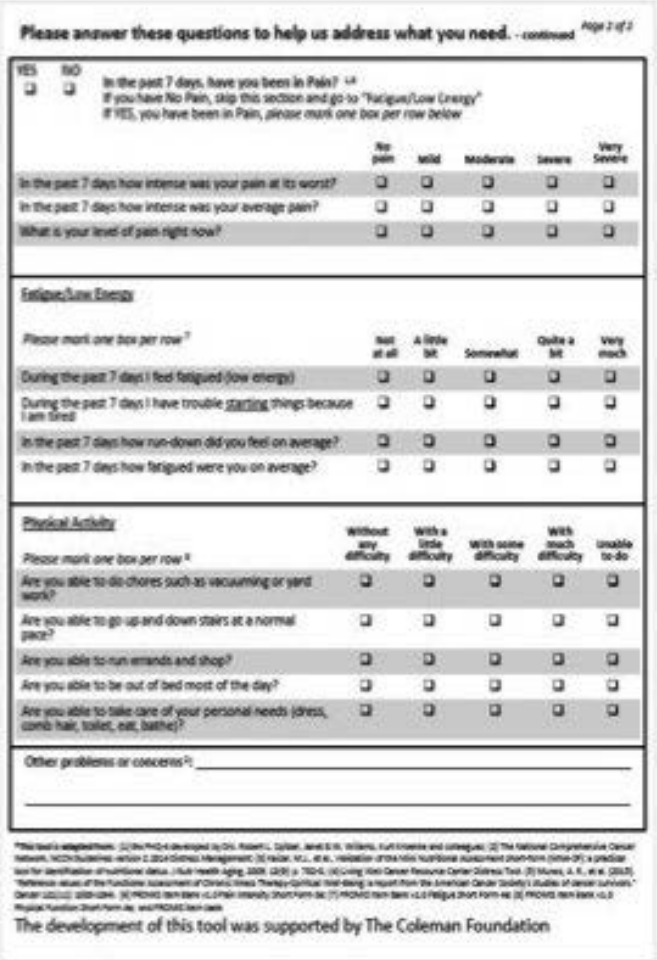
YES	NO	Nutrition Concerns[2, 3]
❑	❑	Weight loss or lack of appetite
❑	❑	Weight gain
❑	❑	Issues with taste
❑	❑	Concerns about nutrition and food

YES	NO	Treatment or Care Concerns[4]
❑	❑	I want to better understand my cancer diagnosis or stage
❑	❑	I want to better understand my prognosis or long term outcome
❑	❑	I have questions about my treatment options, medication, or my plan of care
❑	❑	I want help communicating my wishes for treatment

YES	NO	Physical Concerns[2]
❑	❑	Breathing
❑	❑	Constipation
❑	❑	Diarrhea
❑	❑	Fevers
❑	❑	Nausea or vomiting
❑	❑	Sleep
❑	❑	Changes in urination
❑	❑	Difficulty chewing or swallowing
❑	❑	Mouth sores
❑	❑	Dry mouth
❑	❑	Swollen arms or legs
❑	❑	Feeling full quickly or swollen abdomen
❑	❑	Sexual intimacy or function
❑	❑	Skin dry/itchy, blister/pain
❑	❑	Tingling in hands/feet
❑	❑	Appearance
❑	❑	Use of alcohol/drugs

YES	NO	Spiritual / Faith / Religious Concerns[5]
❑	❑	I have a sense of purpose or meaning
❑	❑	I feel peaceful
❑	❑	I find strength in my faith and beliefs

See reverse side to complete



Please answer these questions to help us address what you need. - continued

Page 2 of 2

YES ❑ NO ❑ In the past 7 days, have you been in Pain? ↳
If you have No Pain, skip this section and go to "Fatigue/Low Energy"
If YES, you have been in Pain, *please mark one box per row below*

	No pain	Mild	Moderate	Severe	Very Severe
In the past 7 days how intense was your pain at its worst?	❑	❑	❑	❑	❑
In the past 7 days how intense was your average pain?	❑	❑	❑	❑	❑
What is your level of pain right now?	❑	❑	❑	❑	❑

Fatigue/Low Energy

Please mark one box per row [7]	Not at all	A little bit	Somewhat	Quite a bit	Very much
During the past 7 days I feel fatigued (low energy)	❑	❑	❑	❑	❑
During the past 7 days I have trouble starting things because I am tired	❑	❑	❑	❑	❑
In the past 7 days how run-down did you feel on average?	❑	❑	❑	❑	❑
In the past 7 days how fatigued were you on average?	❑	❑	❑	❑	❑

Physical Activity

Please mark one box per row [8]	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to do chores such as vacuuming or yard work?	❑	❑	❑	❑	❑
Are you able to go up and down stairs at a normal pace?	❑	❑	❑	❑	❑
Are you able to run errands and shop?	❑	❑	❑	❑	❑
Are you able to be out of bed most of the day?	❑	❑	❑	❑	❑
Are you able to take care of your personal needs (dress, comb hair, toilet, eat, bathe)?	❑	❑	❑	❑	❑

Other problems or concerns [9]: _____

The development of this tool was supported by The Coleman Foundation

Data was collected on an Excel spreadsheet and statistically analyzed. **Result:** We performed initial screening on 138 lung cancer patients. Demographics are shown in table below:

		Male (n=76) (55%)	Female (n=62) (45%)
Insurance			
	Medicare	31 (40)	31 (50)
	Medicaid	20 (26)	16 (26)
	Private	22 (29)	13 (21)
	Self-Pay	0 (0)	1 (2)
	Inmate	3 (4)	0 (0)
	Charity	0 (0)	1 (2)
Stage			
	I	11 (14)	11 (18)
	II	8 (11)	2 (3)
	III	22 (29)	16(26)
	IV	35 (46)	33 (53)
Ethnicity			
	White	14 (18)	8 (13)
	African American	44 (58)	42 (68)
	Hispanic	4 (5)	4 (6)
	Asian	6 (8)	5 (8)
	Other	8 (11)	3(5)
Age *		62.1 ± 8.1	62.1 ± 9.4
	***: Age presented as mean +/- standard deviation (in years)**		

Statistically signifcant correlations were found with the following: --Gender and racial/ethnic minority status correlated with distress/concerns over diagnosis and treatment. --Type of medical insurance correlated with distress/concerns over nutrition (food insecurity) and physical activity. **Conclusion:** Introduction of distress screening tool facilitated identification of some care needs such as patient education and counseling, nutrition services, and physical therapy. Moreover certain demographic groups have especially high burdens in some specific patient concern areas. Our next step is to expand distress screening to determine longitudinal trends, expand supportive oncology services to meet our patients' needs, and to assess impact on unplanned ED visits and patient outcomes.

Keywords: Distress Screening, Coleman Supportive Oncology Collaborative, supportive care

P3.10: NURSING/PALLIATIVE CARE/ETHICS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.10-003 ASSESSING AND ADDRESSING KNOWLEDGE GAPS TO IMPROVE LUNG CANCER SCREENING RATES

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Background: The National Lung Screening Trial showed that annual screening with low-dose computed tomography (LDCT) in high-risk patients reduced lung cancer mortality by 20%. The United States Preventative Services Task Force (USPSTF) now recommends lung cancer screening (LCS) for high-risk individuals. However only about 10% of eligible individuals are referred for LDCT possibly in part due to a lack of familiarity among primary care physicians with LCS guidelines. In this analysis, we sought to obtain a baseline acumen of providers' knowledge and awareness about LCS and develop a series of interventions including embedding USPSTF criteria into electronic medical record (EMR) ordering to educate providers and facilitate more effective use of LCS for high-risk patients. **Method:** A Lung Cancer Screening Program was started in 2015 led by a nurse practitioner. Internal medicine residents at the University of Illinois – Chicago (UIC) General Medicine Clinic (GMC) were surveyed using paper questionnaires. The survey included 6 questions on USPSTF LCS guidelines. Next, educational efforts were addressed through a lecture, email reminders, and informational clinic flyers. Finally the EMR order set was updated to include USPSTF criteria directed ordering. The number of appropriately ordered screens through GMC was tracked monthly. A post-intervention survey was distributed to evaluate if providers' knowledge was improved by these interventions. **Result:** Fifty-three IM residents were surveyed regarding LCS guidelines appropriate for LDCT screening. Of the respondents, 87% knew the correct test for screening was LDCT, 66% knew only smokers with ≥30 pack year history were eligible, 45% knew the minimum age criteria (55 years-old), 28% knew the maximum age (80 years-old), 42% knew interval to re-order screening for a negative test (1 year), and 38% knew the maximum time since quitting (15 years). Following the initial interventions there was an increase in the rate of appropriately ordered LDCT screening tests ordered through GMC clinic (from 6.8 per month [May 2016 to September 2016] to 10.8 per month [Oct. 2016 to Apr. 2017]). Post-intervention knowledge assessment is underway and will be presented. **Conclusion:** Although LCS is recommended by USPSTF, there are gaps in knowledge about eligibility criteria among internal medicine residents. We present data that suggests using educational interventions and changes in EMR to increase awareness and knowledge is associated with an increase in appropriate usage of LDCTs for LCS. Ultimately, we plan to broaden these interventions to additional primary care clinics (eg., Family Medicine, Pulmonary) to improve proper use of LCS at our institution.

Keywords: lung cancer screening, eligibility criteria, low-dose CT scan

P3.10: NURSING/PALLIATIVE CARE/ETHICS - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.10-004 IMMUNOTHERAPY: EMERGENCY DEPARTMENT PROVIDER NEEDS ASSESSMENT SURVEY

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[1]Oncology Research- the Center for Cancer Prevention and Treatment, St. Joseph Hospital, Orange/CA/US, [2]Navigation, St. Joseph Hospital, Orange/CA/US

Background: Globally, lung cancer is the second most common cancer diagnosis and the leading cause of cancer death (WHO, 2017). Over the last decade, many efforts have focused on lung cancer prevention, early diagnosis, and finding more effective treatments. In the last two years, the FDA approved of a new class of medications called checkpoint inhibitors or immunotherapy, with proven efficacy in treating advanced lung cancer and several other malignancies. These drugs incite the immune system, resulting in unique immune-related adverse events (irAEs) which are difficult to diagnose, challenging to manage, and potentially life threatening if not properly assessed and managed. Diagnosis of irAEs are typically made on exclusion. It is vital that the medical team and supportive services have current and accurate knowledge on these therapies when patients present for work up during flare-ups. **Method:** A needs assessment survey was given to St. Joseph Hospital Emergency Care Center (ECC) providers and Registered Nurses at a department staff meeting. A one page pre in-service survey was administered in English only, 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: 20 MD's or PA's and 65 NP's or RN's. Selected questions assisted in identifying knowledge deficits among St Joseph Hospital ECC physicians and registered nurses. We were able to evaluate the effectiveness of teaching, and obtained feedback on the value of implementing an immunotherapy patient identification card. Knowledge of immunotherapy side effect management was measured with an identical pre and post in-service survey. The survey contained 5 items that measured the individual's current knowledge/comfort with managing immunotherapy side effects for oncology patients receiving immunotherapy who are evaluated in St. Joseph Hospital Emergency Department. The questions were developed in conjunction with our current and prior Thoracic Oncology Program Medical Directors. **Result:** Data was analyzed with the Wilcoxon Statistic Responses. We identified a significant knowledge gap by our ECC providers at our institution. These providers are often the first to assess irAEs when patients present to the hospital with significant medical issues. Teaching intervention was effective as evidenced by post test results. **Conclusion:** IrAEs is a vital and relevant topic for our patient populations. ECC providers and our multidisciplinary providers

are supportive of introducing Immuno-Oncology patient wallet cards and further education on Immunotherapy. Future projects include implementation of ISLAC's irAEs management guidelines.

Keywords: IrAEs provider needs/education, I/O patient walletcards, Needs Assessment Survey

P3.10: NURSING/PALLIATIVE CARE/ETHICS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.10-005 NATIONAL UK THORACIC SURGERY PPI GROUP IDENTIFY KEY QUESTIONS IN ROUTINE CLINICAL CARE FOR FURTHER RESEARCH

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Background: Patient and public involvement helps us understand and improve healthcare and treatments. A national UK group incorporating patient and carers who have had experience of thoracic surgery was developed in 2016. Involving this group could enhance thoracic surgery research. The aim of this study was to determine from the patient and carer perspective what could be improved with the thoracic surgery pathway to increase satisfaction and care thus enhancing clinical outcomes. **Method:** 15 patients and carers from the national Thoracic surgery PPI group were sent a questionnaire via post. This consisted of 10 open ended questions regarding the service, education and advice they received before and after their lung surgery. They were also asked to comment on their experience as an inpatient, at the point of discharge and provide any suggestions for improvement. The questions were semi structured which allowed flexibility to follow up responses. Each questionnaire was analysed using phenomenological approach in order to gather a deep understanding of the patients and carer's experiences through an inductive method. **Result:** Three themes were gathered from this audit; ambiguity regarding information; continuous need for reassurance, reflection, interpretation, and finally psychological impact. Overwhelmingly patients felt they needed additional advice and information to cope with the physical and more importantly mental changes which affected their daily lives following thoracic surgery. **Conclusion:** It is evident that patient and public involvement in developing ideas for further research in thoracic surgery is invaluable. Their insight and experience can assist healthcare professionals make appropriate improvements to the service for the benefit of future patients. From this audit it is apparent that receiving sufficient information and advice is vital to patient to managing the surgical journey and enhance recovery, interventions to support patients mental health would be of benefit to the patients. In order to achieve further in depth and detailed understanding of patient experiences post thoracic surgery, qualitative methods such as focus groups or interviews should be conducted with a larger sample size.

Keywords: further research, Thoracic Surgery, Patient and public involvement

P3.10: NURSING/PALLIATIVE CARE/ETHICS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.10-006 THE EFFICACY OF PISTACIA TEREBINTHUS SOAP IN THE TREATMENT OF ERLOTINIB-INDUCED SKIN TOXICITY IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Erlotinib can cause skin toxicity in non-small cell lung cancer patients. This open-labeled phase II, efficacy-finding study evaluated the efficiency and safety of Pistacia terebinthus soap in patients with non-small cell lung cancer who developed erlotinib induced skin toxicity. **Method:** Patients who received erlotinib and developed Grade 2 or 3 skin toxicity were treated twice daily with a soap made of oil extracted from Pistacia terebinthus. During treatment, no topical or oral antibiotics, corticosteroids or other moisturizers were used. Patients were examined 1 week later and their photographs were taken. **Result:** Fifteen non-small cell lung cancer patients who developed skin toxicity while receiving erlotinib were included into the study. Twelve patients were male and the median age was 55 (45-70). Forty percent of the patients (n:6) had Grade 3 skin toxicity. Complete response rates in patients with Grade 2 and Grade 3 skin toxicities were 100 and 33%, respectively. In the remaining patients with Grade 3 toxicity the skin toxicity regressed to Grade 1. The objective response rate was 100%, and no delay, dose reduction or discontinuation of erlotinib treatment due to skin toxicity was necessary. Skin toxicity reoccurred in all patients when patients stopped administering the soap and therefore they used it throughout the erlotinib treatment. **Conclusion:** Pistacia terebinthus soap seemed to be used safely and effectively in the treatment of skin toxicity induced by Erlotinib in non-small cell lung cancer patients.

Keywords: Pistacia Terebinthus soap, erlotinib, skin toxicity

P3.10: NURSING/PALLIATIVE CARE/ETHICS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.10-007 SUDDEN DEATH OF THE PATIENTS WITH LUNG CANCER

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Background: We sometimes experience unexpected sudden death (USD) of in-hospital patients, including the patients with lung cancer. However, information of sudden death of the patients with cancer is limited. The aim of this study is to see the prevalence and the tendency of the patients with lung cancer who died unexpected sudden death. **Method:** This is a cross sectional study. Those who had lung cancer and died at our hospital from Jan 1st to Dec 31st in 2015 were enrolled. Clinical data, such as age, gender, type of lung cancer, department of chief physician (Palliative care physician or not), place of death (palliative care unit or not), duration between the last chemotherapy and death, symptom (dyspnea, appetite loss, and edema), and blood test (number of lymphocyte, Alb and CRP) were corrected. Unexpected sudden death was defined as the death of which symptom occurred within 1 day without expectance. Patients were divided into two groups, expected death (ED) group and USD group and compared with their background information. **Result:** 78 subjects were reviewed and their average age at death was 72.9. 54 were male and 24 were female. The proportion of non-small cell carcinoma, small cell carcinoma, and undetermined subject were 71.8%, 6.4%, and 21.8%, respectively. 9.0% (7/78) of them died unexpectedly. Non-specialist of palliative care, dying in general ward, and good appetite were significantly associated with USD. There were no significant different between the two groups in other factors. **Conclusion:** Our results emphasize the difficulty of "expecting Unexpected SD" and we have to recognize the fact that almost 10% of the patients with lung cancer died unexpectedly.

Keywords: unexpected death, lung cancer, end of life

P3.11: PATIENT ADVOCACY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.11-001 FACTORS CORRELATED WITH TIME AND COST DIAGNOSTIC LUNG CANCER

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Background: Most of lung cancer patients diagnosed in advanced stage. The reasons for the delay of the diagnosis might be from patient and/or health care system. Currently, Indonesia, as a developing country in Asia, has National Health Insurance System (Jaminan Kesehatan Nasional) of which the patients is feasibly referred to the referral hospital without worrying the cost. In Persahabatan Hospital-the National Referral for Respiratory Diseases many cases have diagnostic delayed that might contribute to the prognosis. We had been conducting a study to evaluate diagnostic time and diagnostic cost to diagnose lung cancer. **Method:** We conducted an observational study in Persahabatan Hospital Jakarta of which newly diagnosed lung cancer patients were reviewed. We evaluated the time and cost needed from the first visit until definitive diagnosis by histopatology obtained. We also evaluated the factors that have correlated with time and cost of lung cancer diagnosis. **Result:** One hundred and ten subjects were enrolled in this study. Eighty four (76,36%) were male and 26 (23,64%) were female. The median age was 57 years old with range 26 to 86 years old. Data have shown that 53 (48,2%) subjects were diagnosed under target time (less than 2 weeks) but 57 subjects (51,8%) had diagnostic time more than 2 weeks. The median time of diagnostic was 15 days with the range of 1 to 68 days. Diagnostic delay was correlated with: early stage of the diseases, good performance status, no financial resource. The median cost of diagnosis was 13.025.381 Rupiahs (around 1000 US$) with range Rp. 1.083.000,- to Rp156.285.000,- (<100US$ to 11.000 US$). Subject who came with advanced stage, poor performance status, had complication of lung cancer and reffered to private hospitals had higher diagnostic cost. **Conclusion:** Median diagnostic time of lung cancer in Persahabatan Hospital Jakarta Indonesia was 15 days ranging from 1 to 86 days. Diagnostic time correlated with stage at admission, performance status at admission and financial support. The median cost of diagnosis was Rp. 13.025.381,- (around 1000 US$) with the range of Rp. 1.083.000,- to Rp156.285.000,- (< 100US$ to 10.000 US$). Cost of lung cancer diagnosis correlated with stage at admission, performance status at admission, source of financial support and complication related to lung cancer.

Keywords: diagnostic time, lung cancer, Developing Country

P3.11: PATIENT ADVOCACY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.11-002 IMMUNOTHERAPIES AND LUNG CANCER: EDUCATING THE GLOBAL LUNG CANCER COMMUNITY

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Background: Established in 2001, the Global Lung Cancer Coalition (GLCC) is the international 'voice' of lung cancer patients. Comprised of 35 non-government patient organizations in 24 countries and the UK, nearly half of member organizations

are run by fewer than five staff or are completely volunteer-run. Several meet the criteria of developing countries under the United Nations definition. The option of immunotherapy treatment is still relatively new in lung cancer and smaller, under-resourced member organizations have neither the expertise nor capacity to create credible educational materials on such a complex subject. The goal of this project was to offer information on immunotherapies to educate the global lung cancer community. **Method:** Created by coalition member representatives and reviewed by medical experts, the *Immunotherapy and Lung Cancer* factsheet provides an overview of immunotherapies and how they work. It has been professionally translated into the 17 primary languages of GLCC organizations and is available on the GLCC website. Member and non-member organizations and individuals can download the factsheet to help patients all over the world understand this new treatment option for lung cancer. **Result:** In the first six months after the October 2016 re-launch of the GLCC website, the factsheet was downloaded 276 times. At the December 2016 annual in-person meeting of GLCC, the coalition voted to prioritize and expand the effort to produce and translate additional educational materials. GLCC members are currently working on lung cancer screening and smoking cessation materials that will also be translated. **Conclusion:** An international coalition can take the lead in providing not just members but the broader global lung cancer community access to resources otherwise unavailable to them. Available in Chinese, Japanese, Danish, Slovenian, Dutch, Bulgarian, Swedish, German, Spanish, Italian, French, Norwegian, Turkish, Hebrew and English, the *Immunotherapy and Lung Cancer* factsheet, as well as future materials, are available to individuals, cancer providers and organizations from anywhere in the world to download, print and distribute.

Keywords: Immunotherapy, Education

P3.11: PATIENT ADVOCACY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.11-003 ADDARIO LUNG CANCER FOUNDATION PATIENT EDUCATION HANDBOOKS FILL A HEALTH LITERACY VOID FOR PATIENTS AND NURSE NAVIGATORS

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Background: A lung cancer diagnosis is devastating and patients are often left in shock and seeking trusted resources. The Addario Lung Cancer Foundation (ALCF) provides patient education and support resources, including the patient education handbook. The handbook is a comprehensive resource on lung cancer presented in an easy-to-navigate format, written for the general public, produced in multiple languages and updated to keep pace with emerging advancements. Previous studies have shown that health literacy is correlated with patient engagement and outcomes. The handbook fills a void for patients by providing physician-vetted information on all aspects of lung cancer diagnosis and treatment options. **Method:** Two studies were conducted to assess the value of the handbook to patients and nurse navigators. The first study was a qualitative market research study that included a total of 26 patient interviews, conducted by an independent market research firm in a blinded format. The second study was the COE Impact Study which assessed the usage of ALCF resources by 15 Centers of Excellence (COE) members (a network of community hospitals) through an online survey format. **Result:** Overall, patients had positive ratings for all ALCF resources and rated the handbook highest on a 1-5 point scale system (4.4) among the resources. Patients commented that the handbook is a "one-stop-shop" for everything they need to know about a lung cancer diagnosis. Patients noted it would be most valuable to have at the time of diagnosis but that it can help at any point in their patient journey. It delivers information in a straightforward way, mapping out treatment options and next steps and empowering patients to help them manage side effects and related lifestyle issues. Nurse navigators also rated the handbook highest among ALCF patient resources and many make the handbook part of the diagnosis conversation with each patient. **Conclusion:** The patient education handbook is a valuable tool for patients and nurse navigators, especially at diagnosis when the need for trusted information is greatest. Opportunities exist to continuously improve the patient education handbook including, reformatting it to be modular, coaching patients on how to use the information to dialog with their physicians and training nurse navigators on how to use the book when they first become a COE. ALCF hopes to reach and empower as many lung cancer patients as possible with valuable and accessible information that will guide their treatment options.

Keywords: Patient Education, Nurse navigator

P3.12: PULMONOLOGY/ENDOSCOPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.12-001 LUNG CANCER IN PATIENTS WITH INTERSTITIAL LUNG DISEASE: CLINICAL CHARACTERISTICS AND IMPACT ON SURVIVAL

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Background: Lung cancer (LC) is frequently associated with interstitial lung disease (ILD). However, there are few reports about the frequency or prognostic impact of LC in the ILD patients. **Method:** Patients diagnosed with ILD at Tosei general hospital, from January 2008 to August 2015 were retrospectively reviewed, and a total of 1070 patients with ILD had complete clinical and follow-up data. **Result:** Of the 1070 subjects, 65.8% were male, and the mean age was 68 years. Prevalence of histologically proven lung cancer was 5.6% (n=60). Of the 295 patients with idiopathic pulmonary fibrosis (IPF), 491 with Unclassifiable IIPs (UC-IP), 193 with collagen vascular disease IP (CVD-IP), 6.1% (n=18), 6.1% (n=36) and 2.6% (n=5) were affected by lung cancer. The most frequently encountered histologic types of carcinomas were Adenocarcinomas (n=23, 38%), and squamous cell carcinomas (n=21, 35%). Small-cell lung cancer was encountered for eleven cases (18%). Survival in patients with ILD-LC was significantly worse than in patients with ILD without LC (median survival, 39 months vs 96 months; P<0.001). In patients with UC-IP and with CVD-IP, survival in patients with LC was significantly worse than in patients without LC. However, there was not a significant difference in survivals in patients with IPF (median survival, 42 months vs 54.6 months; P=0.35). **Conclusion:** Prevalence of histologically proven LC was 5.6%. The most frequently encountered histologic types of carcinomas were Adenocarcinomas and squamous cell carcinomas . Survival in patients with LC was worse than without LC. However, in IPF patients, there was not significant difference.

Keywords: ILD, interstitial lung disease

P3.12: PULMONOLOGY/ENDOSCOPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.12-002 PATIENTS WITH MALIGNANT PLEURAL EFFUSION WHO SUCCEEDED PLEURODESIS HAVE A LONGER SURVIVAL RATE - A 10-YEAR FOLLOW-UP

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Background: Pleurodesis is often used to prevent re-accumulation of malignant pleural effusions (MPE). Intrapleural urokinase (IPUK) therapy facilitates lung re-expansion for patients with loculated MPE or trapped lung and allows subsequent pleurodesis. The MPE management has been traditionally regarded as a symptomatic treatment with rare mention of its impact on survival. Our preliminary study involved 26 patients showed successful pleurodesis translates into a longer survival. (BMC Cancer 2016;16:463) The successfully induced inflammatory response by sclerosing agent is supposed to prohibit tumor invasion and metastasis. **Method:** Part I. Three hundred and eighty-nine consecutive patients with symptomatic MPE underwent minocycline pleurodesis with (n = 184) and without (n = 205) antecedent IPUK therapy between September 2005, and August 2015, were recruited for pleurodesis outcome and survival analysis. Part II. The pleural fluid pro-inflammatory (IL-6, TNF-α), or anti-inflammatory (IL-1β, IL-10, TGF-β) cytokines before and after pleurodesis in fifteen patients with MPE between September 2015 and April 2016 were measured using Bio-Plex® Multiplex assays and correlated with the pleurodesis outcome and patient survival. **Result:** Part I. Patients numbering 109 (59.2%) responded to the IPUK therapy. The success rate of the subsequent pleurodesis was similar to that of the simple pleurodesis group (70.5% vs 69.0%; p = 0.804). In both groups, the patients who succeeded pleurodesis had a longer survival rate than those that failed (median, 259 vs 102 days; p < 0.001 and 414 vs 100 days; p < 0.001 respectively). Multivariate analysis showed that successful pleurodesis was an independent prognosticator (hazard ratio, 0.374; p < 0.001 and 0.271; p < 0.001 respectively). The differences remained when lung and breast cancer patients were studied separately. Part II. After instillation of sclerosing agent, pleural fluid IL-1β and IL-10, with a lesser degree were elevated in the group of successful pleurodesis. There was no discrimination in the TGF-β1, and IL-6 level between those succeeded and failed pleurodesis. No consistent change of TNF-α was observed in either group. **Conclusion:** Successful pleurodesis translates into a better survival rate promotes performing pleurodesis on lung re-expansion. The selective elevation of anti-inflammatory cytokines following pleurodesis suggests an anti-tumor effect. The change of TGF-β1 correlated with its dual role in cancer. While chronic inflammation might promote tumor formation, therapy induced acute inflammation might well hamper the process, and is indeed used therapeutically to inhibit tumor. Further studies are warranted to clarify the mechanism and provide opportunities to develop novel therapeutic strategies.

Keywords: malignant pleural effusion, pleurodesis, survival

P3.12: PULMONOLOGY/ENDOSCOPY -
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P3.12-003 OPTIMISED INHALER THERAPY IS SUPERIOR TO SUPPORTIVE CARE ALONE FOR DYSPNOEA IN PATIENTS WITH COEXISTING COPD AND LUNG CANCER

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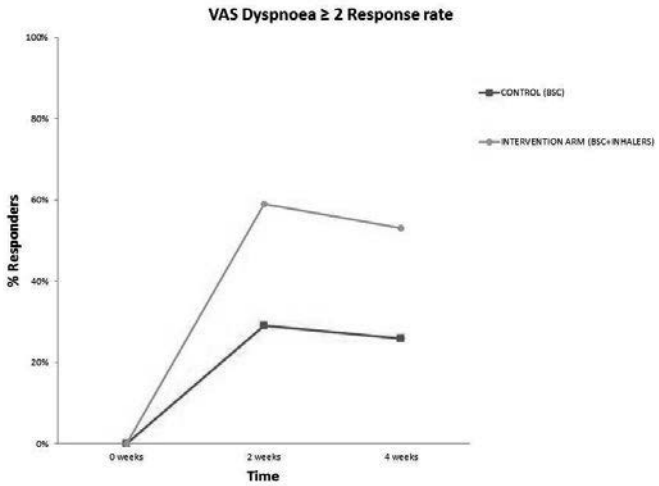
Background: Breathlessness is a common, debilitating symptom associated with both COPD and lung cancer. Opiates remain the mainstay of treatment for breathlessness in oncology. **Method:** Lung cancer patients were prospectively enrolled in this single-centre, open-label, randomised controlled trial. Eligible patients met British

Thoracic Society diagnostic criteria for COPD, had a visual analogue score (VAS) dyspnoea ≥ 4 and had other reversible causes for breathlessness excluded. Patients were randomly assigned (1:1) between the intervention arm of salbutamol 100 mcg, 2 puffs QDS and tiotropium 18 mcg OD +/- salmeterol 50 mcg/fluticasone 500 mcg 1 puff BD (if FEV_1<50% predicted) in combination with best supportive care (BSC) or to BSC alone (control). Control arm patients could continue on any short-acting bronchodilators and BSC included oral morphine and/or benzodiazepines. Patients underwent spirometry, 6 minute walk test (6MWT), VAS dyspnoea and quality of life questionnaires (QOLQ) at baseline and after 2 and 4 weeks. The primary endpoint was the proportion of patients with ≥ 2 point improvement in VAS dyspnoea at 4 weeks. **Result:** Among the intention to treat population (n=63), 53 patients (84%) had NSCLC and 10 (16%) had SCLC. The median baseline VAS was 7.1 and the median baseline FEV_1 was 1.5L (63% predicted). The primary endpoint response rate (RR) was higher in the intervention group n= 32 [RR: 53% (95%CI 35% to 71%)] than in the control group n= 31 [RR: 26% (95% CI 12% to 45%) p = 0.02].



There were no statistically significant differences between the groups for change in 6MWT or QOLQ between baseline and the 4 week assessments. **Conclusion:** For patients with co-existing COPD and lung cancers, VAS dyspnoea is significantly improved by the addition of inhaled therapies to best supportive care. This study highlights the importance of diagnosing and treating COPD in all lung cancer patients.

Keywords: breathlessness, inhalers, copd

P3.12: PULMONOLOGY/ENDOSCOPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.12-004 MAIDONG ON THE PREVENTION AND TREATMENT OF RADIATION PNEUMONITIS IN MICE C57BL/6

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Background: Radiation pneumonia is the most serious complications after radiotherapy of thoracic tumor. We use the Maidong extract as essential prescription, to assess its prevention and control effect of radiation pneumonia, and to explore its possible mechanism. **Method:** 60 C57BL/6 mice were divided into:(1) blank control group, (2)merely irradiated group, (3)Chinese medicine (Maidong) group, and (4) western medicine (dexamethasone combine cefalexin)group, each group of 15 mice. Maidong extract was given 1 times per day to the mice of Chinese medicine group, dexamethasone and cefalexin were given 1 times per day to the mice of western medicine group by intragastric administration from 4 days prior to the irradiation day, last for 2 weeks; merely irradiated group and blank control group were given physiological saline instead. In addition to the blank control group, other groups were given chest a 6MV-X-ray single-wide irradiation of 18Gy.Each group randomly sacrificed 5 mice at 24 hours, 4 weeks, 12 weeks after irradiation. Took the blood, left lungs into homogenate and fixed right lungs in formaldehyde solution for research. **Result:** 1, Compared to the merely irradiated group, the level of plasma IL-6(P<0.01), TNF-α(P<0.05)and TGF-β1(P<0.01), hydroxyproline(P<0.05) and MDA (P<0.01)content of the lung tissue in the Chinese medicine group mice were significantly reduced, SOD activity was significantly enhanced (P<0.01),and the expression of MMP-2(P<0.01) and TIMP-2(P<0.05) proteins were significantly reduced. 2, Compared to the western medicine group, the level of plasma IL-6, hydroxyproline content and SOD activity of the lung tissue, the expression of TIMP-2 protein didn't show significant difference(p>0.05); because of the increase of the level of plasma TNF-α and TGF-β1(P<0.05), MDA (P<0.01)content of the lung tissue in western medicine group mice,the Chinese medicine group were significantly different at 12week; the expression of MMP-2(P<0.05) protein the Chinese medicine group were significantly higher than western medicine group at 4week, but didn't show significant difference at 12week. **Conclusion:** Maidong has certain effect on the prevention and control of radiation pneumonia, the preventive effect may be achieved through the many kinds of approaches: Maidong is relatively more enduring than dexamethasone combine cefalexin, and Maidong had less side effects.

Keywords: Mice, radiation pneumonia, Maidong

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-001 CLINICAL SIGNIFICANCE OF CHEST TOMOGRAPHY CHARACTERISTICS IN NON SMALL CELL LUNG CANCER PATIENTS WHO RECEIVED ANATOMIC RESECTION

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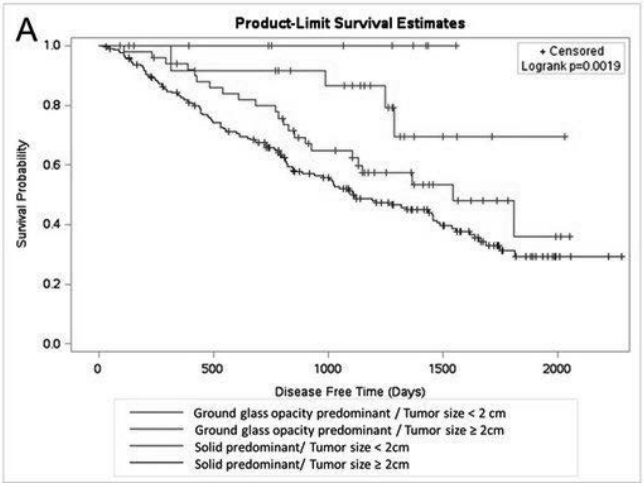
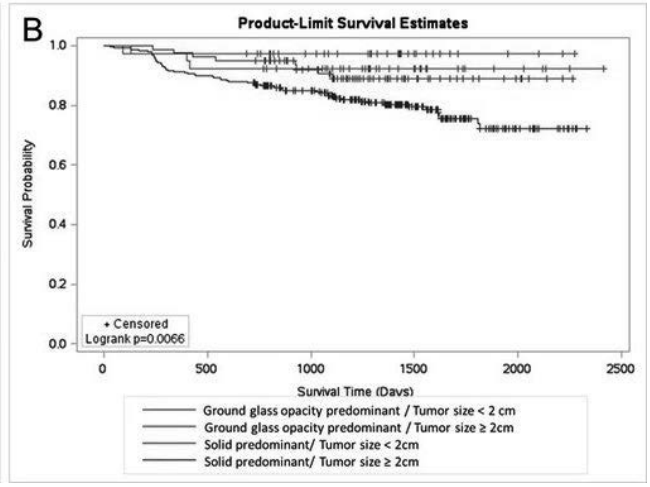
Background: Characteristics of CT image, including tumor size and component were correlated to survival. However, most studies discuss the survival impact of image characteristics in early clinical stage populations. No articles were discussed the issue from the view of pathology stage, ie. actual disease presentations of non small cell lung cancer patients who presented as resectable disease. The aim of study was to analyze radiologic and pathologic findings of non small lung cancer patients who received curative resection in order to clarify he clinical correlation between image characteristics and survival impaction. **Method:** From 2010 January to 2014 May, 440 patients who underwent curative resection, ie. anatomic resection and mediastinal lymph node resection, were included and medical record were reviewed retrospectively. Chest CT characteristics, including tumor size and consolidation-tumor ratio, were re-evaluated and re-measured by radiologists. The correlation between image and pathology characteristics and its survival impaction were analyzed. **Result:** We identified tumor size presented in CT and pathologic measurement were highly coincidence. (p-value<0.001) The presentation of pure GGO and GGO predominant lesion were adenocarcinoma (p< 0.001) Majority of these lesions (61/76, 80.2 %) were well differentiated. (p<0.0001). In addition, pure GGO lesion has less risk for visceral pleura (p < 0.0001), angiolymphatic invasion (p < 0.002), and lower risk with N1 lymph node metastasis (p = 0.004) In addition, we found excellent disease free and disease free survival for patients who was identified GGO predominant lesion with size ≤ 2cm. (Figure 3) The difference of disease free (p= 0.0032, log rank test; Figure 3A) and overall survival (p= 0.0066, log rank test; Figure 3B) of these four subgroups was statistically significance.





Conclusion: Non small cell lung cancer patients who presented with ground glass opacity were corrected with well differentiated adenocarcinoma. In addition, less visceral pleura invasion, less angiolymphatic invasion, and less intrapulmonary lymph node metastases risk were also identified. Our results showed lung cancer patients who presented as GGO predominant lesions and size less than 2 cm may had excellent disease free and overall survival.

P3.13-002 REDUCED DOSE PERFUSION CT OF LUNG CANCER USING A 16-CM COVERAGE SCANNER: EFFECTS OF RESPIRATORY MOTION CORRECTION ON PERFUSION ASSESSMENT

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Background: Perfusion CT parameters have showed promising results for evaluation of tumor response and follow-up. However, clinical implications in patients with lung cancer have been relatively limited due to the fact that perfusion CT is performed while the patient is breathing and high radiation dose. Therefore, the purpose of this study was to evaluate the effects of respiratory motion correction on perfusion assessment of lung cancer in a reduced dose perfusion CT using a 16-cm coverage scanner. **Method:** Eighty four patients with primary lung cancer who underwent a reduced dose perfusion CT (80 kVp, 80 mA) were enrolled in this study. Each perfusion CT study included 25 repeated dynamic CT scans obtained using the volume perfusion software and was reconstructed with hybrid iterative reconstruction at a strength level of 50%. Two observers measured blood flow (BF), blood volume (BV), and permeability of the entire tumor with and without the use of non-rigid registration algorithm. Single-measure intraclass correlation coefficients (ICC) were calculated and interobserver reproducibility for parameters obtained with two different manners were assessed through Bland-Altman analyses. **Result:** CTDIvol obtained with each of the dynamic perfusion CT in this study was 36.16 mGy and the estimated mean effective dose ranged from 2.02 mSv to 4.0 mSv. Using non-rigid registration, all ICC values for BF, BV, and permeability were increased (0.982~0.994 to 0.988~0.997) compared with those obtained before application of non-rigid registration. All ICC values of lower lung tumor (0.991~0.998) or tumor ≤ 3 cm (0.989~0.998) were higher than those of upper lung tumor (0.925~0.984) or tumor > 3 cm (0.975~0.996). Using non-rigid registration, all 95% limits of interobserver reproducibility were narrowed compared with those obtained before application of non-rigid registration, regardless of tumor location or tumor size, except those of BV for tumors located in upper lung and tumors > 3 cm. **Conclusion:** Perfusion assessment of lung cancer using a reduced dose perfusion CT scan is clinically feasible and application of respiratory motion correction using non-rigid registration can reduce measurement errors.

Keywords: Motion correction, lung cancer, perfusion CT

P3.13-003 THE LUNG CANCER PROGNOSTIC INDEX – A RISK SCORE TO PREDICT OVERALL SURVIVAL AFTER THE DIAGNOSIS OF NON-SMALL CELL LUNG CANCER

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Background: Outcomes in Non-Small Cell Lung Cancer (NSCLC) are poor but heterogeneous, even within TNM stage groups. To improve prognostic precision we aimed to develop and validate a simple model for the prediction of overall survival (OS) using patient and disease variables. **Method:** The study population included 1458 patients from three independent cohorts. Associations between baseline variables and OS were estimated in a derivation cohort from a prospective single-centre study (n=695) using Cox proportional hazards regression. Points were allocated to variables based on the strength of association to create the Lung Cancer Prognostic Index (LCPI). Model performance was assessed (by a c-statistic for discrimination and Cox-Snell residuals for calibration) in two independent validation cohorts (n=479 and n=284). **Result:** Three disease-related and six patient-related variables were found to predict OS: stage, histology, mutation status, performance status, weight loss, smoking history, respiratory comorbidity, sex and age. Patients were classified according to predicted LCPI score. Two-year OS rates according to LCPI in the derivation and two validation cohorts respectively were 84%, 77% and 68% (LCPI 1: score≤9); 61%, 61% and 42% (LCPI 2: score 10-13); 33%, 32% and 14% (LCPI 3: score 14-16); 7%, 16% and 5% (LCPI 4: score ≥15). Predictive performance (Harrell's c-statistics) were 0·74 for the derivation cohort, 0·72 and 0·71 for the two validation cohorts. **Conclusion:** The LCPI contributes additional prognostic information which, in conjunction with other validated tools and evidence based management guidelines, may be applied to counsel patients, guide clinical trial eligibility, or standardise mortality risk for epidemiological analyses.

Keywords: Prediction model, Prognosis, NSCLC

P3.13-004 PROSPECTIVE STUDY OF SEQUENTIAL ULTRA-LOW THEN STANDARD DOSE 18F-FDG PET/CT SCANS FOR LUNG LESION DETECTABILITY

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Background: Lung cancer screening with low-dose computed tomography (CT) is better than chest X-rays but is non-specific. Accuracy is improved with positron emission tomography (PET), at a cost of additional radiation. We had previously reported on simulated low-dose PET imaging and demonstrated that $10x10^6$ net true counts is sufficient to generate images with acceptable diagnostic quality. We now hypothesize that we can maintain image quality with a 92% reduction of fluorodeoxyglucose (FDG) tracer activity from 6 mCi to 0.5 mCi. **Method:** Nine patients have been scanned with two sequential PET/CT scans on the same day. The patient is first scanned with 0.5 mCi FDG and a low-dose CT protocol, followed by a routine PET/CT with 6 mCi FDG. PET data from the standard-dose scan were manipulated to emulate various noise (dose) levels, corresponding to nine pre-defined true count levels. Data were matched to the level of the low-dose scan, to compare noise statistics to a ground truth and to directly validate our methods. The data were reconstructed, with many independent noise realizations, and the images were reviewed. Ten lesions, in seven patients, were identified as having the size and uptake consistent with those found in early disease. For a given count level, the corresponding images were determined to be acceptable if lesion detectability was comparable to that found in the full-statistic image set. Detection performance was determined automatically by machine learning, namely, convolution neural networks trained by 4 previous observer responses. **Result:** Lesion detection accuracy was evaluated in 4458 total image sub-volumes. Regions containing both target lesions (2627 samples) and healthy lung background (1831 samples) were used to assess sensitivity and specificity for the task at all noise levels. The table shows data across the 4 observer models.

Mean Sensitivity & Specificity by True Count Groups							
True count/ millions	<0.5	0.5-1	1-2	2-5	5-10	10-20	>20
Mean sensitivity/%	0.35	18.85	62.35	85.40	95.73	96.23	96.42
Mean Specificity/%	6.64	6.93	20.43	66.54	93.55	96.87	98.25

Conclusion: Low-dose PET can provide good performance for lesion detection within the true count range $5\text{-}10\times10^6$.

Keywords: Positron emission tomography, lung nodule, low-dose

P3.13-005 CHARACTERISTICS OF PRIMARY LUNG CANCER ON PET/CT IMAGING IN THE SOUTH AFRICAN POPULATION

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Background: The incidence of primary lung cancer in developing countries has increased and it constitutes the most common cause of cancer related mortality. Some radiological features can be predictive for different histologies and have prognostic utility. One of the features of imaging in the Fleischner Society guideline is common occurrence in the upper lobe with predilection for the right lung. **Method:** A retrospective audit was done to compare the characteristics of primary lung cancer in patients in our environment. Images and patient reports were obtained from our local database archives or from the hospital records. The location of the primary was defined as peripheral if located in the outer third of the lung parenchyma on axial CT or PET/CT images, and defined as central if located anywhere else. Lobe location was also recorded for each primary. **Result:** We reviewed 42 patients with histologically confirmed lung cancer that were referred for PET/CT imaging. The age range was 37-80 years. Sixty nine percent (n=29) were males 31% (n=14) were females. The most common histologic subtype was adenocarcinoma (48%), followed by squamous cell lung cancer (40%), and small cell lung cancer (12%). Most of the primary pathology were in the right lung (60%, n= 25) as compared to the left lung (40%, n=17). The upper lobes were more commonly affected (64%, n=27), followed by the lower lobes (33%, n=14), and right middle lobe (3%, n=1). Sixty percent (n=25) of tumors were centrally located, of which 64% were of the histologic subtype squamous cell ca. Our findings also showed that 26% (n=11) of patients had metastases to ipsilateral lobes, and 24% (n=10) had metastases to the opposite lung. There were 22% (n=22) of patients that had only nodal metastases and 12% (n=5) had both nodal and visceral metastases. Nineteen percent of patients (n=8) had no evidence of nodal or visceral metastases. **Conclusion:** Our findings conform to those found in literature that primary lung cancer involves the right lung more often and involves the upper lobes more commonly. It also showed that squamous cell lung cancers are mostly central and

most adenocarcinomas are peripheral in location.

Keywords: Primary lung cancer, Peripheral, Central, metastases

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-006 CORRELATION BETWEEN CT MORPHOLOGY AT THE DIAGNOSIS AND EGFR STATUS IN PATIENTS WITH ADENOCARCINOMA OF THE LUNG

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Background: Aim of the study was to correlate epidermal growth factor (EGFR) mutation status with computed chest tomography (CT) image patterns at the diagnosis in patients with lung adenocarcinoma. **Method:** Patients diagnosed between January 1, 2015 and March 3, 2017 with available CT and EGFR mutation status were analyzed. The maximal diameter of the nodules, shape (mix, solid) , presence of an air bronchogram and calcification, specula, incision, round shape, central necrosis, pleural connection, UH pre e post were evaluated. **Result:** 87 patients (52 males, median age 66 years, range 43-87) were enrolled. 9, 36 and 42 patients had stage II, III and IV, respectively. EGFR mutations were found in 22 patients (25.3%; 1 exon 18, , 15 exon 19 deletions and 6 exon 21 mutations) and were more frequently among females (45.2% versus 18.6% males, p=0.020) and never smokers (77.8% vs 11.8% smokers, p<0.001). The median maximal diameter of the nodules was smaller in mutated patients (30.5, range 15-74 mm) than in wild-type patients (45.0, range 13-110 mm; p=0.010). Tumors with exon 21 mutations were smaller than wild type tumors (p=0.014). Mutations were statistically more frequent in solid pattern (30.6% vs 0 mixt, p=0.010). A higher number of mutations, not statistically significant, were also found in presence of tumors with regular margins (31.9% vs 17.5% spiculati, p=0.14), no incisions (30% vs 5.9% with incision, p=0.059), no central necrosis or calcification (26.3% vs 14.3% with central necrosis or calcification, p=0.67), no calcification (26.3% vs 14.3% with calcification, p=0.67). Median tumor density was 35 UH in wild type vs 40.0 UH in mutated tumors (p=0.29) and 70 UH in wild type vs 80 UH in mutated tumors (p=0.17), before and after contrast, respectively. **Conclusion:** Adenocarcinomas with EGFR mutations were associated with smaller tumors and with solid pattern.

Keywords: EGFR mutation, CT morphology, NSCLC

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-007 A FEASIBLE FOLLOW-UP PROGRAM USING FDG-PET/CT FOR ASYMPTOMATIC POSTOPERATIVE NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: There is no consensus on the best program for postoperative follow-up and surveillance after curative resection for non-small cell lung cancer (NSCLC) patients at this time. We reported that the diagnostic capability of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was high in postoperative NSCLC patients without clinical and radiological evidence of recurrence (ICVTS 2012). However, there were some problems, such as radiation exposure and its cost. The aim of this study was to propose a more feasible follow-up and surveillance program using FDG-PET/CT for asymptomatic postoperative NSCLC patients. **Method:** Between January 2005 and December 2013, a total of 172 NSCLC patients (98 males and 74 females; mean age: 67.8 years) underwent potentially curative operations, and follow-up FDG-PET/CT was performed in patients without clinical or radiological evidence of recurrence for at least once a year in principle. A total of 481 FDG-PET/CT studies were entered and retrospectively reviewed. **Result:** The histological type was adenocarcinoma in 129 patients, squamous cell carcinoma in 36 and others in 7. The pathological stage was Stage 0 in 2 patients, IA in 106, IB in 28, IIA in 15, IIB in 7, and IIIA in 14 (UICC 7th. edition). Surgical procedures were pneumonectomy in 5 patients, lobectomy in 139, segmentectomy in 14, and partial resection with a sufficient margin in 14. The mean time interval between the initial surgery and latest follow-up was 49.1 months. During the follow-up period, the mean number of times that FDG-PET/CT was performed per patient was 2.8. FDG-PET/CT correctly diagnosed recurrence in 31 of 32 (96.9%) patients and 41 of 42 (97.1%) recurrent sites. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 96.9, 97.1, 88.6, 99.3, and 97.1%, respectively. In 6 (3.5%) patients, other diseases were detected and treated appropriately. On the other hand, FDG-PET/CT performed within 3 years after the operation detected significantly more FDG-positive lesions compared to after 4 years (10.0 vs. 2.0%, respectively, p=0.007). Additionally, in 147 patients with recurrence after curative operations between 2005 and 2013 in our institute, recurrence occurred in 123 patients (83.7%) within 3 years. **Conclusion:** FDG-PET/CT has a high capability to detect recurrence in asymptomatic NSCLC patients after a potentially curative operation. However, it might be sufficient to perform FDG-PET/CT up until 3 years after the operation. A large scale multi-institutional randomized control trial is warranted to ascertain the benefit of surveillance with FDG-PET/CT.

Keywords: Non-small-cell lung cancer, Positron emission tomography/computed tomography, postoperative follow-up and surveillance

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-008 LUNG CANCER ASSOCIATED WITH CYSTIC AIRSPACES: CLINICAL, IMAGING, HISTOPATHOLOGICAL AND MOLECULAR CORRELATION

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Background: "Lung cancer associated with cystic airspaces" is a rare radiological entity that is becoming more frequently encountered on imaging studies and has been gaining more attention since the widespread use of CT for lung cancer screening. The goal of this retrospective study is to investigate and correlate clinical, imaging, histopathological and molecular findings in patients presenting with this type of lung cancer. **Method:** Between January 2014 and April 2017, 13 patients presented at the Multidisciplinary Thoracic Oncology Tumour Board with this rare entity. Clinical, histopathological and molecular data were collected and imaging studies were reviewed for the presence of emphysema, size, morphologic classification and findings on ^{18}F-FDG-PET. **Result:** Median age at the time of diagnosis was 69 years (53-86 years) with a male/female ratio of 8:5. Ten out of 13 patients were smokers. Eleven patients (11/13) had no previous oncological history. Two patients with previous oncological history both had a history of head-and-neck and stage IA lung cancer. Imaging findings showed emphysema in 7 cases. Four patients had type I, 1 patient type II, 4 type III and 4 type IV morphology. Median diameter for the type I, II, III and IV lesions was 20 mm (17-43), 20 mm, 60 mm (25-67) and 46 mm (37-77) respectively. Lesions were more frequent in the right upper (4/13) and lower lobe (4/13). FDG-PET-scan was available in 11 patients and showed high uptake in all patients who presented with a solid aspect of the associated tumour. Four patients (4/13) presented with stage IV at diagnosis. Other stages varied: IA (4/10), IB (1/10), IIA (1/10), IIIA (2/10) and IIIB (1/10). Adenocarcinoma was found in 11 patients (11/13) and squamous cell carcinoma in 2 (2/13). Molecular genotyping for EGFR, ALK and ROS-1 was available in 10 patients (10/13). None of the patients showed positivity for ALK-immunohistochemistry. A single patient showed an exon-18 mutation in the EGFR gene. One patient showed a translocation at the 6q22 breakpoint of the ROS-1 gene. In one patient, a p.Gly469Ala B-RAF mutation was present. Two patients showed a mutation in the exon 2 of the KRAS gene (exon2 c/35G>C;p.Gly 12Ala and c/35G>T;p. Gly 12Val). **Conclusion:** In this series, 5 out of 10 patients with a "lung cancer associated with cystic airspaces" showed a molecular alteration. This suggests that targeted molecular profiling is mandatory in this subgroup. Larger series are needed to confirm these findings.

Keywords: Computer Tomography, molecular profiling, lung cancer associated with cystic airspaces

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-009 RAPID DETECTION OF LUNG CANCER BY FLUORESCENT IMAGING USING A Γ-GLUTAMYLTRANSPEPTIDASE-ACTIVATABLE FLUORESCENT PROBE

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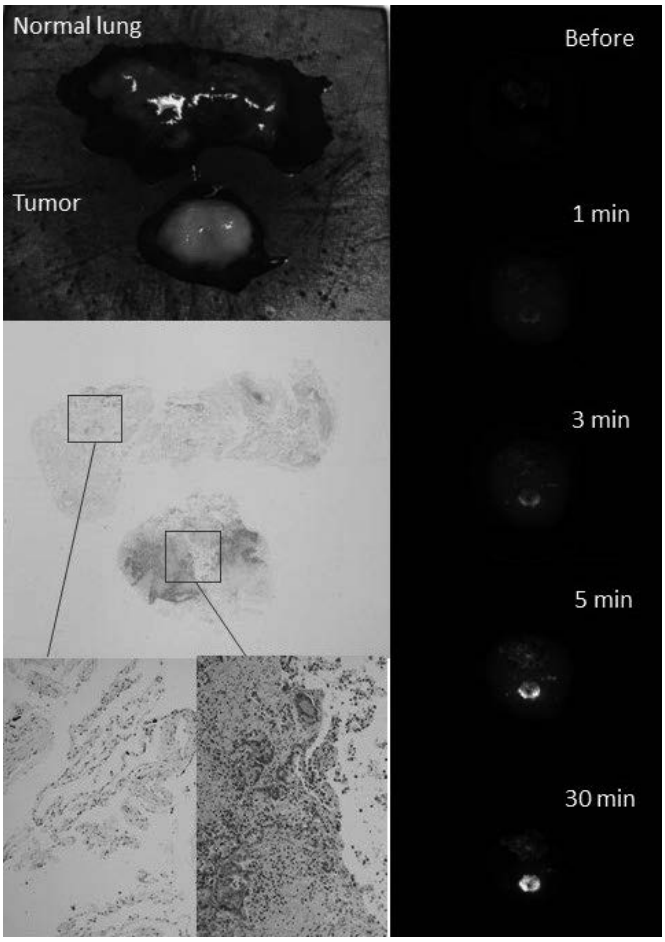
Background: Visualizing the spread of cancer cells in lung cancer surgery is sometimes difficult. γ-Glutamyl-transpeptidase (GGT) is a cell surface-associated enzyme that is overexpressed in various type of human cancers. γ-Glutamyl hydroxymethyl rhodamine green (gGlu-HMRG), an activatable fluorescent probe, is non-fluorescent under a neutral pH and normal cellular environment. However, it becomes highly fluorescent upon reaction with GGT. We evaluated *ex vivo* fluorescent imaging of lung cancers using the GGT-activatable fluorescent probe. **Method:** Between April 2011 to November 2014, 116 resected cancer cells (91 primary lung cancers, 21 pulmonary metastases, and 4 pleural disseminations) were prospectively included in this study. Each tumor was analyzed by first taking a baseline image before gGlu-HMRG was sprayed onto the freshly resected specimen (termed N0; fluorescent intensity of normal lung, T0; that of lung cancer), and then by taking fluorescent images 30 min after spraying (N30 and T30) with the Maestro In-vivo imaging system (PerkinElmer Inc.). Positive fluorescent activity was defined as follows: in cases where fluorescence was observed only in tumor tissues, $\Delta N(=N30-N0) < 0$ and $\Delta T(=T30-T0) < 0$, in cases where fluorescence was observed in both normal and tumor tissues, $\Delta N > 0$ and $\Delta T/\Delta N > 1$.

Result:



In primary lung cancer, 61 of 91 (67%) cases rapidly developed fluorescent activity. In cases with pulmonary metastases, 15 of 21 (71.4%) cases showed positive fluorescent activity. Four disseminated pleural nodules all showed positive fluorescent activity (100%). Age, gender, tumor size, tumor marker, histology (adenocarcinoma (Ad) vs. non-Ad, squamous cell carcinoma (Sq) vs. non-Sq), pleural invasion, and angio-lymphatic invasion were not significant factors influencing fluorescent intensity. **Conclusion:** Fluorescence imaging with gGlu-HMRG may become one of the most powerful tools for accurate staging by rapidly detecting cancer cells and thus become highly useful for cancer resection.

Keywords: activatable fluorescent probe, lung cancer, Fluorescent imaging

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-010 CORRELATION BETWEEN HRCT FEATURES OF PULMONARY PURE GROUND-GLASS NODULES AND THE NEW PATHOLOGIC CLASSIFICATION OF LUNG ADENOCARCINOMA

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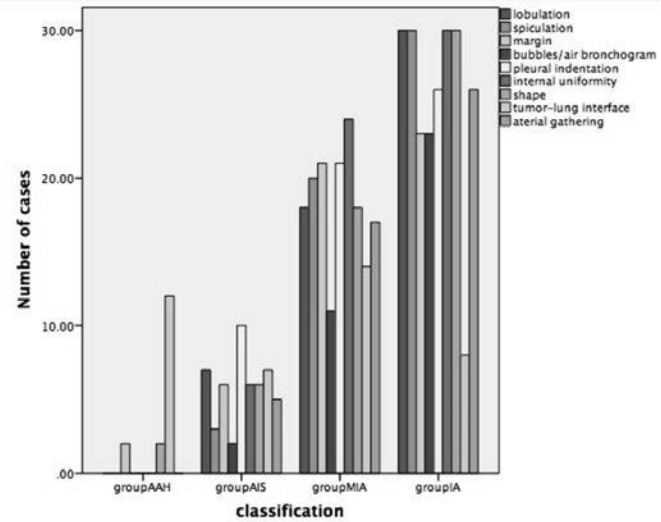
Background: We analysed the correlation between the new pathologic classification of lung adenocarcinoma and radiologic findings of early invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as PGGN on HRCT, and evaluated the values in the diagnosis of pathologic classification of lung adenocarcinoma with PGGN on HRCT. **Method:** Retrospective analysis of 123 lesions (16AAH, 35AIS, 35MIA, 37IA) with PGGN on HRCT with T1N0M0 lung adenocarcinoma or AAH from January 2014 to June 2014 in shanghai chest hospital. There were 93 females and 30 males, with a median age of 58 years old. Statistical relationship between the 2015 World Health Organization Classification of the lung adenocarcinoma and radiologic findings of PGGN were analyzed**,** then sceened out the best predictors, created a modal and verified it. **Result:** The Pearson correlation coefficient(P<0.05) between pathological types and all CT scan morphologic features showed a significant correlation. The logarithm linear correlation cient showed the CT feathures(lobulation, spiculation, pleural indentation, aterial gathering, bubbles/air bronchogram, shape,margin,internal uniformity) had a positive correlation with pathological types excluding tumor-lung interface. These scale variables as maximum lesion area on CT scan, lesion size in cranial-caudal direction, average density of lesion and the corresponding lung's average background density were significant correlation with pathological types. Multinomial logistic regression analysis showed that the best predictors were spiculation, internal uniformity, lesion size in cranial-caudal direction,average density of lesion, gender in turn. Then the multinomial logistic regression model was built, a likelihood ratio test showed that 70.7% of the cases were classified correctly overall, and the predicted value of AAH was up to 92.9%.



Conclusion: The HRCT characteristics of PGGN were significant correlated with the new pathologic classification of lung adenocarcinoma. The pathologic types of PGGN should be evaluated by HRCT, and the best predictors were speculation, internal uniformity, lesion size in cranial-caudal direction, average density of lesion and gender.

Keywords: lung adenocarcincoma, pathologic subtypes, ground-glass nodule

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-011 USE OF VOLUME GROWTH AND FLUOR-DEOXY-GLUCOSE POSITRON EMISSION TOMOGRAPHY IN EVALUATING INDETERMINATE LUNG NODULES IN LUNG CANCER SCREENING

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Background: Indeterminate lung nodules detected during lung cancer screening with low dose computed tomography (CT) present a challenge in distinguishing between malignant and benign disease. Our aim for this study is to compare the sensitivity and specificity of flour-deoxy-glucose positron emission tomography (FDG-PET), volume doubling time (VDT) and a combination of both in the diagnostic workup of indeterminate lung nodules in lung cancer screening. **Method:** The Danish Lung Cancer Screening Trial (DLCST) is a randomized controlled trial with heavy smokers between 50-70 years of age. The screening group underwent 5 annual rounds with low dose CT scan of the thorax. When a lung nodule was detected, participants could either be referred to diagnostic workup, 3-month follow-up or continue with the screening program. We included participants who had a 3-month follow-up scan. Before the follow-up scan was conducted, the participants received a FDG-PET scan. Nodules that were resected or stable for at least 2 years were included. FDG-uptake was categorized from most likely benign (uptake less than background uptake in the mediastinum) to most likely malignant (uptake as mediastinum or higher). VDT was calculated from nodule volume measurements from two time points closest to the FDG-PET scan date. We used a commercially available and validated semi-automated nodule evaluation software. Based on VDT the nodules were divided into three groups. Regressing nodules (VDT<0), slow growing nodules (VDT > 365 days - less likely malignant) and fast-growing nodules (VDT < 365 days – most likely malignant). Finally, we divided combined outcome into three groups: 1. Both tests suggest benignancy, 2. One of the tests suggest malignancy and 3. Both tests suggest malignancy. We used receiver operating characteristic (ROC) curves to compare sensitivity and specificity for the ability to predict a malignant or benign nodule. **Result:** A total of 87 lung nodules in 76 individuals were included. 68/87 (78%) were solid nodules. 41.5% were malignant. Nodule size ranged between 5 mm – 20 mm in largest diameter. The sensitivity and specificity of VDT alone were 61% and 90% respectively. For FDG-PET the sensitivity was 62% and specificity was 90%. Combined use of both tests showed an improvement in test sensitivity to 82% and a specificity of 79%. **Conclusion:** Combined use of FDG-PET and VDT is recommended in the diagnostic workup of indeterminate lung nodules in lung cancer screening.

Keywords: indeterminate lung nodules, FDG-PET, Volume-growth

P3.13-012 FAST FOURIER TRANSFORM ANALYSIS FOR THE OUTLINE OF PULMONARY NODULES ON COMPUTED TOMOGRAPHY IMAGES

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Background: Primary lung cancers show more complicated outline on computed tomography (CT) images of the chest than metastatic lung tumors or benign inflammatory lung disease. This feature is proving to be useful for clarifying the diagnosis of pulmonary nodules. The degree of complexity of pulmonary nodules seen on chest CT images is usually described subjectively by such designations as spiculated, irregular, and so on. Up to now there have been no established methods for evaluating a tumor outline numerically. In this study, we applied fast Fourier transform (FFT) analysis to pulmonary nodules on CT images to evaluate variations in the outlines of primary versus metastatic lesions or benign inflammatory lesions. **Method:** Sequential cases of 72 histologically proven primary lung cancers (group PL), 54 metastatic lung tumors (group MT), and benign inflammatory nodule (group BN) were included in the study. The average ± SD diameters of tumors in groups PL, MT, and BN were 18.9±7.4 mm, 12.2±6.1 mm, and 18.0±5.3 mm, respectively. For the measurements, the outline of each tumor on chest CT images was described using polar coordinates. The data were converted to rectangular coordinates, yielding wave data of the tumor outline. The FFT was then used to analyze the wave data. The complexity index (Cxi) and high frequency percent (HF%) were determined for each tumor. The Cxi was defined as the sum of the amplitude of all harmonics over a fundamental frequency. The HF% was defined as the percent of the high frequency components against Cxi. **Result:** The Cxi was 10.3±6.7 mm, 3.2±2.4 mm, and 8.0±3.8 mm, in groups PL, MT, and BN, respectively. The Cxi was significantly smaller in group MT than group PL ($p<0.0001$) and group BN ($p=0.0003$). Cxi was significantly correlated with tumor diameter in each group. Discriminant analysis showed a significant difference ($P<0.0001$) in Cxi between groups PL and MT with regard to tumor diameter. "Cutoff=0.127*DT+2.23" provided the cutoff value that yielded the highest diagnostic accuracy for distinguishing primary lung cancers from metastatic lung tumors. Use of this cutoff line resulted in a sensitivity of 95.8%, specificity of 81.5%, and accuracy of 89.7%. The HF% was 1.82±2.23%, 3.78±3.93%, and 5.29±1.28, in groups PL, MT, and BN, respectively. The HF% was significantly ($p<0.0001$) smaller in group PL than group BN. **Conclusion:** Fast Fourier transform analysis of tumor outlines appears useful for distinguishing primary lung cancer from the other diseases.

Keywords: Fast Fourier transform analysis, Complexity, computed tomography

P3.13-013 ASSOCIATION OF PLEURAL TAGS WITH VISCERAL PLEURAL INVASION OF PERIPHERAL LUNG CANCER

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Background: Visceral pleural invasion (VPI) is an important prognostic factor for patients with peripheral lung cancer, but its accurate preoperative evaluation with CT is difficult. Pleural tags, which are defined as one or more linear strands that extend from the tumor surface to the pleura, are sometimes seen in peripheral lung cancer that does not abut the pleura. However, studies evaluating the correlation of pleural tags with VPI are limited. The aim of this study was to evaluate the association of pleural tags with VPI of peripheral lung cancer, especially focusing on the type of pleural tags. **Method:** A total of 183 patients were retrospectively analyzed. They underwent pulmonary resection in our hospital between January 2009 and December 2015 for peripheral lung cancer ≦2 cm in solid tumor diameter and dose not abut the pleura. Forms of pleural tag were classified as follows; linear tag, linear tag with soft tissue component at the pleural end, and soft tissue cord-like tag. The relationships between VPI and clinical factors including the forms of pleural tag were analyzed using chi-square for independence tests, and then multivariate logistic regression models were applied. **Result:** Histologically, 23 (12.6%) patients were proven to have VPI. Overlap and multiple forms of pleural tags were frequently seen. Multivariate analysis revealed that tumors with linear tag with soft tissue component at the pleural end had significant association with VPI ($p = 0.008$). Sensitivity and specificity were 47.8% and 83.8%, respectively, in the prediction of VPI with this type of pleural tag. Presence of multiple linear tags also was associated with VPI ($p = 0.036$). **Conclusion:** Specific forms of pleural tag can predict VPI of peripheral lung cancer ≦2 cm in solid tumor diameter and dose not abut the pleura.

Keywords: visceral pleural invasion, peripheral lung cancer, pleural tag

P3.13-014 PREDICTION OF SURVIVAL WITH 18F-FDG-PET/CT EARLY DURING ERLOTINIB TREATMENT IN NSCLC PATIENTS – A COMPARISON OF FOUR EVALUATION METHODS

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Background: Erlotinib treatment is offered to NSCLC patients in a palliative setting also in EGFR wildtype (EGFR-wt) patients because we know that some of these patients will benefit, However, in order to evaluate the effect of treatment, we wait for 8-12 weeks before performing a CT scan, since the effect is rather subtle especially in EGFR-wt patients. The purpose of this study was to evaluate which method for evaluating change in 18F-FDG uptake is the best predictor for survival. **Method:** 18F-FDG-PET/CT scans from 56 NSCLC patients (48 EGFR-wt and 8 EGFR mutated) performed before and after 7-10 days of erlotinib treatment were analysed with four different methods for response to treatment including visual evaluation, and three semi quantitative methods measuring % change in SULpeak, SULmax and TLG, with a range of cut-off levels determining response, stable disease and progression. A direct comparison of the semi-quantitative parameters was performed using univariate cox regression, linear regression and ROC analysis for progression free survival (PFS) and overall survival (OS) < the median. Kaplan-Meier analysis was used to estimate PFS and OS for the response categories. **Result:** Both %SULpeak, % SULmax and %TLG were correlated to PFS and OS. The strongest linear correlation was found for %TLG ($R=0.51$, $p< 0.001$). The ROC analysis showed the highest AUC for predicting OS for %TLG (0.70 (0.56-0.85) with a sensitivity of 0.68 and a specificity of 079. All the semi-quantitative methods showed a statistical overall difference in PFS for the three response categories at some cut-off levels for %SULmax both at 15 and 25%, for %SULpeak at 20 and 25% and for %TLG at 45/75, 50, 30, 25 and 20% cut-off. Visual evaluation failed to differentiate between response categories. For OS %TLG at 4 different cut-off levels and SULpeak at the three lowest cut-off levels showed a statistical overall difference in OS, both visual and %SULmax did not. **Conclusion:** The choice of method for analysis is not clear-cut, but %TLG as suggested by the PERCIST 1.0 is not inferior to other methods, and visual evaluation seems to be the least sensitive at this very early time-point. A lower cut-off level for discriminating between response categories seems to be relevant, we find that 20-25% change for both response and progression is optimal.

Keywords: FDG-PET/CT, response evaluation, Erlotinib

P3.13-015 18F-FDG-PET/CT AFTER INDUCTION CHEMOTHERAPY FOR PREDICTION OF SURVIVAL AFTER RADICAL CHEMO-RADIOTHERAPY IN LOCALLY ADVANCED NSCLC PATIENTS

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Background: The use of 18F-FDG-PET/CT is increasing for radiotherapy planning. We wanted to investigate whether 18F-FDG-PET/CT scans at this time-point can be a tool for selecting patients with locally advanced NSCLC who are likely not to benefit from radical chemo-radiotherapy in order to avoid the potentially harmful side effects in patients undergoing futile treatment, by predicting progression free survival (PFS) and overall survival. **Method:** 18F-FDG-PET/CT scans before and after 2 cycles of induction chemotherapy (carboplatin/vinorelbine) from 91 patients enrolled in a Danish randomized controlled multicenter study (the NARLAL study) was retrospectively evaluated using visual evaluation. Following the induction chemotherapy patients received radical radiotherapy (66 or 66 Gy) with concomitant vinorelbine treatment as according to the NARLAL protocol. Estimates of median OS and PFS was calculated with Kaplan-Meier analysis for the response categories resulting from the visual evaluation, both considering all four response categories and separate analyses for the SMD and PMR groups. Statistical significance was tested using the log rank test, and a significance level of 0.05 was applied. **Result:** The median OS was 25.3 months (95% CI: 21.0-29.6 months), median PFS was 8.6 months (95% CI: 7.9-9.4 months). Overall survival did not differ for PFS or OS when considering all four response categories ($p = 0.424$ for PFS and $p= 0.245$ for OS). Considering only partial metabolic response (PMR) and stable metabolic disease (SMD) no difference for PFS, but we found a median OS of 22.6 (95% CI: 18.9-26.3) months for PMR and 32.4 (28.4-36.3) months for SMD ($p=0.036$). Stratified by histology, the effect was seen in the adenocarcinomas only. **Conclusion:** The median overall survival in patients with a partial response by 18F-FDG-PET/CT evaluation is shorter than for patients with stable disease, in adenocarcinomas. This is surprising and may suggest a differentiation of the treatment for patients with locally advanced NSCLC.

Keywords: FDG-PET/CT, response evaluation, Locally advanced NSCLC

P3.13-016 18F-FDG-PET/CT FOR PREDICTION OF SURVIVAL AFTER INDUCTION CHEMOTHERAPY IN LOCALLY ADVANCED NSCLC – A COMPARISON OF METHODS

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Background: In patients with inoperable, locally advanced NSCLC, radical chemo-radiotherapy is the preferred treatment, and 18F-FDG-PET/CT is increasingly used for radiotherapy planning. Despite the introduction of the PERCIST criteria for evaluation of response with 18F-FDG-PET/CT, various methods are being used making comparisons of studies a difficult task. The aim of this study was to investigate which method for analyses of 18F-FDG-PET/CT provided the best prediction of survival. **Method:** 18F-FDG-PET/CT scans before and after 2 cycles of chemotherapy from 91 patients enrolled in a Danish randomized controlled multicenter study was retrospectively evaluated using four different methods. The change in 18F-FDG-uptake was measured in a single lesion a) SULpeak (according to PERCIST) and b) SULmax (according to the EORTC criteria), c) total disease evaluation qualitatively (visual), and d) total lesion glycolysis measured in all involved measurable lesions with a 45% decrease as cut-off for response and 75% increase as cut-off for progression as according to PERCIST (%TLG). Univariate cox regression was used to evaluate a direct correlation between 18F-FDG uptake at baseline, follow-up and %change and survival (PFS and OS). Estimates of median OS and PFS was calculated with Kaplan-Meier analysis for the response categories from all four methods and, a log rank test performed for evaluation of the statistical significance. A Bonferroni correction for comparison of four methods was applied rendering a $p < 0.013$ the considered level for statistical significance. **Result:** There was no clear correlation between survival (neither PFS nor OS) and % change in FDG-uptake (independent of analysis method), but TLG at baseline showed the strongest correlation to both PFS (p= 0.02) and OS (p= 0.03). %TLG was the only method to show a statistically significant difference in OS, (p=0.004). Visual evaluation and change in SULpeak both succeeded in discriminating between the two largest response groups, PMR and SMD, with median OS for visual evaluation: PMR: 22.6 (95% CI: 18.9-26.3) months versus 32.4 (95% CI: 28.4-36.3) months for SMD; SULpeak: PMR: 20.6 (95% CI: 18.0-23.2) months versus 29.7 (95% CI: 24.2-35.1) months for SMD. Change in SUL max and TLG showed no difference. **Conclusion:** There was no clear correlation between PFS or OS and percentage change in FDG-uptake. The response categories for SULpeak and TLG (PERCIST criteria for cut-off), and visual evaluation predicts OS at various levels. SULmax categories as according to the EORTC criteria did not successfully predict OS. None of the methods predicts PFS.

Keywords: FDG-PET/CT, response evaluation, Locally advanced NSCLC

P3.13-017 REVIEW OF LUNG CANCERS ON THE STAGE AND GROWTH RATE, MATCHED WITH LUNG RADS CATEGORY, IN PREVIOUSLY TREATED WITH BREAST CANCER PATIENTS

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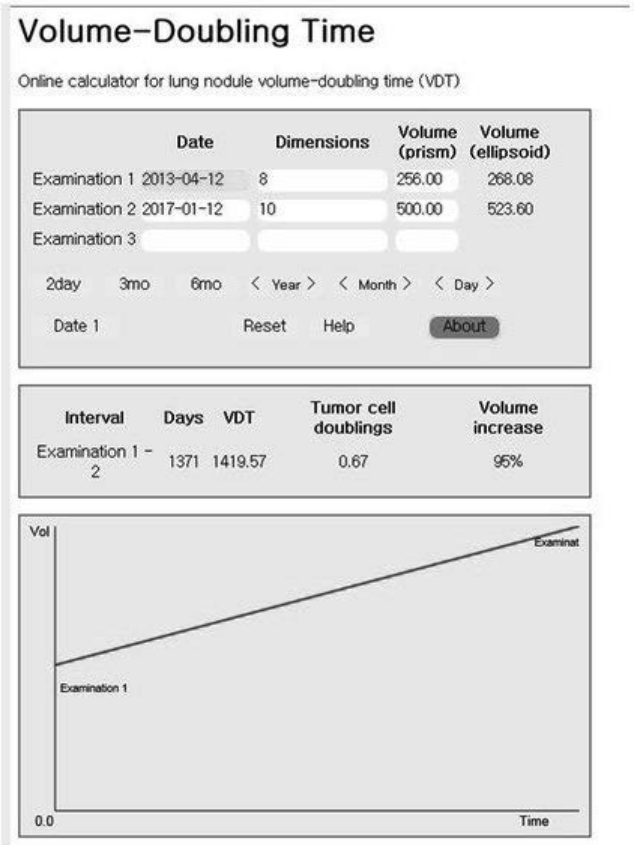
Background: The incidence of lung cancer is dramatically increased. To review the clinical and imaging pattern of lung cancer, diagnosed and treated with breast cancer within 15 years. To evaluate clinical/pathologic stages, doubling time, and lung RADs categories, related with hormone receptor of breast cancers. **Method:** Retrospectively reviewed medical record of breast cancer patients, since 2007. 17 female patients(19 breast cancers)were included. 19 lung lesions were detected. Age range was from 43 to 78 years old(mean 63.8). We reviewed TNM stage, lung RADS, tumor doubling time and the status of hormone receptor. One patient had bilateral breast cancers, mucinous carcinoma (left), and invasive ductal carcinoma(right). Two nodules were shown, invasive ductal carcinoma and one is DCIS. **Result:** The pathology of breast cancer was invasive ductal carcinoma(15), DCIS(2) mucinous ca(1), papillary ca(1). The T stage of breast cancers was T1(17), T2(2) . The subtype of lung cancers was adenocarcinoma, mostly. T stage of lung cancer is T1(16), one is AIS, T3(1), T4(2). The node metastases were not shown and 2/17 showed distant metastases. The primary tumor dimension was from 8mm to 29 mm. The interval between two tumors from 11 days to 14 years. Lung RADs categories were 4A/B(14), 3(2), 2(3) and final category were increased in 5 (from 2 to 4A or B(4 cases), 3 to 4A/B(2 cases)). In 7 interval growing, the tumor doubling time was from70 to 2016 days (mean 712 days).



Conclusion: The receptor (-) breast cancer were higher T stage of lung cancer and lymph nodes metastases were more common. The growth rate of lung nodules are slow as matched with lung RADS category. Volume doubling time of lung cancers ranging from 70 to 2016 days, and exceptionally short in one of them. RADS up scaling in 7 cases are all T1 stage lung cancers, favorable response for the treatment.

Keywords: breast, doubling time, lung nodule

P3.13-018 CT-GUIDED PERCUTANEOUS BARIUM MARKING PRIOR TO VIDEO-ASSISTED THORACOSCOPIC SURGERY (VATS) FOR THE LOCALIZATION OF SMALL PULMONARY NODULES

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Background: Widespread CT scan availability generates the challenge of managing small pulmonary lesions generally undetected on chest radiographs. Preoperative nodule localization is critical for adequate diagnosis and an accurate resection. Metallic hook wire localization under CT is a widely used method but can be associated with pneumothorax, hook related discomfort, and dislodgement. CT-guided percutaneous barium marking (CT-GPBM) can be simpler, low cost procedure, without risk of dislodgement, and radiopaque on fluoroscopy, increasing resection accuracy. Barium marking through bronchoscopy has been previously reported. This study describes our experience with CT-GPBM in the diagnosis and management of ground glass abnormalities and small pulmonary nodules. **Method:** Between January 2013 and May 2017, 36 patients underwent preoperative CT-GPBM and VATS resections at our institution, and were retrospectively reviewed. All cases were discussed in multidisciplinary rounds. After CT localization and local anesthesia, a 21-gauge Chiba needle was utilized, under CT guidance, to inject 0,2 mL of 140% barium sulfate suspension. A control CT confirms the marking and verifies possible complications. CT-GPBM and VATS resection are performed in the same day. VATS resection is performed under fluoroscopy guidance. Finally, the specimen is submitted to fluoroscopy to confirm a complete resection. **Result:** Thirty-six different cases were analyzed (41.7% male / 58.3% female). Median age was 65 (ranging from 32 to 91). 18/36 were never smokers. Most lesions were identified on routine follow-up CT (21/36 - 58.3%). Many had previous history of cancer (24/36 - 66.7%). 31/36 (86.1%) were single nodules - median size of 14mm (ranging from 5 to 47). Solid lesion was the most common radiologic finding (21/36 - 61,8%), while the others were semi-solid or ground glass abnormalities. Pathological findings confirmed primary lung cancer in 41,6% of cases (15/36). Adenocarcinoma was the most common histology. Nine patients had benign diseases. Metastatic lesions represented 33,3% (12/36), most derived from colorectal cancer. No patient had reported

complications. **Conclusion:** This analysis shows that CT-GPBM is an effective, easy and safe pre-operative (VATS) localization procedure, allowing accurate diagnosis and resection of small or faint pulmonary nodules, avoiding thoracotomies in benign diseases and metastatic tumors. Data will be updated for presentation.

Keywords: pulmonary nodule, CT-guided percutaneous barium marking, VATS

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-019 PREOPERATIVE NEEDLE BIOPSY DOES NOT INCREASE THE RISK OF PLEURAL RECURRENCE IN ≤3CM LUNG ADENOCARCINOMA

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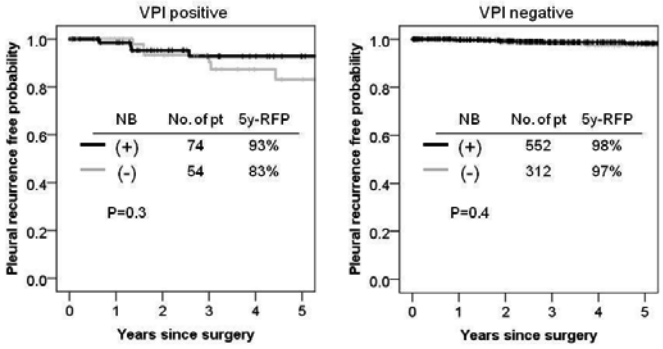
Background: Percutaneous transthoracic needle biopsy (NB) has been widely used for the preoperative diagnosis of lung nodules. It has been proposed that the risk of pleural recurrence is high following lung resection in patients who underwent preoperative NB for sub-pleural nodules (Kashiwabara, et al. *Cancer Invest* 2016; Wang, et al. *Sci Rep* 2017). The aim of this study is to investigate the prognostic impact of preoperative NB for pleural recurrence in patients with early-stage lung adenocarcinoma (ADC). **Method:** Patients who underwent lung resection for pathologic stage I (≤3cm) lung ADC were included in the analysis (1995-2014, n=992; NB group 626 patients and no-NB group 366 patients). We compared the clinicopathologic characteristics and recurrence free probability (RFP, separately analyzed for any, locoregional, pleural, and distant recurrence) between NB and no-NB groups. The risk of pleural recurrence was evaluated in tumors both with and without visceral pleural invasion (VPI). **Result:** The NB cohort was associated with older age and larger tumor size compared to the no-NB cohort ($p<0.05$). There was no statistical difference in the incidence of VPI (VPI in NB, 12% vs. VPI in non-NB, 15%, p=0.2). In RFP analysis by Kaplan-Meier method with log-rank test, there was no statistical difference between NB and no-NB groups (NB vs. non-NB: 5-year RFP for any recurrence, 86% vs. 86%, p=0.8; locoregional recurrence, 93% vs. 94%, p=0.7; pleural recurrence, 98% vs. 96%, p=0.14; and distant recurrence 94% vs. 93%, p=1). In tumors both with and without VPI (n=128 and n=864, respectively), the risk of pleural recurrence was not higher after NB (Figure; 5-year RFP for pleural recurrence [NB vs. no-NB]: VPI positive, 93% vs. 83%, p=0.3; VPI negative, 98% vs. 97%, p=0.4).



Conclusion: Preoperative needle biopsy was not associated with an increased risk of pleural recurrence following lung resection.

Keywords: needle biopsy, lung adenocarcinoma, pleural recurrence

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-020 A PILOT STUDY OF THE AUTOANTIBODIES TO TUMOR ANTIGENS IN LUNG CANCER USING THE EARLYCDT-LUNG TEST IN HONG KONG

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Background: The EarlyCDT-Lung test detects autoantibodies to abnormal cell surface proteins in lung cancer patients. It has been studied in UK[1] and USA[2] in diagnosing lung cancer patients and has a sensitivity of up to 47%, specificity up to 90% and positive predictive value of 16%. It is a potential diagnostic test and when combines with radiological (Computed Tomography) test, the positive predictive value can be enhanced up to 72%[3]. We want to study the performance of the test in a predominantly Asian ethnic city. 1. Caroline J. Chapman et al. EarlyCDT®-Lung test: improved clinical utility through additional autoantibody assays. Tumor Biol. 2012; 33:1319–1326 2. JR Jett et al. Audit of the autoantibody test, EarlyCDT®-Lung, in 1600 patients: An evaluation of its performance in routine clinical practice. Lung Cancer 2014; 83:51–55 . 3. P Massion et al. Autoantibody Signature Enhances the Positive Predictive Power of Computed Tomography and Nodule-Based Risk Models for Detection of Lung Cancer Journal of Thoracic Oncology 2017; 12:578-584 **Method:** Patients who had been referred to our clinic for follow up for lung nodules from March 1st to May 30th, 2017 were included. EarlyCDT-Lung test was performed for those with size greater than 0.8cm or size less than 0.8cm with smoking pack-year more than 30 years. EarlyCDT-Lung test sensitivity and specificity were evaluated. Confirmed lung cancer patients were retrospectively compared with non-lung-cancer patients. **Result:** 10 patients (Chinese: Caucasian=9:1) were included during the study period (Mean age=51.5; male gender=9 (90%); Smoker=2 (20%). 5 patients were diagnosed lung cancer (Mean tumor size=2.9cm; 1 with Stage IA; 1 with stage IB; 1 with stage IIIA, 2 with stage IV; with adenocarcinoma 5/5, EGFR+ve 2/5, ALK+ve 1/5. Mean age=54.8; male gender=4 (80%); Smoker=0 (0%). 5 patients were diagnosed non-lung-cancer (Mean tumor size=0.8cm. Mean age=48.2; male gender=5 (100%); Smoker=2 (40%). EarlyCDT-Lung test was positive in 1/5 lung cancer patients, while 0/5 in non-lung-cancer patients, giving rise sensitivity 20% (1/5), while specificity 100% (5/5). **Conclusion:** This pilot study gives the initial experience of EarlyCDT-Lung test for Asian with high specificity in limited number of subjects. A larger study is warrant for a more accurate result.

Keywords: EarlyCDT-Lung, diagnosis, Cancer

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-021 CAN LYMPH NODES VISUALISED ON PET/CT PREDICT THE OUTCOME OF PATIENTS WITH LUNG CANCER?

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Background: Non-small cell lung cancer (NSCLC) is the common type of histology among all cases of lung cancer. Studies have shown that PET/CT is more accurate than CT for the detection of nodal status due to the increased FDG uptake in very small nodes. In fact, tumor-node-metastasis staging of the mediastinum is currently one the most common indications of PET/CT in lung cancer. The aim of this pilot retrospective review was to assess the role PET/CT as a non-invasive procedure for the visualised lymph nodes in lung cancer. **Method:** Twenty-nine patients [NSCLC (86%), NET (10%), SCL (4%)] underwent PET/CT imaging and were followed for a period of at least 3 years. There were 15 females (51.72%) and 14 males (48.28%) aged between 38-78 years (mean +/- SD= 61.24+/- 9.86) and were referred for staging (86%), restaging (10%) and response to therapy (4%). All patients underwent 18F-FDG PET/CT with a mean time of 71.2 minutes after tracer injection. Tumor and lymph node uptake were evaluated with both visual and quantitative assessment. **Result:** Seven patients (24%) died at 12 months despite treatment induction and by the end of two years follow-up, just a little more than half (51.72%) of the patients died. The majority of those who died were males (r=-0.38; p=0.041). Active lymph nodes were seen in one nodal station in 19 patients. They were also seen in two nodal stations in 12 patients and in three nodal stations in 5 patients. The common stations were as follows: Hilar (33.3%), right lower Para tracheal (22.2%) and subcarinal (19.4%). While no significant association was seen between the primary location of tumor and the occurrence of lymph nodes, patients with positive nodes on PET/CT staging tend to have a reduced survival than those without visualized lymph nodes [odd ratio= 2.33, 95% CI 1.60-9.02; p=0.08]. However, when the analysis was only done for the NSCLC group, a significant reduction of survival was noted in patients who had positive lymph nodes ($p<0.01$). **Conclusion:** This small cohort confirmed the predominance of NSCLC as described in the literature. While this histological predominance could result from a referral bias, it clearly showed that the male gender was associated with a reduced survival. However, a larger cohort must be studied in a prospective analysis to confirm the significantly reduced survival among NSCLC patients with positive lymph nodes during staging, for PET/CT imaging to become a robust predictor of survival.

Keywords: Lung Cancer, 18F-FDG PET/CT, Lymph nodes

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-022 3D CNNS FOR RECOGNITION OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION STATUS IN PATIENTS WITH LUNG ADENOCARCINOMA

J. Xiong[1], T. Jia[2], X. Li[2], L. Fu[1], Z. Xu[2], X. Cai[2], J. Zhang[2], X. Fu[2], J. Zhao[1]

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Background: In this study, we built three 3-dimensional convolutional neural networks (CNN) for recognition of epidermal growth factor receptor (EGFR) mutation status in Chinese patients with lung adenocarcinomas based on non-enhanced computed tomography (CT) images. **Method:** From October 2008 to December 2015, 405 patients with lung adenocarcinomas were included in this retrospective study. Their pathological phenotypes and EGFR mutation status were gained from surgical resections. Their CT images used in this study were taken before any

invasive operation. Tumors with a diameter smaller than 8 mm or have ground glass component were excluded. Region of interest that includes tumors were segmented manually by clinicians and preprocessed to have uniform size and grey-level range before applied to CNNs. The three CNNs have 4 convolutional and 1 full connection layers between input and output layers. The inputs size of three CNNs are 21×21×21, 31×31×31, and 41×41×41, respectively. The outputs of the CNN are the probabilities of mutant and wild status. The CNN classifier's performance was then validated using an independent set and evaluated using area under curve (AUC) values of the receiver operating characteristic. **Result:** 405 patients diagnosed with lung adenocarcinoma staging I to IV were included in this study (195 male, 210 female; 61 smokers, 344 non-smokers). The patients received surgery based treatment and their tumor stage was based on pathological reports. EGFR mutations (mainly 19del and 21L858R) were found in 198/320(61.9%) and 56/85(65.9%) patients in training and validation sets, respectively. The CNN showed an AUC of 0.767 (95% confidence interval: 0.668-0.866, p<0.001) in the validation set. The sensitivity and specificity are 62.5% and 89.7% at best diagnostic decision point. These results were highest among published results of only using images to recognize EGFR. **Conclusion:** The CNN showed potential ability to recognize EGFR mutation status in patients with lung adenocarcinomas and could be improved in the future works to help make clinical decisions.

Keywords: EGFR, CT, CNN

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-023 CLINICOPATHOLOGICAL IMPACTS OF THE SMALL GROUND-GLASS OPACITY SURROUNDING THE SOLID TYPE LUNG ADENOCARCINOMA

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Background: There were many reports and evidences for part-solid nodules with ground-glass opacity (GGO) in small-sized lung adenocarcinoma, and the component of GGO has been known to be a factor of malignant potency of the tumor, although the relation between radiological appearance of >2cm or >3cm lung adenocarcinoma and clinicopathological features were less noted. **Method:** A total of 136 patients with >2cm lung adenocarcinoma with >0.75 of consolidation to tumor ratio (C/T ratio) who underwent lung resection at Shinshu University Hospital from February 2003 through December 2010 were assessed. Among these patients, 83 with pure solid appearance in preoperative thin section computed tomography (C/T ratio = 1.0) were placed into Solid group, and 53 with small GGO surrounding the solid type tumor (0.75 < C/T ratio < 1.0) were placed into Subsolid group in this study. We retrospectively analyzed the clinicopathological features and prognosis after surgery in each groups. **Result:** The maximum standardized uptake value (SUVmax) of the tumor in preoperative radiological assessment using [18F] fluoro-2-deoxyglucose positron emission tomography (FDG-PET) were significantly higher (p=0.0048) in Solid group (7.65±4.36) than Subsolid group (4.82±3.32). The presence rate of vascular invasion (Ly or V) was 54.2% in solid group and 39.6% in Subsolid group. The numbers of node positive patients were 19 with N1, 27 with N2 in solid group, and 8 with N1, 7 with N2 in Subsolid group respectively, and the rate was significantly higher in Solid group (p=0.0019). The prognostic analysis of pathological stage 1 patients (29 patients in Solid group and 37 in Subsolid group) revealed that the overall survival and recurrence-free survival was significantly poorer (p=0.044 and p=0.019 respectively) in Solid group than in Subsolid group. **Conclusion:** The small GGO surrounding the solid type adenocarcinoma as C/T ratio >0.75 indicated lower malignant potency and better prognosis than pure solid tumor without GGO component. Even small GGO component was a clinical factor of favorable oncologic outcomes, it may contribute to regarding the decision making for surgical strategy in preoperative assessment.

Keywords: ground-glass opacity, lung adenocarcinoma, solid type

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-024 IS ALVEOLAR SPREAD MAY BE PREDICTIVE WITH PET CT SCANNING?

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Background: In this study we aim to investigate predictivity of alveolar spread in primary lung cancer by using preoperatively scanning methods **Method:** In order to re-evaluate alveolar spread, pathology preparations of 45 patients had operated for primary lung cancer diagnosis and scanned preoperatively with PET CT all in our hospital which interpreted by same nuclear medicine specialists implicated in this study. As using the patients pet CT findings, CTV (computerized tomography volume), MTV (metabolic tumor volume), TLG(total lesion glycolysis), SUDmax, SUDort values and their relation with alveolar spread analyzed **Result:** Preoperatively PET-CT scanned all in our hospital 45 patients has included and cause of couldn't reach their pathological preparations, 6 of them exluded from the study. 21 of 39 patients were men (53.8%) , 18 of them were women (46.2%) and mean age was 66.67/+-7.88 (42-80). We didn't detect any relation between CTV, MTV, TLG, SUDmax, SUDort values and alveolar spread (p>0.05). However when the CTV/ MTV ratio analyzed, alveolar spread was statistically more common in the group of patients had ratio lower than 1. (62.9% versus 0% , p:0.01) **Conclusion:** High local recurrence risk in sublober rejected patients with alveolar spread has indicated in various studies. Regarding this matter, we recommend re-evaluation of the patients for sublober rejections whose CTV/MTV ratio is lower than 1.

Keywords: PETCT, STAS, lung cancer

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-025 SPINAL CORD AND CAUDA EQUINA COMPRESSION IN LUNG CANCER

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Background: Spinal cord compression is one of the most disabling complications in lung cancer. It may be caused either by the tumor itself or by metastatic involvement of the spine and meninges. The goal of this work is to appreciate characteristic of spinal cord compression in lung cancer. **Method:** Retrospective review of the MRI data of patients with lung cancer presenting with neurological symptoms caused by medullary or cauda equine compression. Only patients with abnormal findings were retained. All exams were performed by a 1.5 T machine. **Result:** From January 2014 to December 2016, only 24 patients (23 males and 1 female) were referred to the imaging department of our institution for medullary compression exploration. Their average age was 57 years. Seventeen patients had adenocarcinoma. Three patients were classed stage IIIB and 18 were classed stage IV. Medullary compression was caused by direct compression (12 cases) of the tumor or by a spine metastases (12 cases). One spine region was involved in 18 patients with dorsal location in 13 patients. In three cases, the compression concerned the cauda equina. Myelopathy was noted in 15 of the 21 patients with spinal cord compression. **Conclusion:** Spinal compression is not frequent in lung cancer. It is mainly observed in advanced stages. It may occur by direct tumor invasion or by vertebral metastatic extension.

Keywords: MRI, lung cancer, spinal cord compression

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-026 NON-SMALL CELL LUNG CANCER: IMAGING OF RECURRENCES AFTER SURGERY

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Background: Lung cancer has a poor prognosis unless patients are operated. However, few patients may undergo surgery. Recurrences are not rare and they increase the mortality. The objective of this study is to appreciate the frequency of recurrences after surgery in non-small lung cancer (NSCLC) in our institution and to correlate them to TNM classification and histological subtypes. **Method:** Retrospective review of 127 patients (106 men and 21 women) aged between 19 and 80 years with NSCLC that were operated. All patients had chest, abdomen and brain computed tomography (CT) in their follow up. We precised for each patient the histological type of the lung cancer, the c and p TNM stages, the resection type and the other treatments prescribed, the recurrence site and the delay between the surgery and the recurrence. **Result:** Recurrences were observed in 35 patients (27.5%). They had either a lobectomy (n=30), a pneumonectomy (n=4) or a wedge (n=1). Recurrences were located to the chest in 36 cases (half of them occurred in the operated lung) and in extra-thoracic organs in 13 cases; the brain was the mostly involved. The delay between surgery and recurrence ranged between 1 month and 7 years. Fourteen patients had a recurrence within the first year after surgical removal of their tumor. Recurrences were mostly observed in patients with T4 stage (23%), N3 stage (66.6%), stage III cancer (49%), and with adenocarcinoma. An under-estimation of the cT and cN stages was observed in 5.6% and 27.5% of patients, respectively. **Conclusion:** Recurrences in patients with surgically removed lung cancer are not rare. They depend on its histological type and on the cT and cN stages.

Keywords: lung cancer, Surgery, recurrence

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-027 UTILIZATION OF PET SCAN IN ADVANCED STAGE NON-SMALL CELL LUNG CANCER IN THE UNITED STATES

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Background: PET scans are used during diagnosis and staging of lung cancer. The role of PET scan in guiding therapy for advanced stage non-small cell lung cancer (NSCLC) is not proven, but it continues to be used during the treatment course at many centers. We studied the Surveillance, Epidemiology, and End Results (SEER) Program database and Medicare claims data to evaluate the use of PET scan in advance stage NSCLC patients in the United States and the impact on patient outcome. **Method:** The SEER-Medicare database was queried to capture patients with stage IV non-small cell lung cancer diagnosed between the years 2000-2011. The cohort of patients that received PET scan after diagnosis were analyzed and compared with the cohort that did not receive PET. The univariate (UV) association between covariates and overall survival (OS) were compared by log-rank tests. Time dependent Cox Model was used in multivariable (MV) analysis, with time from diagnosis to first PET scan as time-dependent variable, while the other covariates as time-independent. All analyses were performed using SAS Version 9.4. **Result:** A total of 52,712 eligible patients with stage IV NSCLC were identified between 2000-2011, out of which 13,873 (26.3%) had received PET scan. Characteristics of PET cohort: median age 74 years, 53% male, 87% white and 82% from metro locations. 87% of the patients that received PET were diagnosed between 2006-2011. In the first year after diagnosis, 70% of the patients had 1 PET, 16% had 2 PETs and 14% had 3 or more PETs. About 64% of the patients had received their first PET scan within 2 months of diagnosis and 19% had it between 2 to 6 months. The average Medicare cost associated with patients that received PET was significantly higher than that of patients that did not receive PET scan ($60,417 vs. $34,287; p<0.001). Chemotherapy and radiation were given in a higher proportion of patients that received PET versus those that did not receive it (56% and 45% versus 26% and 36% respectively; p<0.001). Though univariate analysis revealed that a PET scan within a year of diagnosis was associated with better 1-year survival (HR 0.87, P<0.001), this did not translate into overall survival advantage on multivariable analysis (HR 0.99, P=0.56). **Conclusion:** The utilization of PET scan in stage IV NSCLC patients was associated with higher cost, but without a tangible improvement in survival compared to those that did not have a PET scan.

Keywords: SEER Medicare, Advance stage, PET

P3.13: RADIOLOGY/STAGING/SCREENING -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-028 CONTROVERSIES ON LUNG CANCERS MANIFESTING AS PART-SOLID NODULES

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Background: Questions have been raised about the appropriate treatment of lung cancers manifesting as subsolid nodules (nonsolid nodules (NSNs) and part-solid nodules (PSNs)), as these have very high reported survival rates and have been observed in up to 10% of screening participants. Our goal in this report is to summarize the publications on survival of patients with resected lung cancers manifesting as PSNs and to further the development of consensus definitions of the CT appearance and the workup of such nodules. **Method:** PubMed/MEDLINE and EMBASE databases were searched for all studies/ clinical trials on CT-detected lung cancer in English before Dec 21, 2015 to identify surgically-resected lung cancers manifesting as PSNs. Outcome measures were lung cancer-specific survival (LCS), overall survival (OS), or disease free survival (DFS). All PSNs were classified by the percentage of solid component to the entire nodule diameter into: Category PSNs < 80% or Category PSNs ≥ 80%. **Result:** Twenty studies reported on PSNs < 80%: 7 reported DFS and 2 OS of 100%, 6 DFS 96.3-98.7%, and 11 OS 94.7-98.9% (median DFS 100% and OS 97.5%). Twenty-seven studies reported on PSNs ≥ 80%: 1 DFS and 2 OS of 100%, 19 DFS 48.0%-98.0% (median 82.6%), and 16 reported OS 43.0%-98.0% (median DFS 82.6%, OS 85.5%). Both DFS and OS were always higher for PSNs<80%. **Conclusion:** A clear definition of the upper limit of solid component of a PSN is needed to avoid misclassification because cell-types and outcomes are different for PSN and solid nodules. The workup should be based on the size of the solid component.

Keywords: ground-glass, survival, CT screening

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-029 IMAGING GUIDELINE-RECOMMENDATIONS PRIOR TO TREATMENT FOR NON-SMALL CELL LUNG CANCER DEMONSTRATES VARIABLE COMPLIANCE

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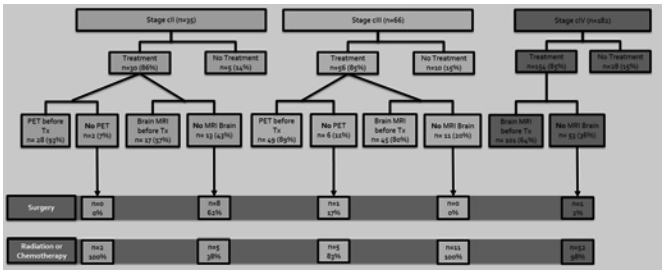
Background: Poor adherence to the recommended guidelines in diagnosing and staging patients with non-small cell lung cancer (NSCLC), with negative downstream effects has been previously shown. In addition, studies have demonstrated benefits of staging with PET, including a reduction in number of non-curative resections performed and a higher rate of identifying M1b disease. Staging with brain MRI has demonstrated a yield up to 10% for detecting metastasis in patients with negative clinical examinations. We aimed to assess the adherence to imaging guidelines for PET and brain MRI in the staging of NSCLC patients prior to treatment within our healthcare system. **Method:** We reviewed patients who underwent initial work-up for primary NSCLC during 6/2013–6/2015, in a hospital network of 7 institutions. Clinical stage II-IV patients were stratified by imaging performed prior to the initiation of treatment. Evidence-based clinical practice guidelines referenced include the American College of Chest Physicians (ACCP) 3rd edition and the National Comprehensive Cancer Network (NCCN) 7th version. Both ACCP and NCCN recommend a PET scan for suspected cIb-III; while ACCP recommends a brain MRI for suspected cIII-IV, and NCCN for suspected cIb-IV. **Result:** The figure demonstrates compliance rates for the 283 included patients. Of cII patients, 7% (2/30) did not receive a PET scan and 43% (13/30) did not receive a brain MRI; while, 11% (6/56) of cIII did not receive a PET scan and 20% (11/56) did not receive a brain MRI.



Conclusion: Variable compliance with imaging guidelines for the use of PET and brain MRI imaging for the staging of our NSCLC patients was seen. Lack of appropriate imaging for NSCLC staging may lead to inappropriate management decisions resulting from incomplete staging information. Quality initiatives are necessary to ensure guideline compliance.

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P3.13-030 METABOLIC PARAMETERS OF FDG PET AT EARLY EVALUATION OF NSCLC DIFFER WITH HISTOLOGICAL SUBTYPES

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Background: Fluorodeoxyglucose Positron emission tomography (FDG PET) is a main tool in diagnosis and staging in patients with non small cell lung cancer (NSCLC). Metabolic parameters as standardized uptake value (SUV) and total lesion glycolysis (TLG) were reported to have independent prognostic and predictive value in different stages of disease and were shown to correlate with tumor activity and tumor burden. However, little is known regarding the correlation of these parameters with histologic subtypes of NSCLC. In this study we aimed to explore associations of FDG PET metabolic parameters in patients diagnosed with NSCLC and histologic subtypes of NSCLC. **Method:** We retrospectively evaluated 87 consecutive patients who underwent FDG PET scans in the workup of pulmonary nodules highly suspicious for malignancy. At total of 62 of them were found to have NSCLC; 44 with adenocarcinoma (ADC) and 18 with squamous cell carcinoma (SQCC). Measurements of hounsfield units (HU), region of interest (ROI), SUVmax, SUVmean, volume of interest (VOI) and TLG were obtained. Follow up for final staging at diagnosis and overall survival (OS) were obtained from electronic medical records. Statistical analysis was made with T-test and Mann-whitney u test. **Result:** In patients with SQCC, the mean ±standard deviation (SD) SUVmax and TLG (±SD) were found to be significantly higher than in patients with ADC (Table 1). Differences in OS showed a trend favoring SqCC but no significance was found (complete results from 16 more patients are pending).

(See table next page.)

Table 1 - Clinical and PET metabolic characteristics according to histologic subtype					
Histological subtype		NSCLC (n=46)	ADC (n=32)	SqCC (n=14)	P value
Clinical characteristics					
Median age [range]		67[43-86]	67 [43-86]	63[44-82]	NS
	female	20	17	3	0.059
	male	26	15	11	NS
stage	1	13	10	3	NS
	2	9	5	4	NS
	3	8	4	4	NS
	4	16	13	3	NS
Median Overall survival [range] (months)		27.6 [0.9-80.9]	19.8 [4.3-80.9]	61.5 [0.9-80.2]	0.267
metabolic characteristics					
Mean HU±SD		34.1±30.2	32.07±35.9	38.5±7.2	0.336
Mean ROI±SD		175.7±116.6	167.12±120.5	195.32±108.8	0.441
Mean SUVmax ±SD (g/mL)		16.2±9.4	14.05±8.2	21.02±10.6	0.019
Mean SUVmean (g/mL)		9.14±4.7	8.3±4.6	11.05±4.4	0.065
Mean VOI±SD		31.1±28.3	26.15±24.4	42.17±34.1	0.077
Mean TLG ±SD (g)		349.8±375.1	250.5±275.3	577.2±475.5	0.005

PET Positron emission tomography, **NSCLC** non small cell lung cancer, **ADC** adenocarcinoma, **SqCC** squamous cell carcinoma, **NS** non-significant **SD** standard deviation, **HU** hounsfield units, **ROI** region of interest, **SUV** standardized uptake value, **VOI** volume of interest, **TLG** total lesion glycolysis

Conclusion: FDG PET Metabolic characteristics such as SUVmax and TLG significantly differ between histological subtypes in NSCLC. This report joins others on the utility of functional imaging studies in NSCLC in assessing not just disease burden but also prognosis and function. Further analyses of the PET parameters prognostic impact according to histology subtype is ongoing and would be presented at the meeting.

Keywords: Fdg pet, NSCLC Histological Subtypes

P3.13: RADIOLOGY/STAGING/SCREENING - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.13-031 PREDICTING FACTOR FOR THE DISSOCIATION OF THE DIAMETER BETWEEN RADIOGRAPHICAL SOLID PART AND PATHOLOGICAL INVASIVE PART IN LUNG ADENOCARCINOMA

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Background: In part-solid nodule of lung adenocarcinoma, the diameter of the solid part in computed tomography(CT) scan correlates with the diameter of the pathological invasive part. However, there are some cases revealing dissociation between them. We analyzed clinical factors predicting the dissociation of the diameter between radiographical solid part and pathological invasive part in adenocarcinoma less than 3 cm. **Method:** Among 291 cases with a lung adenocarcinoma smaller than 3 cm, we identified 91 cases whose solid part in preoperative thin-slice CT scan was less than 5 mm. Based on pathological diagnosis of invasive part, we divided these cases into Adenocarcinoma in situ/Minimally Invasive Adenocarcinoma(AIS/MIA) group (less than 5 mm) and Massive invasion group (5mm or larger), and retrospectively analyzed the clinicopathological factors. We also performed logistic regression analysis to detect the factors predicting the dissociation between radiographical and pathological findings. **Result:** Of 91 cases, 67 cases were in AIS/MIA group (AIS: 57, MIA: 10) and 24 cases were in Massive invasion group. In univariative analysis, cases of Massive invasion group were significantly higher in Brinkman index, CEA, age, and total tumor size than those of AIS/MIA group (p = 0.02, 0.01, 0.04, 0.03 respectively). With these detected four factors, we performed logistic regression analysis after determining threshold by ROC curve, which resulted in Brinkman index equal or larger than 400, and age equal or elder than 67 as significant predictive factors for Massive invasion group ($p < 0.01$, $p = 0.05$ respectively). Among 11 cases positive for these two factors, 7 cases (63.6 %) were in Massive invasion group. **Conclusion:** In the cases of radiographical AIS/MIA, the diameter of pathological invasive part tends to exceed 5 mm if Brinkman index equal or larger than 400, and age equal or elder than 67.

Keywords: Staging, primary lung adenocarcinoma, Part-solid GGO

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P3.13-032 THE IMPACT OF TOBACCO EXPOSURE ON LUNG NODULES AND EMPHYSEMA IN A PILOT SILESIAN STUDY OF EARLY LUNG CANCER WITH LDCT

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Background: Pulmonary emphysema is known to be related to an increased incidence of lung cancer. The risk factors of emphysema and lung cancer are smoking history and envirolmental pollution. Low-dose chest CT is useful method for imaging both: emphysema and solitary pulmonary nodules (SPN). **Method:** We have enrolled a total of 602 healthy volunteers to the Pilot Silesian Study of Early Lung Cancer Detection with LDCT. Retrospectively we analyzed the baseline round of LDCT scans. One person was excluded due to presence of lung cancer symptoms. Gradual accrual period lasted for two years, from 2010 to 2012. The positive result was defined as a presence of solid or part-solid nodule equal to or larger than 5 mm or non-solid equal to or larger than 8 mm. Participants were stratified by exposure to tobacco smoke into five groups: A) current smokers with a history of at least 40 years of smoking - chronic smokers; B) current smokers with a history of smoking at least 40 cigarettes per day - intensive smokers; C) former smokers who quit smoking fewer than 5 years ago; D) former smokers who quit smoking at least 10 years ago; E) exposed to a second-hand tobacco smoke. With the statistical methods we analized corelations between this five groups depending on tobacco exposure and demographic features. **Result:** We identified 1016 lung nodules in 265 individuals. A total of 410 nodules coexisted with emphysema in 99 individuals. In group with emphysema we diagnosed 3 early lung cancers, unlike to the group without emphysema, in which we diagnosed 4 cancers (HR=0.7 95% CI 0.16-1.02). Subsolid morphology and diameter of a nodule larger than 5 mm were associated with higher risk of malignancy. Emphysema and lung nodules were more often found in the group of chronic smokers (>40 years) - 8.1% (A), in comparison to the group of intensive smokers – 0.8% (B). There were no statistically significant differences in both subcohorts of former smokers (for group C and D, 2.1% and 2.3%, respectively). **Conclusion:** In the subgroup of chronic smokers emphysema and lung nodules were more likely to occur. Additional risk factors for the presence of lung nodules and emphysema were: age (above 65 years) and occupational exposure (especially coal miners and welders).

Keywords: pulmonary emphysema, lung cancer screening, nodules

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P3.13-033 DNA METHYLATION OF PTGER4 AND SHOX2 IN LIQUID BIOPSIES FACILITATES THE DIAGNOSIS OF LUNG MALIGNANCY AFTER CHEST CT-SCAN

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Background: Lung Cancer (LC) is the leading cause of cancer-related death worldwide. The Lung Cancer Screening Trial screened 26,723 patients via Low-Dose chest CT-scan. Screening results were positive in 24.2%, however 96.4% were false positive. Therefore, a biomarker helping to discriminate false positive from true positive screening results will limit unnecessary interventions. The aim of this study was to analyze the feasibility of the DNA methylation markers prostaglandin E receptor 4 gene (PTGER4) and short stature homeobox 2 gene (SHOX2) as potential biomarkers in liquid biopsies additional to CT-scan findings suspicious for LC. **Method:** A total of 73 patients with a chest CT-scan suspicious for stage I-IIIA LC were included in this study. LC was histologically confirmed in 50 patients. In the remaining 23 patients benign diagnoses were established. Circulating cell-free DNA was extracted, bisulfite converted and purified from 3.5 ml plasma, using a commercially available kit. Triplicates of bisulfited DNA were assayed with a 45-cycle rtPCR assay detecting methylated DNA of *SHOX2*, *PTGER4* and ACTB as reference assay. Assay result was called positive for PTGER4 if at least two out of three PCR results had cycle threshold (Ct) values below 45; for SHOX2 if the Ct value was below 35. **Result:** PCR-results were valid in 18 (4 organising pneumonias, 5 pneumonias, 3 post-pneumonic residues, 3 hamartochondroma, 1 mycosis, 1 coal-workers pneumoconiosis, 1 aspergilloma) of 23 benign samples (control), and in 43 of 50 LC samples. PTGER4 results were negative in all controls and positive for 18 of 43 LC. These results translate into a specificity of 100 % and a sensitivity of 41.86% for LC detection via PTGER4. The SHOX2 assay was negative in all controls and positive in 9 LC patients, resulting in a specificity of 100 % and a sensitivity of 20.93% for SHOX2. Overall 21 of 43 LC samples were positive in either PTGER4 or SHOX2 and all controls were negative for both measurements. In combination both markers showed a specificity of 100% and a sensitivity of 48.84%. This specificity

would imply a positive predictive value of 100%, further validation in a larger cohort is required. **Conclusion:** DNA methylation of PTGER4 and SHOX2 was highly specific for patients with chest CT-scan findings suspicious for LC. This could help to identify high-risk patients, who should be directly transferred to tissue-based diagnostics, surgery or stereotactic radiation. In the other cases the next diagnostic step should be decided clinically.

Keywords: liquid biopsy, PTGER4, SHOX2

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-034 COMPARISON OF CYTOLOGICAL SMEARS AND CELL BLOCKS OF PLEURAL FLUID DIAGNOSING MALIGNANT PLEURAL EFFUSION IN LUNG CANCER

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Background: In conventional cytology discrimination of the reactive mesothelium cells and malignant cells is the most important diagnostic problem. Cell block (CB) technique is helpful in discriminating cytological abnormalities or well differentiated adenocarcinoma. **Method:** 95 consecutive patients (52% male, mean age 67±12yrs) with malignant pleural effusion in lung cancer were enrolled. 44% of patients had Eastern Cooperative Oncology Group performance score 0-1 and 66% ≥2. In all patients pleural fluid smears were sent for conventional cytological and CB immunocytochemical examination. **Result:** In 69 (73%) cases malignant pleural effusion was the first sign of lung cancer and in 26 (27%) cases developed in disease progression. First pleural fluid immunocytochemistry examination confirmed malignancy in 80 (84%) cases: adenocarcinoma – 70 (88%), small cell carcinoma – 7 (9%) and non small cell carcinoma – 3 (3%). First cytological examination was positive in 81 (85%) smears. Adenocarcinoma cells were identified in 51 (63%) cases although of them CB technique confirmed adenocarcinoma in 49 (96%) smears and reactive mesothelium cells in 2 (4%) smears. Out of 30 (37%) specimens that showed malignant cells in cytological examination, CB method confirmed: adenocarcinoma 15 (50%), small cell carcinoma 6 (20%), non small cell carcinoma 3 (10%) and reactive mesothelium cells 6 (20%). Whether first cytological smear was negative, second smear was positive in 4 (27%) cases and identified 1 (25%) adenocarcinoma and 3 (75%) malignant cells in cytological examination, notably out of them CB examination showed reactive mesothelium in 2 (50%) samples, small cell carcinoma in 1 (25%) sample and adenocarcinoma in 1 (25%) sample. **Conclusion:** Our study aims that pleural fluid cell block immunocytochemistry is more accurate method identifying lung cancer and should be considered as the initial diagnostic approach for malignant pleural effusion in primary investigation in lung cancer, especially in patients with worse performance status.

Keywords: malignant pleural effusion, Adenocarcinoma, immunocytochemistry

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-035 AUTOMATIC ESTIMATION OF MEASUREMENT ERROR ON CT IMAGING

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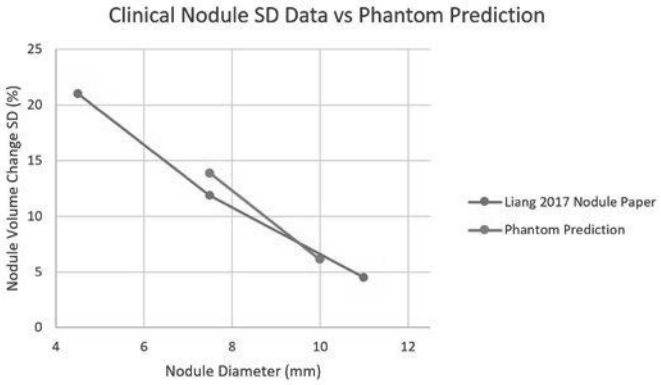
Background: There has been increasing recognition that lung nodule measurement on CT scans is imprecise and that an understanding of the extent of this imprecision is necessary when trying to determine whether actual change in volume has occurred. The various factors that influence this are numerous with two of the most prominent being the overall quality of the CT scan (including all of the adjustable parameters) and the size of the nodule. **Method:** We have developed an automated system whereby a calibration device is scanned on a given scanner with a given protocol and then the system can automatically predict the extent of measurement error for a given size solid nodule. We compared this approach to empirically derived results obtained from a database of 117 screen-detected stable nodule ranging in size from 2.2 to 18.7 mm that were scanned twice on the same CT scanner using the same protocol. Automated volumetric analysis was performed using commercial software. This allowed us to determine the relationship between standard deviation of the measurements versus nodule size. We then scanned our calibration device using the same scanning protocol as was used on those nodules to automatically calculate the size and standard deviation relationship. **Result:** Predicted solid nodule volume standard deviation compared with empirically derived values across a range of nodule sizes was within 20% (see figure)



Conclusion: Results from our automated approach were highly correlated with results obtained from scans obtained in actual clinical practice. The ability to predict extent of error specific to a given scanner and scanning protocol is an essential step in understanding whether change has occurred and has implications for both diagnosis and therapy assessment, including predicting when a follow up scan should be obtained. This type of information will ultimately become a necessary component of all quantitative imaging programs.

Keywords: calibration, measurement error, CT volumetry

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-036 IMMUNOHISTOCHEMICAL AND GENETIC CHARACTERISTICS OF LUNG CANCER MIMICKING ORGANIZING PNEUMONIA

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Background: Lung cancer mimicking organizing pneumonia (LCOP) is a novel radiological entity of lung adenocarcinoma that could be misdiagnosed as inflammatory lesions. However, the characteristic biological and genetic features of LCOP are not fully clarified. **Method:** We used thin-section CT images to select cases of (LCOP) among surgically resected lung adenocarcinoma patients. We compared the clinicopathological characteristics and the immunophenotypes of LCOP (n = 44) and other lepidic-predominant adenocarcinomas (non-LCOP, n = 56). We also analyzed the genomic mutation features of LCOP (n = 4) by whole-exome sequencing (WES). **Result:** All LCOP lesions were lepidic-predominant invasive adenocarcinoma. Patients with LCOP had significantly superior recurrence-free survival, compared to non-LCOP patients (95.5% and 74.4%; P = 0.006, respectively). Vascular invasion and lymph node metastasis were less frequent in LCOP than in non-LCOP patients (P = 0.001 and P = 0.03, respectively). The cancer cell expression levels of aggressiveness-related molecules, including ezrin, ALDH-1, laminin-5 were similar between LCOP and non-LCOP. On the contrary, the number of tumor promoting stromal cells, i.e., podoplanin-positive cancer-associated fibroblasts and CD204-positive tumor associated macrophages, was significantly lower in LCOP (P = 0.021 and P = 0.037, respectively). WES revealed that ABCB1, DNAH3, MSI2, and *SLITRK2* were specifically mutated in LCOP. **Conclusion:** Our results indicate that LCOP is characterized by fewer tumor-promoting stromal cells, which may contribute to the better prognosis of LCOP patients. Moreover, recognition of specific somatic mutations of LCOP patients may provide information regarding the development and progression of this type of lung cancer.

Keywords: lung cancer, microenvironment, stromal cell

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-037 DEEP LEARNING SYSTEM FOR LUNG NODULE DETECTION

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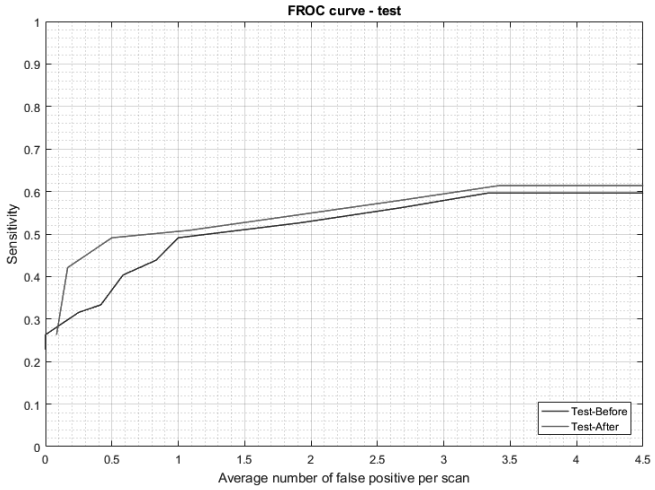
Background: Ever since its first success in large scale image recognition problem, deep convolutional neural networks (DCNNs) have shown their capabilities in solving many challenging visual perceptual tasks, such as image classification, segmentation, object detection. In some cases, DCNNs have already achieved near-human performance. In medical image analysis, DCNNs have also been successfully applied to lesion detection, segmentation, and diagnosis. The power of DCNN lies in its ability to learn a hierarchical representation of raw input data, without hand-crafted features. **Method:** The focus of this study was to improve the performance of DCNN in automatic detection of pulmonary nodule on CT scan. In particular, nodules whose size is less than 4mm were considered. A total of 171 scans were collected at Zhongshan Hospital Fudan University, which was first process by the proposed DCNN

system (12Sigma). The detection results were then carefully reviewed by an experienced physician, all false positives and missed nodules were manually labeled. To refine the system, all false positives and true nodules of sizes 4mm and under were selected. **Result:** The data set was randomly split into training and test sets, where the training set consists of 90% (154 scans) and the test set consists of 10% of data (17 scans). Figure 1 shows the FROC curves on the test set before and after re-training. Overall, the detection sensitivity were improved at all false positive levels, but the improvement was most significant at low FP rate region. For example, when FP is 0.5 per scan, the detection sensitivity increased from 0.36 to 0.49.



Conclusion: This improvement suggests that, even with limited data, the deep neural network can learn from its mistakes and be easily tuned to be more sensitive to small nodules. We believe that when more data is colllected, more significant improve in high FP rate region will be observed.

Keywords: lung nodule detection, Deep learning system, CT scans

P3.13: RADIOLOGY/STAGING/SCREENING -
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P3.13-038 THE ROADMAP STUDY: FEASIBILITY OF IMPLEMENTING A PRIMARY CARE INTERVENTION FOR REFERRAL OF POTENTIAL LUNG CANCER CASES TO SPECIALIST CARE

N. Rankin[1], S. York[2], L. Trevena[3], J. Emery[4], P. Sundaresan[5], P. Beale[6], R. Zielinski[7], S. Vinod[8], T. Shaw[9]

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Background: Pathways to lung cancer diagnosis are complex. General Practitioners (GPs) play a vital role in ensuring that people diagnosed with lung cancer receive timely access to appropriate specialist care. Australian guidelines recommend that the first specialist appointment should take place within two weeks of the initial GP referral. However, local data indicate that up to 60% of patients are not referred within two weeks, while state-based data shows that 11% of patients in New South Wales (NSW), Australia, do not see a lung cancer specialist at all; these patients may be missing out on curative and palliative treatments. We designed a primary care intervention to address these gaps and conducted a feasibility study in three sites across NSW. The RoaDmaP pilot study aimed to develop, implement and evaluate the Referral Decision Prompt (RDP), an intervention that supports GPs to refer patients with a suspicious lung lesion on CT scan for specialist care. Specific objectives were to evaluate feasibility and acceptability with GPs, radiologists and radiology practice staff. **Method:** The RDP intervention was developed with key stakeholder input and was tailored for three participating radiology practices. Eligibility criteria included any patient aged over 18 attending for a chest CT scan. Recruitment and consent procedures were tested to enable collection of patient's medical data from GPs and hospitals to confirm lung cancer diagnoses. The RDP template was integrated into CT scan reports for patients with a suspicious lung lesion. A process evaluation with GPs, radiologists and radiology staff was undertaken through brief surveys and qualitative focus groups. **Result:** Over seven months, 445 patients had a GP-referred chest CT scan; 400 were given study documents; 293 consented (73%). Twelve patients had a suspicious lesion, eight of whom received a confirmed lung cancer diagnosis. Sixty-six percent had a specialist appointment within two weeks. The intervention was rated as highly acceptable by radiologists, radiographers and practice staff; four GPs participated in the evaluation, three recalled the RDP and two used it to change their referral practices. **Conclusion:** The RoaDmaP study presents an innovative approach to identifying lung cancer patients prior to diagnosis and has the potential to improve timely and appropriate specialist referral. The process evaluation findings indicate that this simple, low-cost intervention is feasible and can be easily integrated into radiology reporting practices. It is highly acceptable to radiologists and practice staff, and may positively influence GP referral practices.

Keywords: early diagnosis, primary care, radiology

P3.14: RADIOTHERAPY -
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P3.14-001 IMPACT OF PCI ON PROGNOSIS OF LD-SCLC THROUGH PATTERN OF BRAIN METASTASES AS A FIRST RECURRENCE SITE

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Background: Brain metastases frequently occur in patients with small-cell lung cancer. Therefore, prophylactic cranial irradiation (PCI) is recommended for good responders of initial treatment. The purpose of this study was to investigate influence of PCI on pattern of brain metastases as a first recurrence site (BMFR) after radical treatment for limited disease small-cell lung cancer (LD-SCLC). **Method:** This retrospective study included LD-SCLC patients treated with thoracic radiotherapy and concurrent chemotherapy between January 2006 and December 2014. Induction chemotherapy was permitted. Thoracic radiotherapy was performed with accelerated hyper-fractionated radiotherapy (twice daily, 45 Gy in 30 fractions over 3 weeks) or conventional-fractionated radiotherapy (once daily, 50 Gy in 25 fractions over 5 weeks). Regimen of chemotherapy consisted of intravenous platinum-etoposide. **Result:** One hundred and sixty-two patients were included in this study. The median follow-up duration for surviving patients was 38 months (range, 6-105 months). Among 123 patients (76%) who died, 104 patients died due to disease progression, 11 died due to unknown cause and 8 died due to other cause. Ninety-three patients (57%) underwent PCI, and the 3-year disease specific survival (DSS) rates were 20%(12-35) in patients without PCI and 43%(33-55) in those with PCI ($p<0.001$). Concerning the recurrence pattern, the frequency of BMFR was significantly higher in patients who did not underwent PCI compared with those who did (49% vs 25%, $p=0.008$) although no significant difference in frequency of all site of recurrence was observed between patients without PCI and those with PCI (83% vs 73%, $p=0.109$). Regarding the impact of BMFR on prognosis, patients with BMFR exhibited significant shorter DSS than those whose first recurrence sites was other than brain metastases (3yr-DSS 6% vs 22%, $p=0.007$), and patients who developed BMFR without PCI exhibited significant lower DSS compared with those who developed BMFR with PCI (3yr-DSS 0% vs 17%, $p=0.005$). In addition, 68% of patients who did not underwent PCI exhibited multiple BMFR lesions with 5 or more while 12% of patients who did ($p<0.001$). **Conclusion:** The results of this study indicated that BMFR exhibited significant negative impact on prognosis after radical treatment for LD-SCLC and the difference in the number of metastatic lesions in BMFR between patients with PCI and those without PCI might affect clinical outcomes.

Keywords: recurrence, SCLC, PCI

P3.14: RADIOTHERAPY -
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P3.14-002 MULTIMODALITY MANAGEMENT OF PANCOAST TUMORS; DOES SURGICAL RESECTION NEED TO BE INCLUDED?

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Background: Tri-modality management using chemoradiotherapy followed by surgical resection is the current standard of care for patients with pancoast tumors. Surgical resection is considered the key element to improve patient outcomes, however it involves a lengthy operative procedure with surgical/anesthetics related side effects, long period of rehabilitation, and significant additional cost. In the era of image-guided radiotherapy, we are able to paint the dose around the tumor, targeting it with a high dose of radiotherapy, while avoiding sensitive organs such as spinal cord and brachial plexus. Here we present our institutional experience treating advanced pancoast tumors with chemoradiotherapy. **Method:** Patients are usually staged with chest-abdomen CT scan, upper chest/brachial plexus MRI (if needed), brain MRI and a PET scan. Patients are treated in a supine position, using head and neck mask as the immobilization device; and cone beam image guidance. The radiation dose is 45-70 Gy in 25-35 fractions concurrent with at least 2 cycles of chemotherapy. Patients with resectable tumors have surgery done within 4-6 weeks upon completion of chemoradiotherapy. Patients are followed every 3-6 months with CT scan and/or upper chest MRI for 3 years, then yearly after. **Result:** Of 205 consecutive patients with stage 3-4 NSCLC treated with radical dose radiotherapy at Southlake regional cancer center, 9 patients with pancoast tumor were detected. Two patients (2/9) died; one from a heart attack before completion of his treatment, and the other one from tumor progression (6 months after completion of tri-modality management). All the other 7 patients are still alive and free of disease (table 1, *next page*). **Conclusion:** Selected patients with pancoast tumors treated with high dose radiotherapy, using image guidance, concurrent with chemotherapy may have long term disease free survival. A multi-institutional study is warranted to conclude the management recommendation for these rare tumors.

Keywords: locally advance non-small cell lung cancer, Pancoast tumor, Radiotherapy

Patients	Gender	Age (year)	Tumor size (cm)	Tumor pathology	Tumor invasion	Sugery	RT (Dose/fraction)	Date of completion RT (D/M/Y)	Date of last FU
1	F	61	6.2	Squamous carcinoma	T2, vessels, bone marrow	No	66 Gy/33 fr	06/02/2010	13/10/2016
2	M	62	11.3	Adenocarcinoma	C6-T3 ribs	No	70 Gy/35 fr	05/10/2010	25/01/2017
3	M	72	9	Adenocarcinoma	rib, vessels, neck	No	70 Gy/35 fr	25/01/2011	29/06/2016
4	M	66	9	Squamous carcinoma	C7-T5 vessels	No	66 Gy/33 fr	26/01/2015	11/01/2017
5	F	58	5.6	Adeno carcinoma	ribs	Yes	45 Gy/25 fr	21/03/2016	25/04/2017
6	F	55	6.6	Squamous carcinoma	T2-T4 rib chest wall soft tissue	No	66 Gy/33 fr	04/04/2016	08/06/2017
7	F	74	4.3	Adenocarcinoma	T3-T4 rib	Yes	66 Gy/33 fr	26/05/2016	20/06/2017

P3.14-003 PATTERNS OF FOLLOW-UP CARE AFTER CURATIVE RADIOTHERAPY FOR STAGE I-III NON-SMALL CELL LUNG CANCER

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Background: Evidence regarding optimal follow-up (FU) strategies for patients after curative radiotherapy for NSCLC is limited, resulting in variable FU practice. The aim of this study was to describe the patterns of FU care for patients undergoing curative radiotherapy +/- chemotherapy. **Method:** A retrospective study was conducted of patients with Stage I-III NSCLC, undergoing a course of curative radiotherapy (a minimum dose of 50Gy), between 1/1/2007-31/12/2011 at three institutions. Data was collected from oncology records, including patient demographics, tumour characteristics, treatment and follow-up. At each FU, the reason for FU (routine or symptomatic), specialist seen and imaging performed were recorded, until an event (recurrence or new primary) was diagnosed. The censor date was 31/12/2016. Analysis of FU included univariate chi-square tests for categorical variables, t-tests for continuous variables, multivariate logistic regression analyses, and Kaplan Meier survival curves. **Result:** Two-hundred-and-eighty-three patients (183 males, 100 females) were identified with a median age of 72(36-91) years. Eighty-four (29.7%) were Stage I, 47 (16.6%) were Stage II, and 152 (53.7%) were Stage III. Pathology was large cell in 91 patients (32.2%), squamous cell in 100 (35.3%), adenocarcinoma in 68 (24.0%), and NSCLC NOS in 24 (8.5%). One-hundred-and-sixty-five (56.5%) patients received radiotherapy alone and the remaining 123(43.5%) received chemoradiotherapy. The average frequency of FU visits per year was 5.12, median number of FU visits to first event was 6, and median time to first event was 11 months. 73.7% of FU were routine, while only 16.2% were symptomatic. 1641 imaging tests were performed, equating to an average of 5.8 scans per patient, with only 98 resulting in a diagnosis of an event. Overall, recurrences were diagnosed in 175 patients of whom 85 were symptomatic and 90 diagnosed on routine imaging. New primaries were diagnosed in 23 patients, 15 with symptoms and 8 on routine imaging. Subsequent treatment was curative in 25 (14.3%) patients with recurrent disease and 18 (85.7%) with new primaries. Univariate and multivariate analysis determined that the method of diagnosis of an event (symptomatic vs routine) had no statistically significant impact on the intent of further treatment (curative treatment 13.8% v 7.7%, p=0.089) or on overall survival (2y OS 49.5% vs 51.6%, p=0.772). **Conclusion:** Following curative radiotherapy, patients undergo frequent FU with regular imaging. Despite this only a minority of patients who develop recurrence are suitable for curative treatment. The use of routine imaging did not impact on further curative treatment or improve overall survival.

Keywords: follow-up, Curative radiotherapy, NSCLC Stage I-III

P3.14-004 PATHOLOGICAL STUDY ON THE CLINICAL TARGET VOLUME (CTV) IN LIMITED-STAGE SCLC FOR CT-SIMULATION BASED THORACIC RADIOTHERAPY PLANNING

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Background: The microscopic extension, known as clinical target volume (CTV), of the primary tumor in locally advanced non-small cell lung cancer for chest radiotherapy planning has been well studied. However, the CTV of the primary tumor in limited-stage small cell lung cancer (SCLC) for thoracic radiotherapy planning has not been reported. In this study, we tried to quantify CTV of primary tumor in limited-stage SCLC with pathological approach. **Method:** Patients with stage T1-2N0-1M0 small cell lung cancer, treated with two cycles of etoposide plus cisplatin neoadjuvant chemotherapy or without neoadjuvant therapy were eligible for this study. Routine radical lobectomy and mediastinal lymph node dissection were performed for these patients. After operation, the intact lung lobe specimens were perfused with 10% neutral formalin and inflated as the natural state in the body. Specimens should be fixed for at least 12 hours. The fixed specimens were sectioned at 3mm thickness along the cross-sectional position of the body, and for each slice, the gross tumor and its surrounding 2cm lung tissue was embedded with paraffin and sliced with 4μm thickness. HE routine staining and CD56 immunohistochemical staining were applied. The slides were scanned by KFBIO reading software, and the pathologists confirmed the microscopic extension of the surrounding tumor. The minimal distances between microscopic nidus and the edge of gross tumor were measured. **Result:** Eight patients were enrolled, of whom 4 received 2 cycles of neoadjuvant chemotherapy and 4 received surgery without any neoadjuvant therapy. In patients who received neoadjuvant chemotherapy, one was diagnosed as squamous cell carcinoma after surgery and was excluded for further evaluation of CTV, while 1 patient achieved pathologically complete remission of tumor.The median range of CTV in patients received or did not receive neoadjuvant chemotherapy were 0.4mm (0.05mm-2.76mm) and 1.7mm (0.08mm-12.7mm) respectively, a margin of 1.4mm and 10.2mm could cover 95% of microscopic nidus (P=0.00). **Conclusion:** The preliminary results of this study indicated that to take into account 95% of the microscopic nidus, a 1.4mm and a 10.2mm margin should be need for CT-simulation based thoracic radiotherapy planning for limited-stage SCLC patients who were treated with or without induction chemotherapy. However, the sample size of this study was small and more cases are needed to justify the results.

Keywords: Limited-stage small cell lung cancer, thoracic radiotherapy, clinical target volume

P3.14-005 TREATMENT RESPONSE MEASURED ON CONEBEAM-CT DURING CONCURRENT CHEMORADIATION FOR NSCLC PATIENTS

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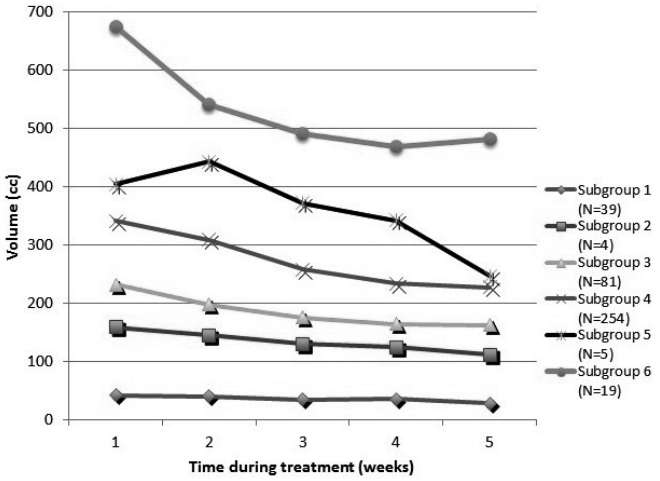
Background: The management of NSCLC-patients has evolved towards a more personalized care approach. Currently, the outcomes of concurrent chemoradiation (CCRT) in NSCLC patients are evaluated after the end of treatment, while individual treatment response during treatment is not taken into account. To pursue adaptive radiotherapy, it is important to distinguish responses during treatment and correlate this with outcome. Therefore, the aim was to identify subgroups that show a distinct treatment response during CCRT and correlate this with treatment outcome. **Method:** NSCLC-patients treated with CCRT between 2007-2013 were included. Treatment consisted of 66Gy/24 fractions with concurrent daily Cisplatin. Deformable image registration of the planning-CT to all Conebeam-CTs acquired during treatment was performed, and the gross tumor volumes on the ConeBeam-CTs were measured. Latent Class Growth Modeling was used to identify subgroups showing a distinct treatment response of the primary tumor during CCRT. Cox survival analysis was performed to assess the association of subgroup 'membership' with overall survival (OS) and progression free survival (PFS). **Result:** 402 patients were included. Median follow-up was 63 months and median OS was 23 months (95%CI 20-26 months) and median PFS was 18 months (95%CI 15–21 month). Six different patterns of treatment response were identified (Figure1). Group 1&2 showed a relatively stable pattern during treatment. Group 5 showed tumor progression in the first week followed by sharp decrease in tumor volume. All other groups showed a decrease in tumor volume from start of treatment. Remarkably, the groups 1&5, that didn't show a decrease in tumor volume from the beginning of treatment, had a significantly improved OS and PFS.



ure 1. Subgroups with distinct treatment response trajectories of NSCLC patients ated with CCRT (N=402).

Conclusion: Six groups showing a distinct treatment response during CCRT were identified. This is an important finding to be able to pursue adaptive radiotherapy. First analyses revealed an association between tumor response during treatment and OS and PFS. In-depth analyses are warranted.

Keywords: Cone beam CT, Concurrent Chemoradiation, adaptive radiotherapy

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P3.14-006 SLOW CT SIMULATION FOR GTV DELINEATION AND PLANNING OF RADIOTHERAPY TO LUNG CANCER PATIENTS; A SUNSHINE TO DEVELOPING COUNTRIES

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Background: In Bangladesh lung cancer stands in the top 3 in both male & female patient. Most of the patients are diagnosed as advanced stage. Radiotherapy plays an important role in the management of lung cancer. Motion management is a big challenge in GTV & ITV delineation, RT planning and minimizing the dose to OAR (Organ at risk). In Bangladesh there are 18 LINAC (12 in private & 6 in Govt. centers) is available. But, only one centre has the facility to do 4DCT simulation (United Hospital Limited). So it is time to consider that slow CT (computerized tomography) simulation can help to delineate GTV more precisely than axial CT simulation in Radiation Center of a developing country like Bangladesh. **Method:** In this study we included ten case of carcinoma of primary lung who have been treated using Radiotherapy. Most of the patients are in stage II or stage IIIA. All patients were treated with Radiotherapy In 3DCRT technique concurrently weekly cisplatin 30mg/m2. All the patients were underwent went 4 modes of CT scan Axial, Helical, Slow & 4D-CT using GE discovery 16 Slice PET-CT scanner. And KV-CBCT for the treatment verification was taken at regular interval. For standardization all the patients underwent different mode of scan using 2.5mm slice thickness and. Slow CT were performed using axial mode scan by increasing the CT tube rotation time as per the breathing period. In 4D-CT scan Respiratory cycle was divided in to 10 phases and scans were performed throughout the entire respiratory cycle. Maxmium Intensity Pixel (MIP), Minimum Intensity Pixel (MinIP) & Average Intensity Pixel (AvIP) were derived from the 10 Phases. GTV or ITV volumes were delineated for all the patients in all the scan modes (ITVAX - Axial, ITVSP - Spiral, ITVSl– Slow, ITVMIP - 4DCT) in the treatment planning system All the GTV or ITV volume were measured, documented and compared with the different modes of the CT scan. We have also done 4 modes of CT scan in moving phantom too. Phantom volume was delineated in all modes of scan (MIP, Slow, Axial and Helical) in treatment planning system and the difference in volume was compared. **Result:** The mean ± sd (range) for MIP, slow, axial, & helical were 36.5 ± 40.5 (2.29-87.0), 35.38 ±39.52 (2.1 – 82), 31.95 ± 37.29 (1.32 – 66.9) & 28.98 ± 33.36 (1.01 – 65.9. Overall underestimate of helical scan and axial scan compared to MIP is 21% and 12.5%. CBCT and slow CT volume has a good correlation with the MIP volume. Ratio of 4DCT and Slow CT scan is 0.97. While we compare volumes (Ratio) of moving phantom of different modes of CT scans, the findings were MIP 50.29cc (1.0), Slow CT 48.83cc (0.97), Axial 35.6 cc (0.71) and Helical 31.68 cc (0.63). Volume comparison in moving phantom also showed good correlation and match in both 4DCT and Slow CT scan. From this study we can draw inference that Slow CT volume has a very good correlation with the MIP volume, the ratio of the Slow CT vs MIP is 0.97 ± 0.12, where as The ratios of GTV(MIP) to GTV (Axial) and GTV(helical) were 0.87 ± 0.14 and 0.79 ± 0.12, respectively, which showed a marked difference in GTV volumes. **Conclusion:** Though, it was limited number of patients in this observational study. But, it showed a very crucial finding to improve the GTV or ITV delineation and to limit the dose to OAR. As slow CT Scan can be done in any CT simulator machine, where there is no facility to do 4DCT scan. Although, 4DCT scan is a gold standard for GTV delineation for the motion management of lung cancer, but, in the absence of 4DCT scan, slow CT can be used. We should need multiple centers, large number of patients' data to validate this finding

Keywords: 4DCT, Slow CT , Radiotherapy

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P3.14-007 A FUNCTIONAL EQUIVALENT UNIFORM DOSE CORRELATES WITH RADIATION PNEUMONITIES IN RADIATION THERAPY

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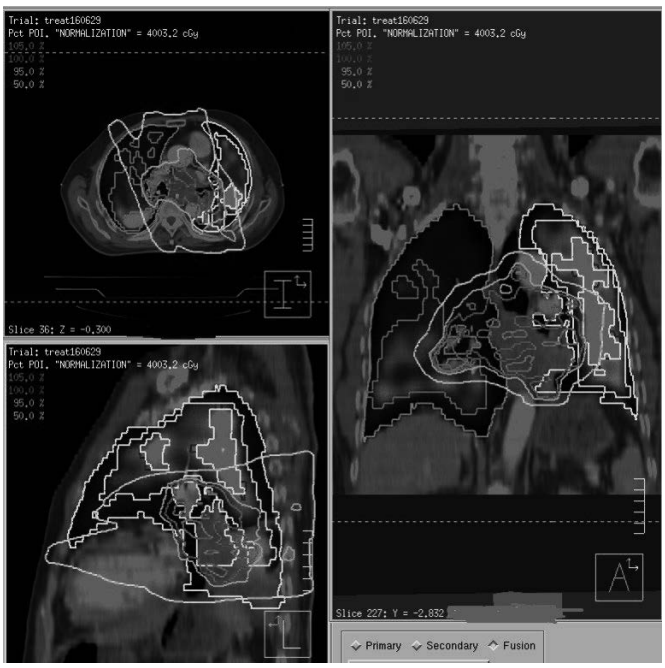
Background: The literature on dose-volume parameters and pneumonitis is extensive, whose results are inconsistent, both for the best predictive metrics and significant comorbid factors. To develop an improved functional equivalent uniform dose (fEUD) with perfusion factors of single photon emission computed tomography (SPECT) images as predictors of radiation peneumonitis (RP) in patients undergoing curative radiotherapy (RT). **Method:**



Functional lung imaging was performed using single photon emission computed tomography (SPECT) for perfusion imaging. Perfusion factors were defined as the mean percentile perfusion levels of the four areas of the top to 75%, 75% to 50%, 50% to 25%, 25% to 0%, respectively. fEUD were calculated from perfusion factors in computed tomography (CT) and SPECT fused images and standard dose-volume parameters were extracted from radiotherapy treatment planning. Total lung (TL) volumes minus GTV, V5 and V20 (the percentage of normal lung tissue receiving more than 5Gy and 20Gy), fEUD (equivalent to 2Gy/fx, α/β=3.3, a=1), and mean dose of TL were analyzed to evaluate correlations between RP, which was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Statistical significance was defined as a P-values of <.05. **Result:** A total of 28 patients treated with intensity modulated RT or 3D conformable RT were analyzed, grades≥3 RP were observed in 6 patients. There was only a significant difference in fEUD between patients with RP and free (p=0.007). Insignificant tendency of difference was showed in the mean dose of TL (p = 0.052). V5 and V20 of whole lung were almost identical between the two groups (p=0.161 and 0.197), as the most values are below the recommended thresholds from published papers. **Conclusion:** SPECT-based equivalent uniform dose presented more significant to predict RP compared to standard dose–volume parameters and mean dose.

Keywords: Radiation pneumonitis, Functional Equivalent Uniform Dose, Perfusion SPECT

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P3.14-008 CLINICAL CHARACTERISTICS MATRIX OF LUNG TUMOR UNDER STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR)

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Background: Early Stage lung cancer can be treated with surgical resection and SABR. In clinical practice, it may be important to find a characteristic matrix for precision radiotherapy. The characteristic matrix for a lung tumor should include: 1) a time factor that incorporates the motion pattern of the tumor, 2) spatial factor which is related to volumetric information including location and surrounding environment, and 3) intrinsic characteristics which are related to the biologic information and could be represented by imaging characteristics. In this investigation, the typical heterogeneous characteristics matrix of lung tumors treated with SABR were studied. **Method:** A total of 38 patients with 41 lung tumors were retrospectively reviewed. All targets were treated with SABR. 4-Dimensional Computed Tomography (4DCT) was used for simulation. The time factor parameter was defined by the breathing cycle signal recorded by an infrared reflector. The internal target volumes (ITV) were generated by the cine image set through phase binning method. The intrinsic characteristics of tumors were described by the image information inside the tumor, which was represented by the ITV. This target image information was described by the minimum Hounsfield Unit (HU), maximum HU, mean HU, and standard deviation. **Result:** For spatial location, there were 23 tumors in the right lung and 18 tumors in the left lung. For phase surrogate signal, the mean amplitude was 0.7 cm with standard deviation (SD) = 0.3 cm. Mean breathing cycle was 3.5 seconds (SD = 1.1). Mean prescription isodose volume (PIV) was 38.3 cc (SD = 37.7) and the mean corresponding diameter was 3.8cm (SD = 1.1cm). Mean ITV volume was 13.4 cc (SD = 20.4) and the corresponding diameter was 2.4 cm (SD = 1.2). With regard to imaging information, ITV minimum HU was -883.1 (SD = 120.3); ITV maximum HU was 222.3 (SD = 487.9); ITV mean HU was -224.9 (SD = 188.2). PTV minimum HU was -937.1 (SD = 62.2); PTV maximum HU was 437.1 (SD = 506.1); PTV mean HU was -482.3 (SD = 192.6). **Conclusion:** A characteristics matrix was computed for SABR treated lung tumors based on time, imaging, and spatial information. The matrix could be further expanded and assessed for intra-fractional and post treatment analysis. Other imaging modalities such as MRI and incorporation of immune system stimulation mechanisms can be combined with big data analysis methodologies for patient treatment options in precision medicine through similarity matching.

Keywords: Characteristic Matrix, Stereotactic ablative radiotherapy, Similarity Matching

P3.14: RADIOTHERAPY -
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P3.14-009 THORACIC RE-IRRADIATION OF LUNG CANCER USING HIGHLY CONFORMAL RADIOTHERAPY IS EFFECTIVE AS SALVAGE TREATMENT OPTION

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Background: Despite wide adoption of intensity-modulated radiation therapy (IMRT), thoracic re-irradiation of lung cancer has been challenged by the tolerance doses of normal tissues such as lung and esophagus. We retrospectively analyzed the local control rate and the toxicity of thoracic re-irradiation using highly conformal radiotherapy. **Method:** Between September 2008 and November 2015, 50 patients received thoracic re-irradiation with 3D conformal therapy (n=6, 12%), linac-based IMRT (n=11, 22%), helical tomotherapy (n=31, 62%), and stereotactic body radiotherapy (n=2, 4%). Total lung mean dose ($_{Total}D_{mean}$) was calculated by the sum of lung D mean of initial radiotherapy (RT) and that of re-RT. **Result:** Twenty-two patients had distant metastasis at the time of re-RT. Median follow-up time was 14.0 months (range; 1.4 - 65 months) from re-RT. At the time of analysis, local progression after re-RT was observed in 40% (n=20) of patients. The 1-year and 2-year local progression-free survival (LPFS) were 60.3% and 47.1%, respectively. Median time to local progression was 8.5 months (range; 1.4 - 65 months) and median survival from re-RT was 13.9 months (range; 1.4 - 65 months). Median total dose was 70.3Gy (range; 33 - 131 Gy) with median fraction size of 2Gy (range; 1 - 10.9 Gy). Local control rate of 3D-conformal RT and that of IMRT was 50% and 61.4%, respectively. When we compared the LPFS of patients who received re-RT using IMRT, smaller PTV volume was associated with greater LPFS with marginal significance: the 1-year LRFR of PTV<57.5 cm^3 and PTV≥57.5cm^3 were 74.5% and 51.7%, respectively (p=0.054). Acute grade 1 and 2 radiation pneumonitis were observed in 16% (n=8) and 10% (n=5), respectively. No acute grade 3 or higher radiation pneumonitis occurred. $_{Total}D_{mean}$ of patients with and without acute radiation pneumonitis showed significant difference: 14.8Gy with acute radiation pneumonitis and 12.0Gy without acute radiation pneumonitis (p=0.048). Acute grade 2 esophagitis was observed in 6 patients (12%), and no grade 3 or higher esophagitis occurred. Chronic grade 2 radiation pneumonitis occured in 5 patients, and no chronic grade 3 or higher complications was observed **Conclusion:** The stratification of patients receiving thoracic re-RT is crucial in extending the indications and improving the efficacy of IMRT. Based on appropriate stratification, thoracic re-RT of lung cancer can be safely delivered using highly conformal radiotherapy with excellent local control and acceptable toxicity.

Keywords: Thorax, conformal radiation, reirradiation

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P3.14-010 MAGNETIC RESONANCE IMAGING (MRI) FOR LUNG CANCER RADIOTHERAPY PLANNING AND TREATMENT

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Background: A potential benefit of integrating MR imaging in the radiotherapy planning and treatment process is the improved soft tissue contrast. However, this benefit may be obscured if there are substantial variations in the way that both target and organs at risk (OARs) are contoured, either at the time of initial simulation or at each fraction. The aim of this work is to develop standardised MR imaging sequences for target and OAR contouring in lung cancer patients for integration into the planning and treatment process for MR image-guided radiotherapy. **Method:** 11 lung cancer patients were recruited across 3 European centres using a standardised MR protocol with various soft tissue contrasts as well as numerous respiratory management techniques. All MR images were acquired at 1.5 T with 3.5 mm slice thickness. 7 radiation oncologists and 3 radiologists reviewed the MR images alongside CT and FDG-PET-CT, rigidly registered to tumour area, to determine the most adequate sequences for OAR and tumour visualisation/delineation. **Result:** The most adequate MR sequences were found to be: Radial 3D T1, Turbo Spin Echo (TSE) fat-suppressed (fat-sat), DIXON TSE and T2 TSE (table 1). The sequences aided in visualisation of tumour, nodes and OARs including oesophagus, proximal bronchial tree, trachea, heart, lungs, spinal cord/canal and brachial plexus. The TSE (fat sat) and DIXON TSE gave strong signal from tumour, nodes and brachial plexus, aiding in their visualisation. The motion averaging characteristics ofthe Radial 3D T1 improve image consistency over slices, whereas the TSE sequences can include motion induced distortions.

Table 1. The most adequate sequences identified for tumour, node and OAR visualisation. These sequences have been acquired with varying contrast and different respiratory management techniques.

Sequence	Respiratory Management	Purpose	Coverage
Radial 3D T1 (fat sat)	Radial k-space sampling	Tumour, nodes, OARs, spatial reference	Ful thorax
TSE (fat sat)	Respiratory triggered	Tumour, nodes, OARs	Tumour (if tumour below aortic arch)
DIXON TSE	Multiple signal averages	Brachial plexus, tumour, nodes	Tumour and Brachial Plexus (if tumour above aortic arch)
T2 TSE	Respiratory triggered	Tumour, nodes, OARs	Full thorax

Conclusion: A set of MR sequences suitable for lung cancer radiotherapy planning have been identified which provide adequate visualisation of tumour, nodes and OARs. The next step is to acquire these sequences in a set of patients and assess

intra-/inter-clinician variability in target and OAR delineation, and develop an MR lung contouring atlas.

Keywords: imaging, planning, MRI

P3.14: RADIOTHERAPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.14-011 MEAN HEART DOSE IS AN INDEPENDENT RISK FACTOR FOR EARLY MORTALITY AFTER CHEMORADIOTHERAPY TREATMENT FOR LUNG CANCER

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Background: Early mortality after (chemo)radiotherapy can be caused by treatment-related toxicities and thus by delivered doses to normal lung and heart tissues. However, prediction models for mortality incorporating dosimetry are lacking. This study explores the prognostic value of common dosimetric features. **Method:** Two prospective cohorts containing 218 and 181 curatively treated stage I-III lung cancer patients from 2003-2007 and 2013-2016 periods, respectively, were studied. Prescribed dose was 66Gy/2Gy (concurrent chemotherapy), 66Gy/2.75Gy (sequential or no chemotherapy) or a similar schedule. Clinical (WHO performance status, age, T stage, N stage and primary gross tumor volume (GTV)) and dosimetric (mean lung dose (MLD) and mean heart dose (MHD)) covariates were analysed. Cox regression models of survival and a logistic regression model for the 12 month mortality endpoint were optimized using forward stepwise selection ($p<0.05$). **Result:** Median follow-up time was 80.2 and 20.2 months in dataset 1 and 2, respectively. MHD (HR=1.023, p=0.001) and WHO performance status (HR=1.25, p=0.03) were selected in the Cox model for dataset 1. Tumor volume (HR=1.0015, p=0.001), WHO performance status (HR=1.023, p=0.02) and MHD (HR=1.0030, p=0.03) were selected in dataset 2. Adding time-dependent covariates revealed a decreasing GTV HR over time in dataset 1 (p=0.02), while MHD risk did not significantly change with time. Worse survival observed in a high MHD subgroup indeed only starts after 8 months (Figure 1). 12 month survival modeling included the covariates MHD (optimal cut-off 22Gy) and GTV (AUC=0.71). In dataset 2, these covariates and cut-off resulted in a model with AUC=0.63.

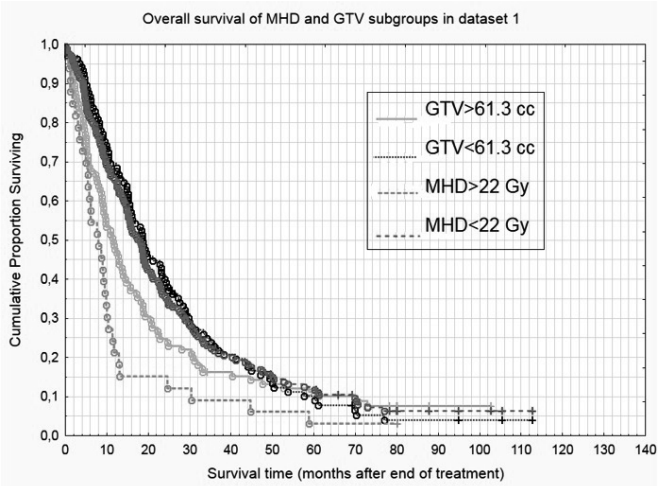

Figure 1 Kaplan-Meier curves for overall survival in dataset 1. Subgroup analysis based on GTV volumes (median value of 61.3 cc as cut-off, green and black curves) and subgroup analysis based on mean heart dose (MHD) (optimal cut-off of 22 Gy, orange and red curves). Later than 8 months survival time, high mean heart dose starts to be an independent risk factor for mortality.

Conclusion: Mean heart dose is an independent risk factor for early mortality in two cohorts with different treatment periods and techniques. The best classifier for 12 month mortality risk was obtained with the MHD<22Gy constraint, which could be used in model-based implementation of proton therapy.

Keywords: Early mortality, Proton therapy, Heart dose

P3.14: RADIOTHERAPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.14-012 RISK OF DEVELOPING PNEUMONITIS INCREASES IN PATIENTS RECEIVING IMMUNOTHERAPY WITH A HISTORY OF LUNG IRRADIATION

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Background: A large proportion of patients with locally advanced/metastatic Non-Small Cell Lung Cancer (NSCLC) present disease progression despite aggressive treatments and will further receive immunotherapy. Pneumonitis is an uncommon but potentially fatal toxicity related to immunotherapy treatment. The association with the history of radiotherapy and the risk of developing pneumonitis have not been well described. We associated the history of radiotherapy with the development of pneumonitis in patients receiving immunotherapy. **Method:** Clinical information was retrospectively obtained from histologically confirmed advanced NSCLC patients treated from February 2013 to February 2017. Clinical and radiologic features of pneumonitis were collected from patients receiving immunotherapy. We sought associations between pneumonitis incidence and clinical characteristics. **Result:** Of 59 patients who received immunotherapy 61.7% were treated with nivolumab, 29.9% with pembrolizumab and 6.7% with the combination durvalumab plus tremelimumab. Immunotherapy treatment was administered in first line in 26.6% of patients, 28.3% received in second line and 36.7% in third or more line of treatment. Twenty-five of the 59 patients (41.7%) received previous radiotherapy, 16 of them (26.7%) to the lung and 9 (15%) to the thoracic spine. Fifteen (15/59) patients (25%) developed pneumonitis; this occurred irrespective of line of therapy in which immunotherapy was received (first line: 38.5%; second line: 33.5%; third line or more: 26.7%). No association was found between line of treatment and pneumonitis development. Median time from therapy initiation to pneumonitis was 4.5 months (range 18 days - 13.1 months). For any grade of pneumonitis, the percentage was of 25% (15 patients) of which 48% (12/25) had received radiotherapy, Grade ≥2 pneumonitis was seen in 10 patients (17%) and 32% (8/25) had history of radiation therapy. All Grade 3 pneumonitis events (n=4) presented in patients with previous lung radiotherapy. The incidence and severity of pneumonitis was higher in patients who had received radiotherapy (OR, 95% CI: 6.8 (1.6 – 28.5); p=0.009). **Conclusion:** The incidence of pneumonitis related to immunotherapy treatment could be underestimated. We observed an increase in the risk and severity of pneumonitis in patients with previous radiation therapy and subsequent treatment with immunotherapy, regardless of used drug or line of therapy. In these patients, we recommend close clinical and radiologic follow-up.

Keywords: Radiotherapy, Immunotherapy, pneumonitis

P3.14: RADIOTHERAPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.14-013 OUTCOMES ACCORDING TO MARGINAL TUMOR DOSE PRESCRIPTION FOR SMALL- TO MEDIUM-SIZED BRAIN METASTASES FROM LUNG CANCER

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Background: At our institution, we commonly treat brain metastases (BM) adjacent to critical structures with a smaller dose prescription (DP) to reduce the likelihood of toxicity. We sought to evaluate the impact of DP on LF and RN for small- to medium-sized BM (≤ 2 cm) from lung cancer. **Method:** A prospective registry of BM patients treated with gamma knife SRS between 2008 and 2016 was interrogated to determine per lesion rates of LF and RN. Each lesion was followed until LF or RN or at last MRI follow-up. Defined criteria were used to differentiate LF from RN. Whole brain irradiation (WBI) was a censoring event. **Result:** From 1,465 potential subjects, 345 small- to medium-sized BM from 151 lung cancer patients were evaluated. Median radiographic follow-up was 10.2 months. Median lesion volume and diameter were 0.17 cm^3, and 0.81 cm, respectively. The DP for 71 lesions (21%) was 15 Gy, and ≥ 20 Gy (median 21 Gy; 20-24Gy) for 274(79%). Most lesions were ≤ 1 cm (65%). Median number of SRS was 2 (1-4) and 36 patients received salvage WBI. Sixteen lesions (4%) developed LF and 12 (3%) developed RN. Freedom from local failure at 1 year (FFLF) for 15 Gy, and ≥ 20 Gy, was 80%, and 95%, respectively (p=0.02). FFLF for lesions ≤1cm, and >1 cm, was 95%, and 78%, respectively (p<0.01). Freedom from RN at 1-year (FFRN) for DP 15 Gy, and ≥ 20 Gy, was 98%, and 96%, respectively (p=0.3). FFRN for lesions ≤ 1cm, and > 1 cm, was 98%, and 93%, respectively (p=0.01). FFLF and FFRN for lesions ≤1 cm and >1 cm, according to DP, are shown in Table 1.

	Lesion size					
	≤1 cm		P value	>1 cm		P value
	DP			DP		
	15 Gy	≥20 Gy		15 Gy	≥20 Gy	
FFLF	88.8%	96.4%	**0.42**	53.4%	88.2%	**0.08**
FFRN	100%	98%	--	98%	92%	**0.43**

Conclusion: Our results suggest that, particularly for lesions >1 cm, DP ≥ 20 Gy correlates with improved FFLF, and similar FFRN rates, compared to DP 15 Gy.

P3.14: RADIOTHERAPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.14-014 LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT): PATIENT'S OUTCOME AND PROGNOSTIC FACTORS

N. Farré[1], E. Acosta[1], J. Balart[1], G. Sancho[1], K. Majercakova[1], P. Carrasco[2], A. Fernández[3], M.D.V. Camacho[3], M. Majem[4], A. Giménez[5], E. Martínez[6], J.C. Trujillo[7], A. Torrego[8], V. Pajares[8], J. Craven-Bartle[1]

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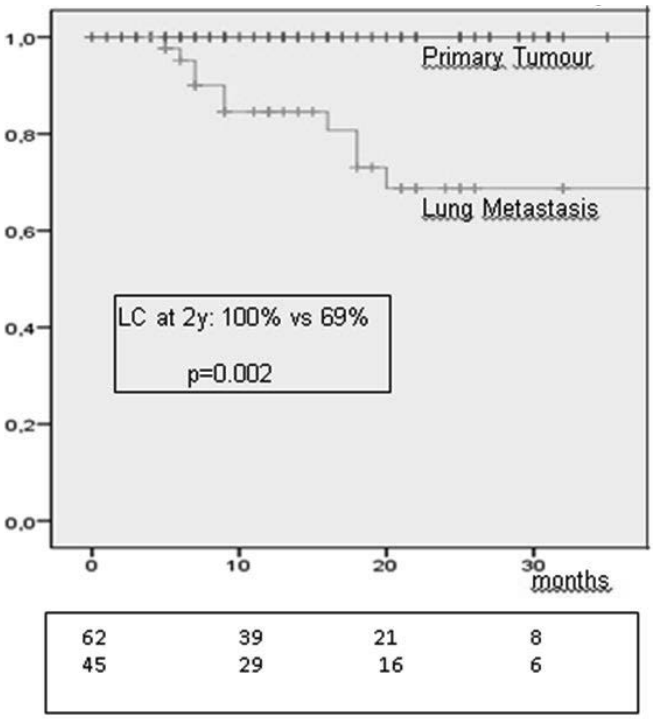
Background: Stereotactic body radiotherapy (SBRT) is the standard of care in patients with medically inoperable early stage NSCLC and an effective method of treatment of lung metastases (LM) in oligometastatic patient.We evaluated local control (LC), overall survival (OS), cause-specific survival (CSS), and related toxicity in the both group of patients treated in our center. **Method:** Between April 2012 and September 2016, 107 lung lesions were treated with SBRT; 62 early NSCLC(58%) and 45 LM(42%). Three risk-adapted fractionation schemes that ensure DBE>100Gy were considered: 3x18Gy, 5x11Gy and 8x7.5Gy. Kaplan-Meier(KM) curves were used to evaluate LC,OS and CSS. We analyzed toxicity and predictive factors. **Result:** The median follow-up was 16 months(range 6-44). For **primary NSCLC**: LC,CSS, and OS at 2 years were 100%,91% and 64%, respectively.19 patients died, 5 because of a lung cancer and 14 due to concurrent disease. Regional relapse was observed in five patients(7.6%).Six patients(9.2%) developed distant metastases. There was no statistically significant difference in OS and CSS when comparing peripheral-central tumors or T1-T2 tumors. However, T2 and central tumors showed lower survival rates. For **lung metastatic lesions**: LC,CSS, and OS at 2 years were 69%, 66% and 66%, respectively. The primary tumors were:colorectal 17(38%), lung 15(33%) and others 13(29%).There was no statistically signficant difference in survival among primary tumor or 1-3 metastatic lesions, but colorectal primary tumors and more than one lung metastases had lower survival.We compared LC and CSS in both group of patients. There was a statistically significant difference in local control(p=0.002) and CSS(p=0.027) among the primary tumors or lung metastases(Figure 1).According to RTOG,≤G2 lung and skin acute toxicity was 5% and 3% respectively.Lung late toxicity ≤G2 was 22.4%. No patients developed >G2 toxicities.



Conclusion: With a 2-year LC rate >95% with limited toxicity, SBRT confirms as state-of-the-art treatment for medically inoperable early stage NSCLC and effective options for oligometastatic patients.

P3.14: RADIOTHERAPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.14-015 A PROPENSITY MATCHED ANALYSIS OF SBRT AND SUBLOBAR RESECTION FOR STAGE I NON-SMALL CELL LUNG CANCER IN PATIENTS AT HIGH RISK FOR LOBECTOMY

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Background: The aim of this study was to perform a survival comparison between stereotactic body radiotherapy (SBRT) and sublobar resection (SLR) in patients with stage I non-small cell lung cancer (NSCLC) at high risk for lobectomy. **Method:** All patients who underwent SBRT or SLR because of medical comorbidities for clinical stage I NSCLC from January 2008 to December 2015 were reviewed retrospectively. Propensity score matching was performed to reduce selection bias between SBRT and SLR patients based on age, gender, performance status, tumour characteristics, pulmonary function. Overall survival (OS) and recurrence-free survival (RFS) were estimated with Kaplan–Meier method. **Result:** Forty-nine patients were matched into each group of SBRT and SLR (include 27 underwent segmentectomy, 22 underwent wedge resection). There were 32 and 30 men with median age of 67 and 69 years, respectively. Median follow-up was 25 months. In terms of treatment-related mortality, the 30- day mortality rates for the SBRT and SLR groups were 0 and 2.0 %, respectively. Patients treated by SBRT had a tendency to increase 3-year OS compared with SLR (94.0% versus 78.1%; P= 0.064).There was no difference between two groups in 3-year RFS (61.8% versus 65.7%; P=0.864). In a subanalysis, 3-year OS after SBRT was greatly better than wedge resection subgroup (94.0% versus 67.4%; P= 0.026), but there was no significant difference between SBRT and segmentectomy in 3-year OS (94.0% versus 88.0%; P= 0.212). **Conclusion:** SBRT had a tendency to increase OS compared with sublobar resection in patients who are not medically fit for lobectomy with clinical stage I NSCLC. However, OS after SBRT was better than wedge resection subgroup. SBRT can be an alternative treatment option to segmentectomy for patients who cannot tolerate lobectomy because of medical comorbidities. A randomized prospective study is necessary to determine survival in compromised SBRT and sublobar resection.

Keywords: SBRT, sublobectomy, NSCLC

P3.14: RADIOTHERAPY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.14-016 RESEARCH ABOUT DIFFERENT ADMINISTRATION MODE OF ENDOSTAR FOR COMBINING WITH CONCURRENT CHEMORADIOTHERAPY IN LOCAL ADVANCED NSCLC

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Background: Radiotherapy is carried out five days in a week. Endostar is a target drug, its adminstration is d1-14 in three weeks. We changed endostar adminstration mode as the same of radiotherpy, five days in a week. Now we evaluate the efficacy and safety of different administration dose of endostar combined with concurrent chemoradiotherapy in ad vanced non-small cell lung cancer(NSCLC). **Method:** From September 2010 to December 2015,40 patients with local advanced NSCLC were recruited. All the patients received radiotherapy with 60Gy and two circles chemotherapy with docetaxel 75mg/m^2 d1 and cisplatin 75mg/m^2 d1~3,combined with two different administration dose of endostar(75mg/m^2 d1-14 in three weeks for two cycles and 75mg/m^2 d1-5 in one week for six cycles concurrent with radiotherapy. Tumor response were evaluated with RECIST1.1 criteria. Acute toxicities were evaluated with NCICTC3.0 and RTOG criteria. **Result:** In group one,2 patients achieved complete response,10 partial response,3 stable disease,5 progressive disease. Overall response rate was 60%. The 1-year progressive-free-survive rate was 40%. The 1-,2-year survival rates were 70% and 25%. The median overall survive is 19.9 month. In group two,overall response rate was 75%. The 1-year progressive-free-survive rate was 50%. The 1-,2-year survival rates were 80% and 45%. The median overall survive is 22.7 month. In group 2 there had a good survival and patient compliance, but there were no significant difference between two groups (P>0.05). **Conclusion:** Endostar combined with concurrent chemoradiotherapy is useful and well-tolerance. Administration mode of endostar combining with chemoradiotherapy, which is five day in a week for six weeks, had a better result and patient compliance.

Keywords: non-small cell lung cancer, Target therapy, Chemoradiotherapy

P3.14-017 DOSIMETRIC EVALUATION OF LUNG SBRT TREATMENT

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Background: To analyse the relation between clinical outcomes and dosimetric indices for SBRT lung treatments. **Method:** 96 lung lesions were treated with SBRT(6MV photons 3DCRT). Planning CT included whole lung. 4DCT of tumor area was used to obtain a MIP-based ITV, with three risk-adapted fractionation schemes [3x18Gy, 5x11Gy, 8x7.5Gy(BED>100Gy)]. In treatment delivery the tumor was centered *online* using CBCT and its movement validated by fluoroscopy adjusting the gating limits to the breathing amplitude. Toxicity and dosimetric indices for PTV and OAR were evaluated and correlated with the clinical outcomes 6 months after radiotherapy **Result:** Table1 shows the dose constraints as well as the results of the dosimetric indices. It was found that 95%/75% of the patients developed G=0 acute/ late toxicity, 3%/0% G=2 acute lung/skin toxicity, 3% G=2 late lung toxicity and no patients developed G>2 toxicities. Figure 1 displays the correlation between V_{100}, V_{90}, CI and the clinical outcomes after 6 months of radiotherapy. Only the CI was statistically significant(t-test p=0.017) as an indicator of the ratio between complete/ partial responses(mean CI=1.1/1.05)

Organ	Index	Dose constrains	mean [range] σ	
			Prescription 3 X18 Gy†	Other prescriptions‡
PTV	$V_{100\%}$(%)		**94.99** [94.90 95.00] 0.03	**98.3** [72.0 95.4] 3.5
	$V_{90\%}$(%)		**99.95** [99.70 100.00] 0.09	**99.4** [90.4 102.8] 1.5
	D_{max}(%)	$110<D_{max}<140$	**129** [113 138] 6	**128** [77 139] 7
	IC	<1.2	**1.14** [1.01 1.40] 0.10	**1.07** [0.83 1.24] 0.09
	V(cc)		**18** [3 52] 14	**28** [2 112] 22
	V(50%)/V(PTV)		**5.9** [4.2 8.6] 1.0	**5.3** [4.1 6.6] 1.8
	D_{max}(@2cm)	27† o <30‡	**27** [22 38] 3	**30** [20 48] 6
	IH		**1.23** [1.11 1.31] 0.05	**1.26** [1.03 1.41] 0.06
Lungs	V_{20}(%)	<15	**3** [1 9] 2	**4** [1 15] 3
	V_{10}(%)	<20	**8** [3 20] 5	**8** [2 28] 5
	V_5(%)	<40	**14** [6 29] 7	**14** [3 42] 8
	$V_{15,0}$(cc) † o $V_{15,5}$(cc) ‡	<1500	**251** [82 548] 158	**205** [3 868] 160
	$V_{10,0}$(cc) † o $V_{10,5}$(cc) ‡	<1000	**229** [77 511] 147	**194** [2 829] 158
	D_{mean}(Gy)		**2.8** [1.2 6.3] 1.4	**3.0** [0.7 9.7] 1.7
	D_1(Gy)		**34** [21 58] 10	**36** [16 66] 1.2
	D_5(Gy)		**15** [6 29] 7	**15** [3 57] 9
homolateral	V_{20}(%)	<15	**6** [2 14] 4	**7** [1 29] 5
	D_{mean}(Gy)		**5** [2 9] 2	**5** [1 16] 3
	D_1(Gy)		**43** [29 61] 9	**46** [22 68] 11
	D_5(Gy)		**22** [12 39] 9	**23** [4 57] 11
Trachea	V_{10}(cc) † o $V_{10,5}$(cc) ‡	<4	**0.01** [0.00 0.10] 0.02	**0.2** [0.0 9.8] 1.2
	D_{max}(Gy)	<30† o <32‡	**3** [0 17] 5	**6** [0 31] 7
	D_{mean}(Gy)		**0.6** [0.1 3.7] 1.0	**2** [0 30] 4
	D_1(Gy)		**2** [0 15] 4	**6** [0 63] 9
	D_5(Gy)		**2** [0 13] 4	**5** [0 32] 6
Bronchial Tree	V_{10}(cc) † o $V_{10,5}$(cc) ‡	<4	**0.01** [0.00 0.10] 0.02	**0.4** [0.0 5.0] 0.9
	D_{max}(Gy)	<30† o <32‡	**10** [2 17] 5	**18** [0 71] 18
	D_{mean}(Gy)		**1.3** [0.1 3.5] 1.0	**2** [0 10] 2
	D_1(Gy)		**7** [1 14] 4	**11** [0 45] 10
	D_5(Gy)		**5** [0 14] 4	**7** [0 35] 6
Spinal Cord	$V_{10,0}$(cc) † o $V_{10,5}$(cc) ‡	<1.2	**0.00** [0.00 0.08] 0.02	**0.1** [0.0 1.2] 0.2
	D_{max}(Gy)	23.2† o <25-30‡	**7** [1 13] 3	**9** [0 20] 5
	D_{mean}(Gy)		**1.3** [0.1 4.6] 1.2	**1.9** [0.0 5.5] 1.3
	D_1(Gy)		**6** [0 12] 3	**8** [0 16] 4
	D_5(Gy)		**5** [0 11] 3	**7** [0 15] 4
Esophagus	$V_{15,0}$(cc) † o $V_{15,5}$(cc) ‡	<5	**0.00** [0.00 0.00] 0.00	**0.0** [0.0 1.7] 0.2
	D_{max}(Gy)	<24-27 o <27-32.5‡	**7** [3 13] 3	**10** [1 27] 6
	D_{mean}(Gy)		**1.1** [0.1 2.5] 0.6	**1.7** [0.1 8.6] 1.3
	D_1(Gy)		**7** [1 15] 3	**8** [0 23] 5
	D_5(Gy)		**6** [0 10] 3	**7** [0 20] 4
Heart	V_{30}(cc) † o V_{30}(cc) ‡	<15	**0** [0 0] 0	**0.04** [0.00 2.40] 0.3
	D_{max}(Gy)	<24-30† o <27-35‡	**8** [0 21] 7	**9** [0 50] 11
	D_{mean}(Gy)		**1.1** [0.0 4.0] 1.4	**1.1** [0.0 7.0] 1.6
	D_1(Gy)		**6** [0 15] 5	**5** [0 28] 7
	D_5(Gy)		**4** [0 12] 4	**4** [0 20] 5
Bronchial Plexus (n=2† y 22‡)	V_{30}(cc) o V_{35}(cc) ‡	<3	**0** [0 0] 0	**0.18** [0.00 3.6] 0.78
	D_{max}(Gy)	<23-26† o <27‡	**0.45** [0.40 0.50] 0.07	**11** [0 48] 15
	D_{mean}(Gy)		**0.11** [0.10 0.13] 0.02	**3** [0 23]5
	D_1(Gy)		**0.30** [0.30 0.30] 0.00	**9** [0 41] 12
	D_5(Gy)		**0.20** [0.19 0.20] 0.01	**7** [0 36] 10
Great Vessels	V_{40}(cc) o V_{45}(cc) ‡	<10	**0** [0 0] 0	**0** [0 0] 0
	D_{max}(Gy)	<39-45† o <45-55‡	**9** [1 24] 6	**16** [0 55] 14
	D_{mean}(Gy)		**1.4** [0.1 3.3] 1.1	**2** [0 11] 2
	D_1(Gy)		**6** [0 19] 5	**11** [0 39] 10
	D_5(Gy)		**5** [0 15] 4	**8** [0 27] 7
Aorta	V_{40}(cc) o V_{45}(cc) ‡	<10	**0** [0 0] 0	**0.05** [0.00 1.19] 0.17
	D_{max}(Gy)	<40† o <45‡	**9** [1 20] 4	**19** [4 63] 14
	D_{mean}(Gy)		**1.4** [0.2 3.6] 0.8	**2.3** [0.2 7.2] 1.6
	D_1(Gy)		**8** [1 16] 4	**13** [1 35] 8
	D_5(Gy)		**6** [0 12] 3	**9** [0 25] 5
Skin	V_{30}(cc) o $V_{35,0}$(cc) ‡	<10	**0** [0 0] 0	**0** [0 0] 0
	D_{max}(Gy)	<30-33† o <40‡	**18** [12 24] 4	**20** [12 33] 5
	D_{mean}(Gy)		**1** [0 1] 0	**1** [0 4] 0
	D_1(Gy)		**9** [7 15] 3	**10** [1 36] 0
	D_5(Gy)		**3.2** [1.1 6.5] 1.7	**4** [0 14] 2
Chest Wall	$V_{35,0}$ (cc) o V_{35}(cc) ‡	<1	**3** [0 18] 5	**5** [0 23] 6
	D_{max}(Gy)	28-30† o <32.5-35‡	**28** [4 44] 11	**47** [1 67] 16
	D_{mean}(Gy)		**4** [2 9] 2	**6** [1 67] 18
	D_1(Gy)		**21** [15 33] 6	**27** [3 50] 10
	D_5(Gy)		**16** [11 25] 5	**19** [2 36] 7

Table1: Shows the restrictions considered, the mean, the range and standard deviation

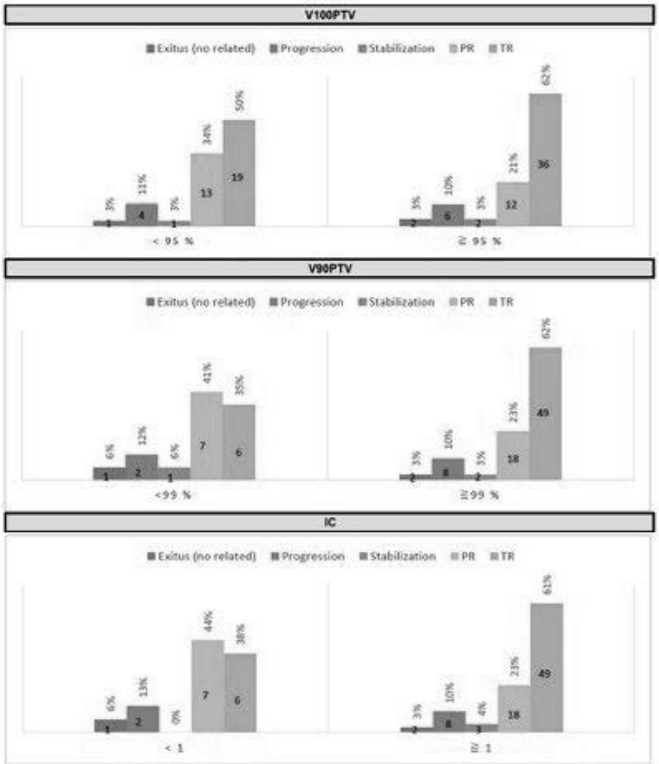

Fig1: Shows tumor progression and survival after 6 months (no related exitus, progression, stabilization, partial response (PR), total response (TR)) as a function of the PTV dosimetric indices, V_{100}, V_{90}, and CI. The dermination of the tumor progression was image-based.

Conclusion: The lung SBRT technique is safe(no G> 2 toxicity has been reported) even for cases with OAR compromise. The CI has been statistically significant as a predictor of complete tumor remission at 6 months.

Keywords: Dosimetric Indices, SBRT, toxicity

P3.15-001 THE IMPACT OF MET INHIBITION ON SMALL-CELL LUNG CANCER CELLS EXHIBITING ABERRANT ACTIVATION OF THE HGF/ MET PATHWAY

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Background: Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers, and is characterized as being extremely aggressive, often displaying rapid tumor growth and multiple organ metastases. In addition, the clinical outcome of SCLC patients is poor due to early relapse and acquired resistance to standard chemotherapy treatments. Several molecular targeted therapies were evaluated in SCLC; however, they failed to improve the clinical outcome. The receptor tyrosine kinase MET is a receptor for hepatocyte growth factor (HGF). Although aberrant activation of HGF/MET signaling is known as one of the crucial mechanisms enabling cancer progression and invasion, the mechanisms in SCLC have not been elucidated clearly. The aim of the present study was to evaluate the effect of inhibiting the HGF/MET pathway on tumor progression in SCLC with multi-organ metastasis. **Method:** We used eight human SCLC cell lines to elucidate the effect of MET inhibition on tumor progression. MET inhibitors, crizotinib and golvatinib, were used in this study *in vitro* and *in vivo*. **Result:** We found that the HGF/MET signaling was aberrantly activated in chemo-resistant or chemo-relapsed SCLC cell lines (SBC-5, DMS273, and DMS273-G3H) by the secretion of HGF and/or *MET* copy number gain. HGF/MET inhibition, induced either by MET inhibitors (crizotinib and golvatinib), or by siRNA-mediated knockdown of *HGF* or *MET*, constrained growth of these SCLC cells via the inhibition of ERK and AKT signals. We also revealed that treatment with either crizotinib or golvatinib *in vivo* suppressed the systemic metastasis of SBC-5 cell tumors in NK cell-depleted SCID mice, predominantly via cell cycle arrest. **Conclusion:** These findings reveal that the therapeutic potential of targeting the HGF/MET pathway for inhibition, to constrain tumor progression of SCLC cells exhibiting aberrant activation of HGF/MET signaling. We suggest that it would be clinically valuable to further investigate HGF/MET-mediated signaling in SCLC cells.

Keywords: SCLC, MET, HGF

P3.15-002 MOLECULAR PROFILING AND NETWORKS RELEVANT TO DISEASE MECHANISMS IN SMALL CELL LUNG CANCER AND LUNG CARCINOID TUMOR

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Background: Small Cell lung cancer (SCLC), which belongs to neuroendocrine tumor (NT), is known for its highly aggressive clinical features and poor prognosis. The molecular underpinnings that may prognosticate survival and could increase our understanding of tumor development and progression are still poor understood in its highly aggressive malignancies. We aimed to describe the proteomic characteristics and biomarker profiling of high-grade NT, SCLC versus low-grade NT, carcinoid tumor (CT) by the state-of-the-art proteomics techniques utilizing clinical specimens. **Method:** In order to obtain the molecular-based differences between SCLC and CT, we performed proteomic analyses for these histological types in lung NTs. Based on definite histological diagnosis, cancerous cells were collected by laser microdissection from FFPE tissues of 6 patients each with SCLC and CT. To elucidate their protein expression profiles, a mass spectrometry-based quantitative proteomic analysis was conducted. After the different profiles were identified using a hierarchical clustering, we applied protein-protein interaction (PPI) network and gene-set enrichment analyses to assess how significantly proteins are expressed and which molecular pathways are activated in SCLC and CT. **Result:** A total of 1,991 proteins were identified from cancerous cell in FFPE tissues throughout these NT subtypes. By hierarchical clustering of the protein expression profiles, 12 cases were clearly classified into two groups of 6 SCLC and 6 CT. We finally identified 11 for SCLC and 44 for CT as tumor-specific proteins, respectively. In brief, our curation-based analysis of PPI networks built from proteins expressed significantly in SCLC cells has revealed that the activations of both mismatch repair system, and its resulted cell cycle pathway but suggested a fatal failure in disruption of mismatched DNA sequences, which suggested an occurrence of carcinogenesis progression simultaneously with an activity trying to return to normal, and which might suggest a heterogeneity of SCLC cells. Proteins expressed significantly in CT cells were the molecules known representatively as the biomarkers of NTs such as neurosecretory protein VGF, chromogranin-A, secretogranin-1 and -2. Besides those, we have found that the certain key network modules controlling cellular proliferation and apoptosis, affecting a series of pathways, as well as regulating genomic instability and DNA damage and repair, which also promotes cell transformation and tumorigenesis. **Conclusion:** Our clinical proteomic profiling of both SCLC and CT revealed their corresponding nature of aggressiveness and extent of prognosis, and detailed curation of PPI networks of interestingly suggested candidates of their therapeutic targets, which might reflect their disease mechanisms.

Keywords: proteomics, small cell lung cancer, carcinoid tumor

P3.15-003 SECOND LINE CHEMOTHERAPY IN SCLC: THE WEST OF SCOTLAND EXPERIENCE

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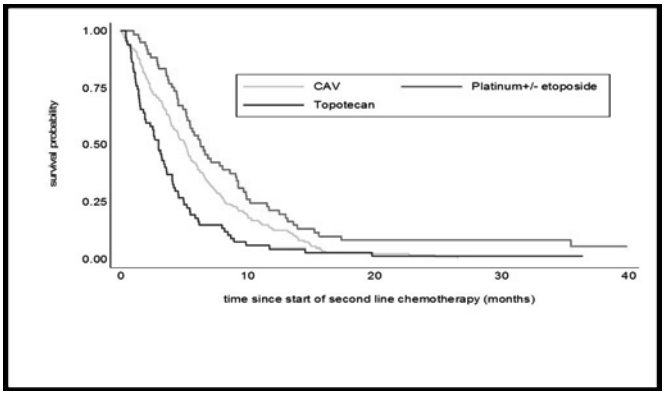
Background: SCLC has a high response rate to first line chemotherapy but this is often short lived. Patients who relapse six months after first line chemotherapy can be retreated with platinum +/- etoposide and patients that relapse early are treated with CAV (cyclophosphamide, doxorubicin and vincristine), Topotecan or best supportive care (BSC). There have been no clinical trials comparing oral Topotecan with iv CAV. **Method:** A retrospective case note review was undertaken of 296 SCLC patients who received second line chemotherapy for recurrent SCLC in the West of Scotland. Results were analysed using STATA version 14. **Result:** SCLC patients that relapsed after first line platinum-based chemotherapy received CAV (n=161), platinum +/-etoposide (n=61), oral topotecan (n=67) and 7 patients received other cytotoxic agents. Median survival for patients who received CAV was 5.1 months (CI 4.1 – 5.7), 6.3 months (CI 5.2-8.6) for platinum/etoposide and 3.0 months (CI 1.9-3.6) for Topotecan. As expected platinum +/- etoposide was superior to CAV (Log rank p = 0.016) and Topotecan (p <0.0001), as these patients had demonstrated platinum sensitivity. CAV appeared superior to Topotecan (p = 0.001) and was better tolerated. 79% of Topotecan patients required a dose reduction versus 29% of CAV patients. 16% of Topotecan, 8% of CAV and no platinum +/- etoposide patients died within 30 days of receiving chemotherapy. 39% of Topotecan and 19% of CAV patients experienced either neutropenic sepsis or myelosuppression requiring a dose reduction or dose delay. There was no difference in time to progression after first line chemotherapy in the CAV and Topotecan populations.



Conclusion: In this West of Scotland retrospective data collection, patients treated with oral Topotecan appear to have a lower median overall survival and experienced more toxicity than those receiving iv CAV.

Keywords: CAV, SCLC, topotecan

P3.15-004 DISTINCT ROLE OF FAK KINASE AND C-TERMINAL DOMAINS ON SMALL-CELL LUNG CANCER PROLIFERATION

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Background: Small-cell lung cancer (SCLC) is a devastating illness with a median five-year overall survival of 5%. Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase which regulates integrin and growth factor signaling pathways involved in cell proliferation, survival, migration, and invasion. FAK is overexpressed/activated in many cancers, including SCLC. We hypothesized that FAK overexpression/activation in SCLC contributes to its aggressive behavior and that FAK may represent a novel therapeutic target in SCLC. **Method:** Two SCLC cell lines, one growing in suspension (NCI-H82) and one adherent (NCI-H446), were treated with a FAK small-molecule inhibitor, PF-573,228 (PF-228) (1 to 5μM), or stably transfected with FAK shRNA and/or FAK-related non kinase (FRNK) domain (doxycycline-inducible) using lentivirus vector. Cell proliferation, cell cycle, apoptosis, motility, and invasion were studied by standard methodologies. FAK expression/activity was evaluated by WB. Active Rac1 expression was evaluated by WB after enrichment of cell lysates in active GTP-bound Rac using Rac pull down columns. **Result:** PF-228 decreased FAK activity by decreasing phospho-FAK (Tyr397) expression in both SCLC cell lines, without modifying total FAK expression. This induced significant inhibition of cell proliferation and DNA synthesis, cell cycle arrest in G2/M phases, and increase of apoptosis dose-dependently. PF-228 also decreased motility in the adherent cell line NCI-H446. Transfection of FAK shRNA decreased total and phospho-FAK expression but this did not affect cell proliferation, DNA synthesis, and cell cycle. We hypothesized that the absence of anti-proliferative effects was due to the loss of the FAK-targeting domain (FAT), normally attached to the focal adhesion complex where it inhibits other proteins supporting proliferation (such as Rac). To test this, we restored FAT function by transfecting FRNK, a physical repressor of FAK activity, into cells stably transfected with FAK shRNA and demonstrated inhibition of cell proliferation and DNA synthesis. Expression of FRNK in SCLC cell lines not previously transfected with FAK shRNA also significantly decreased cell proliferation and DNA synthesis. Moreover, FAK shRNA transfection increased active Rac1 levels, while FRNK re-expression in the cell lines previously transfected with FAK shRNA decreased it. **Conclusion:** This work demonstrates that FAK has a dual role in SCLC: 1/ it supports proliferation, migration, invasion, and inhibits apoptosis through the kinase domain, suggesting that inhibition of FAK kinase activity may represent a suitable therapeutic target for SCLC, and 2/ it inhibits SCLC proliferation through the non-kinase C-terminal domain FRNK, which keeps Rac inactive.

Keywords: small cell lung cancer, RAC GTPase, focal adhesion kinase

P3.15-005 THIRD LINE CHEMOTHERAPY IN SCLC: THE WEST OF SCOTLAND EXPERIENCE

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Background: Scotland has one of the highest incidences of SCLC globally (cancerresearchuk.org). Lung cancer is the leading cause of cancer related deaths in the UK (cancerresearchuk.org), with SCLC having a worse prognosis than NSCLC

and fewer treatment options. Initially, SCLC has a high response rate to first line chemotherapy but rapidly becomes resistant to chemotherapy. There is little evidence to support and guide third line chemotherapy regimens. A West of Scotland (WoS) retrospective database (2007 to 2013) has been developed to gain useful insights into this aggressive disease to improve patient outcomes. **Method:** A retrospective case note review was undertaken of 1325 SCLC patients from the WoS. 58 patients were identified as receiving third line chemotherapy. Information was collected regarding radiological staging, performance status (PS), treatment history, time to progression and survival. Results were analysed using STATA version 14. **Result:** 17% of SCLC patients in this WoS database received no chemotherapy, 60% one line (n= 801), 22% (n= 296) two lines, 4% (n=58) three lines and 0.004% (n= 6) four lines of chemotherapy. Of the 58 patients that received third line chemotherapy 28 had Topotecan, 17 CAV, 7 platinum +/- etoposide and 6 included a variety of other cytotoxics. For all patients receiving third line chemotherapy the median survival was 4.7 months (CI 4.1-5.3) and progression free survival was 3.0 months (CI 2.5 – 3.6). Median survival was 3.5 months (CI 2.6- 5.6) for Topotecan, 4.1 months (CI 2.7-5.0) for CAV and 9.0 months (CI 1.8-12.2) for platinum +/ etoposide. 32 (55%) patients received 3 different regimens for each line of chemotherapy, 25 patients (43%) received a platinum-based chemotherapy regimen twice and 1 patient received a platinum based regimen all three lines of chemotherapy. Only 2 patients received a clinical trial novel treatment for their third line therapy. **Conclusion:** SCLC continues to have a poor prognosis with few patients receiving three lines of chemotherapy. The patients that maintain some sensitivity to platinum based chemotherapy tend to have a marginally better response to third line therapy. Clincial trial opportunities for this group of patients were limited. Patients should be enrolled in clinical trials wherever possible.

Keywords: Third-line, chemotherapy, SCLC

P3.15: SCLC/NEUROENDOCRINE TUMORS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.15-006 COMPREHENSIVE ANALYSIS OF EMT GENE SIGNATURE IN PRIMARY AND METASTATIC SMALL CELL AND NON-SMALL CELL CARCINOMAS OF THE LUNG

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Background: Metastasis are responsible for the death of 90% of patients with lung cancer (LC) indicating the necessity to know the multiple signaling pathways involved. Among them, high-grade neuroendocrine lung carcinomas (NELC) invade and metastasize rapidly. Therefore, biomarkers of aggressiveness in LC remain to be determined, especially in NELC. Epithelial to mesenchymal transition (EMT) genes profile emerge promise as indicator of invasion and metastasis. The aim was to investigate the expression of EMT markers and assessed their relationship with the clinicopathological features and prognosis. **Method:** Fresh frozen tissue from SCLC (n=15) and NSCLC (ADc n=23 and SqCC n=10) and matched normal tissue samples were collected for qRT-PCR analysis carried out on StepOnePlus™ Real-Time PCR with RT² Profiler PCR Array System for the EMT pathway with 84 target genes (Qiagen, Dusseldorf, Germany). Gene expression was correlated with clinicopathological variables in the SCLC and NSCLC groups. Survival curves were calculated using the Kaplan-Meier method and risk factors determined by multivariate Cox regression model. Differences were regarded as statistically significant at P<0.05. **Result:** Female patients presented significant higher expression of EGFR (p=0.03), ILK (p=0.05), JAG1 (p=0.01), MMP2 (p=0.04) and SNAI2 (p=0.04) genes. Tobacco history was associated with increased expression of EGFR (p<0.01), ITGAV (p=0.05), SPP1 (p<0.01) and WNT5A (p=0.02). NSCLC presented similar levels of EMT genes evaluated. Tumors from SCLC and NSCLC in advanced N and M stage expressed significant high levels of genes related to cellular membrane [EGFR (p=0.03), ILK (p<0.01), FR11 (p=0.05), ITGAV (p=0.02), ITGB1 (p<0.01), DSP (p=0.04)], extracellular matrix [COL5A2 (p=0.04), COL1A2 (p=0.04)], cytoplasm [GSK3B (p=0.01), VPS13A (p=0.02), MAP1B (p=0.01)] and nucleus SNAI2 (p=0.04). Interestingly, SCLC tumors expressed higher levels of FR11 (p=0.02), GSK3B (p=0.04), ILK (p<0.01), ITGB1 (p=0.01), JAG1 (p<0.01) and MAP1B (p=0.01) indicating more aggressiveness than NSCLC. A mathematical model controlled for N and M stage, histologic type and the gene expression showed that patients with SCLC expressing high levels of MMP2 and SPARC presented significant high risk of death (OR 5.41 and 4.94, respectively) compared to those with lower expression. Patients with NSCLC with low levels of ILK, SPP1, COL1A2, ITGB1 presented a low risk of death (OR -7.02, -0.4, -1.3 and -3.02, respectively). **Conclusion:** Different expression of EMT genes in SCLC and NSCLC, its relationship with histologic types, advanced stage, lymph node metastasis and death suggest a possible role of these markers in their malignancy, but more importantly provide a potential biomolecular marker to predict outcome.

Keywords: lung cancer, metastasis, epithelial to mesenchymal transition

P3.15: SCLC/NEUROENDOCRINE TUMORS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.15-007 A RETROSPECTIVE REVIEW OF SMALL CELL LUNG CANCER (SCLC) PATIENTS TREATED AT MARMARA UNIVERSITY HOSPITAL

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Background: SCLC accounts for 15%-20% of all lung cancer, and has poor prognosis. The aims of this study were to evaluate the patient characteristics and depict prognostic factors in a series of SCLC patients treated at Marmara University Hospital (MUH) Istanbul. **Method:** Among SCLC patients who were admitted to MUH since 01 January 2010, 154 had satisfactory data to analyse. Demographic data, pathology & radiology reports, lab investigations, information regarding local & systemic therapies were noted from written & electronic patient records. Patient and tumour characteristics were reported descriptively. OS difference between subgroups were analysed with Log-rank & factors that had independent effect on survival detected with Cox regression tests. OS data were calculated with Kaplan-Meier estimator. A *p* value <.05 was accepted as significant unless reported otherwise. **Result:** The median follow-up time was 17 (min-max; 3-84) months. Median survival time of all patients was 10 months; 1 year, 2 & 3 years survival rates were 41%, 22%, and 12%, respectively. Median survival of patients with limited stage and extension stage SCLC were; 22,6 Ms (9,9-35,3), and 9 Ms (7,2-10,8), respectively. On univariate analysis patient with low initial serum haemoglobin (<12 gr/dl), abnormal sodium or ALT (> 40 IU/l) levels, poor ECOG PS (2-3), advanced VA stage, having brain, liver, bone or adrenal mets, and having a paraneoplastic syndrome (PNS) had worse survival estimates. Whereas only ECOG PS (p=0.007, HR 2.2 [1.2-4]), and having a PNS (p=0.04, HR 1.66 [1.02-2.7]) maintained independent prognostic effect on survival in Cox analysis. **Conclusion:** Results of our small retrospective SCLC series showed that median survival of extensive stage SCLC patients is poor (< 1 year) which underlies the need of novel anticancer therapeutics for this group of patients. Our multivariate model pointed out well known prognostic factors but not the VA stage. This may be explained with the small population size of our study.

Keywords: paraneoplastic syndrome, small cell lung cancer

P3.15: SCLC/NEUROENDOCRINE TUMORS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.15-008 [F18]PARPI PET AS AN IN VIVO PHARMACODYNAMIC BIOMARKER OF PARP INHIBITOR THERAPY IN PATIENT-DERIVED XENOGRAFTS OF SMALL CELL LUNG CANCER

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Background: Inadequate drug delivered to target tumors contributes to ineffective treatment. However, the delivered drug concentration is difficult to assess in patients in a timely and clinically-relevant manner. To address this barrier to PARP inhibitor(PARPi) therapy, we evaluated a radiolabeled PARP inhibitor([F18]PARPi) as a pharmacodynamic biomarker. We hypothesized that [F18]PARPi PET imaging can measure PARP inhibitor concentration and activity intratumorally, thereby, predicting therapeutic efficacy. Here, we applied this approach to patient-derived xenografts(PDX) of small cell lung cancer(SCLC). **Method:** To study [F18]PARPi PET as a biomarker of talazoparib(TAL), SCRX-Lu149 PDXs were orally gavaged with different doses of TAL. Mice were injected with [F18]PARPi and imaged with PET, with the expectation that TAL would competitively block [F18]PARPi binding to PARP. Organ retrieval and gamma counting was performed for drug and radiotracer biodistribution. Ex vivo PARP enzymatic activity was measured by ELISA of PAR levels. Differences in PET uptake and the tumor volumetric endpoint (time to reach 1000 mm^3) were analyzed by student t-test and the log-rank test, respectively. **Result:** In PK PET imaging with 0.2 mg/kg TAL, greatest blocking of the radiotracer was noted at 1 hour after gavage with less blocking as time from dosing was extended (avg of 3 mice: 4.5, 2.2, 2.7, 3.1, and 3.4% max injected dose per gram [ID/g] for untreated, 1, 3, 6, and 24 h after drug, respectively). [F18]PARPi PET differentiated between doses of 0.1 and 0.3 mg/kg TAL at 3 h after dosing (3.9 vs 2.1% ID/g or 13% vs 53% relative blocking, respectively; p=0.003). No differences were noted in heart, lung, esophagus, muscle, or bone. PET uptake correlated with ex vivo enzymatic inhibition/PAR levels (p=0.0009). PET measured differences in drug doses corresponded with improved outcomes for PDXs treated with 0.3 mg/kg in combination with radiotherapy(RT; median 84 days, p=0.04) but not 0.1 mg/kg + IR (66 days) compared to RT alone (52 days). **Conclusion:** [F18]PARPi PET can differentiate between multiple doses and timing of orally administered TAL and correlates with drug efficacy. This likely reflects differences in intratumoral drug level and demonstrates the potential of this PET radiotracer to assess differences in drug delivery and efficacy for patients treated with PARP inhibitors.

Keywords: small cell lung cancer, Patient derived Xenograft, PARP INHIBITOR

P3.15-009 IMPACT OF INTERSTITIAL LUNG DISEASE ON CLINICAL OUTCOMES IN SMALL CELL LUNG CANCER PATIENTS

K. Akaike[1], K. Saruwatari[2], Y. Sakamoto[1], T. Jodai[1], S. Sakata[1], S. Iyama[1], R. Sato[1], T. Iriki[1], Y. Tomita[1], S. Saeki[1], H. Ichiyasu[1], K. Fujii[1]

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Background: The impact of interstitial lung disease (ILD) on the clinical outcome in small cell lung cancer (SCLC) patients has not been fully understood. The purpose of this study is to investigate the impact of ILD on treatment and survival in SCLC. **Method:** From April 2006 to March 2016, 67 SCLC patients treated with chemotherapy at Kumamoto University hospital were evaluated. Therapeutic response, progression-free survival (PFS) and overall survival (OS) were compared between SCLC with ILD (n=16) and SCLC without ILD (n=51). **Result:** Patients' characteristics including age, sex, smoking, serum LDH, stage (limited/ extensive disease) between two groups were similar, except for lower proportion of chemoradiotherapy in SCLC with ILD (7% vs. 57%, *P*= <0.001). SCLC with ILD had a significantly lower objective response rate than SCLC patients without ILD (50% vs. 84%, *P*= 0.005). SCLC patients with ILD had a significantly shorter PFS (median, 184 days vs. 290 days, *P*= 0.008) and OS (median, 241 days vs. 704 days, *P*= <0.001) than patients without ILD. In addition, multivariate analysis for PFS and OS revealed that the coexisting ILD was independent predictive factor for poor survival in SCLC patients treated with chemotherapy (PFS, hazard ratio [HR] 2.06, 95% confidence interval [CI], 1.01-4.18, P= 0.046, OS, HR 3.29, 95% CI 1.53-7.08, P= <0.002). Acute exacerbation of ILD was observed in 31% of SCLC patients with ILD. **Conclusion:** This study suggests that coexisting ILD is a predictive factor for poor PFS and OS in SCLC treated with chemotherapy.

Keywords: small cell lung cancer, interstitial lung disease, chemotherapy

P3.15-010 DIFFUSE IDIOPATHIC PULMONARY NEUROENDOCRINE CELL HYPERPLASIA (DIPNECH): NATURAL HISTORY OF THE DISEASE PROGRESSION AND MANAGEMENT

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Background: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare, often benign pulmonary condition which is characterized by diffuse proliferation of neuroendocrine cells in respiratory epithelium. DIPNECH lesions are less than 5 mm in size and are limited to the basement membrane without any invasion. There is limited evidence regarding epidemiology, natural history of disease progression and management of this rare entity. We would like to present our single center experience. **Method:** Retrospective record based descriptive study of all DIPNECH patients managed at University of Kentucky Markey Cancer Center over past 5 years. **Result:** Our patient cohort had 8 females and one male with mean age of 64.5 years at the time of diagnosis. Dyspnea on exertion and dry cough were the commonest presenting symptoms. Three patients were under surveillance without treatment, two patients were treated with short acting somatostatin analog, another three were treated with long acting monthly somatostatin analogs and azithromycin combination, one patient got long acting somatostatin analog and everolimus combination. Two patients had concomitant well-differentiated neuroendocrine tumor of lung. **Conclusion:** DIPNECH is a rare pathology which can have profound effects on patient's quality of life. Paroxysmal coughing spells can be difficult to treat. Our limited single center experience shows encouraging response to use of somatostatin analog, azithromycin and everolimus in the management of debilitating DIPNECH associated symptoms.

Keywords: DIPNECH, azithromycin, everolimus

P3.15-011 CONTEMPORARY TREATMENT AND PROGNOSIS OF NON-METASTATIC ATYPICAL BRONCHOPULMONARY CARCINOID TUMORS

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Background: Despite rising incidence, there remains limited data guiding the prognostication and treatment of patients with bronchopulmonary carcinoid tumors, particularly atypical carcinoids. We report outcomes of a large, modern, single-institutional series of patients treated for localized or locally advanced atypical carcinoid of the lung. **Method:** We retrospectively analyzed the demographic, histologic and treatment histories of 69 patients (74% female) with median age of 65 at diagnosis (range 31-83) who were treated between 2004-2016. The Kaplan-Meier method was used for overall survival (OS) estimates and compared by log-rank. Cox proportional hazards models were used for univariate (UVA) and multivariate analyses (MVA). **Result:** Median follow-up time was 33.6 months. The majority (96%) of patients underwent surgical resection (86% R0, 9% R1, 3% R2) with common approaches being lobectomy (59%), wedge resection (13%) and pneumonectomy (9%). Three patients (4%) received definitive radiotherapy as their local treatment. Nearly half (49%) of patients had nodal involvement with a stage distribution of 39% stage I, 25% stage II and 36% stage III. Twenty-one patients received chemotherapy as part of their initial treatment, 81% of whom had stage III disease. Sixteen patients received radiotherapy (median 50.4 Gy, range 18-66 Gy) as part of their initial treatment, most of whom received postoperative radiation for N2 disease (63%). Five patients (31%) received postoperative radiotherapy due to concern of incompletely resected disease. Higher stage was significantly associated with poorer OS (p=0.04). 3-year OS for Stage I, II and III disease was 96%, 88% and 72%, respectively. Stage I disease also had a significantly lower risk of distant metastasis compared to Stage II/ III disease (17% vs. 31% at 3 years p=0.04). On UVA, Stage III disease was significantly associated with poorer OS (HR 4.7, p=0.021) and risk of distant failure (HR 2.8, p=0.039). Multivariate modeling showed that older age (HR 1.05, p=0.03) and stage III status (HR 6.6, p=0.009) were predictive of poorer OS. For stage III patients treated surgically, receipt of adjuvant therapy (chemotherapy and/or radiotherapy) was not significantly associated with OS (p=0.36) or distant failure (p=0.69). **Conclusion:** This is one of the largest reported series of atypical pulmonary carcinoid patients treated with curative intent. We observed generally favorable prognosis in this cohort that was primarily treated with surgery. We did not observe a significant impact of adjuvant therapy on outcomes, but small patient numbers limit our ability to quantify their potential effect.

Keywords: Atypical Carcinoid, carcinoid, neuroendocrine

P3.15-012 SURGICAL OUTCOME IN EARLY STAGE SMALL CELL LUNG CANCER

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Background: Chemo-radiation is considered to be the standard treatment for the management of limited disease of small cell lung cancer (SCLC). Even in this early stage, the role of surgery in SCLC is still controversial. We sought to examine the role of surgery; complete resection in terms of survival in SCLC. **Method:** A retrospective review was undertaken of patients who underwent surgery for SCLC between 2001 and 2015. Patients were staged according to the 7th edition of the Tumor, Node, Metastasis classification of lung cancer. Actuarial survival estimated with Kaplan Meier method and comparisons were undertaken using Cox regression hazard model. Clinicopathological factors and predictors of survival were analyzed. **Result:** We identified 49 patients who underwent complete resection. The mean follow up period was 1343 days. The mean age was 70.7 years. 40 patients were men and 9 were women. The number of patients of clinical stage was stage IA :21, IB: 15, IIA: 4, IIB: 6, IIIA:3. Operative procedure was lobectomy in 43, segmentectomy in 1, wedge resection in 5. The number of patients of pathological stage was stage IA :15, IB: 11, IIA: 14, IIB: 7, IIIA:2. Adjuvant chemotherapy was performed in 26 patients (53.1%). The 5-year overall survival (OS) rate in all patients was 58.8%. The 5-year OS was 61.3% in c-stage I, 54.5% in c-stage II, and 50% in c-stage III. The 5-year OS were 66.2% in p-stage I, 55.4% in p-stage II, and 50% in p-stage III. The 5-year OS of patients with adjuvant chemotherapy was significantly better than that of patients without adjuvant chemotherapy (77.8% vs. 39.8%, p=0.005). Multivariable Cox regression hazard model demonstrated that adjuvant chemotherapy was prognostic factor of overall survival (OS) (hazard ratio 0.255 (.095-.688), p=0.007) **Conclusion:** Surgical outcome for early stage SCLC was satisfied one. The role of surgery for this group seemed to be important. Adjuvant chemotherapy may improve prognosis and long-term survival will be expected.

Keywords: chemotherapy, small cell lung cancer, Surgery

P3.15-013 THE ADDITION OF ANTIANGIOGENIC AGENTS TO CHEMOTHERAPY FOR PATIENTS WITH EXTENSIVE-STAGE SMALL CELL LUNG CANCER: A META-ANALYSIS

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Background: The combination chemotherapy of etoposide and a platinum salt represents the standard therapy for almost 30 years in patients with ED-SCLC (extensive-disease small-cell lung cancer). While, the survival benefit of chemotherapy is not obvious. Antiangiogenic agents have been confirmed to have survival benefits for patients with NSCLC (non-small cell lung cancer). However, there is no established role for antiangiogenic therapy in SCLC **Method:** we conducted this meta-analysis to evaluate antiangiogenic agents plus chemotherapy in patients with ED-SCLC. Pub-med, EMBASE, Cochrane Library and ClinicalTrials.gov website were systematically searched for RCTs (randomized controlled trials) that compared antiangiogenic

agents plus chemotherapy with chemotherapy alone in ED-SCLC. **Result:** We firstly found that antiangiogenic agents plus chemotherapy was well tolerated and could provide a statistically significant improvement in PFS (progression-free survival) for patients with ED-SCLC (HR = 0.76 [95% CI 0.65, 0.88], P = 0.0003). The results of ORR (objective response rate) (RR = 1.06 [95% CI 0.96, 1.18], P = 0.23) and OS (overall survival) (HR = 0.98 [95% CI 0.80, 1.21], P = 0.85) showed no benefit for antiangiogenic agents plus chemotherapy. **Conclusion:** Our study firstly shows that the addition of antiangiogenic agents to standard chemotherapy is well tolerated and can provide a statistically significant improvement in PFS for patients with ED-SCLC. Further, maintenance therapy with antiangiogenic agents is an effective treatment option for ED-SCLC patients who received four to six cycle of chemotherapy. Additionally, four-drug chemotherapy plus antiangiogenic agents may be better for ED-SCLC patients with PS of 1 to 2. However, whether antiangiogenic agents plus chemotherapy can influence OS for ED-SCLC needs further validation.

Keywords: small cell lung cancer, chemotherapy, antiangiogenic agents

P3.15: SCLC/NEUROENDOCRINE TUMORS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.15-014 CASE SERIES OF SMALL CELL LUNG CANCER TRANSFORMATION AS RESISTANCE MECHANISM TO EPIDERMAL GROWTH FACTOR RECEPTOR-TYROSINE KINASE INHIBITOR

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Background: Patients with epidermal growth factor receptor (EGFR) mutant advanced non-small cell lung cancer (NSCLC) developed resistance to first- or second-generation EGFR-tyrosine kinase inhibitor (TKI) after 9-13 months and third-generation EGFR-TKI after 10 months, respectively. Small cell lung cancer (SCLC) transformation is a rare resistance mechanism in these patients. **Method:** Tissue re-biopsy was performed in 35 patients with EGFR mutant advanced NSCLC who failed first-line EGFR-TKI; and 4 patients with acquired T790M mutant advanced NSCLC who failed third-generation EGFR-TKI, to look for SCLC transformation **Result:** SCLC transformation was identified in 2 out of 35 (5.7%) patients who failed first-line EGFR-TKI and 1 out of 4 (25.0%) patients who failed third-generation EGFR-TKI. The first patient was a 70-year-old never-smoker male who was diagnosed with stage IV lung adenocarcinoma harboring exon 19 deletion mutation in April 2014. He had partial response (PR) to gefitinib 250 mg daily but developed symptomatic progressive disease (PD) after 26 months. Re-biopsy of his enlarging primary lung lesion showed SCLC transformation. The second patient was a 43-year-old never-smoker male who was diagnosed with stage IV lung adenocarcinoma harboring exon 19 deletion mutation in November 2015. He had PR to gefitinib 250 mg daily but developed symptomatic PD after 15 months. Re-biopsy of his rapidly enlarging primary lung lesion showed SCLC transformation. His plasma cell-free tumour DNA (cftDNA) was positive for T790M mutation. The third patient was a 62-year-old never-smoker female who was diagnosed with stage IV lung adenocarcinoma harboring exon 21 L858R mutation in November 2015. She had PR to gefitinib 250 mg daily but experienced symptomatic PD after 8 months' of gefitinib therapy. Re-biopsy of her primary lung tumor revealed the presence of T790M mutation and her treatment was switched to osimertinib 80 mg daily. After an initial PR, she developed PR in the 12th month of osimertinib treatment. Biopsy from a metastatic inguinal lymph node showed SCLC. The first and second patients were given standard SCLC chemotherapy with carboplatin and etoposide but did not respond. The third patient sought treatment in another hospital. **Conclusion:** Re-biopsy is recommended in all patients with symptomatic PD while on EGFR-TKI treatment. SCLC transformation under the pressure of first, second and third-generation EGFR-TKI is an emerging challenge to the management of advanced NSCLC. Other than conventional carboplatin and etoposide chemotherapy, new treatment strategies should be explored to improve the outcome of patients who develop SCLC transformation.

Keywords: Epidermal growth factor receptor, resistance mechanism, small cell lung cancer

P3.15: SCLC/NEUROENDOCRINE TUMORS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.15-015 LCNEC TUMOR LOCATION, DIVIDED INTO CENTRAL AND PERIPHERAL TYPE, HAS DISTINCT CLINICOPATHOLOGIC FEATURE, GENOMIC CHARACTERISTICS AND SURVIVAL

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Background: Pulmonary large cell neuroendocrine carcinoma (LCNEC) represents a rare entity in lung cancer. Due to poor understanding of its biologic characters, optimal treatment strategy for patient with LCNEC remains undetermined. Recent data reveals that LCNEC can be divided into SCLC and NSCLC type based on distinct genomic signatures. It has been considered that SCLC is a central-type lung cancer and LCNEC usually locates in peripheral or midzone of lung. In the present study, we examined that whether there are significant differences between central tumors and peripheral tumors of LCNEC, in terms of clinicopathologic features, survival, and genomic profiles. **Method:** A total of 126 cases (113 cases with surgical samples) of pulmonary LCNEC were included in the present study. The tumors with invasion of the segmental and/or lobar bronchus were classified as central LCNEC and those without as peripheral LCNEC. EGFR mutations, ALK translocations, ROS1 translocations, Kras mutations, RET translocations and BRAF mutations were detected. Overall survival (OS) was determined from the date of operation until reported death or last follow-up visit. OS was analyzed by the Kaplan-Meier plots and the log-rank test was used to calculate the significance between groups. The prognostic factors for OS were analyzed using univariate and multivariate COX analyses. **Result:** Central tumors were associated with smoking history (p=0.047), higher T stage (p<0.001), N stage (p=0.001), TNM stage (p=0.014), and larger tumor size (p<0.001) compared with peripheral tumors. Although neuroendocrine marker expression of CD56, CGA, and SYN was not significantly different according tumor location, central tumors had higher expression of NSE (p=0.003). Moreover, peripheral tumors had higher incidence of EGFR mutations (18.8 vs. 0%, p=0.023) and similar incidence of Kras mutations (10.4 vs. 8.0%, p=1.000). Tumors harboring EGFR mutations were all pure LCNEC. No ALK translocations, ROS1 translocations, RET translocations and BRAF mutations were identified. The median OS was 3.71 years. TNM stage (p=0.039) and N stage (p=0.068) were associated with survival. Interestingly, central tumors had poorer survival compared with peripheral tumors, in terms of median OS (1.51 vs. 4.04 years), 1-year OS rate (54.0 vs. 83.9%), 2-year OS rate (37.0 vs. 75.9%), 3-year OS rate (31.7 vs. 59.9%). After multivariate analyses, tumor location was still an independent prognostic factor for OS (HR, 2.675, 95% CI, 1.384-5.171, p=0.003). **Conclusion:** Primary tumor location of LCNEC, divided into central and peripheral type, has distinct clinicopathologic feature, genomic characteristics and survival, which may help classify and manage patients with LCNEC.

Keywords: Pulmonary large cell neuroendocrine carcinoma, central tumors, Peripheral tumors

P3.15: SCLC/NEUROENDOCRINE TUMORS -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.15-016 THE ROLE OF SURGERY IN COMBINATION TREATMENT OF PATIENTS WITH SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) as the most aggressive tumor deserves a special attention. The aim of this research was to define the place of surgery of patients with SCLC in order to improve the results of treatment. **Method:** Clinical material for research consists of 49 patients in stage IA-IIIA with SCLC, which were radically operated in Ugra (region Russia) between 1999 and 2015. Among patients predominate males 41 (83,7%), versus females – eight (16,3%). **Result:** All patients underwent radical operations R0. All resection types were included (pneumonectomy, bilobectomy, and lobectomy). By 37 patients (75,5%) systematic nodal dissection (SND) was carried out, by 5 (10,2%) - mediastinal lymph node sampling (MLS) and by 7 patients mediastinal node dissection was not carried out. By SCLC combination treatment was used more often – 35 (71,4%). By that only in 11 cases additional adjuvant of thoracic radiotherapy was used. In 14 cases only surgical resection was used (28,6%). 5-year and 10-year overall survival (OS) rate was 47,6% and 37,2%. Median survival rate was 49 months. Five and ten-year OS rate by surgery combined with adjuvant chemotherapy was 53,8% and 39,5%, as compared to only surgical treatment – 35,6%. Median survival rate was 67 and 25 months, respectively. At I stage satisfactory results were achieved: 5-year and 10-year OS rate was 68,8% and 62,5% (p<0,05), – that corresponds with results of treatment of patients with non-small cell lung cancer with similar stage of process. Median survival rate was not achieved. At II stage 5-year and 10-year OS rate was 41,7 and 41,7%. Median survival rate was 36 months. At III stage unsatisfactory results were obtained. 5-year OS rate was 25,1%. Median survival rate was only 13 months. **Conclusion:** SCLC at I and II stages is the indication to radical treatment, mandatory including surgical resection with SND and adjuvant chemotherapy. The main method of treatment at III stage is chemotherapy or chemoradiotherapy.

Keywords: systematic nodal dissection, Surgical treatment, small cell lung cancer

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-001 FEASIBILITY OF 20 ML OF SALINE FOR PLEURAL LAVAGE CYTOLOGY IN NON-SMALL CELL LUNG CANCER

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Background: Pleural lavage cytology (PLC) is an independent prognostic factor for resected non-small cell lung cancer (NSCLC). However, there has been no standard method for the test and the optimal dose of saline is still unclear. We investigated the feasibility of 20 mL saline in this retrospective study. **Method:** From January 2001 to December 2011, 466 consecutive patients who underwent a curative resection for NSCLC and received both a pre- and post- PLC by using 20ml of saline were enrolled. The prognostic significance of each PLC status and other clinicopathological factors were investigated. **Result:** Patients with a positive pre-(n=24) or post-PLC(n=28) had significantly worse 5-year survival rates than those with negative results

(pre-PLC positive/negative; 32.6%/69.9%, p=0.001, post-PLC positive/negative; 21.4%/71.1%, p<0.001, respectively). The post-PLC (p<0.001) was found to be an independent prognostic factor for the overall survival by a multivariate analysis, whereas the pre-PLC was not (p=0.95). In stage I disease, patients with a positive post-PLC had a significantly worse survival regardless of the pre-PLC status. These results were comparable to those of the past reports by using more saline of 50-1000mL. **Conclusion:** Using 20 mL of saline would be feasible for PLC and may be helpful to simplify the procedure.

Keywords: dose of saline, pleural lavage cytology, lung cancer surgery

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-002 POSTOPERATIVE PROGNOSTIC FACTORS IN NON-SMALL CELL LUNG CANCER PATIENTS WITH LYMPH NODE METASTASIS

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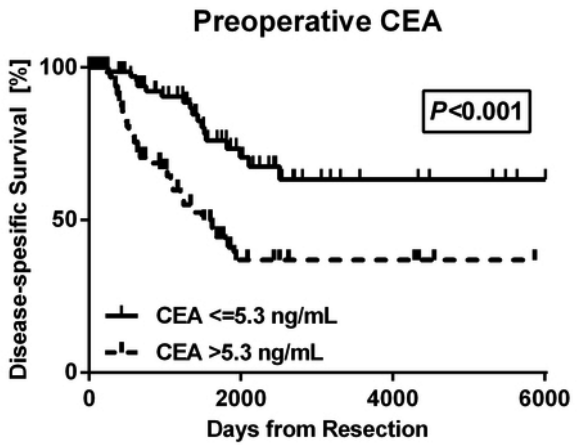
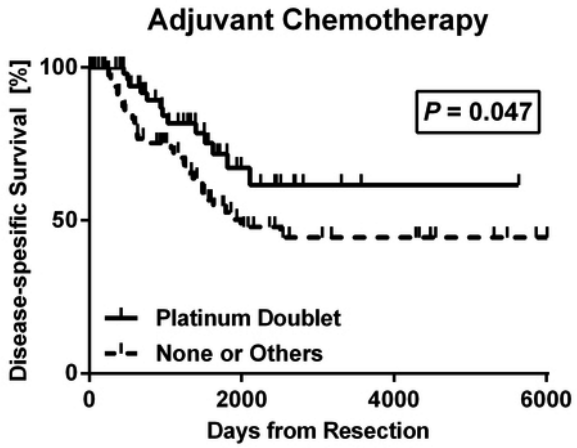
Background: Postoperative outcome for NSCLC patients with lymph node metastasis is unfavorable even after surgery with/without adjuvant chemotherapy. We sought to investigate postoperative prognostic factors in NSCLC patients with lymph node metastasis. **Method:** We retrospectively reviewed NSCLC patients with pathologically identified lymph node metastasis who underwent complete resection. Demographic, clinical, and pathologic factors (sex, age, smoking index, Performance Status, preoperative carcinoembryonic antigen [CEA], surgical procedure, lymphadenectomy extent, histology, tumor differentiation, tumor size, pT factor, metastatic node site, 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 disease-specific survival (DSS). **Result:** Of the 146 eligible patients, 113 were male and 33 were female. The median age and preoperative CEA were 67 years and 5.3 ng/mL, respectively. Lobectomy or greater resection and segmentectomy were performed in 140 and 6 patients, respectively. Tumor histology was adenocarcinoma in 58 patients, squamous cell carcinoma in 70, and others in 18. Node metastasis was identified in hilum only in 85 patients and mediastinum in 61. Adjuvant chemotherapy was performed in 61 patients (platinum doublet in 56 and tegafur/uracil in 5, respectively) and was not performed in 85. The 5-year DSS was 58%. The CEA ≤5.3 ng/mL (HR: 0.368), without mediastinal node metastasis (HR: 0.436), and platinum doublet adjuvant chemotherapy (HR: 0.491) were identified as significant predictors of favorable DSS. The 5-year DSS in patients with CEA ≤5.3 and >5.3 ng/mL were 73% vs 41%, respectively (p<0.001). The 5-year DSS in patients who underwent platinum doublet chemotherapy or none/others were 67% vs 53%, respectively (p=0.047).





Conclusion: Even if NSCLC patients have lymph node metastasis, favorable postoperative prognosis may be expected in patients with low preoperative CEA. Platinum doublet adjuvant chemotherapy should be considered in patients with lymph node metastasis on pathological examination.

Keywords: lymph node metastasis, Surgery, Locally Advanced Cancer

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-003 THE CLINICAL SIGNIFICANCE OF IMMUNE-NUTRITIONAL PARAMETERS IN SURGICALLY RESECTED ELDERLY PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: The world's population is rapidly aging, and the age of patients with lung cancer will increase as well. The prognostic nutritional index (PNI), controlling nutritional status (CONUT), and the geriatric nutritional risk index (GNRI) are useful parameters for evaluating immune-nutritional status. We aimed to perform a multicenter retrospective study to investigate the correlations of these immune-nutritional parameters with postoperative comorbidities or surgical outcomes of elderly patients with non-small cell lung cancer (NSCLC). **Method:** We selected 272 consecutive patients with NSCLC aged >75 years treated from January 2005 to December 2012 and evaluate three preoperative immune-nutritional parameters as potential predictive factors of postoperative comorbidities or as prognostic factors for surgically resected elderly patients with NSCLC. **Result:** Both PNI and GNRI as well as sex and preoperative respiratory comorbidities, were significantly associated with postoperative comorbidities (P =0.0287, 0.0443, 0.0191 and 0.0177, respectively). Multivariate analyses showed that preoperative GNRI (P= 0.0161) as well as sex (P< 0.0001), preoperative serum carcino embryonic antigen levels (P= 0.0128), preoperative serum cytokeratin 19 fragment levels (P= 0.0125), pleural invasion (P= 0.0214) and lymphatic vessel invasion (P= 0.0165) significantly affected overall survival (OS). Abnormal GNRI was significantly associated with histology (P = 0.0419) and outcome (P =0.0077). In Kaplan–Meier analysis of OS by preoperative GNRI, the abnormal GNRI group had significantly shorter OS than the normal GNRI group (5-year OS, 45.15% vs. 64.10%, P= 0.0007, log-rank test). CONUT score did not have any correlation with postoperative comorbidities or surgical outcome. **Conclusion:** Preoperative GNRI is a novel preoperative predictor of postoperative comorbidities as well as a prognostic factor that may identify high-risk elderly patients with NSCLC.

Keywords: non-small cell lung cancer, elderly patients, immune-nutritional parameters

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-004 SURGERY FOR PATIENTS WITH LUNG CANCER ASSOCIATED WITH INTERSTITIAL PNEUMONIA

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Background: Treatment of patients with lung cancer associated with interstitial pneumonia (IP) is difficult because of post-operative complications or treatment-related deaths. Indeed, post-operative acute exacerbation of IP in patients with lung cancer and IP is associated with a high mortality rate. In our institute, we have unified surgical methods and improved peri-operative management of such patients since 2013. In the current study, we retrospectively studied the clinical features, surgical methods, and peri-operative management, and analyzed the clinicopathologic features of patients with lung cancer associated with IP. **Method:** We selected patients with lung cancer associated with IP who underwent surgery from January 2004 to May 2017. A presumptive diagnosis of IP or an IP pattern on computed tomography (CT) was confirmed histologically by examination of resected specimens and/or the presence of the clinical diagnostic criteria. Acute exacerbation of IP was defined according to the guidelines of the Japanese Respiratory Society when the following criteria were fulfilled within 1 month: (1) increased respiratory distress; (2) fibrosis, newly developed ground glass opacity and infiltrative shadow on high-resolution computed tomography (HRCT); and (3) > 10 Torr decrease in PaO_2 under the same oxygenation conditions. (4) no evidence of pulmonary infection, heart failure, pneumothorax, and pulmonary embolism. We studied the following clinicopathologic features in patients with lung cancer associated with IP: gender, age, surgical methods, pathologic stages, mortality rate, and post-operative complications, including acute exacerbation of IP. **Result:** Fifty-three patients underwent surgery. The mean age was 70.8 years (50 males and 3 females). Forty-three, 1, and 9 patients underwent lobectomies, a segmentectomy, and partial resections, respectively. Twenty-three, 17, and 13 patients were stage I, II, and III, respectively. Eight patients had post-operative acute exacerbations of IP and there were three in-hospital deaths

caused by acute exacerbations. Of note, there have been no in-hospital deaths since 2013. **Conclusion:** It is possible to prevent severe post-operative complications in patients with lung cancer associated with IP with the aid of intra-operatively and optimal peri-operative management.

Keywords: lung cancer, Interstitial pneumonia, Surgery

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-005 OUTCOME, MORTALITY AND MORBIDITY AFTER LUNG CANCER THORACIC SURGERY

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Background: Introduction:Lung cancer is the most common form and cause of cancer death world-wide. Radical surgical resection, with or without adjuvant treatment, is still a prerequisite for cure.In European countries the proportion of patients who undergo surgery for this disease varies between 10 and 30% .Advances in operative and postoperative care have led to a decline in complications and mortality rates during the last two decades.In spite of different additional modes of treatment, survival is still poor. **Method:** The study comprised 388 consecutive patients referred to University Hospital of Lung Disease Tirane, from a defined population, during a 12-years period (2004-2017).There were in total 968 patients who underwent lung resection for bronchogenic carcinoma.There were 690 males and 278 females included 15-87 years with a mean age of 65.5 years.Postoperative events studied were divided into major and minor complications or death during the first 30 days after surgery. **Result:** Early mortality (within 30 days) after lung cancer surgery. During the study period an increasing number of women and of patients older than 70 years underwent surgery.The 30 day mortality rate was 3.4% (33 patients), 1.2% after single lobectomy(11 patients) and 3.1 % after pneumonectomy(22 patients). Major complications occurred in 48 patients (4.9%). Minor complications occurred in 75 patients (7.7%).Male gender, smoker, FEV1 70% of expected value, squamous cell carcinoma and pneumonectomy were risk factors predicting adverse outcome . **Conclusion:** Our results show low mortality and morbidity after lung cancer surgery. However, patients with reduced lung capacity and those undergoing pneumonectomy should be treated with great care, as they run a considerable risk of major complications or death during the first 30 days postoperatively.Older age (>70 years) does not appear to be a contraindication to lung cancer surgery, but patients in this group should undergo careful preoperative evaluation.

Keywords: outcome, Compications, after thoracic surgery

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-006 IMPACT OF LIMITED RESECTION OR OMITTED ADJUVANT THERAPY IN PATIENTS WITH PATHOLOGIC STAGE II AND III NON-SMALL-CELL LUNG CANCER

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Background: There is consensus for the treatment modalities of lung cancer. However, there were cases in which inadequate treatments were performed due to unavoidable reasons which could make different oncologic outcomes. So authors investigated factors affecting oncologic outcomes in patients with pathologic stage II and III lung cancer who underwent limited resection or omitted adjuvant therapy. **Method:** From January, 2010 to December, 2012, 231 patients underwent operation for non-small-cell lung cancer in our hospital. Of them, 63 patients who were diagnosed as pathologic stage II and III were enrolled in this research, and medical records of them were reviewed including demographic factors, treatment modalities, 5-year overall survival rate, 5-year recurrence and so on. **Result:** The mean age was 64.03±7.94 years old and preoperative performance status was good in all patients. The median follow-up duration was 58.7 [1.3, 88.4] months. Patients (group A) with resection more than lobectomy and adjuvant therapy were 50, patients (group B) with limited resection were 4, and patients with omitted adjuvant therapy were 13 (group C). 5-year overall survival rate of group A was 69.7% (stage IIA-84.4%, IIB-40.0%, IIIA-48.5%), but, all of group B were recurred and passed away. Of group C (stage IIA-9, IIB-1, IIIA-3), 5 were recurred and dead. Multi-variable analysis (Cox proportional hazard regression analysis) of prognostic factors for overall survival (OS) and recurrence (R) was performed, which showed limited resection (OS; hazard ratio 32.179, p=0.001 and R; hazard ratio 61.337, p=0.000) and pathologic stage (OS; hazard ratio 1.898, p=0.017 and R; hazard ratio 1.517, p=0.037) were presented as significant poor prognostic factors. And omitted adjuvant therapy didn't significantly affect oncologic outcome, but had negative influence (OS; hazard ratio 8.102, p=0.074 and R; hazard ratio 5.528, p=0.13). **Conclusion:** This study has many weak points including small sample size, retrospective study and so on, but this study suggests that several factors affect prognosis in advanced stage non-small-cell lung cancer but, especially, the limited resection in advanced stage has been a significantly negative impact and should be considered carefully.

Keywords: advanced non-small-cell lung cancer, omitted adjuvant therapy, limited resection

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-007 INCIDENCE AND OUTCOMES OF POSITIVE PARENCHYMAL MARGINS AFTER LUNG RESECTION – AN ANALYSIS OF 1428 CASES

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Background: Positive margins after pulmonary resection for cancer is an uncommon and challenging occurrence, with no consensus currently available to guide best adjuvant treatments. Our objective was to determine the rate of positive parenchymal margins after non-pneumonectomy lung resection with an assessment of adjuvant treatment strategies and outcomes. **Method:** Ethics board approval was obtained for a retrospective analysis of prospectively collected data on all lung resections performed at the Ottawa Hospital during the period 2008-2014. Individual patient records were then examined to confirm margin status by a review of the final pathology report. Survival and disease-free intervals were analysed using log-rank statistics, with significance set at 5%. **Result:** Over the study period, 1428 patients underwent non-pneumonectomy lung resection. A total of 29 cases (2%) were identified with a positive lung parenchymal margin (PPM). A matched subset (n=662) of the remaining 1379 patients with negative parenchymal (NPM) were used as control group. Median followup for NPM was 36.7 [0-105.6] and for PPM was 29.1 [0.5-71.5]. Overall, lobectomy was the most common pulmonary resection performed; wedge resections represented the majority of the PPM (n=16, 55%) followed by lobectomy (n=9; 31%) and segmental resections (n=1; 3%). Overall survival (Figure) and disease-free survival (not shown) were significantly ($p<0.0001$) worse for the PPM (Hazard ratio 5.59, 95%CI [2.05-15.6]) with a median survival of 31.5 months; the control group had not reached median survival. Stage I and II NSCLC were predominant in both groups; however postive margins were more often associated with metastatic disease (24% in PPM; 0.9% in NPM). The majority of PPM went on to receive additional treatment (n=17; 68%) consisting of adjuvant chemotherapy (n=7; 28%), radiotherapy (n=4; 16%), chemoradiotherapy (n=5; 20%) and re-resection in one case. The remaining patients were observed. Recurrence was found at the staple line in 7 cases (24%); the remainder recurred at distant sites. **Conclusion:** The overall rate of PPM in this study is low (2%) as compared to reported rates of 5-15%. Wedge resection for metastases was associated with most cases of PPM; most patients received additional treatment and had distant sites of recurrence. Overall survival was significantly worse for PPM despite adjuvant therapy, which likely reflects the underlying disease.

Keywords: Adjuvant therapy, Margins, Surgery

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-008 THYMIDINE PHOSPHORYLASE INFLUENCES CLINICAL OUTCOME FOLLOWING SURGERY IN PATIENTS WITH STAGE I AND II NON-SMALL CELL LUNG CANCER

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Background: Expression levels of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), and orotate phosphoribosyltransferase (OPRT) may predict the clinical efficacy of 5-fluorouracil (5-FU) -based chemotherapy in patients with cancer. We investigated the differences in mRNA expression levels of these enzymes in non-small-cell lung cancer (NSCLC) and evaluated them as prognostic factors for NSCLC treated by surgical resection. **Method:** Intratumoral mRNA levels of TS, DPD, OPRT, and TP were quantified in 71 patients following a complete resection in pathological stage I and II NSCLC (adenocarcinoma or squamous cell carcinoma) using the Danenberg tumor profile (DTP) method. **Result:** TP was the only significant prognostic factor for overall survival (OS) following complete resection of stage I and II NSCLC. Median values of TP mRNA expression significantly differed between the high and low mRNA expression groups for OS. OS at 5 years was significantly better in the low TP mRNA expression group than the high TP mRNA expression group (82.5% vs. 63.6%, $p<0.001$). The Cox's proportional hazard model indicated that the pathological stage, sex, and TP expression were independent prognostic factors for OS. Univariate analysis for disease free survival (DFS) indicated that the pathological stage was the only prognostic factor for DFS. However, DFS at 5 years tended to be better in low TP mRNA expression group than in high TP mRNA expression group (88.9% vs. 67.3%, $p=0.083$). **Conclusion:** TP mRNA expression presents an independent prognostic factor for OS in patients with stage I and II NSCLC following complete resection.

Keywords: thymidine phosphorylase, Danenberg tumor profile method, non-small cell lung cancer

P3.16-009 REOPERATION FOR HEMOSTASIS WITHIN 24 HOURS CAN GET A BETTER SHORT-TERM OUTCOME WHEN INDICATED AFTER LUNG CANCER SURGERY

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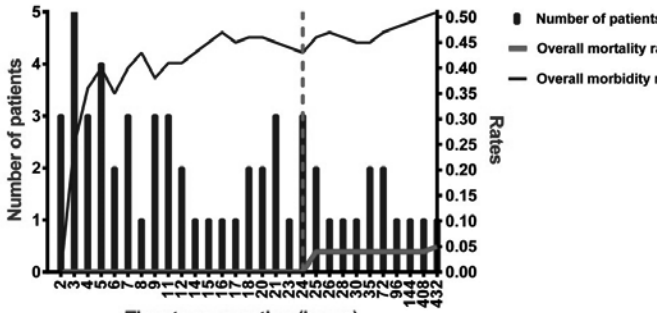
Background: Postoperative hemorrhage after lung cancer surgery is a potentially fatal complication. This study aimed to investigate the indications and timing of reoperation for postoperative hemorrhage after lung cancer surgery. **Method:** We identified all patients who underwent lung resection and mediastinal lymph node dissection for lung cancer between October 2001 and September 2015 at Sichuan Cancer Hospital, identifying 57 who had undergone reoperation for hemostasis. The records of these 57 patients were reviewed and analyzed. **Result:** The most common postoperative hemorrhage site was the separation surface of the original pleural adhesions (29.8%). The median time interval between the initial operation and reoperation was 12 hours (range, 2-432 hours), and most patients (77.2%) underwent reoperation within 24 hours. The overall morbidity and mortality rates of reoperation were 50.9% and 5.3%, respectively. The morbidity rates of early reoperation group (≤ 24 hours) and late reoperation group were 43.2% and 77.0%, respectively, which were significantly different (P=0.033). The mortality rates of early reoperation group and late reoperation group were 0 and 23.1%, respectively, which were also significantly different (P=0.010).

Table 1 Origin of postoperative bleeding for reoperation

Origin of bleeding	Number of patients (n=57)	Percentage
Pulmonary resection surface	1	1.8
Pulmonary artery trunk	1	1.8
Pulmonary artery branch	2	3.5
Chest wall invasion resection surface	4	7.0
Intercostal blood vessel	4	7.0
Bronchial artery	6	10.5
Hemothorax-unknown origin	11	19.3
Lymph node dissection surface	11	19.3
Pleural adhesion separation surface	17	29.8



Conclusion: Once indications of reoperation for postoperative hemorrhage after lung cancer surgery are identified, reoperation within 24 hours after the initial operation can get a better short-term outcome.

Keywords: lung cancer surgery, postoperative hemorrhage, reoperation

P3.16-010 PREOPERATIVE SIX-MINUTE WALK DISTANCE IS ASSOCIATED WITH COMPLICATIONS OF PNEUMONIA AFTER LUNG RESECTION

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Background: Postoperative pulmonary complications such as pneumonia are significant negative predictors of short- and long-term survival after thoracic surgery. A preoperative cardio-pulmonary function is known as a predictor for postoperative pulmonary complications in patients with lung cancer. However, little is known about the relationship between preoperative exercise capacity and complication of pneumonia after lung resection. The 6-min walk distance (6MWD) measured by the 6-min walk test (6MWT) is a simple, safe, and inexpensive field test that can be used to evaluate the functional exercise capacity. We examined the association between preoperative 6MWD and development of postoperative pneumonia. **Method:** A retrospective study was conducted on patients with malignant lung tumors who were scheduled to undergo lung resection at Nagoya University Hospital from January 2014 to December 2015 (Institutional Review Board approval No. 2015-0413). Preoperative pulmonary function tests and 6MWT were assessed. A logistic regression model and receiver operating characteristic (ROC) curves were used to analyze clinical variables and compare the performance on 6MWD and percentages of predicted values of forced expiratory volume in 1 s (%FEV_1) and diffusion capacity of the lung for carbon monoxide (%DLco). **Result:** The data from a total 321 patients including 283 with primary lung cancer and 38 with metastatic lung tumors were analyzed. Preoperative 6MWD significantly correlated with age, FEV_1, forced vital capacity (FVC), %DLco, and serum albumin level. Pneumonia developed in 13 patients (4.0%) and the 6MWD of patients with pneumonia was significantly lower than that of patients without (413.9±89.0 vs. 495.2±93.2 m, p=0.002). Incidences of smoking history and comorbidity of COPD and interstitial lung disease were significantly higher and %FEV_1, FEV_1/FVC, %DLco, and serum albumin level were significantly lower in patients with pneumonia than in those without. Length of hospital stay after surgery was significantly longer in patients with pneumonia than in those without (30.4±29.6 vs. 7.4±7.0 days, p<0.001). In ROC analysis, 6MWD ≤450 m was a threshold for predicting postoperative pneumonia with 69.2% sensitivity and 71.1% specificity. A 6MWD ≤450 m, %FEV_1<80%, %DLco <80%, serum albumin <3.5 g/dL, and blood loss during surgery >200 g were significantly associated with development of postoperative pneumonia in a logistic model adjusted by age, sex, and primary lung cancer. **Conclusion:** Preoperative 6MWD is associated with development of pneumonia after lung resection for malignancies. Preoperative 6MWT is a useful screening tool in patients with primary and metastatic lung tumors.

Keywords: 6-min walk test, lung resection, pneumonia

P3.16-011 CORRELATION BETWEEN PULMONARY VEIN STUMP THROMBUS AND CEREBRAL INFARCTION AFTER LEFT UPPER LOBECTOMY OF THE LUNG

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Background: Arterial embolism including cerebral infarction is the major concern after surgery, because it can leave fatal or serious results. Recently, it is reported that pulmonary vein stump thrombosis is easy to occur after pulmonary resection, particular left upper lobectomy. However, it is unknown whether pulmonary vein thrombus is actually associated with cerebral infarction. **Method:** A totally 296 patients, underwent postoperative enhanced CT after left upper lobectomy in our hospital from September 2002 to December 2013, were retrospectively evaluated. We examined the association with pulmonary vein thrombus and cerebral infarction in both groups with thrombosis and without thrombosis formation. The relationship of patients' background, clinical stage, pulmonary vein stump thrombus and postoperative cerebral infarction were analyzed. **Result:**

a pulmonary vein stump thrombus	n	cerebral infarction (n = 61)	No cerebral infarction (n = 98)
+	21	0 (0%)	21 (100%)
−	275	15 (5.5%)	260 (94.5%)

21 patients (7.1 %) had a pulmonary vein thrombus, however all cases were asymptomatic and cerebral infarction was not developed. On the other hand, cerebral infarction developed in 15 patients of 275 patients without pulmonary vein thrombus formation. Only clinical stage was significantly relevant to cerebral infarction in univariate analysis. Table 1. Incidence of cerebral infarction according to a pulmonary vein stump thrombus **Conclusion:** Left upper lobectomy of the lung is well known to be a high risk of pulmonary vein stump thrombosis and cerebral infarction in all surgical procedures of the lung. However, pulmonary vein thrombus was not necessarily associated with the cerebral infarction after left upper lobectomy of the lung in this study.

Keywords: pulmonary vein stump thrombus, left upper lobectomy of the lung, cerebral infarction

P3.16-012 LUNG CANCER: SYSTEM APPROACH

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Background: Search of optimal diagnosis and treatment strategies for non-small cell lung cancer (LC) patients (LCP) (T1-4N0-2M0) realized. **Method:** We analyzed data of 708 consecutive LCP (age=57.5±8.3 years; tumor size=4.3±2.4 cm) radically operated (R0) and monitored in 1985-2017 (m=613, f=95; lobectomies=461, pneumonectomies=247, mediastinal lymph node dissection=708; combined procedures with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=192; only surgery-S=563, adjuvant chemoimmunoradiotherapy-AT=145: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=269, T2=251, T3=131, T4=57; N0=460, N1=130, N2=118, M0=708; G1=178, G2=216, G3=314; squamous=394, adenocarcinoma=266, large cell=48; early LC=164, invasive LC=544. Multivariate Cox modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine any significant dependence. **Result:** Overall life span (LS) was 2196.3±1764.1 days and cumulative 5-year survival (5YS) reached 71.1%, 10 years – 63%, 20 years – 43.4%. 451 LCP lived more than 5 years (LS=3125.7±1560.3 days), 128 LCP – more than 10 years (LS=5123.1±1547.9 days). 195 LCP died because of LC (LS=560±372.1 days). AT significantly improved 5YS (58.3% vs. 34.1%) (P=0.001 by log-rank test) only for LCP with N1-2. Cox modeling displayed that 5YS of LCP significantly depended on: phase transition (PT) early-invasive LC in terms of synergetics, PT N0—N12, cell ratio factors (ratio between cancer cells- CC and blood cells subpopulations), G1-3, histology, glucose, RH, AT, blood cell circuit, prothrombin index, heparin tolerance, recalcification time, weight (P=0.000-0.030). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT early-invasive LC (rank=1), PT N0—N12 (rank=2), healthy cells/CC (3), lymphocytes/CC (4), thrombocytes/CC (5), eosinophils/CC (6), erythrocytes/CC (7), segmented neutrophils/CC (8), glucose (9), monocytes/CC (10), stick neutrophils/CC (11), leucocytes/CC (12). Correct prediction of 5YS was 100% by neural networks computing (area under ROC curve=1.0; error=0.0). **Conclusion:** 5YS of LCP after radical procedures significantly depended on: 1) PT early-invasive cancer; 2) PT N0--N12; 3) cell ratio factors; 4) blood cell circuit; 5) biochemical factors; 6) hemostasis system; 7) AT; 8) LC characteristics; 9) anthropometric data. Optimal diagnosis and treatment strategies for LC are: 1) screening and early detection of LC; 2) availability of experienced thoracic and cardiothoracic surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymph node dissection for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for LCP with unfavorable prognosis.

P3.16-013 PROGNOSTIC EFFECT OF EGFR GENE MUTATION FOR RECURRENCE IN COMPLETELY RESECTED LUNG ADENOCARCINOMA

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Background: Prognostic effect of EGFR gene mutation in disease progression which affecting recurrence pattern and recurrence dynamics after complete resection of lung adenocarcinoma has not been well established. We investigated the relationship between EGFR gene mutation and recurrence dynamics in completely resected lung adenocarcinoma. **Method:** We retrospectively review 527 patients who underwent curative surgery for lung adenocarcinoma from January 2006 to December 2009. Demographics, clinic-pathologic data, and prognosis data were obtained by review of medical records. The EGFR gene mutation was analyzed by nested polymerase chain reaction followed by bidirectional direct sequencing in case of recurrence. Adenocarcinoma patients who experienced recurrence and had data of EGFR mutation were included in the analysis. Pathologic stage IV were excluded. Patients were divided into M group (mutant EFGR gene) or W group (wild-type EGFR gene). Sites of recurrence and disease-free times (DFT) of two groups were compared. **Result:** Median follow-up duration was 72 months. Overall 5-year survival rate was 80.1%. Recurrence was detected in 153 patients and 5-year disease-free rate was 58.2%. EGFR gene sequencing was performed in 118 (77.1%) patients. There were 38 (32.2%) loco-regional recurrences and 80 (67.8%) distant metastases. Any mutation of EGFR gene was detected in 66 (59.9%) patients (M group) and 52 patients had wild-type EGFR gene (W group). Sites of recurrence in M group were loco-regional in 25 (37.9%) and distant metastasis in 41 (62.1%) patients. Site of recurrence in W group were loco-regional in 13 (25%) and distant metastasis in 39 (75%) patients. Sites of recurrence of both groups were not significantly different. (p=0.14) Median DFT of two groups were significantly different (M = 20.3 months vs W = 15.1 months, p=0.039). Visceral pleura invasion (p=0.045) and EGFR gene mutation (p=0.039) were prognostic factor for DFT in univariable analysis. In multivariable analysis, EGFR gene mutation was the only prognostic factor for DFT. (HR – 0.676, 95% CI – 0.371 ~ 0.986, p=0.042) No significant factor for DFT was identified in loco-regional recurrence. EGFR gene mutation, however, was the only significant prognostic factor for DFT of distant metastasis (HR – 0.561, 95% CI – 0.356 ~ 0.885, p=0.013) in univariable and multivariable analysis. **Conclusion:** In recurrent lung adenocarcinoma, EGFR gene mutation group showed longer DFT than wild-type EGFR group. EGFR gene mutation is a prognostic factor in lung adenocarcinoma and slow-growing nature of adenocarcinoma with EGFR gene mutation should be considered in surveillance after surgery.

Keywords: Epidermal growth factor receptor, Adenocarcinoma, Prognosis

P3.16-014 POST-RECURRENCE SURVIVAL ANALYSIS OF STAGE I NON-SMALL CELL LUNG CANCER-PROGNOSTIC SIGNIFICANCE OF LOCAL TREATMENT

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Background: The aim of this retrospective study was to review recurrence patterns of stage I non-small cell lung cancer (NSCLC) and identify prognostic factors for post-recurrence survival (PRS). **Method:** Among 940 patients with pathological stage I NSCLC who underwent curative resection between 2001 and 2009, 261 patients who had experienced a recurrence were included in this study. A total of 188 patients had adenocarcinoma (ADC), and 62 had squamous cell carcinoma (SCC). Oligo-recurrence was defined as one to three locoregional or distant recurrent lesions restricted to a single organ. Potentially curative local treatment (PCLT) included surgery, stereotactic radiotherapy (SRT), and photodynamic therapy. **Result:** The median follow-up duration was 65 months (range: 4–186 months), and the median disease-free interval (DFI) was 23 months (range: 2–95 months). The most common site of recurrence was the lung in 145 patients, followed by a mediastinal lymph node in 49 patients, pleura in 30 patients, and brain in 27 patients. Local treatment for recurrent tumors included surgery in 59 patients, SRT in 46 patients, photodynamic therapy (PDT) in 2 patients, and other radiotherapy in 41 patients. Seventy-eight patients received chemotherapy only, and thirty-five patients received conservative treatment. Among 125 patients who were evaluated for an epidermal growth factor receptor (EGFR) gene mutation study, positive results were detected in 63 patients, and 31 were treated with a EGFR-tyrosine kinase inhibitor (EGFR-TKI). The 3- and 5-year PRS rates were 49.1% and 33.8%, respectively. Age at recurrence, ADC cell-type, DFI, TKI, and PCLT were independent prognostic factors in a multivariate analysis. **Conclusion:** local treatment for recurrent tumors could be a good option for selected candidates. Local treatment seems to be a reasonable modality for treating oligo-recurrence, even an extrapulmonary recurrence. Use of an EGFR-TKI is applicable if an EGFR mutation has been detected. Further study is required to identify patients who are optimal candidates for local treatment.

Keywords: survival, Local treatment, oligo-recurrence

P3.16-015 RAPID IDENTIFICATION OF MICROPAPILLARY OR SOLID COMPONENT FOR EARLY-STAGE LUNG ADENOCARCINOMA

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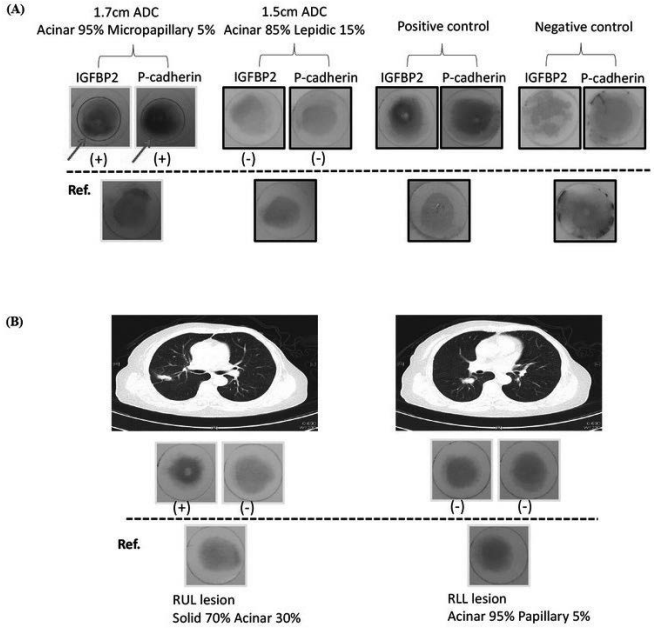
Background: Sublobar resection may be less than ideal for lung adenocarcinoma (ADC) with even minor micropapillary (MIP) or solid (SOL) component, given that they carry a higher incidence of locoregional recurrence. Rapid identification of these subtypes would help decision-making on the extent of resection for early-stage ADC. **Method:** Antibody arrays of adhesion and apoptosis molecules were applied for 8-pair ADCs with (≥5%) or without (<5%) MIP/SOL component to identify the differentially expressed proteins, which were further validated by Western blot. A semi-dry dot-blot (SDB) system that visualizes the presence of the target proteins, modifying from the dot-blot method, was used to for diagnosing MIP/SOL existence in a prospective cohort of 45 clinical stage I ADCs that received operation. Resected specimens were reviewed according to the new IASLC/ATS/ERS classification and each component was recorded in 5% increments. **Result:** Insulin-like growth factor-binding protein 2 (IGFBP2) and P-cadherin was found more frequently in the MIP/SOL positive group and thereby setting as the target proteins in the SDB system for detection. A total of 46 nodules with a mean size of 2.4±0.8 cm was enrolled, including 10 (21.7%) with MIP and 16 (34.8%) with SOL component. The specificity and sensitivity for detecting MIP/SOL existence through SDB method were 72.0% and 90.5%, respectively. The average test duration was 25.6±1.9 minutes. Interestingly, the test successfully diagnosed one of the two synchronic lesions to have SOL component (Figure 1). **Conclusion:** Detecting IGFBP2 and P-cadherin via SDB method may have a potential role in the rapid identification of MIP/SOL components in early-stage lung ADC. Figure 1. (A) Semi-dry dot-blot system identified the expression of IGFBP2 and P-cadherin by the comparison of chromogen density to reference. The positive result indicated the existence of micropapillary or solid components. (B) Synchronous lesions with or without solid component showed different test result.



Keywords: lung adenocarcinoma, micropapillary, solid

P3.16: SURGERY -
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P3.16-016 PROGNOSIS OF PATIENTS WITH REMNANT TUMOR AT BRONCHIAL STUMP AFTER PULMONARY RESECTION FOR NSCLC: BASED ON CASE SERIES STUDY

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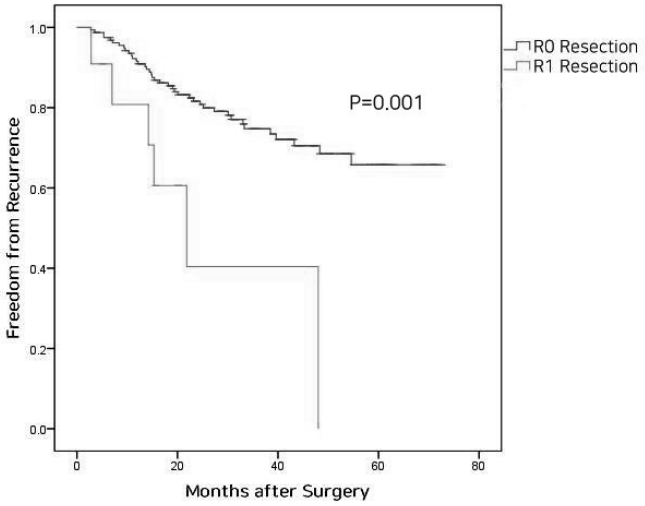
Background: Current guidelines recommend adjuvant therapy for positive margins after surgical resection. However, there is no strong evidence for those adjuvant therapies. In this study, we analyzed series of patients with microscopically tumor-positive bronchial stump (R1) and compared it with patients with complete R0 resection. **Method:** From 2011 to 2015, 172 patients underwent surgical treatment for NSCLC at out center. Excluding three patients with pleural seeding and residual tumors at parenchymal resection margin, 10 patients were bronchial R1 resection. We performed a retrospective analysis of patients' data during follow-up (mean 36.6 months). **Result:** All patients with R1 disease received adjuvant therapies. Mode of adjuvant therapy was not related to recurrence (P=0.683) within R1 group. Kaplan-Meier analysis showed that recurrence rate in R1 group was higher compared to R0 resection group (P=0.001) when no stratification for staging was done. However, overall survival was not different between two groups (P=0.087).



Conclusion: In this study, R1 resection group was revealed as a risk factor for tumor recurrence while it did not significantly affect overall survival. The type of adjuvant therapy had no relation to the recurrence of NSCLC. But further investigation with large cohort is necessary to find out the exact effect of adjuvant therapy and stage.

Keywords: R1 resection, Bronchial microscopic residual disease

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-017 THE ROLE OF SKIP METASTASES AND THE NUMBER OF METASTAC LYMP NODES IN THE SURVIVAL OF OPERATED PATIENTS

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Background: The IASLC staging committe hase rased the question of the role of skip metastases and single and multple metastases in a sigle station in the hillar and mediastinal regions in survival of lung cancer **Method:** Based on a database with 1068 operated patients we will try to establish an aswer to these questions. We have just this week received the dataset so we did not have time for making the necessary calculations before abstract deadline **Result:** The reults wil be added before the next deadline **Conclusion:** Will be added before the next deadline

Keywords: Surgery, Skip metastases, Staging

	Patient no.	Operation	Stage Group	Cell Type	Adjuvant Treatment	Recurrence	Site of Recurrence	Recurrence Free (mo)	Survival (mo)
Limited to epithelium	1	Bilobectomy	1B	Sqcc	Chemotherapy	Yes	Lung(s), pleura	15	64*
	2	Lobectomy	2A	Sqcc	Chemoradiation	Yes	Lung(s)	22	36
Submucosal Invasion	3	Bilobectomy	1B	Sqcc	Radiotherapy	No		20	20
	4	Lobectomy	2A	Sqcc	Chemoradiation	No		5	5*
	5	Lobectomy	3B	Adeno	Chemotherapy	Yes	Lung(b), pleura, brain	7	32
Peribronchial invasion	6	Lobectomy	1A	Adenoid cystic	Radiotherapy	No		18	18
	7	Lobectomy	2A	Adeno	Chemotherapy	No		16	16
	8	Lobectomy	3A	Sqcc/Adeno	Chemotherapy	No		20	20
	9	Lobectomy	3A	Adeno	Chemotherapy	Yes	Lung(b), mediastinal LN, stump	14	27*
	10	Lobectomy	3A	Adeno	Chemotherapy	Yes	Lung(b), mediastinal LN	48	61

Sqcc, Squamous cell carcinoma, *Adeno*, Adenocarcinoma, *s*, same lobe, *b*, bilateral, *, Mortality case

P3.16-018 NULL 30-DAYS MORTALITY AFTER 72 CONSECUTIVE LEFT OPEN PNEUMONECTOMIES FOR LUNG CANCER

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Thoracic Surgery, Oncology Institute Bucharest, Bucharest/RO

Background: The authors evaluate the 30-days mortality after open pneumonectomy for lung cancer and compare the results obtained for left-right pneumonectomy. **Method:** Between 2008 and 2011 there were radically resected 326 consecutive cases of lung cancer. There were 117 pneumonectomies – 72 on left and 45 on right, all performed through thoracotomy. **Result:** Overall 30-days mortality rate was 3,41% after pneumonectomy for lung cancer. After left pneumonectomy there was 0% mortality and after right pneumonectomy - 8,88% mortality. In 37 cases the patients received induction therapy – on those cases the mortality was 2,7% at 30 days, meaning 5% for right and 0% for left pneumonectomies. Without induction therapy the 80 patients operated per primam presented 3,75% 30-days mortality (12% for right and 0% for left pneumonectomies). These values are excellent for left pneumonectomies and similar to the literature for the right ones. The case selection is not the "cause of success" since 40,17% of cases were pathological stage III (TNM 6-th edition - valid at that time) and 29,05% were pathological stage II. Neither the limitation of the resection affected the mortality since the authors have performed 64,1% of pneumonectomies (75 cases) with intrapericardial approach, of which 21 pericardiectomies, 17 pericardioplasties and 3 atrial resections. All resection included mediastinal lymph node dissection. From best of our knowledge mediastinal lymph node dissection doesn't affect 30-days mortality after pneumonectomy for lung cancer. **Conclusion:** A null mortality rate at 30-days after left pneumonectomy for lung cancer is possible, without case selection.

Keywords: pneumonectomy, 30-days mortality, lung cancer

P3.16-019 PROGNOSTIC FACTORS FOR RESECTED NON-SMALL CELL LUNG CANCER IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Background: For diabetic patients with lung cancer, blood glucose levels and medications such as metformin and statins may impact survival. This retrospective study defined prognostic survival factors for diabetic patients with resected non-small cell lung cancer. **Method:** Between January 2005 and December 2013, 301 patients with type 2 diabetes mellitus who underwent curative resection for non-small cell lung cancer were identified and reviewed retrospectively. Prognostic factors for lung cancer–specific and overall survival were evaluated using the Cox proportional hazards regression model. **Result:** The median follow-up period was 48 months (interquartile range, 30–72). In a multivariate analysis for lung cancer–specific survival, older age, forced expiratory volume in 1 second (FEV1) < 80 % predicted, and advanced pathologic stage were significant negative prognostic factors; statin use was a positive prognostic factor [hazard ratio, 0.468; 95% confidential interval, 0.258–0.849]. In a multivariate analysis for overall survival, male sex, older age, FEV1 < 80 % predicted, and advanced pathologic stage were significant negative prognostic factors; proper glycemic control (hazard ratio, 0.645; 95% confidence interval, 0.436–0.952) and statin use (hazard ratio, 0.602; 95% confidence interval, 0.390–0.931) were positive prognostic factors.

Prognostic factors related to overall survival		
Variable	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)**
Male	2.682 (1.603–4.486)	2.628 (1.287–5.366)
Age	1.041 (1.016–1.066)	1.070 (1.042–1.099)
Smoking	1.927 (1.247–2.979)	0.988 (0.527–1.850)
FEV1% predicted <80	1.843 (1.254–2.708)	1.647 (1.073–2.530)
Obesity (BMI ≥25)	0.573 (0.387–0.848)	0.752 (0.496–1.138)
Proper glucose control	0.700 (0.487–1.006)	0.645 (0.436–0.952)
Cardiovascular comorbidity	1.315 (0.896–1.929)	
Neoplastic comorbidity	1.259 (0.815–1.946)	
Renal insufficiency	1.338 (0.871–2.055)	
Metformin	1.131 (0.781–1.638)	
Insulin	1.465 (0.886–2.422)	
Statin	0.602 (0.398–0.911)	0.602 (0.390–0.931)
Non-adenocarcinoma	1.724 (1.203–2.470	0.905 (0.571–1.435)
Pneumonectomy	2.386 (1.364–4.175)	1.520 (0.806–2.864)
R1 (vs R0)	1.841 (0.452–7.492)	
Stage		
I	Reference	
II	2.594 (1.694–3.973)	3.315 (1.837–5.983)
III/IV	3.818 (2.445–5.961)	6.515 (3.471–12.226)
Adjuvant treatment	1.545 (1.076–2.217)	0.606 (0.361–1.018)

Conclusion: Proper glycemic control (HbA1C <7.0) is recommended for diabetic patients undergoing lung cancer surgery. Statin use was associated with improved overall survival and lung cancer–specific survival. Further studies are required to elucidate associations between type 2 diabetes mellitus and anti-neoplastic effects of statins and to evaluate statins as a novel adjuvant treatment for lung cancer.

Keywords: Non-small cell lung cancer, type 2 diabetes mellitus, prognostic factor

P3.16-020 LONG TERM CHANGES OF PULMONARY FUNCTION AFTER LOBECTOMY

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Background: Postoperative pulmonary function changes after lung resection and that decline is determined by the extent of lung resection. It has been known that pulmonary function after surgery recovers gradually within 3 months to 1 year and finally reaches a steady state. However, the long-term respiratory function is unknown. We investigated the changes in respiratory function after thoracic surgery in patients who performed more than segmentectomy to evaluate the long-term effect of lung resection. **Method:** A total of 99 patients who underwent lobectomy followed up serial pulmonary function at postoperative 1month, 6months, 1,2,3 and 5 years. We investigated the serial changes of forced expiratory volume per 1 seconds (FEV_1%), diffusion capacity of carbon monoxide (DL_{co}%) by groups of minimal invasive surgery and adjuvant chemotherapy. **Result:** The reduced postoperative FEV_1% recovered to preoperative value until postoperative 6 to 1 year and declined yearly. The value of DL_{co}% increased to preoperative value until postoperative 2 years and remained steady state. There was no significant change in at more than 2 years follow-up (Fig.1). The value of DL_{co}% was decreased significantly during adjuvant therapy (p=0.031) (Fig.2) and the patients performed VATS lobectomy showed faster recovery in FEV_1% and DL_{co}% compared to thoracotomy group (p=0.001) (Fig.3 and 4).

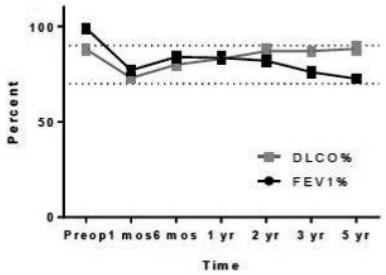

Fig.1 Postoperaive changes of FEV_1% and DL_{CO}% for 5 years after lobectomy

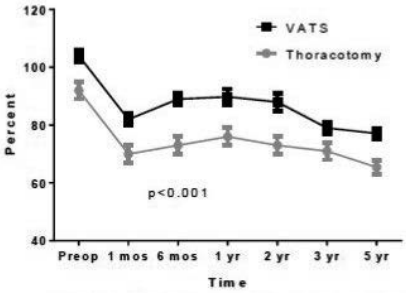

Fig.3 Postoperaive changes of FEV_1% for 5 years after lobectomy by operative method

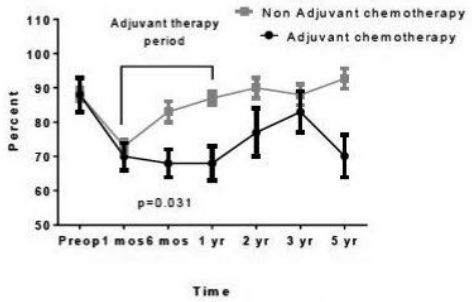

Fig.2 Postoperaive changes of DL_{CO}% for 5 years after lobectomy by adjuvant chemotherapy

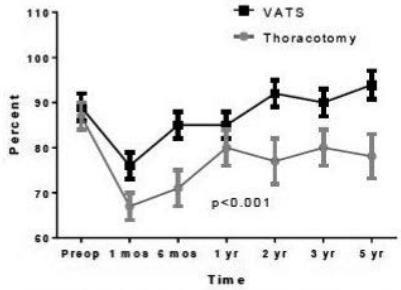

Fig.4 Postoperaive changes of DL_{CO}% for 5 years after lobectomy by operative method

Conclusion: The respiratory function after lung lobectomy recovered gradually over postoperative 2 years. Adjuvant chemotherapy or thoracotomy showed negative impact on the postoperative pulmonary function.

Keywords: Pulmonary Function, Thoracic Surgery, lung cancer

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-021 THORACIC MORBIDITY AND MORTALITY SYSTEM IN ANALYSIS OF POSTOPERATIVE COMPLICATIONS AFTER PNEUMONECTOMY IN NSCLC PATIENTS

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Background: Postoperative complications after pneumonectomy for NSCLC depend on the extension of surgery, comorbidities and accurate registration of any adverse event. The aim of the study was to evaluate the short-term results after standard and extended pneumonectomy in NSCLC patients according to the TMM (Thoracic Morbidity and Mortality) grading system. **Method:** We included 216 NSCLC patients consecutively submitted to pneumonectomy at our institution from January 2011 to December 2015 in the retrospective study performed on data prospectively collected in an electronic clinical database. All patients were divided into two different groups: standard (n=142) and extended (n=74) pneumonectomy, where resection of adjacent organs was indicated. The patients undergone extended pneumonectomy were subdivided into single (n=49) and multi-organ resection (n=25) groups. Systemic mediastinal lymph node dissection was carried out in all cases. Morbidity and mortality rate was analyzed according to the definitions proposed by the ESTS and TMM classification system. **Result:** Postoperative morbidity and mortality rate after standard pneumonectomy (23,9% and 3,5%) was significantly lower than extended procedure (43,2% and 10,8%) (p=0.02). Multi-organ resection was an independent prognostic factor of unfavourable outcome: morbidity and mortality was significantly higher in the multi-organ group (48,0% and 16,0%), while in the single-organ group it was 40,8% and 8,2% respectively (p=0.01). The incidence of the BPF was the only one variable in the ESTS complications definition which differs significantly between the groups of standard, single- and multi-organ resection: 3,5%, 6,1% and 16,0% respectively (p=0.02). Major complications rate (grade IIIA and higher according to the TMM) was significantly higher in the multi-organ group (40,0%) than in the single-organ (28,6%) and standard (14,8%) group (p=0.01). **Conclusion:** TMM classification system is more accurate in grading and further analysis of postoperative complications after pneumonectomy in NSCLC patients in compare with ESTS criteria. Multi-organ resection should be carried out with caution due to unacceptable high morbidity and mortality rate.

Keywords: pneumonectomy, complications, morbidity and mortality

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-022 SEGMENTECTOMY FOR LUNG ADENOCARCINOMA: THE IMPACT OF EGFR MUTATION STATUS ON RECURRENCE

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Background: In this study we sought to identify long-term predictors for recurrence in patients who underwent thoracoscopic segmentectomy for lung adenocarcinoma with a curative intent. We especially focused on the association of surgical outcome with the presence of molecular driver gene mutation. **Method:** We retrospectively reviewed the medical records of 194 patients who underwent thoracoscopic segmentectomy for NSCLC from July 2009 to August 2015. Mutation status was tested in treatment-naive patients who had complete resection of NSCLC using direct sequencing or multiplex polymerase chain reaction-based assay. **Result:** 134 cases were available for molecular data and 48.5% were EGFR mutation-positive. These 134 cases included 52 compromised segmentectomies (39%) for patients with poor pulmonary reserve or other limiting factors. The median follow-up period was 38.8 months. Of the 134 patients, 9 developed distant site recurrence and 4 local recurrence. The 3- and 5-year recurrence free survival were 91% and 87%, respectively. Multivariate Cox regression analysis showed recurrence was affected by female sex (hazard ration (HR), 0.12; 95% CI, 0.01-0.56; p=0.02), intentional segmentectomy (HR, 0.08; 95% CI, 0.01-0.70; p=0.02), and surgical margin of 2 cm or more (HR 0.05; 95% CI, 0.01-0.58; p=0.02). Vascular invasion and p-factors such as size and visceral pleural invasion failed to gain significance after adjusting pathologic nodal status. Also, driver gene mutations were not found to be an independent predictor of recurrence (EGFR mutation; HR, 0.840; 95% CI, 0.28-2.51). **Conclusion:** Apart from lobectomy, driver gene mutation profile does not provide any additional information both in recurrence prediction after segmentectomy and in deciding whether to proceed segmentectomy for mutation-positive patients. This study again emphasizes surgical principle of resection margin of 2 cm should be kept for oncologic clearance when performing segmentectomy.

Table. Predictors for Recurrence in Segmentectomy Patients

	Univariate analysis		Multivariate analysis	
Predictor Variable	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Female	0.14 (0.03-0.65)	0.012	0.12 (0.01-0.56)	0.022
Age (years)	1.06 (1.00-1.14)	0.062	1.06 (0.95-1.20)	0.305
Smoking stasus	2.02 (1.01-4.06)	0.048	1.16 (0.20-6.60)	0.869
EGFR mutation	0.84 (0.28-2.51)	0.760		
KRAS mutation	1.21 (0.16-9.31)	0.857		
Visceral pleural invasion	6.31 (2.06-18.3)	0.001	0.17 (0.01-2.05)	0.164
Lymphatic invasion	1.34 (0.41-4.36)	0.629		
Vascular invasion	7.83 (1.69-36.3)	0.009	0.00 (0.00-infin)	0.999
Number of dissected lymph nodes	1.02 (0.96-1.07)	0.578		
Pleural margin (cm, 0 vs. >0)	2.48 (0.76-8.07)	0.132	6.22 (0.36-108)	0.209
Surgical margin (cm, >2)	0.13 (0.02-1.07)	0.058	0.05 (0.01-0.58)	0.017
Size (cm)	1.97 (1.27-3.06)	0.002	1.73 (0.57-5.27)	0.337
Pathologic nodal status (N+ vs. N0)	7.58 (1.67-34.5)	0.009	0.00 (0.00-infin)	0.999
Type of segmentectomy (Intentional vs. Compromised)	0.15 (0.04-0.56)	0.005	0.19 (0.05-0.84)	0.028

Keywords: segmentectomy, EGFR, Adenocarcinoma

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-023 INTRAPULMONARY LYMPH NODE METASTASIS OF NON-SMALL CELL LUNG CANCER: DISTRIBUTION PATTERN AND THERAPEUTIC RELEVANCE

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Background: Intrapulmonary lymph node retrieval is important for pathological staging and omitting this procedure may affect the outcome evaluation for patients of pN0. In this study, we aim to investigate the incidence and distribution pattern of intrapulmonary nodes involvement (level 13-14) in a pathological N1 cohort. Meanwhile, survival benefit of adjuvant chemotherapy for patients with N1 nodes involvement only limited in intrapulmonary levels was explored. **Method:** From January 2006 to December 2014, 1979 cases admitted to Peking University Cancer Hospital were treated with standard lung resection and systematic lymph node dissection and intrapulmonary lymph nodes retrieval, of which 160 cases of pathological N1 status entered the analysis. Surgeons collected intrapulmonary nodes after operation according to the protocol and all samples were sent for pathological examination. The data was prospectively collected and retrospectively analyzed. For those with N1 nodes involvement only limited in intrapulmonary levels, adjuvant chemotherapy was suggested by oncologists and patients may or may not follow the advice due to insufficient evidence in this condition. The outcome of those receiving adjuvant chemotherapy and those not was compared. **Result:** In this group, 104 cases (65%) reported level 13-14 nodes metastasis and 57 cases (36%) of N1 spreading only limited in level 13-14. The average levels and numbers of intrapulmonary node involvement were 1.09±0.29 and 1.54±0.85, respectively. For peripheral lung cancer, 38 of 89 cases (42.7%) showed non-tumor-located level 13-14 metastasis. Level 13-14 involvement in non-tumor-bearing segment of the right upper lobe was more frequent than that of the lower lobe (44.4% vs 13.3%, p=0.032), but this trend didn't occur in the left side(56.5% vs 45.8%, p=0.464). In 25 cases with tumor diameter

≤ 2cm, 13 cases (52%) presented non-tumor-bear segment metastasis(right side 38.5% vs left side 52.0%). Among 57 cases of pN1(13-14 only), 38 cases showed all three stations' collection and examination from level 10 to 12 in pathological reports, of which 19 had adjuvant chemotherapy and remaining 19 did not. Survival analysis in this 38 cases revealed survival benefit for patients receiving adjuvant chemotherapy (5-year OS 100% vs. 73.7%±11.6%, p = 0.043; 5-year DFS 53.9%±12.8% vs. 74.6%±8.5%, *p*=0.563). **Conclusion:** High incidence of intrapulmonary node metastasis and frequent spreading to non-tumor-located (sub)segments in pN1 group may indicate the clinical relevance of intrapulmonary node retrieval. The oncological outcome may be improved by adjuvant chemotherapy for those with N1 nodes involvement only limited in intrapulmonary levels.

Keywords: NSCLC, adjuvant chemotherapy, intrapulmonary lymph node

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-024 FEASIBILITY OF THE FIT4SURGERY APP - CAN IT REPLACE CONVENTIONAL PULMONARY REHABILITATION IN THE SURGICAL POPULATION?

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Background: Perioperative exercise and physiotherapy is increasingly recognised as beneficial for preparation and recovery in patients undergoing lung cancer surgery. Time and resource constraints may be a barrier to referral for rehabilitation prior to lung cancer surgery. We aimed to establish if provision of an exercise app to use at home would enable patients to exercise more frequently than attendance at classes and determine what the patient experience of using the app was. **Method:** We developed an app for an Apple iPad which utilised a Bluetooth connection to a pulse oximeter to provide patients with realtime feedback on their pulse rate and oxygen saturations during exercise. The app guides patients in doing pulmonary rehabilitaton exercises, which can be made more intense or gentler depending on baseline fitness. We conducted a prospective cohort study to test use of the app by patients at home before and after lung cancer resection. Incremental shuttle walk tests were performed before and after using the app to investigate the difference in preoperative functional capacity. Patients were asked to complete semi structured telephone interviews to comment on their experience of the app. Transcripts of interviews were analysed using content analysis to categorise and highlight the important messages from patients. **Result:** During the 14 month study 37 patients were recruited. A variety of patients participated; the age range was 33 to 84 years and FEV1 range was 45% to 124% predicted. The average number of sessions completed on the app was 4, double the amount if they were attending pulmonary rehabilitation classes prior to lung cancer surgery. All patients except one improved their incremental shuttle walk distance before surgery. Interviews yielded five key messages about the app; patients had a range of motivations for taking part in the study, it was simple to use, patients had a positive experience using it, they had tips for improving it and they thought it had had an impact upon their fitness levels. All the patients found the app convenient to help them perform exercises outside of hospital. **Conclusion:** Patients welcomed the app and immediate provision of the app eliminated any delay in accessing support to exercise. Patients were able to perform more sessions of exercise by using it at home as opposed to hospital based exercises classes. It was feasible to use the app in all types of patients attending for surgery and a multi-centre study is indicated to assess the impact upon postoperative outcomes.

Keywords: Enhanced Recovery, lung surgery, Rehabilitation

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-025 DEVELOPMENT AND VALIDATION OF A SURVIVAL NOMOGRAM IN ELDERLY PATIENTS WITH RESECTED NON-SMALL-CELL LUNG CANCER

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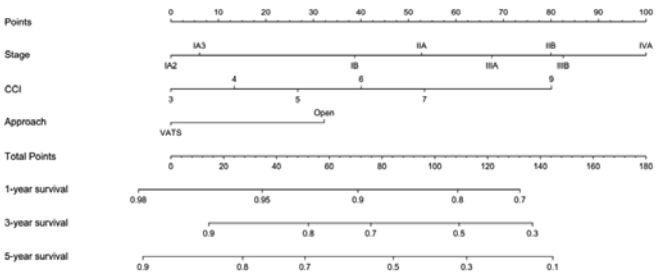
Background: The outcomes of elderly patients with resected lung cancer were less predictable due to shorter life expectancy and increased comorbidities. We sought to develop a nomogram based on the 8th TMN staging system for predicting survival of elderly patients with resected non–small-cell lung. **Method:** Data of patients aged≥70years with resected NSCLC between 2000 and 2016 in Peking University People's Hospital were analyzed. Multivariate Cox proportional hazards regression was used to build a nomogram. The performance of the nomograms was subjected to internal validation and to external validation by Harrell's concordance index (C-index), calibration plots and risk group stratification. **Result:** A total of 453 elderly patients with resected NSCLC were included in the study. The median follow-up time was 45 months. The 8th TNM staging system, Charlson Comorbidity Index and surgical approach (VATS versus Open) were independent prognostic factors to predict overall survival (OS). The nomogram for predicting OS demonstrated a sufficient level of discrimination according to the C-index (0.694, 95%CI 0.645-0.743), which was stronger discriminatory power than the 8th TNM stage system 0.652(0.603-0.701). The calibration curves for probability of 1-, 3-, and 5-year overall survival (OS) showed optimal agreement between nomogram prediction and actual observation. In the external validation cohort of 269 cases, the model also demonstrated a sufficient level of discrimination according to the C-index (0.715, 95%CI 0.657-0.780).



Conclusion: We developed and validated a nomogram that could predict individual accurate prognosis for elderly patients with resected lung cancer. This tool might help the clinicians for individualized treatment decision making.

Keywords: elderly, lung cancer, Nomogram

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-026 CLINICAL IMPLICATION OF OCCULT LYMPH NODE METASTASIS IN THE REMAINING LOBES AFTER LOBECTOMY IN NON-SMALL CELL LUNG CANCER

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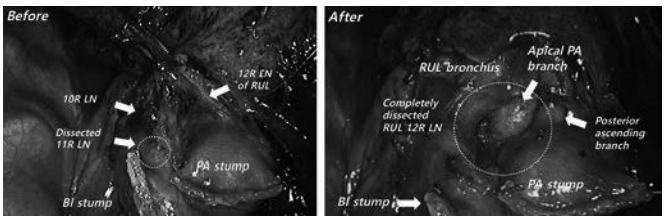
Background: The presence of lymph node metastasis in the ipsilateral remaining lobe and its clinical implication after lobectomy have not been evaluated or discussed. **Method:** We sampled station 12 node of the remaining lobe during the surgery and completely dissected all the segmental nodes if cancer cell metastasis was either confirmed or suspicious. We retrospectively reviewed such patients and analyzed clinicopathologic characteristics. **Result:** Between 2010 and 2016, we found 20 cases where a complete lymph node dissections of the remaining lobes were performed (male 19, female 1, median age 55 (29-71) years). The location of primary cancer was predominantly in the RLL (RLL 17, RML 2 and LLL 1) and the surgical procedure performed were mainly bi-lobectomy (RLL and RML 11, RLL 6, RML 2, LLL 1). The site of lymph nodes in the other lobe were predominantly located in the RUL (RUL 18, RUL and RML 1, LUL 1). Clinical N-stages were N0 in 6, N1 in 9, and N2 in 15 patients. Preoperative CT and PET-CT failed to predict presence of metastasis of other lobe lymph nodes. The pathologic N-stages were N0 in 3, N1 in 4 and N2 in 13. The metastasis in the other lobe was present in 14 patients whereas, 6 were negative. Twelve out of 14 patients with positive lymph node in the other lobe had mediastinal lymph node metastasis (85.7%). The overall survival rates were 94.4% at one year and 74.4% at 2 years. However, as many as 8 patients (40%) recurred at the time of the study.



Conclusion: In conclusion, we found some patients possessed occult metastasis in N1 nodes of the remaining lobe especially in lower lobe cancers and the majority had occult N2 metastasis as well. The prognostic and clinical implication of knowing lymph node status of the remaining lobe needs further investigations.

Keywords: Other lobe, lymph node metastasis, Prognosis

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-027 EFFECTS OF SURGICAL WAITING TIME ON PROGNOSIS IN PATIENTS WITH LUNG CANCER

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Background: The effect of surgical waiting time on prognosis in patients with lung cancer remains unknown. The purpose of this study is to examine the impact of surgical waiting time on outcome in patients with lung cancer. **Method:** We retrospectively reviewed all patients who underwent complete surgical resection in a single center between January 2006 and May 2016. Waiting time is defined as the interval between the date of initial visit to the department of respiratory

medicine or thoracic surgery and the date of surgery. The patients were divided into two groups based on surgical waiting time: group A (n=160), 0-37 days; group B (n=150), 38 days or longer. Patients who had received neoadjuvant therapy, history of previous primary lung cancer and waiting time greater than 6 months were excluded. **Result:** 310 patients met inclusion criteria (65.8% men; median age: 67yrs; c-stage I / II / III 249 / 41 / 20, p-stage I / II / III 212 / 47 / 51, median waiting time: 37 days). Waiting time tends to be shorter as c-stage of disease (I / II / III 38 / 35 / 31.5 days) becomes more advanced. Bronchoscopy or CT guided biopsy before surgery was performed in the group A / B, 160 / 150 patients, respectively. Charlson Comorbidity Index (CCI) (0 / 1 / 2 / 3 / 4 / 5 / 6 / 7) was in the group A: B; 97 / 20 / 33 / 7 / 1 / 0 / 1 / 1: 72 / 27 / 37 / 11 / 2 / 0 / 0 / 1, respectively; group B was significantly associated with higher comorbidity rate. The 5-year RFP in the group A / B was 60.7 / 67.6% (p=0.19) (c-stage I / II / III 70.8 / 31.3 / 21.4%, 68.7 / 66.6 / 50%(p=0.92/0.32/0.3)), respectively. The 5-year OS in the group A / B was 75.6 / 82.6% (p=0.3) (c-stage I / II / III 83.3 / 68 / 21%, 85.7 / 79.3 / 0%(p=0.77 / 0.82 / 0.62)), respectively. **Conclusion:** Surgical waiting time from initial visit to operative intervention does not adversely affect recurrence and survival.

Keywords: lung cancer, Prognosis, waiting time

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-028 NECROSIS IS A PREDICTOR OF RECURRENCE IN PATIENTS WITH SMALL LUNG ADENOCARCINOMA ≦2CM

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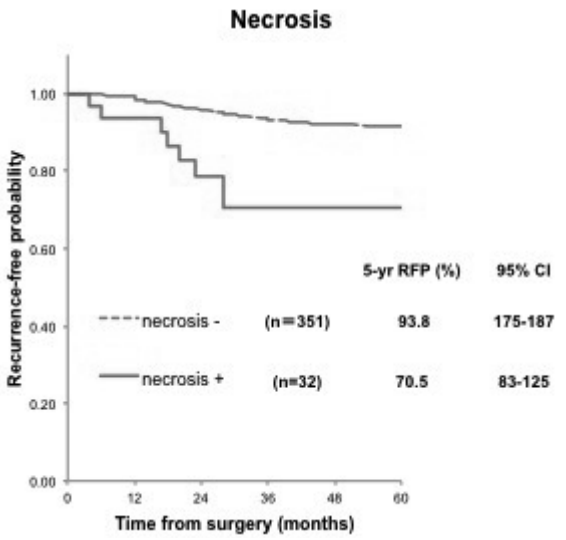
Background: The prognostic significance of pathological necrosis in small lung adenocarcinoma has not been investigated. The purpose of this study is to investigate the prognostic role of pathological necrosis in patients with completely resected small lung adenocarcinoma ≦2cm. **Method:** All available tumor slides from patients with surgically resected lung adenocarcinoma ≦2cm in size (1998-2015) were retrospectively reviewed. Exclusion criteria: patients who received induction therapy and lung cancer surgery within preceding 2 years. Recurrence free probability and overall survival were assessed using the Kaplan-Meier method. **Result:** 351 patients met inclusion criteria (48% women, median age 67yr (34-86 yrs), 50% never-smokers; 324 Stage IA, 27 Stage IB; 111 and 240 patients underwent sublobar resection and lobectomy, respectively). Presence of pathological necrosis was identified in 32 patients (9%). Presence of pathological necrosis was significantly associated with sex, smoking, clinical T classification in the 8th edition and pathological tumor size (p<0.01, p<0.001, p<0.01, p<0.001, respectively). Presence of pathological necrosis correlated with an increased risk of recurrence, compared with those without pathological necrosis (5-year RFP, 70.5%vs 93.8%; p<0.001). Presence of pathological necrosis did not affect OS (5-year OS, 80.8%vs 92.3%; p=0.21).



Conclusion: In patients with small lung adenocarcinoma ≦2cm, presence of pathological necrosis was significantly associated with increased risk of recurrence.

Keywords: small lung adenocarcinoma, necrosis

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P3.16-029 RECURRENCE WITHIN A YEAR AFTER COMPLETE RESECTION OF PRIMARY LUNG CANCER

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Background: Optimal postoperative follow-up method for lung cancer patients is not determined. Investigation of early recurrence risk may help differentiating the patients who should be intensively follow up, and further lead to improve prognosis of those cases. We clinicopathologically evaluated the lung cancer patients with recurrence within a year after complete resection. **Method:** We retrospectively reviewed 63 patients with recurrent diseases after complete resection of lung cancer between 2006 and 2016 in our institution. **Result:** We found 32 patients (50.1%) who had recurrent disease within a year after resection (former group), 31 patients (49.2%) over a year after resection (latter group). Average ages of each group were 70.1 years for the former, and 68.4 years for the latter. As for histological types, the former were composed of Adenocarcinoma (Ad) 12 / non-Ad 20, and the latter composed of Ad 27/ non-Ad 4 cases. Ad was found more frequently in the latter than the former, significantly (p<0.0001). Pathological stage (I/ II-IV) of each groups were 8 / 24 cases for the former, 18 / 13 cases for the latter. The former had more advanced stages than the latter, not significantly. Average tumor size (mm) was 45.5 for the former, 32.3 for the latter, not significantly. Pleural invasion (-/+) were 11/32 cases for the former, 11/31 for the latter, not significantly. On the other hand, Lymphatic invasion (-/+) were 24/32 cases for the former, 16/31 for the latter (p=0.0168). Vessel invasion (-/+) were 23/32 for the former, 14/31 for the latter (p=0.0313). The former had more Lymphatic invasion (+), Vessel invasion (+) patients than the latter, significantly. Postoperative survival times were 503.6 days for the former in average, 1704.1 days for the latter. The prognosis of the latter was better than the former (p<0.05). The number of deaths were 19 for the former (including 1 case with intercurrent disease death), 9 for the latter (same 2 cases). The former had more cases of death (p=0.0238)than the latter, significantly. **Conclusion:** Lung cancer patients with recurrence within a year after resection showed non-Ad histology and lymphovasclar invasion positivity more frequently, than those over a year after resection. Such patients had shorter survival time and more number of deaths than those over a year, showing poorer prognosis.

Keywords: Lung cancer, Surgery, Recurrence

P3.16: SURGERY -
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P3.16-030 VENOUS THROMBOEMBOLISM AFTER LUNG CANCER SURGERY AND ITS RISK FACTORS: A SINGLE CENTER, RETROSPECTIVE, COHORT STUDY FROM CHINA

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Background: The high Venous Thromboembolism (VTE) incidence has been perceived in post-surgery lung cancer patients. However, there is lack of effective data from such area in China. To evaluate the incidence of VTE and define risk factors for primary lung cancer, we conducted a retrospective single center cohort study. **Method:** 252 patients were enrolled in this study, included 131 primary lung cancer patients and 121 benign lung disease patients after lung surgery from July 2016 to March 2017. The Color Doppler Ultrasonography was performed before and after operation for VTE confirmation. Patients experienced new postoperative VTE, unexplained dyspnea, hemoptysis, chest pain, highly suspected PE and other symptoms, further CTPA examination was required. The VTE incidence was evaluated after discharge. Caprini RAM was performed; relative outcomes had been recorded for all patients. Caprini scores 0 to 4 were defined as low-risk, 5 to 8 as moderate-risk and over 9 as high-risk. Single factor analysis was constructed to define risk factors associated with VTE. **Result:** The overall VTE incidence was 12.3% (31 of 252). The VTE incidence after primary lung cancer surgery was 16.0% (21 of 131), much higher than the VTE incidence of benign lung diseases 8.3% (10 of 121), but did not reach statistical significance (P=0.061). Among 21 VTE lung cancer patients, 4.8% was SVT (1), 81.0% DVT (17), and 14.3% was DVT+PE (3); 15 patients (71.4%) have manifested intramuscular venous thrombosis. Those 21 VTE patients possessed high Caprini scores, which was significantly higher than non-VTE patients in benign lung disease group (Score: 7 versus 4, P<0.001). Postoperative VTE incidence was correlated with increasing Caprini scores. The VTE incidence in the low, moderate, and high-risk groups was 0%, 13.4% and 35.3% respectively. The high-risk patients group had significant higher incidence than the low and moderate groups (P=0.049). In lung cancer patients, pre-operative D-Dimer concentration from VTE patients was 2 times higher than non-VTE patients (0.42 versus 0.21, P=0.015) and 1.7 times higher than patients postoperatively at day 3 (1.24 versus 0.71, P=0.008). FDP concentration in VTE patients postoperatively at day 3 was 1.8 times higher than non-VTE patients (6.40 versus 3.60, P<0.001). **Conclusion:** The overall incidence of VTE after primary lung cancer surgery was 16.0%. High-risk patients had an incidence of 35.3%. High Caprini scores suggest extended chemoprophylaxis for patients after discharge. Pre-operative high D-Dimer, POD3 high D-Dimer and POD3 high FDP concentration indicate high VTE risk.

Keywords: venous thromboembolism, Thoracic Surgery, Caprini RAM

P3.16-031 SURVIVAL AND PROGNOSTIC FACTORS OF SYNCHRONOUS MULTIPLE PRIMARY NSCLC AND FURTHER DIFFERENTIATION FROM INTRAPULMONARY METASTASIS

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Background: The diagnosis, staging, and therapeutic strategy for synchronous multiple primary non-small-cell lung cancer (SMP-NSCLC) remain unclear. Distinguishing SMP-NSCLC from intrapulmonary metastasis is difficult but of great importance for selecting the surgical procedure and prognoses. **Method:** Fifty-two patients diagnosed with SMP-NSCLC according to the modified Martini-Melamed criteria in the thoracic surgery department of the China-Japan Friendship Hospital from November 2004 to December 2015 were enrolled in this retrospective study. A total of 106 tumors were subjected to pathological examination. Close follow-up and survival analysis were performed. **Result:** The perioperative morbidity rate was 5.8%, with no cases of perioperative death. The overall 5-year survival rate was 40.6%, the cancer-specific 5-year survival rate was 54.5%, and the median survival time was 52 months. Older age (p=0.553), sex (p=0.600), smoking history (p=0.496), tumor distribution (p=0.461), video-assisted thoracoscopic surgery (p=0.398), and adjuvant chemotherapy (p=0.078) did not affect survival. Preoperative percentage of forced expiratory volume in the first second (p=0.022), Charlson comorbidity index (p=0.034), surgical procedure (p=0.040), and highest pT stage (p=0.022) were independent risk factors in the multivariate analysis. Different pathological subtypes were identified in 13 of 18 cases of multiple adenocarcinomas. Different gene mutation types and correlations between tumors were identified through next generation sequencing in those with the same pathological subtype. **Conclusion:** Postoperative survival rates in SMP-NSCLC were satisfactory. Non-radical resection might improve the prognosis for patients with a tolerable general condition and pulmonary function. Higher pT stage might result in poorer survival rates. Larger sample size and future study are still needed to identify the prognostic factors. Comprehensive histologic assessment and next generation sequencing could be effective methods for screening SMP-NSCLC.

Keywords: multiple primary lung cancer, survival analysis, next generation sequencing

P3.16-032 PREDICTION OF POSTOPERATIVE LUNG FUNCTION IN PATIENTS WITH LUNG CANCER BY LUNG LOBE

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Background: Prediction of postoperative lung function is important in preoperative evaluation of patients with lung cancer. Postoperative predictive lung function includes a calculation method predicting from the number of bronchial branches in the non-occlusion area and a method using perfusion scintigraphy. We compared the lung function predicted from these two methods with the actual postoperative lung function and examined the correlation with each method for each lobe. **Method:** Forty seven patients underwent lung lobectomy with lung cancer of 2 cm or less from November 2015 to February 2017 were targeted. All patients were performed preoperative lung function test and perfusion scintigraphy using technetium-99m-labeled macroaggregate of albumin. In this study, cases with right middle lobectomy and bilobectomy were excluded. In all cases, lung function test was reexamined at the third to six month after surgery. The assessment of pulmonary perfusion was performed with planar imaging. Regional quantitation of lung perfusion was first assessed using the traditional method by drawing 2 regions-of-interest (ROIs) of equal size over each lung, dividing the lung into upper, middle, and lower lung zones. The mean of the counts in each of the 4 zones was calculated and compared. **Result:** Surgery was performed in 22 cases of right upper lobectomy, 10 cases of right lower lobectomy, 10 cases of left upper lobectomy and 5 cases of left lower lobectomy. Both calculation method and perfusion scintigraphy predicted postoperative FEV1 well in patients who underwent lobectomy (R= 0.94 vs R = 0.91) (both, $p < 0.001$). We studied upper lobectomy 32 cases and lower lobectomy 15 cases. Both methods showed significantly lower values compared with actual postoperative FEV1. In upper lobectomy cases, the average of the difference between the actual postoperative FEV1 and predicted postoperative FEV1 in calculation method was 193ml, and the average difference from predicted postoperative FEV in perfusion scintigraphy was 168ml. There was no significant difference between the two methods. In lower lobectomy cases, the average of the difference between the actual postoperative FEV1 and predicted postoperative FEV1 in calculation method was 263ml, and the average difference from predicted postoperative FEV1 in perfusion scintigraphy was 144ml. The FEV value of the calculation method was significantly lower than that of perfusion scintigraphy (p=0.0021). **Conclusion:** The conventional calculation method and perfusion scintigraphy method showed a strong correlation with actual postoperative FEV1. In lower lobectomy, the perfusion scintigraphy method showed the possibility of predicting more accurate postoperative FEV1.

Keywords: perfusion scintigraphy, predicting postoperative FEV1, lobectomy

P3.16-033 SIGNIFICANCE OF SPREAD THROUGH AIR SPACES IN RESECTED PATHOLOGICAL STAGE I LUNG ADENOCARCINOMA

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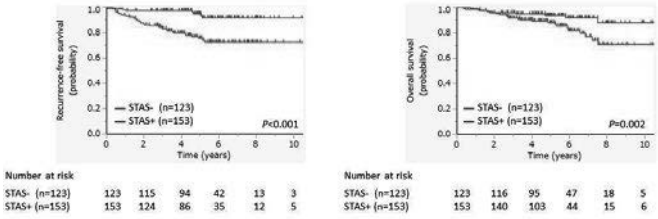
Background: Spread through air spaces (STAS) is a novel invasive pattern of lung cancer, which spreads within air spaces beyond the edge of the main tumor, but not necessarily accompanying stromal invasion. In the current study, we investigated the significance of STAS in patients with pathological stage I adenocarcinoma. **Method:** STAS was assessed in a total of 276 patients with resected pathological stage I adenocarcinoma. STAS was classified as either no STAS, low STAS (1-4 single cells or clusters of STAS), or high STAS (≥5 single cells or clusters of STAS) using a 20x objective and a 10x ocular lens. We evaluated the association between STAS and the clinicopathological characteristics and postoperative survivals. **Result** Among 276 patients, 123 (44.6%), 48 (17.4%) and 105 (38.0%) were classified as having no, low and high STAS, respectively. Fisher's exact test demonstrated that positivity for STAS was significantly associated with a larger radiological tumor diameter (P=0.008), a higher consolidation/tumor ratio (P<0.001), a higher maximum standard uptake value (P<0.001), a pathologically larger tumor size (P=0.004), the presence of pleural invasion (P=0.027) and a histologically invasive type (P<0.001), while STAS was not significantly associated with *epidermal growth factor receptor* mutations or programmed death ligand-1 expression (P=0.129 and P=0.872, respectively). Patients with the STAS had significantly shorter recurrence-free and overall survivals than those without (P<0.001 and P=0.002, respectively). According to a multivariate analysis, positivity for STAS remained an independent prognostic parameter for both the recurrence-free and overall survivals. **Conclusion:** STAS was associated with clincopathologically invasive features and was predictive of a worse survival.



Keywords: Spread Through Air Spaces, Surgery, lung adenocarcinoma

P3.16-034 IMPACT OF TRAVEL DISTANCE TO TREATMENT INSTITUTION ON SURVIVAL FROM STAGE I TO III LUNG CANCER

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Background: Over the last decade, attention and emphasis on regionalization of care for tertiary hospitals have increased in order to improve outcomes, especially in complex surgical procedures such as resection of lung cancer. On the other hand, the growing centralization of cancer services increases patient displacement and may delay access to specialized services and treatment. Impact of travel distance on patients' outcome from lung cancer is poorly described. The objective of this study is to evaluate whether distance to treatment institution has an impact on survival from patients with lung cancer. **Method:** This is an observational, retrospective study, which included patients with stage I-III lung cancer that performed curative resection at Hospital São Lucas da PUCRS, Brazil. Data was collected from medical charts including demographic, clinical-pathological features and survival. Survival was estimated using the Kaplan-Meier method and log-rank test was used to perform multivariate analysis for prognostic factors. Chi-squared test was used to compare variables between groups. **Result:** Between January 2011 and December 2015, 234 patients with stage I-III lung cancer performed curative resection at Hospital São Lucas da PUCRS. The median age was 65 years (24-85 years) and 50.85% were male. 147 (62.82%) patients were from public health insurance and 87 (37.18%) had private coverage. The distribution of clinical stage (AJCC 8th ed) was : 116 (49.57%) stage I, 71 (30.34%) stage II and 47 (20.09%) stage III. The median distance to institution was 19.7 (2-1086 km). Patients with public health insurance traveled higher distance than those with private coverage (p= 0.0004). The 3-year overall survival was 86.13% for stage I, 77.74% for stage II and 48.95% for stage III. The distance to institution had no impact in overall survival (p=0.85 for stage I, p= 0.63 for stage II and p= 0.46 for stage III). **Conclusion:** Our study shows that the distance

between residence and treatment institution was not found to influence survival of the patients with lung cancer treated by surgery. Importantly, patients with public health insurance, which are in general poorer, have to travel longer distances for curative treatment.

Keywords: distance, lung cancer, survival

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P3.16-035 THE UNKNOWN: DOES BODY MASS INDEX (BMI) INFLUENCE OUTCOMES POST LUNG CANCER RESECTION SURGERY?

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Background: Higher BMI is well known to increase the overall intraoperative & post operative surgical risk in obese patients with BMI>30 . Well –published studies have showed that these group of patients have higher affinity for surgical related complications & risks in other surgical specialities , but its impact in patients undergoing pulmonary resections is uncertain. This study looks into this aspect in our cardiothoracic unit . **Method:** A well-conducted retrospective cohort study was performed on all patients undergoing lobectomies for primary lung cancer between year 2011 to 2015 . These data was extracted using the operating theatre ORSOS database and cross referencing with the surgical unit database . Sole exclusion criteria was any patients with BMI<18 . Numerous statistical analysis of demographics & outcomes were tabulated . **Result:** Patient demographics , operation type & side with post operative surgical complications were analysed . Elements of lung function tests were also evaluated **Conclusion:** Identifying the outcomes post lobectomy in patients with BMI>30 will help plan better outstanding and resources for post operative care in this sub group in order to get them thru the post operative course .

Keywords: lobectomy , complications , BMI

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P3.16-036 FEASIBILITY OF LUNG CANCER SURGERY IN SEPTUAGENARIANS

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Background: Lung Cancer is most common cancer in the world . It has progressively become a disease of older people as radiological & clinical detection improves rapidly with advances in anatomic lung resections . As population grows older demographically , it poses various distinct treatment & management challenges . Thus , we looked into outcomes & factors associated with long-term survival following lung cancer resections in patients older than 70 years of age . **Method:** A retrospective study was conducted , all septuagenarians patients with lung cancer who underwent pulmonary resections , between years 2011 to 2015 , were reviewed . These data was cross-referenced & checked with the operating theatre ORSOS & national mortality data **Result:** 80 patients in total . Male predominantly between ages 70 to 79 years old . Average age is 73.5 years . 19 patients were non-smokers . Average in-hosp stay was 9.9 days .5 patients needed post op ICU admission for hypotension & one patient had failed extubation needing prolonged ventilation . 67 patients had epidural catheter for post-op pain management which expedited their pain recovery process . Minor complications includes 6 patients with superficial drain site infection . No one suffered any strokes . No major complications noted . Survival at 30 days – 100% , 1 year – 10 out of 80 patients died - 87.5 % survival rate . At present – 54 out of 80 patients are alive – 67.5 % **Conclusion:** Strict operative patient selection thru MDM will identify groups of patients that will benefit from these surgeries .These group of patients did extremely well post operatively . Important factors associated with these successful surgeries were indicative of the better survival rates. Septuagenarians with lung cancer can be given a new lease of life with continued survivability following major pulmonary resections .

Keywords: lung cancer , NSCLC , septuagenarians

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P3.16-037 SUPERIOR VENA CAVA REPLACEMENT COMBINED WITH VENO-VENOUS SHUNT FOR LUNG CANCER AND THYMOMA: CASE SERIES

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Background: Superior vena cava (SVC) replacement is infrequently performed and technically challenging in low-volume centers. Veno-venous shunt (VVS) technique is used to reduce SVC pressure during SVC replacement and has not been well reported. This study aims to add experience on this subject and evaluate the surgical outcomes of patients who undergo SVC replacement combined with VVS in our center. **Method:** A retrospective analysis of six patients who received SVC replacement combined with VVS from September 2011 to February 2017 was performed. Clinical characteristics, pathological features, operative characteristics, postoperative outcomes and survival of six patients were reviewed. **Result:** There were four males and two females with a median age of 44 years (range, 35-69 years). There were three lung cancer patients and three thymoma patients at a stage from IIIA to IVA. Five patients underwent induction therapy. Complete resection was performed on five patients. One case underwent internal VVS, and the other five cases underwent external VVS. Prosthesis grafts were employed in five cases and autologous pericardium in one case. Three cases underwent single-vein reconstruction, and the other three cases underwent double-vein reconstruction. The median SVC clamping time was 75 minutes. There were no postoperative deaths and major complications. All follow-up patients were alive, and no thrombosis was found in all the grafts.

(See table next page.)

Table 1 Clinical and pathological characteristics of six patients								
Case	Year	Age (years), sex	Tumor	Status	Treatment	Response after induction	Histology	Stage
1	2011	35, male	Thymoma	Primary	CRT+S+CT+S	PR	B2 thymoma	IVA
2	2012	46, male	Lung cancer	Primary	CT+S+CT	PR	Adenocarcinoma	pT4N2M0, IIIB
3	2015	37, female	Thymoma	Primary	CRT+S+CT	PR	B2 thymoma	III
4	2015	42, female	Thymoma	Recurrence	S+RCT	-	B1 thymoma	III
5	2016	54, male	Lung cancer	Primary	CT+S+CRT	SD	Squamous cell carcinoma	pT4N2M0, IIIB
6	2017	69, male	Lung cancer	Recurrence	CRT+S+CT	SD	Squamous cell carcinoma	pT4N0M0, IIIA

CRT, chemoradiotherapy; CT, chemotherapy; PR, partial response; RT, radiotherapy; S, surgery; SD, stable disease **Conclusion:** SVC replacement combined with VVS is technically feasible and safe. Although VVS technique is not a must, it may make SVC replacement safer in inexperienced centers. Surgery-based multidisciplinary treatment for selected patients with type T4 lung cancer and SVC involvement or thymoma and SVC involvement may achieve a favorable long-term outcome.

Keywords: Superior vena cava replacement, Veno-venous shunt, Vena caval bypass

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P3.16-038 EXPERIENCE OF 180 BRONCHIAL SLEEVE RESECTIONS FOR MALIGNANT TUMORS

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Background: Sleeve lobectomy can expand the indications to radical organ-saving operations and avoiding pneumonectomy increase the number of operated ones, and also significantly improve the quality of life and rehabilitation conditions of patients, which is of special importance for persons with limited functional reserves. **Method:** One surgical team performed 180 bronchial sleeve resections for malignant neoplasms of the lung. In all cases an invagination technique was used to form an anastomosis per 1 cartilage semicircle. There were 168 (93,3%) patients with primary tumors and 12 (6,7%) with solid metastatic lesions. Non-small cell lung cancer (NSCLC) was performed in 149 (88.7%) cases, carcinoid tumors - in 19 (11.3%) cases. Ia stage was diagnosed in 7.4%, Ib stage in 6.7%, IIa in 25.5%, IIb in 16.1%, IIIa in 37.6% and IIIb - 6.7% of cases. There were 80.6% (145) males and 19.4% (35) females. The average age of patients was 56.9 (from 18 to 82 years). 21 variants of bronchoplastic reconstructions was performed, lobectomy - in145 (80,6%) patients, bilobectomy – in 24 (13,3%), segmentectomy – in 6 (3,3%), isolated resection of bronchus – in 5 (2,8%) patients. In common 63 (35%) bronchoangioplasty interventions were performed. Resection of the pulmonary artery was performed in 49 cases (40 - circular, 9 - edge), vena cava resection - in 9 patients (6 - circular, 3 - edge), segmental arteries were resected in 5 patients (3 - circular, 2 - edge). In all cases of NSCLC extended ipsilateral mediastinal lymph node dissection was performed. **Result:** Complications were noted in 35 patients (19.4%): pneumonia (6.1%), atelectasis of the lobe (0.6%), insufficiency of bronchial sutures (3.9%), granulation stenosis of bronchial anastomosis (1.1 %), PE (1.7%), chylothorax (1.1%), recurrent nerve paresis (1.1%), cardiac rhythm disturbances (1.7%), hemothorax (1.7%), AMI (0.6%). Postoperative mortality was in 3.9% cases. The cause of death in 3 patients was massive PE, in 1 - AMI, in 3 - failure of bronchial sutures. Long-term results were obtained in 128 patients. The one-year observed survival rate in patients after reconstructive resections was 90.6%, 3-year - 57.4%, 5-year - 42.4% (with median 48.8 months). One-year recurrence-free survival was 89.1%, 3-year - 63.8%, 5-year - 51.6% Median relapse-free survival was 55.2 months. **Conclusion:** Using the invagination technique for the bronchial anastomoses is characterized by the simplicity of technical execution and is accompanied by satisfactory immediate and long-term results.

Keywords: sleeve lobectomy, sleeve resection, bronchoplastic

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P3.16-039 RIGHT UPPER LOBECTOMY WITH SVC RECONSTRUCTION AFTER INDUCTION CHEMORADIOTHERAPY FOR A PATIENT WITH BULKY N2 NSCLC

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Background: The treatment strategy for N2 IIIA non-small cell lung cancer (NSCLC) is still controversial. Some believe that patients with bulky N2 are not good candidates for trimodality treatment. In addition, with regard to the survival of patients underwent lung resection with SVC reconstruction, patients with SVC involvement due to direct invasion of the main tumor have longer survival compared to those with SVC involvement due to mediastinal lymph node (LN) metastasis. We encountered a patient with bulky N2 NSCLC with SVC involvement. **Method:** A 69-year-old man complaining of cough was referred to our hospital for examination of a chest abnormal shadow. Chest CT showed a 58-mm pulmonary mass lesion in the right upper lobe and mediastinal LN swelling (#4R: 31 mm, #2R: 15 mm), which resulted in stenosis of the SVC. Transbronchial biopsy of the mass and EBUS-TBNA of the #4R LN showed squamous cell carcinoma. Since distant metastasis was not apparent, the patient was diagnosed with locally advanced IIIA lung cancer with bulky N2. After induction of concurrent chemoradiotherapy (2 cycles CDDP+VNR + 45 Gy radiotherapy), the lesion showed 9.5% reduction and was defined as stable disease according to the RECIST criteria. **Result:** Since it would be difficult to dissect the SVC and #4R LN, and this procedure would require substantial time, we approached by median sternotomy and right fourth intercostal thoracotomy and established the shunt between the left brachiocephalic vein and the right atrial appendage prior to cross-clump of the SVC. The SVC was resected because of extensive firm adhesion of the #4R LN, and reconstructed with a 12-mm reinforced polytetrafluoroethylene graft. The anastomosis was performed using a 5-0 Plorene suture. The patient underwent right upper lobectomy with mediastinal dissection and combined resection of the SVC. The operation time was 494 min and blood loss was 700 g. The patient was discharged on postoperative day 16. Pathological examination revealed the effect of chemoradiotherapy was Ef2, and viable cells were present in the #4 LN (ypN2). **Conclusion:** While the long-term outcome of this patient is unknown, we believe the trimodality treatment is an option for bulky N2 NSCLC with SVC involvement.

Keywords: SVC reconstruction, bulky N2, NSCLC

P3.16: SURGERY -
WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.16-040 INTRAPLEURAL PERFUSION THERMO-CHEMOTHERAPY FOR PLEURAL EFFUSION CAUSED BY LUNG CARCINOMA UNDER VATS

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Background: The aim of this study was to assess the effectiveness of Intrapleural Perfusion Thermo-Chemotherapy (IPTC) under video-assisted thoracoscopic surgery (VATS) for malignant pleural effusion (MPE) caused by lung carcinoma. **Method:** In this retrospective study, fifty-four patients with moderate or large amounts of ipsilateral malignant pleural effusion (MPE) secondary to non-small cell lung cancer (NSCLC) underwent pleural biopsy and IPTC under VATS. IPTC was performed by perfusing the pleural cavity with 43.0°C saline solution containing cisplatin (200 mg/m^2) using a devised circuit through mechanical circulation for 60 minutes. Blood pressure, heart rate, oxygen saturation (spo2), and esophageal and rectal temperatures were monitored throughout the surgery. At the end of the perfusion, pleural biopsy was performed again for histological analysis. **Result:** The temperature at the pleural surface was stabilized at 43°C, and pleural effusion was controlled in all patients. KPS scores increased in 89.3% of patients. No patient developed bone marrow suppression reactions with noticeable bleeding after treatment, and no liver and kidney malfunctions were observed. Apoptosis was detected by light and electron microscopy after IPTC. CEA markedly decreased in all patients 1 month after IPTC. The median survival time was 21.7 months, with a one-year survival rate of 74.1%. **Conclusion:** Intrapleural Perfusion Thermo-Chemotherapy under VATS is a new, safe, less invasive and more effective approach for malignant pleural effusion (MPE) caused by lung carcinoma.

P3.16-041 PLEURAL PHOTODYNAMIC THERAPY AND SURGERY FOR PLEURAL METASTASIS BY NON-SMALL CELL LUNG CANCER

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Background: Photodynamic therapy (PDT) is one of the established treatment modality for non-small cell lung cancer (NSCLC). Early-stage lung cancer and superficial endobronchial lesions less than 1 cm in thickness can be e ectively treated with external light sources. Thicker lesions and peripheral lesions may be amenable to interstitial PDT, where the light is delivered intra-tumorally. The primary adverse event, phototoxicity, is expected to be minimized with the introduction of new photosensitizers that have shown promising results in phase I and II clinical studies. Moreover, the addition of PDT to standard-of-care surgery and chemotherapy(or target therapy) can improve survival and outcomes in patients with pleural dissemination. Therefore, pleural PDT with surgery has shown promise in the treatment of non-small cell lung cancer with pleural spread. **Method:** Between January 2007 and January 2017, we retrospectively reviewed the clinical characteristics, treatment course and outcome of 39 patients with pleural seeding by non-small cell lung cancer. The eligibility criteria are as follows: pathologic diagnosis of lung cancer or thymoma with pleural spread, medical feasibility for PDT and surgery. The exclusion criteria are as follows: younger than 18 years old, leukopenia, or thrombocytopenia; chronic renal insufficiency with serum creatinine > 2.5 mg/dL; significantly impaired liver function; pregnancy or lactation. Patients underwent anatomic resections in whom it was possible to remove all gross tumor. After finishing the procedure, the parietal pleura were stripped from the bony hemithorax as radical parietal pleurectomy. Debulking of all gross tumor was performed in the mediastinum, too. For thymoma patients, the radical thymothy- mectomy was performed concurrent with radical pleural pleurectomy. The goal was to remove all detectable tumor in the operation field before proceeding to the photodynamic therapy. . **Result:** Thirty-nine patients enrolled in this study. There are 18 men and 21 women included in this study. The mean patient age was 52.6 ± 11.9 years. Using Kaplan-Meier survival analysis, the 3-year survival rate and the 5-year survival rate were 69.4% and 59.5%, respectively. There is one ARDS occurred immediately after the procedure. After medical treatment, the condition gradually improved. Other minor complications included prolonged air-leakage (five patients) and skin redness (six patients). The complications were successfully treated using medication. There was no procedure-related mortality. **Conclusion:** Photodynamic therapy and surgery for pleural dissemination in patients with non-small cell lung cancer is feasible and associated with a good soutcome.

Keywords: pleural metastasis, photodynamic therapy, non-small cell lung cancer

P3.16-042 INTRAOPERATIVE HYPER-THERMOTHERAPY WITH DISTILLED WATER FOR STAGEIV LUNG CANCER

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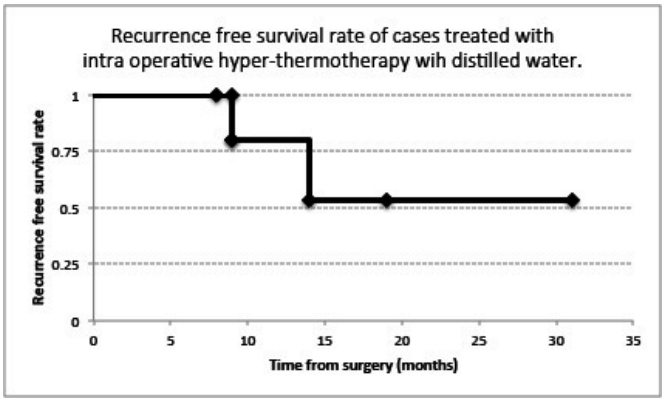
Background: Non-small cell lung cancer (NSCLC) with dissemination are classified as Stage IV lung cancer and usually considered inoperable. However, dissemination detected primarily during thoracotomy has been reported to show better prognosis compared with dissemination diagnosed clinically. Here, we present a case series of surgically treated stage IV lung cancer treated with intraoperative hyper-thermotherapy with distilled water. **Method:** Clinical records of 912 consecutive NSCLC patients who underwent surgery intended for complete resection between 2006 and 2016 were retrospectively reviewed. 5 M1a cases and 1 M1b (posterior mediastinum) case were treated with intraoperative hyper-thermotherapy with distilled water. Thoracic cavity was filled with distilled water heated to 43 degrees Celsius, following segmentectomy / lobectomy and lymphadenectomy. **Result:** All cases were pathologically T2 adenocarcinomas. 3 had pN2 status, and 3 had pN0 status. 3 had EGFR mutation, with adjuvant EGFR-TKI therapy. Recurrence was confirmed in 2 cases; 1) pT2aN2M1a, tumor size 3.5 cm with no EGFR mutation, 2) pT2aN0M1b tumor size 2.5 cm with no EGFR mutation. The median observation period was 14 months (8-31) with 2year recurrence free survival rate of 53.3% and 2year overall survival rate of 66.6%. 2 cases showed a significant decrease of serum CEA post operatively. No pleural effusion was confirmed post operatively among the surviving cases.



Conclusion: Stage IV lung cancer cases with dissemination detected during thoracotomy have tolerable survival rates when combining intraoperative hyper-thermotherapy with distilled water post segmentectomy / lobectomy and lymphadenectomy. Multidisciplinary treatment, including surgery, for Stage IV lung cancer requires further consideration as it has potential for better prognosis.

Keywords: dissemination, Surgery, intraoperative hyper-thermotherapy

P3.16-043 RESECTION AND RECONSTRUCTION OF TRACHEAL CARINA IN LUNG CANCER SURGERY

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Background: Resections of the tracheal carinal have a special place in thoracic surgery, which is determined by the anatomical arrangements in this area, technical difficulties associated with lung ventilation and airway reconstruction. **Method:** 108 operations with carinal sleeve resection were perfomed from 1998 to 2016. Histopathologically : squamous cell carcinoma (80), adenocarcinoma (15), dimorphic cancer (2), carcinoid (4), other forms (7). As for the stages of NSCLC the patients were distributed: IIA -7 (6,7%), IIB – 4 (3,8%), IIIA – 59 (56,2%), IIIB – 33 (31,4%), IV – 2 (1,9%).LN metastases were detected in 64 (61%) patients: N1 lesions in 17 patients, N2 in 45 patients, N3 in 2 patients. Direct invasion of metastatic LN into carina was detected in 13 patients (12%). All patients underwent mediastinal LN dissection, in 8 cases bilateral. Tracheobronchial anastomoses were formed by single nodal sutures using invagination technique,then were perfomed obligatory myoplasty of the anastomosis area.Pneumonectomy with carinal sleeve resection was performed in 82 patients (on the right 77, on the left 5). In 26 cases (24%), organ-preserving interventions were performed: isolated carinal resection or lob(bilob)ectomy with a double-sleeve reconstruction of the carina. In total, 7 different variants of reconstructions of the tracheal carina were performed. In 61 patients (56,5%), resection of other extra-pulmonary structures as simultaneously performed. 66 patients (61%) received combined treatment. **Result:** Postoperative complications occurred in 33% of patients (36), mortality was 10.2% (11). The causes of in-hospital mortality were tracheobronchial anastomotic leakage (5), pneumonia of the single lung (2), arrosive bleeding (1), PE (1), ADHF (1), ARDS (1). Mortality after organ-preserving resections was significantly lower in comparison with carinal pneumonectomy (7.5% vs 12.1%, $p < 0.05$). Preservation of lung parenchyma ensured significantly better quality of life and early rehabilitation in comparison with patients who underwent carinal pneumonectomy. The overall 5-year survival rate was 28.5%, median survival was 24.2 + 2.3 months. In multivariate analysis, the most important prognostic factor was the status of the regional lymph nodes (N). In stages N0-N1, 5-year survival rate significantly prevailed over that in N2-N3 stages (35.1% vs 14.4%, $p < 0.05$). Combined treatment compared with only surgical treatment allowed to improve 5-year results of treatment (38.5% vs. 18.1%, $p < 0.1$). **Conclusion:** Surgery with carinal sleeve resection provide satisfactory results in the treatment of locally advanced lung cancer . Perfection of the technique of carinal "double-sleeve" resections with preservation of the lung parenchyma provides better results in comparison with carinal pneumonectomy.

Keywords: lung cancer, carinal sleeve resection, tracheobronchial anastomosis

P3.16-044 FEASIBLE OUTCOME OF RADICAL EXTENDED SURGERY IN T4 LOCALLY ADVANCED NSCLC; 23-YEAR JAPANESE SINGLE CENTER EXPERIENCE

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Background: T4 NSCLC is sometimes considered as an unresectable disease due to the surgical difficulties and expected poor outcome. Especially, pulmonary resections accompanied with carinal resection and resections under extracorporeal circulation (ECC) have huge surgical invasiveness and risks of postoperative life-threatening complications. On the other hand, in practice, such surgery plays an important role to control disease in highly selected T4 cases. We reviewed our 23-year experience to clarify the benefit and risk of radical extended surgery in T4 locally advanced NSCLC. **Method:** All patients underwent curative-intent radical extended surgery such as pulmonary resection accompanied with carinal resection or resection under ECC for cT4 NSCLC (UICC ver.7) at Fukuoka University, between 1993 and 2016. All relevant data were retrieved from our institutional database and analyzed retrospectively. **Result:** 27 patients were enrolled with a mean age of 57.9±11.2 (35-74) at surgery. 25 patients (92.6%) were male, and only 2 were female. 17 patients underwent pulmonary resection with carinal resection (CR group), 11 underwent pulmonary resection under ECC (ECC group). 1 case required both CR and ECC procedure. As an extent of pulmonary resection, pneumonectomy was performed in 24 patients, lobectomy in 2, and bilobectomy in 1. In CR group, all of 17 patients underwent carinal pneumonectomy (Rt; 12, Lt; 5). In ECC group, reason for ECC use were as follows; resection and reconstruction for descending aorta 6, left atrium 3, aortic arch 1, and pulmonary artery trunk 1. As ECC, cardiopulmonary bypass was used in 5 patients, extracorporeal membrane oxygenation in 6. In this cohort, multimodality approach was indicated only in 10 patients (37%). R0 resection was achieved in 22 patients (81.5%). Regarding pathologic N status, N0 was in 10 patients, N1 in 4, N2 in 12, and N3 in1. Overall survival (OS) in the whole cohort was 62.6% at 1-year, 58.1% at 3-year, 43.6% at 5-year, respectively. OS in CR group was 63.6% at 1-year, 42.4% at 5-year, OS in ECC group was 64.2% at 1-year, 48.1% at 5-year. 30-day mortality was observed in 3 patients (11.1%), in-hospital mortality was observed in 7 (25.9%). No significant difference in surgical and survival outcome was observed between two groups. **Conclusion:** Our long-term results of extended surgery in T4 NSCLC were feasible. Outcome of carinal resection was equal to resection under ECC. However, surgical and short-term outcome could be improved. Individualized approach combined with other modality therapy will be a next step to better short- and long-term outcome.

Keywords: Surgery, Locally advanced NSCLC

P3.16-045 EVALUATION OF THE SAFETY AND EFFICACY OF VATS PNEUMONECTOMY IN THE TREATMENT OF LOCALLY ADVANCED LUNG CANCER

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Background: VATS technique has been increasingly used worldwide for the management of lung cancer[1]. VATS lobectomy has been shown to be superior to traditional open lobectomy with shorter length of stay, fewer perioperative complications and improved quality of life[1]. There remain concerns regarding the use of VATS for larger oncological resections including pneumonectomy and sleeve resections. We add more confirmatory data to several retrospective cohort studies demonstrating the safety of VATS pneumonectomy in selected patients[1,2]. **Method:** With ethics approval, a retrospective cohort study was performed at a single-centre in Melbourne, Australia. It included all patients who had undergone a pneumonectomy between 1999 and 2017. The primary outcome was overall survival. Secondary outcomes included: 30-day and 90-day mortality, disease free survival and length of stay. **Result:** 79 patients underwent pneumonectomy between 1999 and 2017. 27 patients underwent pneumonectomy via VATS approach. There were 76 patients with NSCLC, two with carcinoid and one with melanoma. There was no difference in the tumour size between the two cohorts (VATS median 47mm versus open median 50mm, p=0.12). There was no significance difference in node positive disease between the two cohorts (p=0.14). The 30-day and 90-day mortality rate was 3.8% and 5.1% respectively, with all events occurring in the open cohort. Median overall survival for all patients was 22 months, with a median disease-free survival of 14 months. There was no statistically significant difference in overall survival depending on operative access (median survival VATS 86 months versus open 26.2 months, p=0.12). There was no difference in disease-free survival from NSCLC between the two groups (VATS median 86 months versus open median DFS 15.9 months, p=0.21). The length of stay was shorter in the VATS cohort (7 days versus 8 days, p=0.008). The number of lung cancer cases performed as VATS at our institution has increased from 41% between 2002 and 2011 to 84% since 2014. The rate of VATS pneumonectomy has increased from 18% between 2002 and 2011 to 58.6% since 2014, however this increase lagged three years behind less major resections (i.e. lobectomy). **Conclusion:** In concordance with other recent retrospective cohort studies, our study demonstrates both the safety of VATS pneumonectomy and the oncological efficacy in appropriately selected patients. References: 1. Sahai RK, Nwogu CE, Yendamuri S et al. Is thorascopic pneumonectomy safe? Ann Thorac Surg. 2009;88:1086-1092. 2. Nagai S, Imanishi N, Matsuoka et al. Video-assisted thorascopic pneumonectomy: retrospective outcome analysis of 47 consecutive patients. Ann Thorac Surg. 2014;97(6):1908-1913.

Keywords: VATS, pneumonectomy

P3.16-046 PNEUMONECTOMY AFTER INDUCTION/NEOADJUVANT TREATMENT FOR NSCLC: MORBIDITY, MORTALITY AND LONG-TERM SURVIVAL

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Background: To compare the effects of neoadjuvant/induction chemotherapy or chemoradiation on morbidity, mortality, and long-term survival in patients with locally advanced NSCLC undergoing pneumonectomy. **Method:** All pneumonectomies following neoadjuvant treatment performed for NSCLC between 2000 and 2016 were retrospectively reviewed. The study included 162 patients (28 females; median patient age, 55.4 years [range, 31–73]). Neoadjuvant treatment consisted of chemotherapy in 115 patients (71%, group I) and chemoradiation in 47 patients (29%, group II). Chemotherapy was cisplatin-based, and 2–6 cycles of treatment were completed. Radiotherapy was administered sequentially (dose, 45–60 Gy). Surgery was performed 3–6 weeks after neoadjuvant treatment. Both groups were assessed for 90-day mortality, morbidity, and long-term survival. **Result:** Right pneumonectomy was performed in 60 (37%) patients, and the procedure was completed in a standard manner in 64.2% of the patients. Morbidity was observed in 27.7% of the patients (27,8% in group I; 27.6% in group II,p=0.98). The incidence of bronchopleural fistula was 4.3% (4.2% in group I; 4.3% group II). The 90-days mortality rate was 3.1% (5 patients in group I, 0 in group II,p=0.17). The mortality rates for right and left pneumonectomy were 3.3 (2/60 patients) and 3% (3/102 patients), respectively (p=0.61). The 5-year survival rates were 46.2% in group I and 54.2% in group II, (P = 0.16). **Conclusion:** Pneumonectomy after neoadjuvant chemotherapy or chemoradiation appears to be safe with an acceptable morbidity, mortality, and long-term survival. Chemoradiation did not improve long-term survival compared to chemotherapy despite comparable 90-day mortality and postoperative morbidity.

Keywords: pneumonectomy, mortality, Neoadjuvant treatment

P3.16-047 SALVAGE SURGERY FOR LOCOREGIONAL RECURRENCE OR PERSISTENT RESIDUAL TUMOR AFTER DEFINITIVE CHEMORADIATION THERAPY

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Background: There are few treatment options with curative intent for locoregional recurrence or residual tumor of locally advanced lung cancer after definitive chemoradiation therapy. Lung resection; salvage surgery is likely to be one of the options for local control in this situation. However, perioperative complications and survival benefit of salvage surgery are not well-reported. **Method:** Patients who underwent lung resection after definitive chemoradiation therapy for the treatment of non-small cell lung cancer were selected. Frequency and content of perioperative complications, 5-y overall survival rate and disease free survival rate were retrospectively analyzed. **Result:** A total of 13 patients treated between January 2001 and December 2016 were eligible for evaluation. (12 men and 1 women, mean age 54 years, Median follow-up was 39.7 months.) The indication for surgery was primary tumor regrowth (69%) or tumor persistence (31%). The prior median radiation therapy dose was 60Gy (range 60-77Gy). The indication of for surgery were primary tumor regrowth (8 patients)or tumor persistence(5 patients). All patients underwent an anatomical resection, surgical procedure included lobectomy in 10 patients, pneumonectomy in 2 patients, bilobectomy in 1 patients. 2 patients underwent a bronchoplasty. Median estimated blood loss was 247ml, and median operative duration was 278 min. Compared with anatomical resection we usually perform, salvage surgery needs longer operative duration. Postoperative complications occurred in 4 patients(31%) without perioperative death within 90 days : arrhythmia, delayed pulmonary fistula, acute exacerbation of interstitial pneumonia and empyema. the 5-y overall survival and 5-y recurrence free survival rate were 73.3% and 55.0%,respectively. **Conclusion:** Salvage surgery for locoregional recurrence or residual tumor after definitive chemoradiotherapy was acceptable in safety. It should be considered as a treatment option for selected patients. However, the technique of salvage surgery is complicated, it needs an adequate experience.

Keywords: lung cancer, salvage surgery, chemoradiation

P3.16-048 THE ROLE OF PULMONARY RESECTION IN STAGE IVA NON-SMALL CELL CARCINOMA PATIENTS

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Background: In non-small cell lung cancer (NSCLC), pulmonary resection for stage IV patients was not recommended in standard therapy. However, various new treatments for advanced or recurrence NSCLC patients such as molecular-targeted therapy for driver oncogenes or immune checkpoint therapy have improved the survival of those patients in these days. Therefore, we need to review the role of surgery for advanced NSCLC patients again. **Method:** Clinical records of 334 patient diagnosed stage IV in Shiga University of Medical Science between 2006 and 2015 were reviewed and clinicopatholocgial features and overall survival were analyzed retrospectively. **Result:** 32 patients underwent surgery in this period, and the patients included 25 men and 7 women, with median age of 70.0 years (52-82 years). There were 22 adenocarcinomas, 8 squamous cell carcinomas and 2 other histological subtypes. Surgery included 19 pulmonary resections, 3 spinal fixation surgery, 7 intracranial surgery and 3 other surgery. Median overall survival following surgery or non-surgery was 15.8 month and 9.9 months, respectively (P=0.002). Moreover, in 19 cases of pulmonary resection, there were 7 patients with pleural disseminations (IVa) and 12 patients with distant metastases (IVb). In case with disseminations (IVa), median overall survival was also significantly longer in patients with pulmonary resection than in those of non-operative 31 patients in the same period (42.2 months *vs* 8.3 months, P=0.038). **Conclusion:** Although further study in larger sets of patients would be warranted, surgery should not be excluded from treatment modality for stage IV patients, especially IVa cases if we could selected appropriately.

Keywords: Non-small cell carcinoma, dissemination, pulmonary resection

P3.16-049 SURGERY WITH CONTINUED TKI THERAPY AFTER ACQUIRING RESISTANCE TO EGFR OR ALK TKI

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Background: Lung cancer with ALK or EGFR activation inevitably acquires resistance to respective TKIs despite an initial good response. Relapses with only a limited number of regions, so-called oligo-recurrences, occur in a subset of such patients. Here, we present two cases of lung cancer treated with surgery and continued TKI therapy after acquiring resistance to EGFR or ALK TKI. **Method:** Retrospecive review of patient charts. **Result:** Case1: A 46-year-old man was diagnosed as having ALK-positive adenocarcinoma with pleural dissemination by exploratory thoracotomy. After 2.5 years' treatment with alectinib, the primary tumor in the left lower lobe gradually progressed. Left S6 segmentectomy was performed. Genetic analyses of resected specimens revealed ALK G1202R resistant mutation. Alectinib treatment was resumed after surgery and the patient is free of disease 1.5 year after surgery. Case2: A 65-year-old woman presented with lung cancer with ureteral metastasis. Genetic analyses of resected ureteral tumor revealed EGFR L858R point mutation. Gefitinib was initiated and partial response was observed. After 1 year treatment with gefitinib, right middle lobectomy was performed to resect the remaining tumor. Gefitinib treatment was continued and recurrence-free survival of 2 years was achieved. **Conclusion:** These two patients appear to benefit from surgery and continued TKI therapy after acquiring resistance to EGFR or ALK TKI. It may be one of the treatment strategy in selected patients.

Keywords: EGFR, ALK, oligo-recurrence

P3.16-050 STROMAL PDGFR-B EXPRESSION INFLUENCES POSTOPERATIVE SURVIVAL OF NSCLC PATIENTS RECEIVING PREOPERATIVE CHEMO- OR CHEMO-RADIOTHERAPY

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Background: Platelet-Derived growth factor beta (PDGFR-β) is a functional regulator of mesenchymal cells. It is reported that PDGFR-β is expressed by cancer associated fibroblasts, and PDGFR signaling supports cancer cells. Stromal expression of PDGFR-β is reported to be associated with poor prognosis in prostate, breast, pancreas, and gastric cancers. However, the significance of stromal PDGFR-β expression in non-small cell lung cancer (NSCLC) in patients undergoing preoperative chemo- or chemoradio-therapy had not been undetermined. **Method:** Seventy-two patients with NSCLC undergoing preoperative chemo- or chemoradio-therapy between 1996 and 2006 were assessed for expression of stromal PDGFR-β by immunohistochemistry using resected specimens. After cancer cells and stromal tissues were identified by HE staining, stromal PDGFR-β expression was defined as positive when it was observed in >5% of the stromal area. Relationships between stromal PDGFR-β expression and disease-free survival (DFS) and disease-specific survival (DSS) were analyzed. **Result:** The mean age of the 72 patients was 59.7 years. Sixty-one (85%) were male and 11 (15%) female. Forty patients (56%) underwent preoperative chemoradiotherapy and 32 patients (44%) underwent preoperative chemothearapy. Indications for preoperative chemotherapy were N2 disease in 51 (71%), T3 or T4 disease in 20 (28%), and other reasons in the remaining patient (1%). Regimens for preoperative chemotherapy were cisplatin (CDDP)-based in 34 patients (47%) and carboplatin (CBDCA)-based in 37 (52%). Type of resection were pneumonectomy in 7 (10%), bilobectomy in 6 (8%), lobectomy in 57 (79%), and sublobar resection in 2 (3%) patients. Complete resection were achieved in 59 patients (82%). The pathologic stage (7th ed.) was IA in 11 (15%), IB in 12 (17%), IIA in 6 (8%), IIB in14 (19%), IIIA in 19 (27%), IIIB in 5 (7%), and IV in 5 (7%) patients. The histological type were adenocarcinoma in 32 (44%), squamous cell carcinoma in 35 (49%), and others in 5 (7%) patients. On immunohitological examination, stromal cells expressed PDGFR-β in 47 cases (65%). Five-year DFS and DSS in the stromal PDGFR-β-positive group was significantly worse than in the negative group (29.1%-vs-64.6%, p=0.01 and 40.2%-vs-66.1%, p=0.02, respectively). **Conclusion:** Stromal PDGFR-β expression is negatively associated with DFS and DSS in patients with NSCLC undergoing preoperative chemo- or chemoradio-therapy.

Keywords: Surgery, lung cancer, chemotherapy

P3.16-051 IMPLICATIONS OF PREOPERATIVE SERUM TUMOR LEVELS ON PATHOLOGICAL CHARACTERISTICS IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: Although preoperative serum tumor marker levels, such as carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC) are often evaluated in non-small cell lung cancer patients, the implication of these levels are still unknown. This study examined the predictive effect of preoperative tumor marker levels on pathological characteristics of lung adenocarcinoma. **Method:** We retrospectively reviewed patients with lung adenocarcinoma who underwent macroscopic complete resection. The pathological metastasis and/or involvement was defined that positive pleural effusion or lavage cytology, 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, tumor markers (CEA, SCC, Sialyl Lewis^x-1 [SLX], cytokeratin-19 fragments [CYFRA], neuron-specific enolase [NSE], and pro-gastrin-releasing peptide [ProGRP]), and demographic and clinical factors were analyzed by a univariate analysis and multivariate logistic regression analysis. For the significant tumor markers, optimal cutoff points were determined with a receiver operating characteristic analysis. **Result:** Of the 263 eligible patients, 138 were male and 125 were female. The median age was 70 years. The median preoperative CEA, SCC, SLX, CYFRA, NSE, and ProGRP levels were 3.7 ng/ml,0.8 ng/ml,28 U/ml,1.8 ng/ml,8.4 ng/ml,and 46.9 pg/ml, respectively. According to the 7th edition of the TNM classification, 186 patients (71%) had c-stage IA disease, 48 (18%) had c-stage IB disease, 26 (10%) had c-stage II disease, and 3 (1%) had c-stage III disease. Positive pleural effusion, positive pleural lavage cytology, pleural involvement, pulmonary metastasis, lymph node metastasis, lymphatic permeation, and vascular invasion were identified in 3 (1%), 4 (2%), 48 (18%), 9 (3%), 28 (11%), 20 (8%), and 35 patients (13%), respectively, and in total, 83 patients (32%) developed the pathological metastasis and/or involvement. The univariate analysis identified CEA, smoking index, size, solid size, and c-stage as significant predictors. A multivariate analysis revealed CEA (OR: 1.113, p=0.005) and solid size (OR: 1.052, p<0.001) as significant predictors. The optimal cutoff point was determined as 6.0 ng/ml for the preoperative CEA, and 35 of the 63 patients (56%) with ≥6.0 ng/ml of CEA developed the pathological metastasis and/or involvement whereas 48 of the 200 patients (24%) with <6.0 ng/ml of CEA developed pathological metastasis and/or involvement. **Conclusion:** Our results suggested the predictive effect of the high preoperative CEA level on pathological metastasis and involvement in patients with lung adenocarcinoma, and thus, we may consider preoperative CEA to decide surgical procedure for these patients, such as the extent of pulmonary resection and lymphadenectomy.

Keywords: tumor marker, Adenocarcinoma, carcinoembryonic antigen

P3.16-052 USE OF DECELLULARISED PORCINE INTESTINAL SUBMUCOSA EXTRACELLULAR MATRIX IN AIRWAY RECONSTRUCTION TO ENABLE LUNG-SPARING ONCOLOGICAL SURGERY

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Background: Reconstruction of the airways following tracheal resection, tracheo-oesophageal complications and lung-sparing oncological surgery is challenging. Airway reconstruction materials ideally must possess balanced properties of rigidity, flexibility and have an intact surface of epithelium to maintain a functional airway. A novel approach is the use of bio-scaffolds which allow regeneration of respiratory epithelium and eliminate the need for immunosuppressive treatment. Initial experiences with decellularised porcine small intestine submucosa extracellular matrix (CorMatrix®) as a scaffold for vascular, cardiac and pericardial tissue repair and reconstruction has been encouraging. The properties of extracellular matrix are potentially suitable for airway reconstruction. **Method:** We initially used the bio-scaffold for repairing tracheal defects and tracheo-oesophageal fistulae (n=6). We then extended its use to reconstruct distal airways to facilitate lung-sparing oncologic resections of intermediate grade lung tumours (n=3). These patients would otherwise have required pneumonectomy (Case 1 and 2) or bi-lobectomy in a patient with borderline lung function (Case 3). We describe our experience using extracellular matrix for airway reconstruction in lung-sparing oncological surgery. **Result:** Three patients underwent complex sleeve resections with varying degrees of bronchial airway reconstruction using extracellular matrix. The lung tumours were: (1) muco-epidermoid tumour of the left upper lobe and left main bronchus; (2) typical carcinoid of the right main bronchus; (3) typical carcinoid of the intermediate bronchus and right middle lobe. All patients underwent frozen section pathology examination at the time of surgery and formal histology confirmed pT1N0 and R0 resection status. There were no perioperative complications. All patients underwent bronchoscopy prior to discharge and serial bronchoscopies were carried out 6 weeks, 3 months and at >1 year. All patients had complete integration of the scaffold by epithelialisation and the patch was not evident at 3 months. All segmental bronchi were widely patent. At 18 months there was no tumour recurrence. **Conclusion:** The use of decellularised porcine intestinal submucosa extracellular matrix (CorMatrix®) as a bio-scaffold is safe and shows remarkable epithelialisation and integrity. It is an option for airway reconstruction to facilitate lung-sparing surgery without compromising oncologic margins.

Keywords: oncological surgery, airway reconstruction, extracellular matrix

P3.16-053 GENOMIC CHALLENGES FOR LUNG CANCERS WITH MULTIPLE PULMONARY SITES OF INVOLVEMENT

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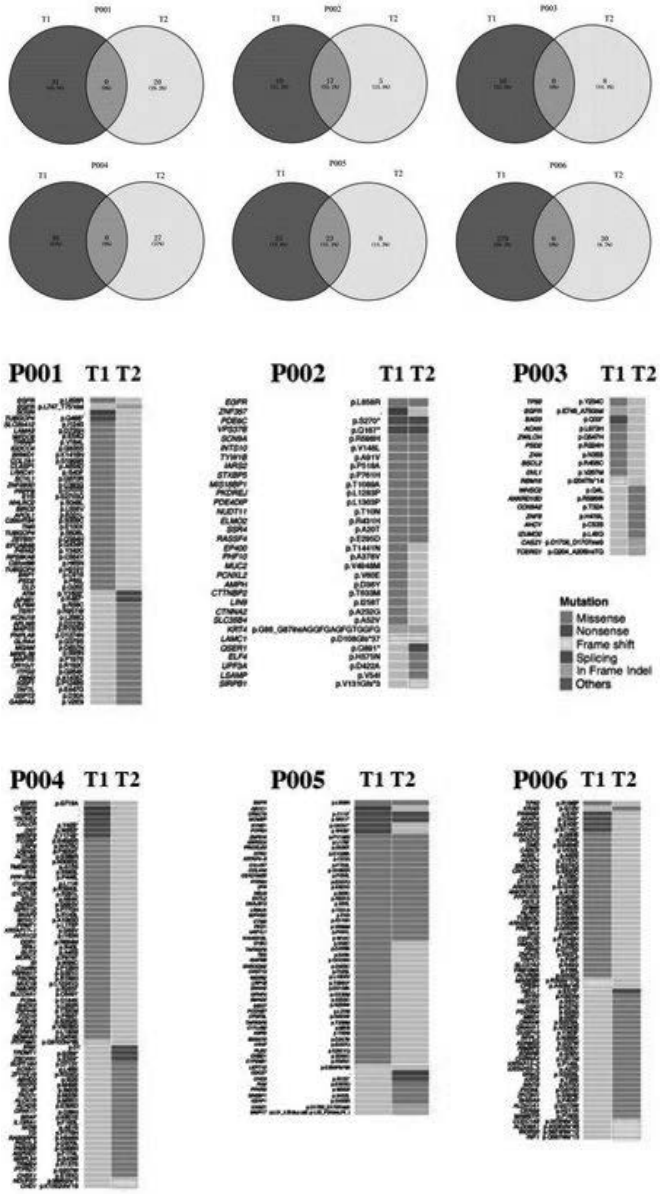
Background: Patients with lung cancer who harbor multiple pulmonary sites of disease have been challenging to classify. Although the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee propose to tailor TNM classification of multiple pulmonary sites of lung cancer to reflect the unique aspects of four different patterns of presentation, tough challenges faced by clinicians are still not easily overcome. **Method:** Surgical tumor and normal tissue specimens were collected from six patients who were diagnosed with pathologically confirmed multiple lung cancers, with each tumor in the separate lobe, and treated at Beijing Cancer Hospital, Peking University, Beijing, China. Whole-exome sequencing was used to depict the genomic profiles of each tumor, and the average sequencing depth was 123× per sample (range, 84× to 154×; s.d., 19×). **Result:** In this study, we analyzed genomic profiles of 12 tumors from 6 patients with multiple lung cancers. Eight tumors from 4 patients demonstrated distinct genomic profiles, suggesting all were independent primary tumors, which were consistent with comprehensive histopathological assessment. Noteworthy common genomic characteristics were seen in 4 tumors from 2 patients. Compared with TCGA lung cancer cohort, one out of 6 patients carried significantly higher somatic nonsynonymous mutational burden, which were also discrepant between two separate lesions.



Conclusion: The current findings suggest that the tailor TNM classification of multiple pulmonary sites of lung cancer still encounter real-world challenges. A deeper understanding of the spatial and temporal dynamics of the carcinogenesis and evolution of lung cancer will be required to address these challenges.

Keywords: lung cancer, genomic, Whole exome sequencing

P3.17-001 THE PROGNOSTIC ANALYSIS OF POSTOPERATIVE RADIOTHERAPY FOR ESOPHAGEAL SQUAMOUS CELL CARCINOMA WITH DIFFERENT STATUS OF LYMPH NODE METASTASIS

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Background: Lymph node metastasis is a significant prognostic factor in patients with resected esophageal cancer. Although the role of postoperative radiotherapy has not been confirmed, a large number of studies have shown that postoperative radiotherapy can improve the local control and survival, especially for stage III and lymph node positive patients. This study retrospectively analyzed the prognostic factors of postoperative radiotherapy for locally advanced esophageal squamous cell carcinoma (ESCC), and evaluated the prognostic value of different status of lymph node metastasis. **Method:** Data from 121 patients with locally advanced ESCC who underwent radical resection and received postoperative radiotherapy from 2006 to 2013 were reviewed retrospectively. OS and DFS were estimated using Kaplan-Meier. Univariate analysis and multivariate analysis were performed to investigate prognostic factors by the Log-rank test and the Cox regression model. The effects

of different status of lymph node metastasis on OS and recurrence patterns were compared. **Result:** The median DFS of all patients was 22.57 months, and median OS was 32.90 months. Multivariate analysis showed that Karnofsky Performance Status, length of tumor and positive lymph nodes ratio (LNR) were independent prognostic factors of DFS and OS. For patients with lymph nodes metastasis, LNR has better prognostic value for OS (AUC=0.673, *P*=0.04) compared with the number of positive lymph nodes (AUC=0.584 *P*=0.31). The median OS of patients with LNR≤ 15% and LNR>15% were 33.43 and 19.20 months, *P*=0.04. Patients without lymph node skip metastasis (NSM) had better OS than that with NSM, but the difference was not statistically significant. Among the patients with both LNR>15% and NSM, OS was significantly worse than other lymph node positive patients, with median OS of 14.33 vs. 32.50 months, P=0.02. The analysis of the treatment failure patterns showed that more distant metastases were observed in patients with LNR>15%, while more local and regional recurrences were observed with LNR≤ 15%. **Conclusion:** The status of lymph node metastasis was related to the prognosis of postoperative radiotherapy for locally advanced ESCC. LNR has better prognostic value for OS, treatment failure patterns varied in different LNR. The patients with both high LNR and NSM have significantly poorer prognosis.

Keywords: Esophageal squamous cell carcinoma, postoperative radiotherapy, lymph node metastasis

P3.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.17-002 COMPARISON OF SINGLE- AND MULTI-INCISION MINIMALLY INVASIVE ESOPHAGECTOMY FOR TREATING ESOPHAGEAL CANCER: A PROPENSITY-MATCHED STUDY

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Background: To compare the perioperative outcome of minimally invasive (MIE) esophagectomy performed with a single- or a multi-incision in treating esophageal cancer. **Method:** Patients with esophageal cancer who underwent MIE from 2006 to 2016 were evaluated. A 3–4-cm incision was created in both the thoracoscopic and the laparoscopic phases during the single-incision MIE procedures. A propensity-matched comparison was made between the two groups of patients. **Result:** We analyzed a total of 48 pairs of patients with propensity-matched from the cohort of 360 patients undergoing MIE during 2006–2015. There is no statistical difference in terms of postoperative ICU and hospital stay, number of dissected lymph nodes and presence of major surgical complications (anastomotic leakage and pulmonary complications) between the two groups of patients. The pain score one week after surgery was significantly lower in the single-incision group ($p < 0.05$). There was no surgical mortality in the single-incision MIE group. **Conclusion:** Minimally invasive esophagectomy performed with a single-incision approach is feasible for treating patients with esophageal cancer, with a comparable perioperative outcome with that of multi-incision approaches. The postoperative pain one week after surgery was significantly reduced in patients undergoing single-incision MIE.

Keywords: Single incision, Multiple incisions, Minimally invasive esophagectomy

P3.17: THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES - WEDNESDAY, OCTOBER 18, 2017 - 09:30-16:00

P3.17-003 A SELECTIVE SMALL MOLECULE INHIBITOR OF C-MET KINASE, BPI-9016M, HAS SYNERGISTIC EFFECTS WITH RADIATION ON ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Background: c-Met is overexpressed in cancer cells and plays a crucial role in apoptosis evasion. BPI-9016M, a small-molecule inhibitor of c-Met, could enhance the cytotoxicity of various DNA-damaging agents and promote the cell apoptosis. Here, we evaluated the radiosensitizaion potential of BPI-9016M in Eca109 human esophageal squamous cell carcinoma (ESCC) cell line. **Method:** Cell viability was determined by CCK8 assay. The radiosensitization effect of BPI-9016M was evaluated by clonogenic survival and progression of tumor xenograft. Cell apoptosis were determined by flow cytometric analysis and TUNAL. Cell apoptosis regulators were detected by western blot analysis. Radiation-induced DNA double strand break (DSB) and homologous recombination repair (HRR) were detected by the activation of ATR-Chk 1/ATM-Chk2 pathways. **Result:** BPI-9016M induced radiosensitization in Eca109 cell of ESCC cell line, associated with 1) down-regulating mutation P53 and Bcl-2; 2) decreases phosphorylated ATR and ATM focus formation, and the expression of γ-H2AX; 3) up-regulates the rate of cell apoptosis protein cleaved-Caspase(Figure 1). The combination of BPI-9016M with irradiation delayed the growth of ESCC tumor xenograft to a greater extent compared with either treatment modality alone ($P < 0.05$). Figure 1. BPI-9016M enhanced radiation induced apoptosis and inhibited ATM- and ATR-dependent DNA damage homologous recombination repair (HRR) pathways analyzed by western blot. **Conclusion:** Our findings suggest that the enhanced apoptosis and the inhibition of HRR contribute to radiosensitization by c-Met inhibitor BPI-9016M in ESCC cell.

Keywords: c-Met, ESCC, radiosensitivity

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PUB001 EPID-BASED IN VIVO DOSIMETRY FOR ACCURATE DELIVERY OF LUNG STEREOTACTIC RADIOTHERAPY USING BREATH-HOLD SEGMENTED VMAT

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Background: In vivo dosimetry (IVD), a direct method of measuring radiation doses to cancer patients during treatment, has shown unique features to trace deviations between planned and actually delivered dose distributions. Lung stereotactic ablative radiotherapy (SBRT) involves the delivery of high doses in a few fractions for ablative purposes. Then SBRT treatments strongly benefit from IVD procedures, as any uncertainties in dose delivery is more detrimental for treatment goals. We assessed the feasibility of EPID-based IVD for clinical lung SBRT treatments using VMAT technique. **Method:** 8 patients with lung metastases treated with Elekta VMAT were enrolled. Dose prescription was 50Gy in 5 fractions. Patients were simulated and treated using the Active Breath Coordinator (Elekta), a spirometer enabling a temporary controlled interruption of patient breathing at the end of inspiration phase. VMAT plans were generated with Ergo++ TPS with a single 360° arc; the VMAT delivery sequence was divided into multiple subarcs according to the patient predefined breath-hold periods. IVD was performed using SOFTDISO software (Best Medical Italy). IVD tests were evaluate by means of (i) R ratio between isocenter daily in-vivo dose and planned dose and (ii) g-analysis between EPID integral images in terms of percentage of points with g-value smaller than one (g%) and mean g-values (gmean), using a global 3%-3 mm criteria. Alert criteria of ±5% for R ratio, g% <90% and gmean > 0.67 were chosen., the last two in order to accept only 10% of the values to exceed 3%/3mm and an average discrepancy of the order of 2%/2mm, respectively. **Result:** A total of 40 transit EPID images were acquired. Two images (5%) were removed from analysis for image deterioration and/or electronic acquisition failures. The overall mean R ratio was equal to 0.999 ± 0.021 (1 SD) for all patients, with more than 98% of tests within 5% alert criteria. The 2D portal images g-analysis show an overall gmean of 0.29±0.13 with 100% of tests within alert criteria, and a mean g% equal to 97.9±3.2% with 100.0% of tests within alert criteria. The results are supplied in quasi real-time, with IVD tests performed and displayed after only 1 minute from the end of arc delivery. **Conclusion:** Our results showed that the integration of ABC multi-segmented breath-hold control into the VMAT-SBRT delivery strategy translated in high reproducibility treatments.

Keywords: SBRT, In-vivo dosimetry, Breath-hold

PUB002 NIVOLUMAB IN SECOND-LINE TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER WITH SQUAMOUS CELL HISTOLOGY: A COST-EFFECTIVE CHOICE

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Background: The introduction of active new agents, such as nivolumab, for the second-line treatment of advanced non-small cell lung cancer (NSCLC) with squamous cell histologyis associated with a relevant increase of costs and it is therefore important to make a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest such as progression free survival (PFS) and overall survival (OS). **Method:** The analysis was conducted to assess the effect of front-line chemotherapy on the PFS and OS on each arm of the evaluated trials. Only phase III randomized controlled trials (RCTs) were considered. We calculated the pharmacological costs necessary to get the benefit in PFS and OS, for each trial. We have also applied the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to the above pivotal phase III RCTs **Result:** We evaluated the 2 pivotal phase III RCTs, including 815 patients. The application of ESMO-MCBS reached high scores for the two pivotal phase III RCTs (grade 5for Brahmer et alTrial and grade 4for Broghaei et alTrial). Concerning both PFS and OS, the most relevant increase of costs was associated with the use of nivolumab, with the highest costs for month of PFS-gained (31 294 €), but with the lowest cost for month of OS-gain (from 5856 € to 6846 €) . **Conclusion:** Combining pharmacological costs of drugs with the measure of efficacy represented by the OS, nivolumab is a cost-effective second-line treatment for patients with advanced NSCLC with squamous cell histology. The lack of correlation between PFS and OS is a well known phenomenon with the clinical use of check point inhibitors and reinforces the importance of the evaluation of OS as a strong end-point, even on a pharmaco-economic perspective.

Keywords: squamous cell histology, Advanced Non-Small Cell Lung Cancer, Nivolumab

PUB003 METASTASES IN T1-T2 CLASSED LUNG CANCER

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Background: Lung cancer is the first cancer responsible for metastases. They can be either intra-or extra-thoracic. Their diagnosis when the cancer is locally non-advanced modifies completely the treatment. The aim of this work is to find out variables influencing metastases occurrence in T1-T2 classed lung cancer. **Method:** Retrospective review of data of 63 patients (60 males and 3 females) with confirmed lung cancer, which were classed T1 or T2 according to the TNM 7 in the work up of their disease and who were explored in the imaging department of our institution between January 2011 and December 2016. Patients were subdivided into two groups: with or without metastases. The variables tested to find out a relationship with metastases occurrence were age, T1 or T2 status, N status and histological type of the cancer. A significant statistical relationship was retained when p was ≤0.05. **Result:** The mean age of the included patients was 61 years (ranging between 43 and 73 years). Adenocarcinoma was the most common histological type (71%). Twenty seven patients (43%) had metastases; 21 of them (77%) had extra-thoracic ones. Comparing patients with and without metastases, no significant relationship was found between the T1 or T2 stage (p= 0.147), the age (p=0.745) and metastases occurrence. In the opposite, they were statistically related to N2-N3 lymph nodes stage (p=0.032) and to adenocarcinoma (p=0.006). **Conclusion:** Metastases are quite frequent in T1-T2 classed lung cancer. Their occurrence was related to the N stage and to the adenocarcinoma.

Keywords: lung cancer, Metastases, T1- T2

PUB004 INHIBITION OF IPLA$_2$ REGULATES E2F3 PATHWAY AND CELL CYCLE CHECKPOINTS TO INDUCE APOPTOSIS IN NON-SMALL CELL LUNG CANCER CELLS

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Background: In India, around 556400 people died of cancer in 2010, according to estimates published in *The Lancet* (Dikshit *et al.,* 2012). According to GLOBOCAN, 2015 estimated 1,514,000 number of new cancer cases in South Central Asia. Lung cancer is the leading cause of cancer death among males in both more and less developed countries (Torre *et al.,* 2015). The E2F3 is believed to have an essential role in the control of cellular proliferation by regulating the transcription of genes involved in cell cycle progression, cell cycle re-entry and tumor development. iPLA$_2$ are reported to play a significant role in cancer cell growth and possibly carcinogenesis. Expression of these enzymes has been noted in several types of cancer cells including pancreatic, kidney, and brain. Additionally, other groups have shown strong statistical associations between iPLA$_2$ over expressing haplotypes and the initiation of colon cancer in humans. Human lung adenocarcinoma epithelial cells (A549) were transfected with E2F3 siRNA and/or treated with the bromoenol lactone (BEL). **Method:** Cell viability was determined by MTT assay. Cell proliferation was determined by BrdU incorporation assay. Apoptosis was detected by cell morphologic observation through AO/EtBr staining and DAPI, cell cycle analysis, and immunoblot analysis on the expression of protein associated with cell cycle arrest. To investigate the effect of the blocking of the endogenous E2F3 in lung cancer cells, we used small interfering RNA (siRNA) against E2F3 alone or in combination with BEL for inhibition of iPLA$_2$, and expected that the cell sensitivity to BEL would increase, when blocked with the E2F3 and iPLA$_2$ gene and treated with E2F3 siRNA and BEL. **Result:** We demonstrated that the targeted inactivation of E2F3 with BEL treated results in elevated p27^{kip1}, p21^{WAF1}, p16^{INK4A} and p14^{ARF} protein levels, loss of E2F3 and MDM2 target gene expression. The lung cancer cells treated with BEL alone without inactivation of E2F3 gene results in elevated p27^{kip1}, p16^{INK4A} and p14^{ARF} but not p21^{WAF1} protein levels, loss of iPAL$_2$ target gene expression. P53 gene express invariably in both E2F3 siRNA and BEL treated lung cancer cells. E2F3 knockdown by siRNA further decreases the cell growth of lung cancer cells that are treated with BEL alone, confirming that single agent drug targeting does not achieve a maximal biological effect. **Conclusion:** The combination of a potent, irreversible iPLA2 inhibitor such as BEL, with E2F3-specific siRNAs should be further investigated as a new strategy in the treatment of lung cancer

PUB005 CT FINDINGS REDUCE THE RISK OF EBUS-TBNA

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Background: Endbronchial ultrasound guided-trans-bronchial needle aspiration is useful methods for the diagnosis of lung cancer and benign disease. In EBUS-TBNA, we should pay attention for complication and fail. Mediastinitis is a sever complication by EBUS-TBNA. Some reports were paid attention to necrosis findings by EBUS, for example coagulation necrosis sign, heterogeneous echogenicity, and blood poor

finding. And then, we couldn't collect lesion with EBUS-TBNA, because of size and bronchus artery. We should avoid bronchus artery. If bronchus artery was punctured, Bleeding was failed sampling. **Method:** In this study, we revealed CT finding is enhanced LN size and necrosis. 43 lesions were enrolled retrospectively from Jan 2015 to May 2017. **Result:** Malignancy were 23. In CT finding, aspiration axis's means were 34.4±12.3 mm. In plain CT, low intensity area was detected 36.6% (14/43). In enhanced CT, low density area was detected 47.2% (17/36). CT size was enhanced EBUS size (r2=0.45, p<0.001). Indeed, we avoided sampling for 10mm or less in EBUS. CT low density area wasn't enhanced EBUS necrosis sign's. These CT findings were low sensitivity and specificity. We avoided sampling from necrosis leions in EBUS. **Conclusion:** CT size were enhanced EBUS sampling axis diametter. However, CT low density area wasn't reflect necrosis finding in EBUS.

Keywords: EBUS-TBNA, CT, bronchoscopy

PUB006 THE LEVEL OF PROGRAMMED CELL DEATH LIGAND 1 (PD-L1) COULD PREDICT SURVIVAL OF PATIENTS WITH RESECTABLE SMALL CELL LUNG CANCER

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Background: Programmed cell death ligand 1 (PD-L1) expression has recently been associated with survival of patients with malignance. Given faint results of PD-L1 expression and survival, we evaluated PD-L1 expression patterns and clinical outcomes in patients with small cell lung cancer (SCLC) who underwent complete resection. **Method:** PD-L1 immunohistochemistry was performed with the rabbit monoclonal antibody (M4424, Spring Bioscience, CA) on resection specimens from patients with complete resectable SCLC. Membranous expression of PD-L1 in 5% tumor cells was defined as positive (+). **Result:** Between January 2009 and December 2011, a total of 61 patients were collected to detect PD-L1 expression. Among of them, 26 (42.6%) patients expressed PD-L1 less than 1%, 23 (37.7%) patients and 13 (21.3%) patients expressed PD-L1 equal to or greater than 5% and 10%, respectively. For PD-L1 (+) patients, 47.8% (11/23) was in T2 patients, while 43.5% (10/23) in N0, 52.2% (12/23) in pathological stage I-II. For entire group, the median survival time (MST) was not reached (range, 6 - 89 months), and 1-, 3- and 5-year survival rates were 90.0%, 57.3% and 54.2%, respectively. The survival in PD-L1 (+) patients was significant longer than that of PD-L1 (-) patients (MST: not reached vs. 34 months, $p = 0.032$). The 3-year survival rate was 72.3% in PD-L1 (+) patients, which was higher than 47.5% in PD-L1 (-) patients. The MST and 3-, 5-year survival rates were similar between PD-L1 (+) and PD-L1 (-) patients regardless of the definition of PD-L1 positivity was PD-L1 expression in ≥ 1% or ≥ 10% tumor cells. Multivariate analysis revealed that postoperative chemotherapy (HR = 0.322, $p = 0.023$) and PD-L1 expression (HR = 0.253, $p = 0.008$) were positively independent prognostic factors for OS. **Conclusion:** PD-L1 highly expresses and plays a positive role on the prognosis of patients with resectable SCLC.

Keywords: PD-L1, SCLC, overall survival

PUB007 SCREENING AND VALIDATION OF LUNG ADENOCARCINOMA RELATED LONG NON-CODING RNA BASED ON PROFILING MICROARRAY

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Background: A large number of long noncoding RNAs (lncRNAs) have been found to be implicated in varieties of tumors. However, the contributions of lncRNAs to tumorigenesis in lung adenocarcinoma (LAD) remain largely unknown. We performed a genome-wide analysis of lncRNA expression in LAD and matched nontumor (NT) tissues to identify new targets for further study of renal carcinoma. **Method:** The genome-wide analysis of lncRNA expression in 3 LAD and matched NT tissues were conducted using 4×180K Agilent lncRNA Chips and 6 lncRNAs were selected and validated by qRT-PCR in 90 LAD patients. The differentially expressed lncRNAs and mRNAs were recognized through P value and fold-change (FC) filtering. Potential targets associated with LAD were identified by gene ontology and pathway analyses. Construction of the co-expression network was accomplished using Cytoscape. **Result:** A total of 460 lncRNAs and 771 mRNAs were deregulated and 134 lncRNAs and 466 mRNAs were upregulated in LAD tissues, compared with paired NT tissues. PCR results showed the expressions of these 6 lncRNAs were consistent with the chips. Moreover, the co-expression network analysis portended 641 nodes and 571 connections between 109 lncRNAs and 532 coding genes. Lastly, LINC00578 could be involved in the pathogenesis of LAD and its expression level was closely related to disease-free survival (DFS) and overall survival (OS) in patients without distant metastasis. **Conclusion:** Our results indicated that these abnormal lncRNAs could respond to lung carcinoma progression and LINC00578 may act as a potential target for future treatment of LAD.

Keywords: Lung Adenocarcinoma; LINC00578; Nuclear factor-kappa B (NF-κB), Long non-coding RNA; Microarray

PUB008 SUCCESSFUL TREATMENT WITH APATINIB PLUS HUMAN ENDOSTATIN FOR REFRACTORY RECURRENT ADVANCED PULMONARY CARCINOSARCOMA: A CASE REPORT

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Background: Primary pulmonary carcinosarcoma composed of a mixture of carcinoma and sarcoma elements is exceedingly rare. Advanced pulmonary carcinosarcoma is associated with a poor prognosis. This study aimed to review the efficacy and safety of Apatinib combined with recombinant human endostatin in patients with advanced pulmonary carcinosarcoma who failed in the second-line chemotherapy. **Method:** A 53-year-old male was diagnosed with recurrent pulmonary carcinosarcoma and failed in the prior chemotherapy (including first-line chemotherapy: epirubicin plus ifosfamide, and second-line chemotherapy: gemcitabine plus cisplatin). The patient was treated with oral apatinib and intravenous injection human endostatin. Apatinib was administered at a dose of 500mg/d P.O, while continuous intravenous pump of 30mg/d human endostatin was given for 7 days, with 4 weeks in a cycle. **Result:** The patient achieved partial response evaluated by Chest computerized tomography (CT) after 4 weeks medication and had an progression-free-survival of 24 weeks. The common side effects related to treatment was hand-foot syndrome and hypertension; however, the toxicity of apatinib plus human endostatin was controllable and tolerable. **Conclusion:** The preliminary results of this case indicate that apatinib plus human endostatin has outstanding efficacy for refractory primary pulmonary carcinosarcoma, but this still warrants further investigation.

Keywords: Recombinant human endostatin, Apatinib

PUB009 CSO'S ROLE IN SAVING LIVES FROM TOBACCO USE IN ASEAN

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Background: Since non-communicable diseases (NCDs) were ignored in Millennium Development Goals (MDGs), it is very important to make it as the priority in post 2015. NCDs are the majority cause of deaths in ASEAN region. With the soaring burden of NCDs, tobacco control is the single 100% preventable factor which contributes to all NCDs in both developed and developing countries. Therefore, it is crucial to make sure that governments understand the importance of role of civil society organization in saving the lives of ASEANers. Southeast Asia Tobacco Control Alliance is a multi-sectoral alliance established to support ASEAN countries in developing and putting in place effective tobacco control policies. Our vision is to lead towards a healthy, tobacco free ASEAN. Tobacco control measures need comprehensive strategies and innovative approach to deal with fast growing tobacco industry in ASEAN. To be able to do that, financing is a major problem in many countries especially in low and middle income countries where human resource and funding are very limited. Civil society organization's role is to advocate policy makers with evidences for evidence based policy making in countries. To prevent the upcoming deaths due to tobacco consumption in ASEAN countries, it is very important for different organizations such as government organizations, UN agencies and civil society organizations to work together. Our role in protecting the lives of the people in ASEAN is through collaboration, establishing and encouraging multi-sectoral involvement, networking, coordination among ASEAN countries to share best practices, in-time technical assistant for countering tobacco industry attacks in ASEAN countries and providing the knowledge hub. **Method:** Section not applicable **Result:** Section not applicable **Conclusion:** As a result of civil society organization like SEATCA, there are many smoke free cities and smoke free heritage sites in ASEAN. ASEAN region also has a regional network for smoke free cities to prevent citizens who are suffering from secondhand smoke. Different policies such as smoke free law, regulations on pictorial health warning, ban on advertising are also developed in ASEAN countries as a result of country leadership with assistant from civil society organization. Therefore, civil society plays an important in saving lives of people in ASEAN to reduce the burden of disease and deaths which will lead to productivity loss and economic impact in ASEAN region.

Keywords: tobacco control, advocacy, multi-sectoral collaboration

PUB010 RESULTS AFTER INTERDISCIPLINARY MANAGEMENT OF 5 PATIENTS WITH ASKIN TUMOR

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Background: Askin tumors are rare but highly malignant chest wall tumors, which require multimodal therapy including often extensive resection of the thoracic wall. This study evaluated the outcomes of Askin tumor in five patients; imaging features and surgical results were reviewed to improve knowledge of the disease with an interdisciplinary approach. **Method:** Patients' records, treated between 2008 and 2017, were reviewed retrospectively. Five patients (three male, two female; mean age 21.3 years; range 17-56 years) were included. All patients received neoadjuvant chemotherapy. After reduction of initial tumor volume, radical tumor resection and thoracic wall reconstruction were performed. All survivors were evaluated in 2016

by clinical examination and lung function test. **Result:** Five-year survival rate in our group of patients is 60 %. There were two mortalities. Two patient passed away 4 years after the primary management, mainly attributed to tumor progression, which demanded aggressive surgical procedures and irradiation. Another patient died 18 months after the first diagnosis after several surgical interventions for recurrent multiple pulmonary metastases. Three years after the first diagnosis, one patient suffered from local recurrence of Askin. The large chest wall defects arising after surgery have been successfully reconstructed using combination of latissimus dorsi muscle flaps and biomaterials. **Conclusion:** Data of patients with Askin tumor is scarce. Analysis of our five patient series indicates that improved outcomes can be achieved by aggressive interdisciplinary management including radical surgery and chemotherapy. Chest wall stability can be achieved by utilization of local muscle flaps and biomaterials to cover surgical chest wall defects.

PUB011 AN ASSESSMENT OF ORAL HEALTH STATUS, TOBACCO USE AND CANCER AWARENESS AMONG TEA PLANTATION WORKERS (IRULA TRIBES), NILGIRI HILLS, INDIA

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Background: Tea is an important agro-industry of India, which contributes immensely to the countries economy. Tea garden population constitutes approximately 1/12th of tea growing state's population. Poor socio-economic conditions, ignorance due to illiteracy, over-crowded and unhygienic living conditions in the residential colonies make tea garden population vulnerable to various communicable diseases and malnutrition. Hence this study was contemplated with an aim to assess the oral health status, tobacco use and cancer awareness among tea plantation workers, Nilgiri Hills, Tamil Nadu, India. **Method:** A cross-sectional descriptive study was conducted to assess the tobacco use and cancer awareness among tea plantation workers, Nilgiri Hills.Data was collected using a pretested Questionnaire, which included Demographic data, tobacco habits, its frequency and form. The data collected was analysed using SPSS version15. **Result:** .Results showed that among 900 study population, showed 57% had no formal education, 34.5% had not visited dentist before. 64.5% had indigenous brushing habits. 52% of oral mucosal lesions and 6% malignant oral tumors were observed. A very high prevalence of periodontal disease, tobacco chewing, deep rooted beliefs and customs regarding dentition and dental treatment was observed in this community. Prevalence of oral mucosal lesions in the study population was due to tobacco usage and lack of awareness regarding the deleterious effects of the products used. **Conclusion:** The dangers from smoking and chewing tobacco are well documented within the literature but the public's lack of knowledge of the risks is a concern. Health professionals are encouraged to ensure that the public is made aware of these risks, especially those within high-risk groups.

PUB012 QUANTITATIVE ANALYSIS OF CTDNA DIFFERENTIATES NECESSITY FOR REPEAT BIOPSY IN NSCLC PATIENTS DEVELOPED EGFR-TKI RESISTANCE

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Background: Circulating tumor DNA (ctDNA) testing could serve as a non-invasive alternative to guide subsequent treatment post EGFR tyrosine kinase inhibitor (TKI) resistance. However, whether plasma genotyping can replace tissue biopsy regarding treatment decisions calls for further investigation. In this study, we explored the clinical application of liquid biopsy by next generation sequencing (NGS) in patients who have progressed on 1st generation EGFR-TKI and tried to identify sub-populations who might benefit from additional tissue biopsy. **Method:** We performed capture-based NGS on matching tissue biopsy and plasma samples from 32 patients who have progressed on 1st generation EGFR-TKI and conducted qualitative and quantitative analysis to identify features and concordance between tissue and plasma among this population. **Result:** The concordance between tissue and plasma is 93.5% for EGFR sensitizing mutations while only 58.1% for T790M. Patients with an EGFR sensitizing mutation allele frequency (AF) less than 2% from plasma ctDNA are more likely to have false negative results on T790M mutation detection (p=0.007). Patients with a T790M relative allele frequency (RAF) less than 20% are more likely to carry concurrent resistant mutations (p=0.018). **Conclusion:** We demonstrated that after acquiring EGFR-TKI resistance, two subsets of patients require repeated biopsy after plasma testing: patients who are T790M negative yet have a low EGFR sensitizing mutation AF, and patients who are T790M positive but with a low T790M RAF.

Keywords: Circulating Tumor DNA, next-generation sequencing, Repeat Biopsy

PUB013 DEPLETION OF STAT6 SUPPRESSES PULMONARY CANCER PROGRESSION BY DECREASING M2 MACROPHAGES IN THE LUNG

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Background: We found signal transducer and activator of transcription 6 (STAT6) highly expressed in human lung adenocarcinoma and squamous carcinoma and expressed mainly in interstitial immune cells and little in epithelial cells. STAT6 has been reported suppressing breast cancer metastasis, but its function in lung cancer is poorly understood. **Method:** Urethane induced primary lung cancer model was built in wild type (WT) and STAT6 knock out ($STAT6^{-/-}$) mice to explored the role of STAT6 in tumorigenesis. Male mice were treated with urethane (1g/kg) dissolved in PBS by intraperitoneal injection at two months of age. Lung tumors from mice induced with carcinogen were harvested at 16, 24, 36 weeks after injection in the balb/c mice and $STAT6^{-/-}$ mice.To identify the role of STAT6 gene itself in cancer cell proliferation. We performed short interfering RNA (siRNA)-mediated knockdown of STAT6 gene and analyzed the cancer cell activity and proliferation in vitro. Fluorescence-activated cell sorting (FACS) analysis, co-culture system, CCK8 assay, cell cycle assay, immunenohistologic stainig, PCR and immunofluorescence were used in this study. **Result:** Primary lung cancer nodules of $STAT6^{-/-}$ mice resulted in smaller volume, less weight, slower growth rate than that of WT mice. In vitro, lung cancer cell lines with STAT6 knock down exhibited no difference in tumor growth. Thus we interfered interaction between STAT6 and lung tumor microenvironment (TME). $CD11b^+$ cells were less accumulated and migrated to the lung in $STAT6^{-/-}$ mice. $CD11b^+$ cells from $STAT6^{+/+}$ mice promoted tumor growth in nude mice, while same number of $CD11b^+$ cells from $STAT6^{-/-}$ mice could suppressed this heterotopic transplantated tumor progression. This indicated that $STAT6^{-/-}$ mice derived $CD11b^+$cell resisted lung tumor growth. Among $CD11b^+$ cells, $Ly6G^+Ly6C^{int}$ neutrophils had no change, while tumor associated macrophages showed marked polarization difference in this primary tumor-bearing model between $STAT6^{+/+}$ and $STAT6^{-/-}$ group in vivo and in vitro. Co-culture of $STAT6^{-/-}$ macrophages and tumor cells contributed to less M2 differentiation. **Conclusion:** Deficiency of STAT6 suppressed lung cancer progression through decreasing $CD11b^+$cells and M2 migration to the lung. STAT6 deficiency inhibited macrophage polarization through regulating lung cancer cell secreted factors like IL-4.

Keywords: lung cancer, macrophage, STAT6

PUB014 COLLAGEN XVII ACTIVATES OCT4 AND ALTERS METABOLIC REPROGRAMMING THROUGH UPREGULATION OF AKT/GSK-3B/B-CATENIN PATHWAY IN LUNG CANCER

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Background: Collagen XVII, a type II integral transmembrane protein, is found to be associated with the maintenance of EMT phenotypes and metastasis ability in lung cancer stem cells (CSCs). Pluripotency genes, such as Oct4 and Nanog, constitute the core regulatory network that suppresses differentiation-associated genes, thereby maintaining self-renewal and the pluripotency of the cells. Oct4 can regulate the transcription of the glycolytic enzymes Hk2 and Pkm2, which determine the rate of glycolytic flux in embryonic stem cells. This study aimed to investigate whether Collagen XVII can activate the pluripotent gene expression and subsequently alter the metabolic state of lung CSCs, thus enhancing tumor invasion, chemoresistance and initiation in lung CSC. **Method:** Several single cell clones of A549 lung cancer cells with overexpression of Collagen XVII were set up to examine the link and possible mechanism among Collagen XVII and pluripotent gene expressions in lung CSCs and investigate if dysregulation of Collagen XVII can cause metabolic reprogramming through activation of Oct4. Extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) are measured using the Seahorse XF24 extracellular flux analyzer. CRISPR/Cas9 system was used for knock-out of Collagen XVII expression in lung cancer cells. **Result:** We demonstrated that overexpression of Collagen XVII in lung cancer cells increased cancer stemness including migration, invasion, chemoresistance, decreased DNA damage, increased EMT markers and enhanced tumor formation in vivo. Oct4 expression was activated in lung cancer cells with overexpression of Collagen XVII through AKT/GSK-3β/β-catenin pathway. Overexpression of Collagen XVII also increased glycolytic capacity and the lactate level, compared to parental A549 lung cancer cells. The expression of Oct4 was downregulated by knock-out of Collagen XVII, thus resulting in decreased extracellular acidification rate and oxygen consumption rate in lung cancer cells. **Conclusion:** We found for the first time that Collagen XVII can activate Oct4 through upregulation of AKT/GSK-3β/β-catenin pathway, and thus alter metabolic reprogramming including glycolysis and oxygenation consumption in lung cancer cells. Further investigation to elucidate which metabolism associated proteins is responsible for the stemness of lung cancer stem cells is mandatory.

Keywords: lung cancer, Collagen XVII, Oct4

PUB015 A POOLED ANALYSIS OF EFFICACY AND SAFETY OF CTLA-4 ANTIGEN IN THE TREATMENT OF CANCER

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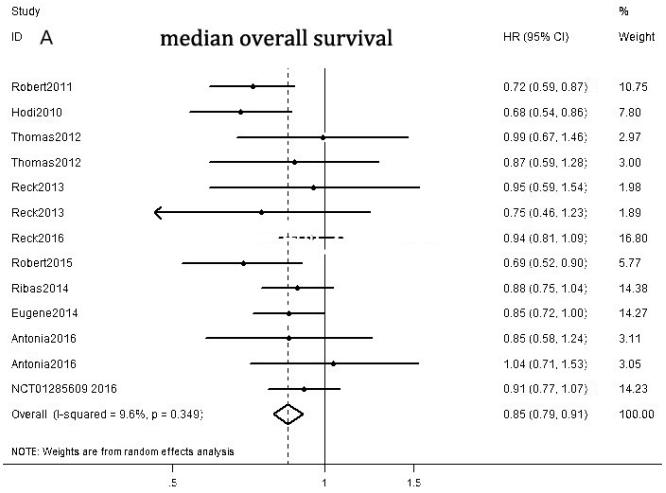
Background: Anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), including ipilimumab and tremelimumab, showed significantly improve survival in patients with melanoma. However, treatment of CTLA-4 antigen in patients with other cancers, especially lung cancer, showed inconsistent survival benefit. We conducted this meta-analysis to explore the efficacy and safety of CTLA-4 antigen compared to the conventional regimens or other immunotherapy during cancer treatment by reviewing randomized trials. **Method:** Until January 2017, an electronic systematic literature search was performed up in Pubmed and Cochrone Library. ASCO and ESMO were reviewed seriously as well. Median overall survival (mOS), median progression-free survival (mPFS), hazard ratio (HRs) and their corresponding 95% confidence intervals (CIs) were calculated. **Result:** We found that mOS and mPFS were significantly improved in all cancers (HR=0.83, 95%, CI=0.76-0.90; HR=0.77, CI=0.72-0.83, respectively), showing advantage benefit for CTLA-4 antigen over other treatment. Subgroup analysis demonstrated significant outcome of mPFS in SCLC and NSCLC (HR=0.85, CI=0.77-0.94; HR=0.85, CI=0.74-0.96). Combination with chemotherapy got significant outcome in mOS and mPFS (HR=0.88, CI=0.79-0.97; HR=0.85, CI=0.79-0.92), whereas combination with immunotherapy only demonstrated promising benefit in mPFS but not mOS(HR=0.80, CI=0.72-0.89; HR=0.82, CI=0.66-1.01).



Conclusion: These results indicate that CTLA-4 antigen take advantage over conventional treatment, and provide evidence for further study to explore the best medicine timing and administration mode in CTLA-4 antigen treatment.

Keywords: CTLA-4, Ipilimumab, tremelimumab

PUB016 OXIDIZED LOW DENSITY LIPOPROTEIN RECEPTOR 1 PROMOTES LUNG METASTASES THROUGH REGULATING THE EPITHELIAL-TO-MESENCHYMAL TRANSITION

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Background: Oxidized low density lipoprotein receptor 1 (OLR1), a type II membrane protein, has been identified as receptor for oxidized low-density lipoprotein. Previously, we described that high expression of OLR1 was associated with poor prognosis in squamous non-small cell lung cancer (NCSLC), and could construct a prognosis predictive model. The current study firstly provided evidence that OLR1 regulated EMT and thus promoted lung metastases in osteosarcoma (OS). **Method:** All relevant experiments were conducted according to the manufacturer's protocols. In vivo tumor xenograft experiments were carried out in 6- to 16-week-old mice, then maintained in our animal facility under pathogen-free conditions in accordance with the Institutional Guidelines and approval by local authorities. For the use of the clinical materials for research purposes, prior patient's consent and approval from the Institute Research Ethics Committee were obtained. All statistical analyses were performed using IBM SPSS Statistics 22.0 for Windows (SPSS Inc, Chicago, IL). **Result:** *(See next page.)*

Microarrays were adopted to explore the underlying epigenetic mechanisms related to metastasis. 44 genes were identified among total 26890 differentially expressed genes. After validated in paired primary and metastatic tissues, OLR1 was selected in the current study. The expression levels of OLR1 were tested in 4 widely used cell lines. Cell proliferation, migration and invasion could be enhanced when OLR1 was overexpressed. OLR1 overexpression also triggered G1 to S+G2 phases of cell cycle. Accordingly, cell proliferations, migration and invasion would be reduced when OLR1 was silenced. OLR1-silencing blocked G1 to S+G2 phases of cell cycle. Also, OLR1 silencing effectively suppressed local tumor carcinogenesis and lung metastases in vivo. Moreover, silencing OLR1 repressed the expression of mesenchymal markers (Snail, Twist, and N-cadherin), but induced an epithelial marker (E-cadherin). **Conclusion:** This study indicated a novel molecular mechanism involving the role of OLR1 in lung metastases of osteosarcoma, strengthened the correlation between OLR1 and lung metastases.

Keywords: lung metastases, Epithelial-to-mesenchymal transition, OLR1

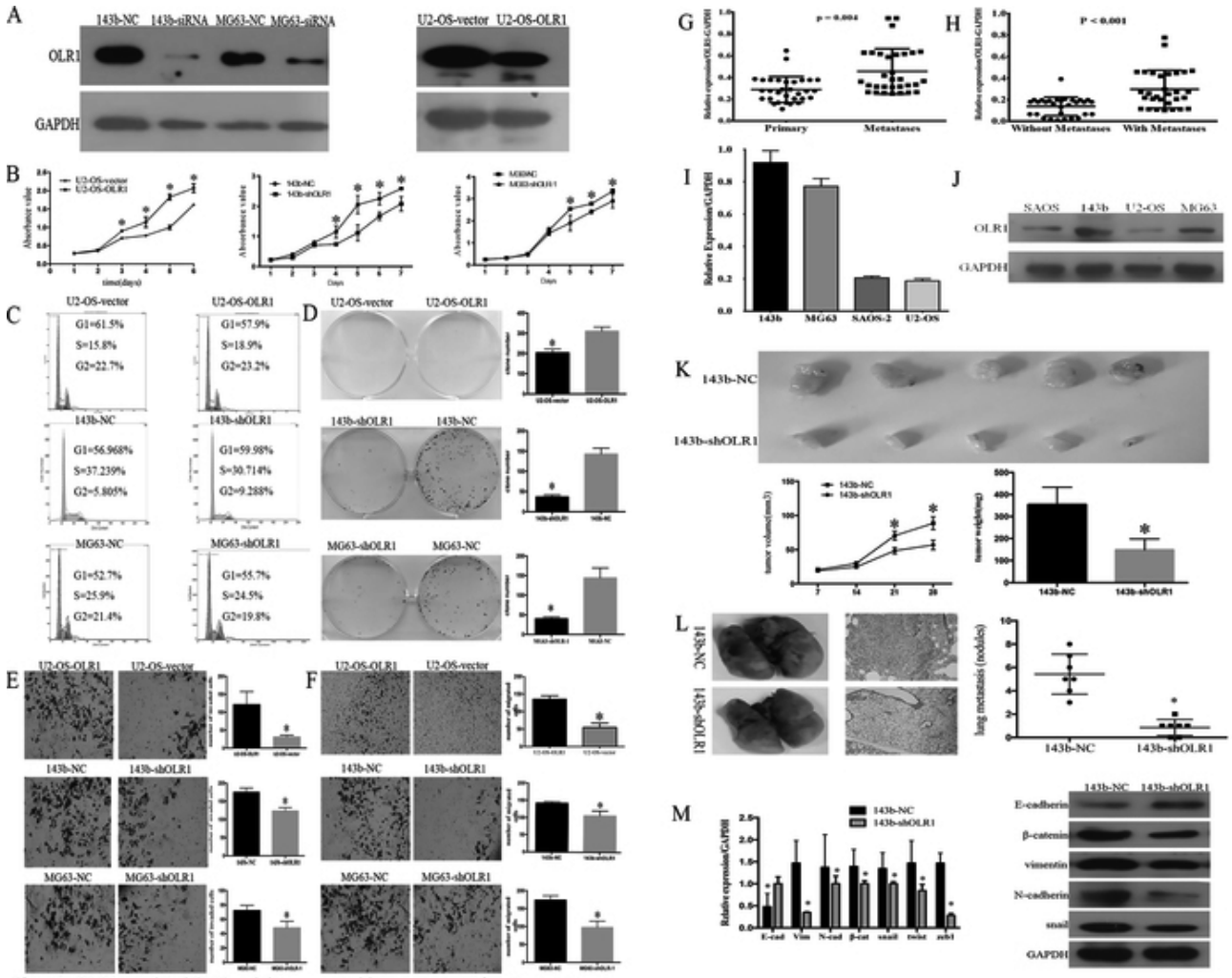

Figure1. OLR1 regulated EMT and thus promoted lung metastases in osteosarcoma

A: Overexpression and silencing of OLR1 in osteosarcoma cell lines, U2-OS, 143b, and MG63. B: Cell proliferations of OLR1-overexpressing cells were found to be significantly enhanced by MTT assays, whereas OLR1-silencing cells being significantly reduced. C: OLR1 overexpression triggered G1 to S+G2 phases of cell cycle, while OLR1-silencing blocking G1 to S+G2 phases of cell cycle.D: Much higher cell densities for the OLR1-overexpressing cells were observed by colony formation assays when compared to the vector controls. Accordingly, much lower cell densities for the OLR1-silencing cells were observed by colony formation assays when compared to the controls. E: The ectopic overexpression of OLR1 in U2-OS cells increased their invasive abilities. OS cells invasive abilities were significantly suppressed when OLR1 was silenced. F: The ectopic overexpression of OLR1 in U2-OS cells increased their migratory abilities. OS cells migratory abilities were significantly suppressed when OLR1 was silenced. G: The expression level of OLR1 was significantly upregulated in metastatic OS tissues in comparison to the primary OS tissues. H: Significantly higher OLR1 expression level in the primary OS tissues from metastatic patients. I: The expressions of OLR1 were investigated in four OS cell lines (U2-OS, SAOS-2, 143b, and MG63) by qRT-PCR. The results indicated that the expression levels of OLR1 were low in U2-OS and SAOS-2 cell lines, but high in 143b and MG63 cell lines. J: The expressions of OLR1 were investigated in four OS cell lines (U2-OS, SAOS-2, 143b, and MG63) by Western blotting. The results indicated that the expression levels of OLR1 were low in U2-OS and SAOS-2 cell lines, but high in 143b and MG63 cell lines. K: OLR1 silencing effectively suppressed local tumor carcinogenesis of OS cells in vivo. L: OLR1 knockdown in 143b cells caused a significant reduction in the number of lung metastases. M: Silencing OLR1 repressed the expression of mesenchymal markers (Snail, Twist, and N-cadherin), but induced an epithelial marker (E-cadherin).

PUB017 AK2 IS OVEREXPRESSED AND CORRELATED WITH INCREASED METASTASIS POTENTIAL AND TUMORIGENICITY IN LUNG ADENOCARCINOMA

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Background: Lung adenocarcinoma (LAD) is considered to be a highly aggressive disease with heterogeneous prognosis and the molecular mechanisms underlying tumor progression remain elusive. Adenylate kinase 2 (AK2), an isoenzyme of the AK family, is critical in the control of energy metabolism and may have momentous extra-mitochondrial functions, especially in tumourigenesis. However, the roles and molecular mechanism of AK2 in LAD has been rarely investigated. **Method:** A total of 345 LAD cases were immunohistochemically analyzed by using a monoclonal antibody against AK2. Celigo cell imaging analyzer, flow cytometric analysis, cell transwell assays, Immunofluorescence test and western blotting were performed to assess the effects of AK2 on proliferation, apoptosis, cell cycle, autophagy and epithelial-to-mesenchymal (EMT) phenotypes in LAD cells in vitro. Colony formation assay and xenograft transplantation were employed to demonstrate the antiproliferative effect of AK2 knockdown in combination with hydroxychloroquine (HCQ), an effective autophagy inhibitor, in vitor and in vivo . **Result:** AK2 expression upregulation was significantly associated with unfavorable prognosis in LAD. Silencing AK2 inhibited cell proliferation, migration and invasion in cell lines. Mechanismly, we found that AK2 promoted LAD cell migration and invasion via regulating EMT phenotypes. Furthermore, we observed that AK2 deletion induced autophagy and co-treat with HCQ led to reinforced growth suppression in vitro and in LAD xenografts mouse models. **Conclusion:** Our results indicate that AK2 is essential in LAD tumorigenesis. Inhibition of AK2 may have potential as a therapeutic target for patients with pulmonary cancer and co-treat with HCQ could synergistically improve therapy outcome in LAD patients.

Keywords: lung adenocarcinoma, Adenylate kinase 2, Epithelial-to-mesenchymal transition

PUB018 ANALYSIS OF THE SAFETY AND USEFULNESS OF NAB-PACLITAXEL THERAPY IN PATIENTS WITH NON-SMALL CELL CARCINOMA

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Background: Nab-paclitaxel (nab-PTX) is used as primary therapy in the treatment of non-small cell carcinoma. However, we frequently use it as secondary or later therapy, or for patients with performance status (PS) of >=2. Therefore, we analyzed the response to and safety of nab-PTX therapy in the treatment for patients with non-small cell carcinoma in our hospital. **Method:** Between January 2014 and March 2017, 46 patients received chemotherapy with nab-PTX, or nab-PTX and carboplatin for non-small cell carcinoma in our hospital. We used the standard nab-PTX 100 mg/m^2 and carboplatin AUC5, except in older patients and those with PS of >=2, for whom we reduced the medication dose. **Result:** The median age of the patients was 66 years (range, 26–78 years), and 17 patients were older than 75 years. Of the patients, 39 were male and 7 were female, and 41 patients were smokers. Ten patients had preexisting pulmonary fibrosis, and 30 had preexisting emphysema. The tissue types of the tumors were squamous cell carcinoma, adenocarcinoma, other types, and not diagnosed in 32, 10, 2, and 2 of the patients, respectively. The PS of 7, 33, and 6 patients before treatment were 0, 1, and 2, respectively. The tumor stage was IIB, IIIA, IIIB, A, B, and postoperative recurrence was observed in 3, 4, 11, 15, 9, and 4 cases, respectively. The treatments were used as primary, secondary, or third or later therapy in 8, 25, and 13 patients, respectively. Twenty-five patients received the combination therapy. The median follow-up period was 8.5 months. The response rate (RR) was 11%. The disease control rate (DCR) was 20%. The median progression-free survival (PFS) was 3 months. Twenty patients experienced adverse events of grade 3 or higher. These events included leukocytopenia (14, 70%), anemia (3, 15%), anorexia (3, 15%), febrile neutropenia (3, 15%), fatigue (1, 5%), and thrombopenia (1, 5%). In addition, the data of the patients treated with nab-PTX as secondary or later therapy indicated a RR of 13%, DCR of 18%, and median PFS of 3 months. The data of the patients with PS of >=2 indicated a RR of 0%, DCR of 16.7%, and PFS of 1.5 months. **Conclusion:** Nab-PTX is used as secondary or later therapy in patients with non-small cell carcinoma and PS of >=2. Nab-PTX therapy is useful and safe at a constant rate. We will analyze more cases, including patients under observation, and will report the data during the presentation.

Keywords: nab-paclitaxel, Non-small cell carcinoma

PUB019 EGFR MUTATION CORRELATES WITH UNINFLAMED PHENOTYPE AND WEAK IMMUNOGENICITY, CAUSING IMPAIRED RESPONSE TO PD-1 BLOCKADE IN NSCLC

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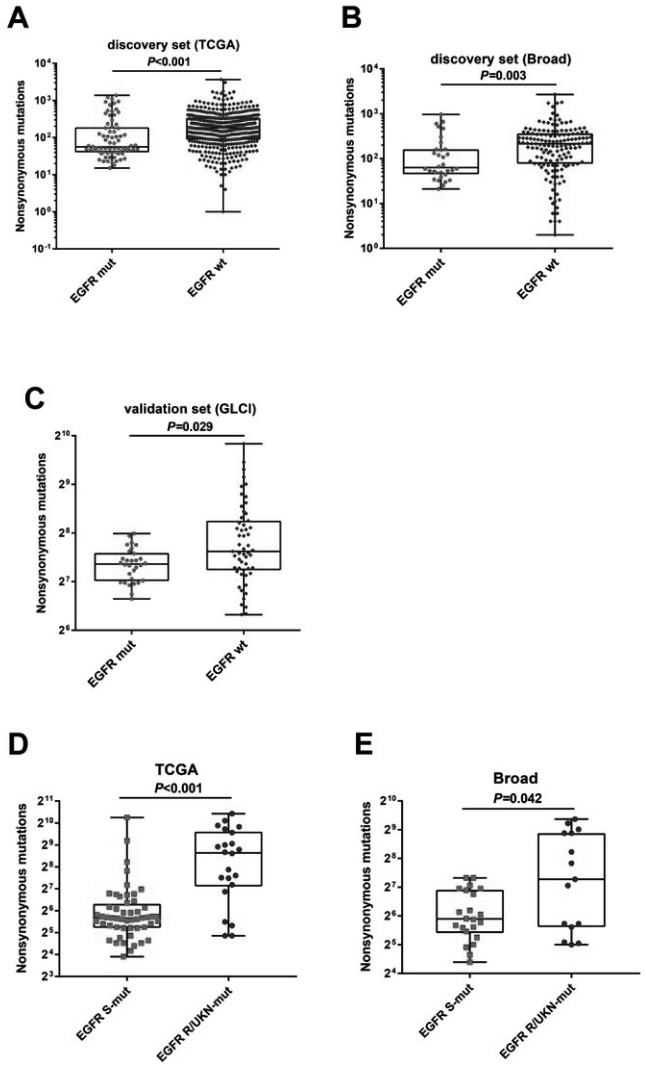
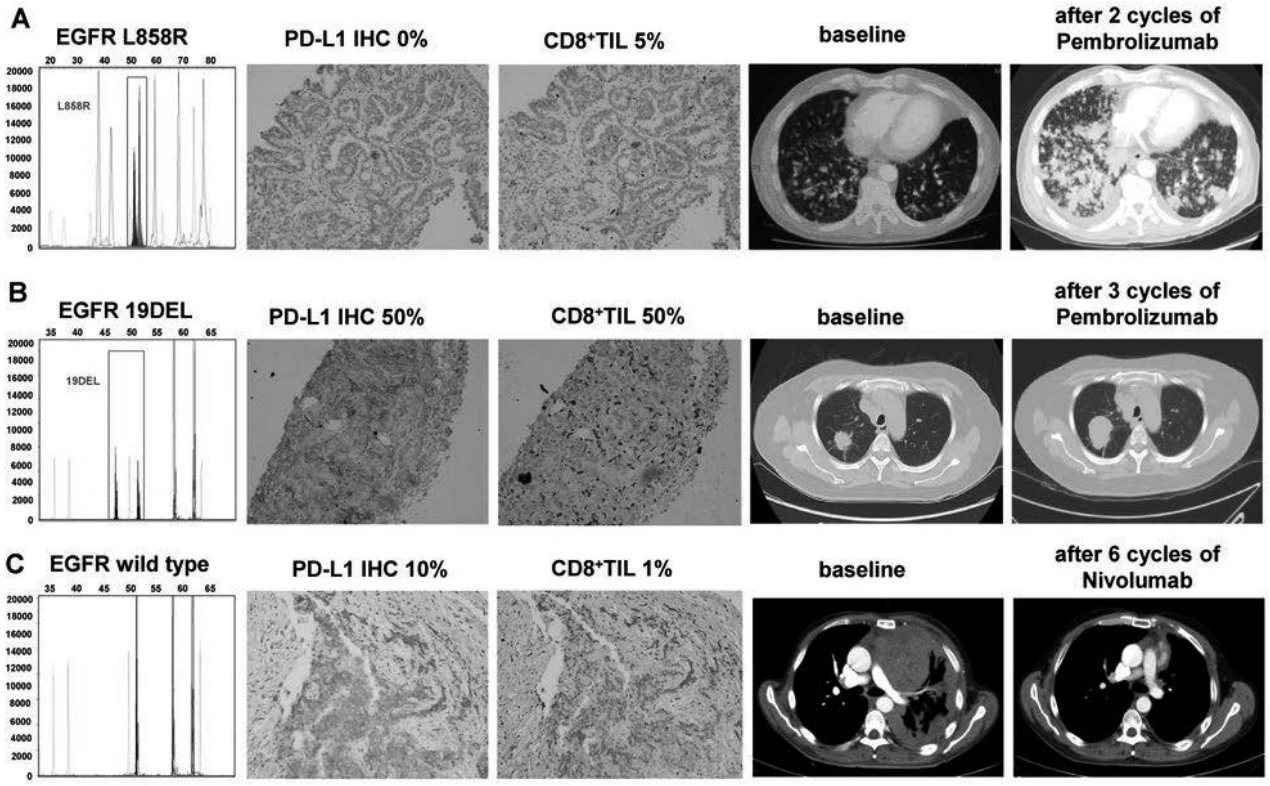
Background: Patients with EGFR mutations showed unfavorable response to programmed cell death-1 (PD-1) blockade immunotherapy in non-small cell lung cancer (NSCLC). Yet the underlying association between *EGFR* mutation and immune resistance remains largely unclear. **Method:** We performed an integrated analysis of PD-ligand 1(PD-L1)/CD8 expression and mutation profile based on the repository database and resected early-stage NSCLC in Guangdong Lung Cancer Institute (GLCI). Meanwhile, two pool-analyses were set to clarify the correlation between *EGFR* mutation and PD-L1 expression, and the association of *EGFR* status with response to anti-PD-1/L1 therapy. **Result:** Pool-analysis of 15 public studies suggested that patients with *EGFR* mutations had decreased PD-L1 expression (odds ratio: 1.79, 95% CI: 1.10-2.93; P = 0.02). Analysis of The Cancer Genome Atlas (TCGA) and the GCLI cohort confirmed the inverse correlation between *EGFR* mutation and PD-L1 expression. Furthermore, patients with *EGFR* mutation showed a lack of T-cell infiltration (P = 0.003) and shrinking proportion of PD-L1$^+$/CD8$^+$TIL (P = 0.005). Importantly, patients with *EGFR* mutations, especially the sensitive subtype (exon 19Del, L858R, L861Q, G719X, S768I), showed a significantly decreased mutation burden, based on analysis of the discovery and validation sets. Finally, a pool-analysis of 4 randomized control trials confirmed that patients with *EGFR* mutation did not benefit from PD-1/L1 inhibitors (Hazard ratio [HR] = 1.09, P = 0.51) while patients with EGFR wild-type did (HR = 0.73, P < 0.00001). Three cases treated with PD-1 inhibitor in our center also supported that EGFR mutation was unfavorable to PD-1 blockade even when those with strong positive of PD-L1 and CD8$^+$ TIL.





Conclusion: This study provided evidence of a correlation between *EGFR* mutations and an uninflamed tumor microenvironment with immunological tolerance and weak immunogenicity, which caused an inferior response to PD-1 blockade in NSCLCs.

Keywords: programmed cell death protein-1, Mutation burden, EGFR

PUB020 BARRIERS IN ENROLMENT IN LUNG CANCER STUDY

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Background: Objective - To find out the barriers in enrolment for clinical trial. Introduction- The success of a clinical trial is the recruitment and retention of a study population of an adequate sample size. In all clinical trials, the process starts with a screening period. The screening period starts with the signing of the informed consent. During the screening period, inclusion/exclusion criteria for the study participation is checked. Subjects who meet all inclusion criteria and exclusion criterion are eligible to be randomized . Significant proportion of patient do not participate in clinical trial in spite of meeting exclusion and inclusion criteria. It is important to find out the reasons for not participating in clinical trials. This will help in developing strategies to overcome it. **Method:** We retrospectively analyzed a prospectively maintained database during 2015. We have entered the reason for not participating for a specific study of targeted therapy in lung cancer. We have done descriptive analysis of data. **Result:** Information concerning 92 patients with EGFR mutation positive in non small cell lung cancer who were treatment naive and ECOG 0-2 were included in this analysis. In the year 2015 out of 92 patients, 61 patient were randomized (66%) with met protocol eligibility criteria for a particular study and agreed to participate in clinical trial .So, 31 (33%) patient were screen failure. The reason for screen failure were16 of 31 patients were ECOG 3 (17%); 9 of 31patient were already started treatment (9%) in the OPD because they did not want to wait for the report; 5 of 31patient did not want to participate as they preferred oral targeted therapy(5%).1 of 31 had financially constraint(1%) **Conclusion:** Barriers to cancer clinical trial accrual can be prospectively identified. This will help us in addressing these barriers for futures studies.

Keywords: randomized ,participate,EGFR mutation

PUB021 SLK CAUSES RESISTANCE TO EGFR-TKI IN LUNG CANCER

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, such as gefitinib and dacomitinib are effective for non-small cell lung cancer with activating EGFR mutations. However, relapse typically occurs after an average of 6-12 months of continuous treatment. Although some mechanism(s) of resistance have been identified, approximately 30% of acquired resistance cases remain unknown. Targeted therapies that inhibit EGFR tyrosine kinase activity (EGFR-TKI, Gefitinib) are of particular interest in lung adenocarcinomas with activating mutation of EGFR . However, all patients will escape after several months of treatment and ultimately develop progressive disease. A better understanding of the molecular mechanisms underlying resistance to EGFR-TKIs is a critical challenge as it can help design new drugs and therapeutic strategies to overcome resistance. The aim of this study was to explore additional mechanisms of EGFR-TKI resistance in lung tumors. We generated resistant clones of the sensitive EGFR exon 19 mutant NSCLC cell lines PC9 and HCC827 by exposing them to increasing concentrations of gefitinib or dacomitinib for several months. We identified a specific deregulation of SLK in resistant clones and unraveled a SRSF2/SLK pathway as a new mechanism of lung tumor progression following gefitinib treatment. **Method:** Generation of Gefitinib and Dacomitinib resistant PC9 and HCC827 clones Cell growth assay, Apoptosis Western blotting Small interfering RNA (siRNA) transfection, RNA extraction and RT/qPCR analysis Indirect Immunofluorescence Stastistical Analysis **Result:** Some resistant clones had absence of known mechanisms of resistance including the EGFRT790M mutation, MET gene amplification and Small-cell lung cancer histology but exhibited a lower growth kinetic compared to sensitive cells. Focusing on these clones we found that some of them had undergone Epithelial to Mesenchymal Transition (EMT). In one clone with EMT, overexpression of a truncated SLK protein was detected. Overexpression of normal sized SLK protein was observed in the others independently of EMT status. Neutralization of the splicing factor SRSF2 sensitized resistant cells to gefitinib-induced apoptosis and strongly inhibited SLK expression. SLK: a potential target of SRSF2 These results demonstrated for the first time that a SRSF2-dependent pathway is an important determinant of acquired resistance of lung tumors to EGFR-TKI **Conclusion:** Collectively these data highlighted the SRSF2/SLK module as a new component of EGFR signaling network and strongly suggested that activation of a survival SRSF2/SLK pathway is a new mechanism of lung tumor progression following gefitinib treatment.

Keywords: EGFR-TKI, resistance, SLK

PUB022 A CROSS-SECTIONAL STUDY OF DIAGNOSTIC EXAMINATIONS AND FIRST-LINE TREATMENT PATTERNS OF LUNG CANCER IN JIANGSU PROVENCE, CHINA

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Background: Purpose: Jiangsu Provence was among the top in economic and cultural development in China, and so did the prevalence of lung cancer. The objective of this study was to explore the usually used auxiliary examinations in diagnosis of lung cancer, first-line anti-cancer regimens, as well as gene aberration test status of patients with lung cancer in Jiangsu Provence, China. **Method:** 22 tertiary hospitals in Jiangsu Provence were involved in this study. Patients who were diagnosed with Lung cancer between March and May in 2016 and had never been treated before were enrolled. Patients information including demographics, histological subtypes, stages, family history of lung cancer, clinical manifestations, auxiliary examinations, gene aberration test status and first-line anti-cancer regimens were collected 1-2 days after patients discharging from hospitals. Descriptive statistics about diagnostic examinations, gene aberration test conditions, and first-line treatment patterns were performed. **Result:** A total of 928 patients from 22 comprehensive and specialist hospitals in Jiangsu Provence were enrolled. Chest computerized tomography (CT) was the most commonly used auxiliary examination (95.7%) for screening of high-risk populations of lung cancer. If pathology needed, TBLB and TTNA were often performed. For SCLC, only patients staged T1-2N0M0 tend to select surgery, the other mostly cisplatin and etoposide chemotherapy. For NSCLC with stage I and II, surgery was the preferred option while for stage III and IV, chemotherapy dominated the first-line regimen, which mainly referred to cisplatin and pemetrexed regimen. As for gene aberration test, detection rate of EGFR gene mutation was 28.0% in non-selective NSCLC, 33.2% for locally advanced or metastatic NSCLC, and 39.3% for advanced non-squamous NSCLC, and the positive rate was 49.3%, 53.8% and 54.5%, respectively. The frequency of ALK gene fusion, c-MET gene amplification, ROS1 gene fusion and RET gene rearrangement were 4/111, 3/11, 5/26 and 0/3 respectively. 72.7% of patients with EGFR mutation were treated with TKIs, while it was only 5.5% for patients with EGFR mutation negative or unknown. **Conclusion:** In Jiangsu Provence, chest CT scanning was the most commonly used screening method for diagnosis of lung cancer. First-line treatment patterns were basically in accordance with stage and EGFR mutation status, although some disparities unavoidable.

Keywords: Cross-sectional, Lung Cancer, first-line therapy, gene aberration, Jiangsu Provence

PUB023 CONCOMITANT CHEMORATIOTHERAPY TREATMENT FOR INOPERABLE BRAIN METASTASES IN NON-SMALL CELL LUNG CANCER PATIENTS:CLINICAL EXPERIENCE

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Background: Aim of this study was to evaluate tumor response, Quality of life (QoL) and median survival of concomitant chemotherapy cisplatin/etoposide (P/E) protocol with WBI (whole brain irradiation) follow by P/E protocol until progression or appearance of serious adverse effects in NSCLC patients with multiple brain metastases. **Method:** From December 2012 to April 2014, 12 patients were enrolled in this study. All of the patients received one or combination of previous treatments, chemotherapy and radiotherapy. Selected patients had multiple brain metastases detected on CT and/or MRI, and the brain is only one site of disease dissemination, no extracranial metastases were assessed and they were at younger age. Conventional megavoltage external beam radiotherapy was administered with linear accelerator (energy 6 MV). Two lateral opposed fields were used for WBRT, covering up to C2 vertebral body. Dose administered was 30 Gy/10 fractions or 40 Gy/5 fractions. Concurrently with WBRT, patients received systemic chemotherapy cisplatin 60-75 mg/m^2 and etoposide 100 mg/m^2 and, after 4 weeks, patients received chemotherapy protocol P/E cisplatin 75 mg/m^2 etoposide 100 mg/m^2 on 21 days until progression or appearance of serious adverse effects. Tumor response was assessed according to RECIST criteria on the follow-up visits first on 2 months and then on every 3 months with CT or MRI of the brain and other investigations. We analyzed tumor response from the beginning of the concomitant chemotherapy and WBRT continuously with adjuvant chemotherapy until tumor progression or detected severe toxicity. Assessment of QoL was performed by patients' subjective answers, subjective improvement and without subjective improvement. Adverse effects were performed according to WHO criteria. Overall survival was analyzed from the beginning of the concomitant chemotherapy and WBRT and adjuvant chemotherapy until death or patient's last control. **Result:** We assessed PR (partial response) at all patients included in the study. Common adverse events were neurotoxicity and hematology toxicity according to WHO criteria. No patient was withdrawn from the study because of the adverse events. All patients reported subjective improvements. Overall median survival was 7.5 months (95% CI 6.32-8.73), presented with Kaplan-Meir curve. **Conclusion:** We performed this study to treated selected group of patients with non-small cell lung cancer with good performance status, no extracranial metastases and younger age. Combination of WBRT with new drugs is optional. Considering our clinical results, we recommend this treatment as safe and effective for NSCLC patients.

Keywords: NSCLC patients, brain metastase, concomitant chemoradiotherapy

PUB024 CLUSTERS SPATIAL ARRANGEMENT OF TUMOR INFILTRATING LYMPHOCYTE AND CANCER NUCLEI PREDICTS RECURRENCE IN EARLY STAGE NON-SMALL CELL LUNG CANCER

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Background: Increased TILs is associated with improved outcome in several solid tumors including NSCLC. However, the current approach to TIL quantification involves manual grading of TILs was subject to inter-observer variability. We evaluated the computerized feature analysis algorithms to evaluate the relationship between the spatial arrangement of TILs and cancer nuclei in NSCLC with disease recurrence. **Method:** Two independently collected H&E based tissue microarrays (TMAs), YTMA140 (n=70) and YTMA79 (n=119), of ES-NSCLC were used in this study. TILs and cancer nuclei were initially segmented by using a convolutional neural network based approach in conjunction with shape and color features of the individual cells. Cell clusters for both lymphocytes and cancer nuclei were constructed by aggregating proximally located TILs and nuclei respectively. For each cluster (TILs and cancer nuclei), a total of 50 measurements including the density, arrangement and spatial distribution of proximal clusters were extracted. The top 12 most predictive measurements were identified via feature selection and used to train a prediction model (quadratic discriminant analysis (QDA)) using YTMA140. YTMA79 was used for independent validation.

(See figure next page.)

Result: The most predictive features identified were (1) the average number of co-located TIL and cancer nuclei clusters and (2) ratio of TIL clusters to cancer nuclei clusters. The QDA classifier yielded an area under the receiver operating characteristic curve (AUC) of 0.78 on the validation set (Figure 1). Cancers where the cancer nuclei clusters were more tightly surrounded by lymphocyte clusters showed a statistically significant correlation (p-value < 10-7) with better outcome as measured by increased disease-free survival time. **Conclusion:** Our results showed that computer extracted features of the spatial arrangement of TILs and cancer nuclei was predictive of recurrence in ES-NSCLC. Additional independent multi-site validation of these features is needed.

Keywords: non-small cell lung cancer, recurrence, tumor infiltrating lymphocyte

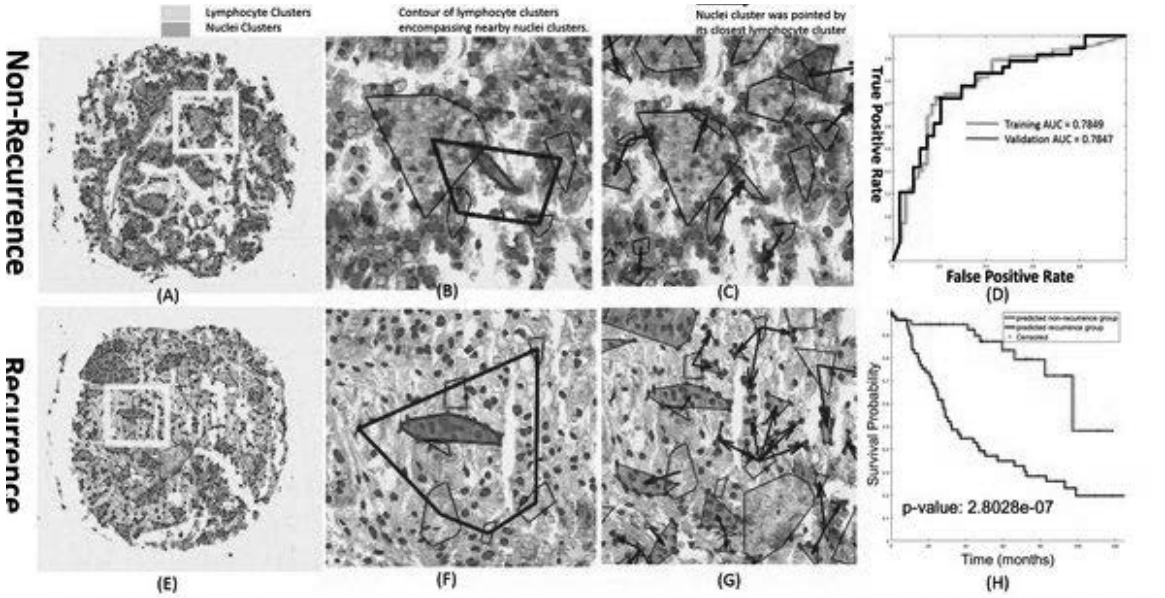

Figure 1. (A) Non-recurrent and (E) Recurrent NSCLC patient images. (A, E) TIL (green) and cancer nuclei cluster (red) construction, (B, F) number of proximal TIL clusters circumscribing each nuclear cluster, (C, G) Arrows show location of closest TIL cluster with respect to each cancer nuclei cluster, (D) receiver operating curve for both training and validation sets (AUC=0.78 for both sets) for the quadratic discriminant analysis in conjunction with the 12 most predictive features. (H) Kaplan-Meier curves showing separation between the recurrent and non-recurrent cases on the test set via the quadratic discriminant analysis in conjunction with the 12 most predictive features ($p < 10^{-7}$). *Note: nuclei cluster are closely encompassed by proximal lymphocyte clusters for patients with better outcome (see area and vertex of blue contour in B and F); nuclei cluster are guarded tightly by surrounding lymphocyte cluster (see the arrow source point in C and G).*

PUB025 EFFICACY OF ALK INHIBITORS IN THE TREATMENT OF ALK-REARRANGED NON-SMALL CELL LUNG CANCER AND BRAIN METASTASES: A META-ANALYSIS

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Background: Several anaplastic lymphoma kinase inhibitors (ALKi) have been developed to treat non-small cell lung cancer (NSCLC). However, few trials have been conducted thus far to directly compare the efficacy of different ALK inhibitors. **Method:** A search of three databases (PubMed, Web of Science and the Cochrane Library) was performed from the inception through May 28, 2017. We have pooled the overall response rate (ORR) and progression-free survival (PFS) of patients treated with alectinib, brigatinib, ceritinib and crizotinib. We also analyzed the results of 4 random-controlled trials comparing the efficacy of ALK inhibitors and chemotherapy. In addition, we attempted to generate a curve of the pooled probability of progression-free survival in order to compare the efficacy of different ALK inhibitors. **Result:** Patients treated with ALK inhibitors have higher ORR (OR=5.85, 95%CI 3.79-9.04) and PFS (HR=0.74, 95%CI 0.69-0.79) than those treated with chemotherapies. Subgroup analysis showed that among ALKi-naïve patients, the ORR of brigatinib-treated patients was the highest (100%, 95%CI, 63-137%), followed by alectinib (87%, 95%CI 78-96%), ceritinib (70%, 95%CI 64-76%) and crizotinib (63%, 95%CI 57-68%), while for ALKi-pretreated patients, the ORR difference of patients treated with different ALK inhibitors were not significant. For patients with brain metastases, alectinib has the highest ORR (61%, 95%CI 49-72%) followed by brigatinib (53%, 95%CI, 39-66%) and ceritinib (51% 95%CI 42-59%). **Conclusion:** The efficacy of ALKi was superior to that of chemotherapy. The efficacy of second-generation ALKi in ALKi-naïve patients was superior to that of crizotinib. Alectinib was more effective than ceritinib or brigatinib for patients with brain metastases.

Keywords: non-small cell lung cancer, brain metastases, ALK inhibitors

PUB026 PD-L1 EXPRESSION, USING SP142 AND 22C3 ANTIBODY CLONES, IN NSCLC PATIENTS WITH KNOWN STATUS OF EGFR AND ALK GENES

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Background: Currently available immune-checkpoint inhibitor therapies in NSCLC patients have different, approved PD-L1 expression assays. These assays have similarities, but also some differences. In our study, we estimated usefulness of two immunohistochemical (IHC) tests in patients with different pathological diagnosis of lung cancer and known most common genetic abnormalities. **Method:** The study included 48 NSCLC patients (median age: 65 years old) with known status of *EGFR* and *ALK* genes. PD-L1 expression examination was carried out using two IHC assays with SP142 (Ventana) and 22C3 (Dako) antibodies. The analysis was performed in histological (resected tissue) and cytological (cellblocks from bronchoscopy biopsies) material in a form of formalin-fixed paraffin-embedded blocks, on corresponding analysis platforms. **Result:** The expression of PD-L1 of ≥5% and ≥50% on tumour cells (TCs) was significantly ($p<0.05$) higher in assay with 22C3 (66.7% and 45.8%) than with SP142 antibody (39.6% and 22.9%). The median percentage of PD-L1-expressing TCs was significantly ($p<0.0001$) higher in test with 22C3 than with SP142 antibody. PD-L1 expression on TCs was observed significantly higher in squamous cell carcinoma (SCC) patients than in PD-L1-positive non-SCC patients (p=0,0224). We have observed low percentage of PD-L1-positive cases among patients with common *EGFR* mutations and *ALK* rearrangement. **Conclusion:** Our results support that the highest PD-L1 expression on TCs occurs in SCC patients and in adenocarcinoma patients without common, druggable genetic abnormalities. The obtained results were clearly visible in assays with 22C3 antibody, whereas the SP142 antibody showed more diverse results in the same cases.

Keywords: PD-L1, Immunohistochemistry, non-small cell lung cancer

PUB027 ASSOCIATION OF SOME DEMOGRAPHIC VARIABLES AND RISK FACTORS WITH LOCALIZATION AND HISTOPATHOLOGICAL FORMS OF LUNG CANCER

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Background: Cancer represents a challenge for modern epidemiology with its frequency and high mortality as well as with many etiological unknown facts. The leading type of cancer in the world is the lung cancer (LC). In the Republic of Macedonia LC is on the first place among the ten most common primary sites of cancer. The **aim** of this study was to analyze the eventual causal associations between some variables and the risk factors with the localization, as well as with the histological forms of LC. **Method:** A total of 139 persons of the whole territory of Macedonia diseased from LC were included in the investigation. Disease diagnosis and its pathohistologic verification were done by biopsy analysis, taken within the process of brochoscopy. Eventual existence of an association, i.e. determination of the significance in the difference analyzed among separate statistical series has been tested by Pearson's X^2 test and Kolmogoroff-Smirnoff test (K-S test), for one and two samples. **Result:** Structure of the diseased according to anatomic criteria is with identical sequence in both genders: right–men (51,2%); women (50%);left-men (48,8%); women (50%). Data analysis showed that there was no significant difference in localization of the pathologic process according to anatomic criteria between men and women (Mann-Whitney z=-0,06;p>0,05). According to pulmologic criteria, the process was localized, in greatest percent of the cases, in the right upper lobe (men-26,8% bilaterally; women-33,4% right; 25% left). There was no significant difference concerning the localization of pathologic process among smokers, non-smokers and ex-smokers (Kruskal-Wallis X^2=0,16;DF=2;p>0,05). In the structure of patients, being smokers, malignant process was most frequently localized in the right and left upper lobes (28,4%-bilaterally).The structure of the individuals according to histological characteristics and gender showed that, the most frequent form in men was squamous cell carcinoma (SQC), present in 49,6%. The small cell (SCLC) and adenocarcinoma (ADC) followed with 30,7% and 13,4%, respectively. In women, the first place was taken by ADC with 66,7%. Then followed SCLC (16,7%), and SQC (8,3%). There was statistically significant difference between both genders in relation to the histological type of LC (Mann-Whitney z=-3,32;p<0,01). **Conclusion:** Distribution of the diseased according to anatomic criteria was almost identical in both genders. In majority of patients, the process was localized in the right and the left upper lobes. Smokers were the most represented among the patients with malignant process localized in the lung upper portions.

Keywords: smoking cigarettes, lung cancer, histologic type

PUB028 THE USE OF AN EBUS TBNA FRIENDLY LARYNX MASK

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Background: Optimal performance of endobronchial ultrasound guided trans-bronchial needle aspiration (EBUS-TBNA) requires both anaesthesia care and procedural sedation with the aim of providing patient with as much comfort as possible while also ensuring the operating physician has optimal working conditions. By managing the airway with a supraglottic airway , the upper para-tracheal nodes will be accessible. Deep anesthesia can be avoided, due to effective usage of local topical anesthesia will ensure stable operating conditions without coughing or other discomfort for the patient. The Ambu AuraGain is a second-generation supraglottic airway with a short wide airway tube, combined with a flat back plate creates a stability after placement and a better access of the EBUS-TBNA scope. The oral part of the tube prevents the posibilty of harming the scope if the patient bites the teeth together The objective of this study was to assess the clinical performance of the AuraGain used as a conduit for EBUS-TBNA. **Method:** The study included 20 cases, ASA II-III, eligible for a size 3, 4 or 5 supraglottic airway. The assessment included insertion, working as a conduit for bronchoscopy, fibreoptic assessment of anatomic fit and complications. After each procedure the performance were avaluated by the anaestetist and the endoscopist. **Result:** First attempt insertion success rate was 95% with an overall success rate of a 100%. Average intra cuff pressure to obtain seal was 55.55 cmH2O, and ventilation was performed without leak at up to pPeak of 35 cmH2O which was the maximum pressure permitted. Assessment of ease of maneuvering an EBUS scope via the AuraGain was evaluated. Especially the resistance to advance, retract and rotate the scope in the trachea and the bronchial tree was evaluated based on a 3-point scale, defined as: little resistance, moderate resistance or high resistance. 90% recorded passing a scope as being with little resistance, moderate resistance was felt in 2 cases, and no records of high resistance was experienced. One episodes of patient coughing and biting was recorded, which was due to inadequate anesthesia , but because of the integrated bite absorption area, no dental damage or damage to the scope occurred. Fiberoptically assessment of alignment of AuraGain and the trachea was recorded as 100% satisfactory to accommodate performance of the EBUS procedure with needle aspiration of lymphoid nodes of down 3.mm. **Conclusion:** The AuraGain was effectively utilized for airway management and with a high degree of success for as a conduit for EBUS-TBNA.

Keywords: EBUS TBNA Lanrynx Mask

PUB029 EUDRAGIT COATED CHITOSAN NANOPARTICLES FORCOLON CANCER

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Background: Cancer is the second leading cause of death worldwide, the deaths projected to continue rising, with an estimated 12 million deaths in 2030. Aim of the present investigation is to prepare and compare the uncoated (U-CH NP) and eudragit S 100 coated (E-U-CH NP) chitosan nanoparticles encapsulating a caspase 3 activator (UCN 01), by ionic gelation method. **Method:** The prepared formulations were studied for various parameters like particles size, zeta potential, transmission electron microscopy, atomic force microscopy, *in vitro* release study, *ex vivo* study using Caco 2 colon cancer cell line and *in vivo* studies. **Result:** Developed formulation showed particle size of 168 ± 3.7 nm and 265 ± 4.1 nm for U-CH NP and E-U-CH NP, respectively. The cytotoxicity of prepared formulations was performed on Caco2 cell line by MTT assay. U-CH NP showed enhanced cytotoxicity as compared to blank (without drug) formulation. There was an increase in caspase 3 activity of U-CH NP as compared to UCN 01 alone. The E-U-CH NP showed better in vitro release than uncoated formulation in SCF (pH 6.8) than in SGF (pH 1.2) due to eudragit S 100 coating. E-U-CH NP showed better tumor regression ability than U-CH NP. **Conclusion:** The results obtained demonstrated that E-U-CH NP has continuous release profile of UCN 01 and comprehensive residence time. Thus, it is better acceptable than free UCN 01 and may be a potential delivery system for the targeting and treatment of colon cancer.

PUB030 A NOMOGRAM TO PREDICT THE SURVIVAL OF STAGE IIIA-N2 NON-SMALL CELL LUNG CANCER AFTER SURGERY

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Background: There are concerns regarding heterogeneous survival of stage IIIA-N2 non-small-cell lung cancer (NSCLC) after surgery. The goal of this study was to construct and validate a nomogram, using prognostic variables, to predict the survival following resection for stage IIIA-N2 non-small-cell lung cancer. **Method:** Stage IIIA-N2 NSCLC patients who underwent surgery during the period from 2004 to 2009 in SEER were identified and extracted (N=1765). And external validation was conducted using cohort (N=122) from Jiangsu Cancer Hospital Lung Cancer Center. Cox regression was performed. The nomogram was developed using significant prognostic factors from multivariable analyses and was evaluated internally using bootstrap validation. The performance of the model was evaluated by concordance index(C-index) and calibration curve. **Result:** Cox multivariable analyses identified age, sex, grade, tumor size, lymph node positive radio and surgery type as independent prognostic factors. A nomogram was developed by these factors. The C-indexes of the model were 0.67 (95%CI, 0.64 to 0.70) in training cohort and 0.66 in validation cohort (95%CI, 0.60 to 0.72). The calibration plot showed an optimal consistent between nomogram predicted survival and actual observed survival. Different subgroups stratified by prognostic score showed significant distinctions by survival analysis. **Conclusion:** This study established an effective nomogram for survival outcomes prediction of stage IIIA-N2 NSCLC after surgery and stratified patients by outcomes.

Keywords: Nomogram, Prognosis, Surgery

PUB031 RESEARCH ON CLINICAL EFFECT AND CYTOKINES DYNAMIC CHANGE OF PATIENT WITH ADVANCED MALIGNANT TUMOR TREATED BY PD-1 INHIBITORS

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Background: PD-1 inhibitors hve made breakthrough in the treatment of advanced tumors. But there is no comprehensive understanding of the biomarker related to the clinical effect of PD-1 inhibitors. So we have conducted cytokines detection on patients receiving PD-1 inhibitors treatment and analyzed the possible relation between the dynamic changes and the clinical effect . **Method:** 146 malignant tumor patients receiving Nivolumab or Pembrolizumab for multi-line therapy in our center from January 2015 to January 2017 were collected. And 33 of them took the peripheral blood cytokines test and 35 healthy volunteers are detected as normal control. **Result:** The short-time survival analysis was made after the first cycle treatment, and the clinical effect reached PR 20 cases (13.7%), SD 102 cases (69.9%), PD 24 cases (16.4%).The ORR was 13.7% and the DCR was 83.6%. Up to the end of follow-up, the median PFS was 4.1 months (95%CL: 3.1-5.0) and the median OS was 11.1 months (95%CL: 8.9-13.2). The initial serum concentration of IL-2, IL-7, Basic FGF, GM-CSF and PDGF-bb in the normal control groups is obviously higher than that of advanced tumor patients, and the initial serum concentration of IL-5, IL-6, IL-8, IL-15, IP-10, MIP-1a, MIP-1b and TNF-a in the advanced tumor patients is obviously higher than that of normal control group. The concentration of IL-10 and IP-10 upon the progress of PD-1 inhibitors treatment is obviously higher than before. The concentration of Eotaxin in the disease control group one cycle after

PD-1 inhibitors treatment is obviously higher than that of the progress group; upon three cycles of treatment, the concentration of IL-6 and IL-8 in the progress group is obviously higher than the disease control group. It can be found during the course of 3-cycle and 6-cycle treatment that: cytokines, including IL-1b, IL-6, IL-8, IL-9, MIP-1a and MIP-1β rather steadily change in PR+SD group and fluctuate greatly and even rise sharply in PD group; IL-1ra, IL-2 and IL-15 show crosscurrent, which means they are on the rise in PR+SD group while overall change steadily or lower in PD group. **Conclusion:** Malignant tumor patients after multi-line therapy can benefit from the PD-1 inhibitors and the concentration change of some peripheral blood cytokines may related to the clinical effect of PD-1 inhibitors.The increase in the cytokines, including IL-1ra, IL-2 and IL-15 may hint better clinical effect; however, the increase in cytokines such as IL-1b, IL-6, IL-8, IL-9, MIP-1a and MIP-1β may hint poorer clinical effect of PD-1 inhibitor treatment.

Keywords: cytokines, clinical effect, PD-1 inhibitors

PUB032 THE ASSOCIATION BETWEEN SOX2 AND PD-L1/CD8 EXPRESSION AND THEIR PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH RESECTED LUNG SQUAMOUS CELL CARCINOMA

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Background: *SOX2* gene alterations have been recognized as the candidate driver mutations of lung squamous cell carcinoma (LSCC). The aim of the present study was to evaluate association between SOX2 expression and PD-L1/CD8 expression and their prognostic value in patients with resected LSCC. **Method:** A total of 198 patients with resected LSCC together with matched lymph node metastases (LNM, n = 42) were included. The expression levels of SOX2, PD-L1 and CD8 in both primary tumor and metastatic lymph nodes were evaluated by immunohistochemistry. **Result:** There are no correlation between SOX2 or PD-L1 expression and clinicopathlogical features including age, sex, smoking history, differentiation, pathological stage, surgical procedures and pleural/angiolymphatic invasion. Low differentiation and pleural invasion were significantly associated with high CD8 expression ($P < 0.001$). In cases with matched LNM, PD-L1 expression in primary tumor was consistent with it in LNM, while SOX2 and CD8 expression in primary tumor were not consistent with those in LNM. In addition, SOX2 ($r = 0.146$, $P = 0.040$) or CD8 ($r = 0.214$, $P = 0.002$) expression level was significantly associated with PD-L1 expression level in primary tumor. Patients with positive SOX2 expression had markedly better DFS (HR, 0.492; 95% CI, 0.206-0.851; $P = 0.016$) but marginally longer OS (HR, 0.560; 95% CI, 0.243-1.040; $P = 0.065$). CD8 expression was associated with significantly longer OS (HR, 0.413; 95% CI, 0.220-0.774; $P = 0.005$) but marginally longer DFS (HR, 0.579; 95% CI, 0.321-1.045; $P = 0.069$). PD-L1 expression was not associated with DFS or OS. Moreover, the combination of SOX2 and CD8 expression could be well stratified the total populations into four different groups with distinct prognosis. In multivariate analysis, SOX2 expression was dramatically correlated with longer DFS (HR, 0.502; $P = 0.023$) and CD8 expression was associated with significantly longer OS (HR, 0.505; $P = 0.026$). **Conclusion:** The expression of PD-L1 in primary tumor was consistent with that in LNM. There was a positive correlation between SOX2 or CD8 expression and PD-L1 expression. The combination of SOX2 and CD8 expression was a promising prognostic factor in patients with resected LSCC. The results of our study may be expected to serve as useful information to predict the postoperative prognosis and for immunotherapy in patients with resected LSCC.

Keywords: non-small cell lung cancer, Programmed cell death ligand 1, sex determining region Y-box 2

PUB033 THE ROLE OF REMOTE ACCESS PLATFORMS FOR CONTINUOUS ENGAGEMENT OF MESOTHELIOMA PATIENTS AND COMMUNITY MEMBERS

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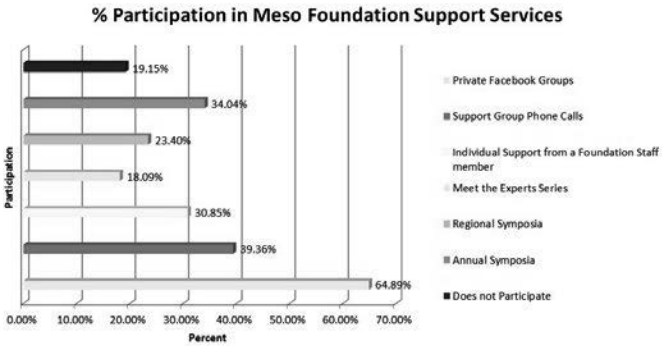
Background: Mesothelioma, a rare cancer known to be caused by exposure to asbestos fibers, has not decreased in incidence over the past 15 years (CDC). As treatments and technologies continue to advance, there is a growing need for support networks. **Method:** Mesothelioma community members were surveyed through our database to assess demographics and engagement with the foundation. An electronic survey platform was used to collect the data. **Result:**



Of those that participated in this survey, 69.66% are not in active treatment. The demographics of those that participated in the survey are as follows: Patients (44.68%), Caregiver (29.79%), Bereaved (24.47%), Other (1.06%); Male (30.43%), Female (69.57%). Of those surveyed, individuals were disseminated over 28 states. **Conclusion:** These data highlight the importance of an online platform as an interface of support communication. Because of the rare and remote nature of mesothelioma, accessible and consistent in-person support networks do not exist. We found that the primary mode of community member engagement was through private Facebook groups, and that participating through this online platform constructs a comprehensive community interface. Facebook groups, while remote, provide real-time access to others in similar situations, enhancing the feeling of community and decreasing the feeling of isolation globally. For rare cancers, it is imperative that remote care is comprehensively cultivated to accommodate the disseminated geographic nature of individuals and to permit continuous engagement of mesothelioma patients and community members.

Keywords: Mesothelioma, support groups, social media

PUB034 AUTOMATED QUANTIFICATION OF KI-67 INDEX ASSOCIATES WITH PATHOLOGIC GRADE AND PROGNOSIS OF PULMONARY NEUROENDOCRINE TUMORS

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Background: Pulmonary neuroendocrine tumors (PNETs) can be classified as four variants: typical carcinoid (TC), atypical carcinoid (AC), small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC). Classification of the four tumor categories is a step-wise process identified by the presence of necrosis and number of mitoses per $2mm^2$. In NE tumor pathology, Ki-67 was first described as prognostic factor in the pancreas and was incorporated into the grading system of digestive tract NE neoplasms in the 2010 World Health Organization (WHO) classification. However, the significance of Ki-67 has not been fully studied in PNETs. The purpose of our research is to investigate the potentially diagnostic value of Ki-67. **Method:** We retrieved 160 surgical specimens of pulmonary neuroendocrine tumors (37 TC, 2 AC, 30 LCNEC, 91 SCLC) based on mitotic rate and histologic features. A nuclear quantitation algorithm was used to calculate the Ki-67 proliferative index (PI). Six equivalent fields (500 × 500μm) at 10× magnification were manually annotated for digital image analysis. The mitotic activity was manually quantitated in the most cellular areas on whole-slide images, eight 40× high power fields were calibrated as 2 mm^2. **Result:** The median mitotic count and Ki-67 index for TC, AC, LCNEC, and SCLC were 1 and 3.96%, 6 and 28.91%, 58 and 57.62%, 118 and 79.3%, respectively. However, the Ki-67 index overlapped among the four groups, with ranges of 0.38-13.49% for TC, 16.34-41.48% for AC, 30.67-93.74% for LCNEC, and 12.43-96.87% for SCLC. The Ki-67 index was positively associated with mitotic number ($P<0.001$). Neuroendocrine carcinomas can be separated into two groups, high grade (Ki-67>10%) and low grade (Ki-67≤10%). However, there is no adequate threshold to separate pulmonary AC from TC and no statistic difference of Ki-67 index between LCNEC and SCLC. For the univariate survival analyses in PNETs, both the Overall Survival (OS) and Progression Free Survival (PFS) correlated with Ki-67 index, mitotic number and nodal metastasis . But none of them was proved to be an independent prognostic factor. In high grade PNETs, multivariate analysis revealed that tumor size has a trend of being an independent prognostic factor, but did not reach significant level ($P=0.085$). **Conclusion:** Our results indicate that software-automated quantitation of Ki-67 index is a reliable method to predict the prognosis of PNETs. In addition, Ki-67 index can be a useful adjunct to pathologic grade in pulmonary neuroendocrine carcinoma.

Keywords: mitotic number, Ki-67 index, Pulmonary Neuroendocrine tumors

PUB035 CONFIRM: A PHASE III RANDOMIZED TRIAL TO EVALUATE THE EFFICACY OF NIVOLUMAB VERSUS PLACEBO IN RELAPSED MESOTHELIOMA

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Background: Mesothelioma is an incurable, apoptosis-resistant cancer caused in most cases by previous exposure to asbestos and is increasing in incidence. It represents a growing health burden but remains under-researched, with limited treatment options. Despite a significant number of clinical studies in the second line setting, no randomized study has been positive. Early promising signals of activity relating to both PD-L1 and PD-1 targeted treatment in mesothelioma implicate a dependency of mesothelioma on this immune checkpoint, and support the development of a randomized phase III trial to evaluate the efficacy of nivolumab. CONFIRM is the first ever placebo controlled, randomized phase III trial of a PD-1/PD-L1 immune checkpoint inhibitor in mesothelioma. **Method:** The primary objective is to determine whether nivolumab increases overall survival (OS) in relapsed mesothelioma. Secondary objectives are to determine whether nivolumab a) increases progression-free survival, b) increases response rate, c) has good safety/tolerability, and d) results in acceptable patient quality of life and cost per quality adjusted life year. A translational study will be undertaken to determine the correlation between OS and i) PD-L1 expression, ii) mutational burden (estimated by genome-wide analysis of copy number alterations), iii) immunotranscriptomic profile. Developed by researchers at the Universities of Leicester and Southampton on behalf of the UK NCRI Lung Clinical Studies Group the trial is co-ordinated by the Cancer Research UK Southampton Clinical Trials Unit in the UK, within the Centre of Cancer Immunotherapy. The trial will recruit 336 patients with pleural or peritoneal mesothelioma who have received at least two prior lines of therapy, from UK sites between March 2017 and 2021. We are also investigating opening recruitment to international sites. Patients will be randomized 2:1 (treatment: control), stratified according to epithelioid vs. non-epithelioid and center, to receive 240mg nivolumab (anti PD-1 antibody) monotherapy or saline placebo as a 30-minute intravenous infusion. Allocation will be double-blind. Treatment will be on day one of each 14-day cycle, until disease progression for a maximum of 12 months. Trial follow up will continue for 6 months after the last participant has progressed, or completed or discontinued treatment. The trial is powered (80%, with 2-sided 4% significance level) to detect a hazard ratio of 0.7 using an adjusted Cox regression model (time-to-event) and will be analyzed using intention-to-treat. This trial is funded by Cancer Research UK (C16728/A21400) and Bristol Myers Squibb (CA 209-841). Trial registrations: NCT03063450 and ISRCTN79814141. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Nivolumab, Mesothelioma, Immunotherapy

PUB036 IS PREOPERATIVE EGFR-TKI COMPARABLE WITH CHEMOTHERAPY FOR STAGE II-IIIA LUNG ADENOCARCINOMA?

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Background: Although it has been proved that preoperative chemotherapy could improve disease-free survival (DFS) and overall survival in stage IB-IIIA resectable NSCLC, the role of neoadjuvant targeted therapy has not been established. Our purpose is to investigate the efficacy and safety of induction EGFR-TKI compared with neoadjuvant chemotherapy, in order to explore optimal strategy for the treatment. **Method:** From 2013 to 2016, we retrospectively reviewed clinical records of stage I-IIIA lung adenocarcinoma patients, who had received at least two cycles of neoadjuvant chemotherapy or at least 4 weeks of induction targeted therapy followed by surgery. Gathered data were tested for significance between chemo and targeted therapy group. Tumor samples were collected and analyzed by sequencing to explore EGFR-TKI resistance mechanisms. **Result:** 60 patients were enrolled in this study, of whom 80% were stage II-IIIA. Of all the cases, 17 harboring EGFR mutation received induction EGFR-TKI, whereas 39 received chemotherapy. Another 4 received TKI following chemo before surgery. Among EGFR mutant patients, objective response rate (ORR) was 47.6% for neoadjuvant EGFR-TKI, and 32.6% for chemotherapy (p=0.300). In subset analysis, for stage II to IIIA EGFR mutant patients, neoadjuvant targeted therapy had significant tumor response compared with chemotherapy (ORR: 66.7% vs. 34.8%, p=0.020). Of 21 preoperative EGFR-TKI cases, 10 patients received continued administration (47.6%): a further tumor size reduction was noted by the second month of TKI administration if clinical response was achieved initially, whereas no apparent shrinkage was observed by the third month's TKI. No further shrinkage was achieved by continued administration if initial tumor size reduction was little. No difference in postoperative complication, drainage volume and hospital days was seen between chemo and targeted therapy. A series of molecular mechanisms of EGFR-TKI resistance including BIM deletion polymorphisms, T790M mutation, loss of PTEN, AKT and PIK3CA mutation were detected. **Conclusion:** Compared with chemotherapy, neoadjuvant EGFR-TKI is an efficacious approach for stage II-IIIA EGFR mutant NSCLC patients. A second month's extended TKI administration could be recommended if initial clinical response was achieved. These results, together with molecular detection, might provide evidence for further investigation of the treatment by randomized controlled trials.

Keywords: lung adenocarcinoma, EGFR mutation, neoadjuvant targeted therapy

PUB037 18 FLUORODEOXYGLUCOSE: BEYOND DIAGNOSIS TO USE IN NOVEL THERAPY

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Background: PET CT scan has revolutionized the treatment of several types of cancer especially Lymphoma (Hodgkin's Disease and aggressive Non Hodgkin Lymphoma), Non Small Cell Lung Cancer, Head and Neck Squamous Cell Cancers and various other cancers that express 18-FDG avidity. 18FDG PET CT provides structual and functional imformation and provides more accurate extent of disease spread and localization of malignancy. The high FDG concentration may be used to selectively kill all FDG avid tumor cells. **Method:** 18 Fluorodeoxyglucose is preferentially concentrated in tumor tissue due to high tumor activity (reportedly 200 times more glycolysis than normal tissue cells). Alkylating chemotherapy agents like Cyclophosphamide have high non cell cycle specific tumoricidal property. If we can successfully conjugate an alkylating agent with an 18FDG radio isotope, we can attain high concentrations of the chemotherapy drug within the tumor tissue while normal tissues are selectively spared (less toxicity). Massive preferential killing of tumor cells can be expected in such a situation producing a Complete Response (CR) or a Partial Response (PR) of the tumor tissue be it localized disease or the distant metastasis. **Result:** Section not applicable **Conclusion:** The new approach usincg FDG seems to be promising as it's expected to target both local and metastatic disease. The discussion provided here may be put into preclinical studies for studying the efficacy of this new therapeutic modality before clinical trials may be carried out.

Keywords: Targeted therapy, NSCLC, Fdg pet

PUB038 PROGNOSTIC IMPACT OF FOXP3-POSITIVE TUMOR INFILTRATING LYMPHOCYTES IN SMALL-CELL LUNG CANCERS

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Background: Backbone of treatment for small-cell lung cancer (SCLC) is chemo-radiotherapy while surgery is performed in highly selected patients with limited disease. The outcome is disappointing and more effective management is needed. Aim of the study is to evaluate prevalence, correlation with clinicopathological features and prognostic impact of PD-L1 expression and tumor infiltrating lymphocytes (TILs) in SCLCs. **Method:** We have retrospectively reviewed SCLCs referred to our Institution from 1996 to 2015. 127 patients were included: 48 underwent multimodal treatment including surgery, 25 chemo-radiotherapy, 54 received chemotherapy for metastatic disease. PD-L1, CD3, CD8 and FOXP3 expression was assessed by immunohistochemistry. Staining in >5% of tumor cells defined PD-L1 positivity. CD3, CD8 and FOXP3 were evaluated by semiquantitative score (0 to 3+). Bcl-2 and p53 expression, mitotic count and necrosis were also evaluated. **Result:** 48 surgically resected SCLCs were analyzed. PD-L1 was positive in 30 (62%) samples. All cases were scored positive for CD3 and CD8: 20, 24 and 4 cases were classified as 1+, 2+ and 3+ for CD3, whereas 21, 22 and 5 cases were classified as 1+, 2+ and 3+ for CD8, respectively. Regarding FOXP3, n=12 cases were scored as 0, n=31 as 1+ and n=5 as 2+. Positive correlation between CD8 and FOXP3 was noticed (p<0.001); Bcl2 expression was inversely associated with FOXP3 and positively with PD-L1 (p=0.02 and p=0.03). Median overall survival (OS) was 62.3 (95% CI: 32.4-82.1) months. The presence of FOXP3-positive TILs (score>0) was associated with improved outcome: median OS was 69 (95% CI: 42.7-95.3) and 20 months (95% CI: 0.1-59) for FOXP3-positive and negative patients, respectively (log-rank p=0.004). In multivariate analysis including other confirmed prognostic factors FOXP3 maintained significant association with OS. Molecular analyses in the other groups of patients are ongoing.

Clinical and biological prognostic factors: univariate and multivariate analysis			
		Univariate analysis HR (95%CI)	Multivariate analysis HR (95% CI)
FOXP3	0 1+/2+	- HR: 0.34 (0.16-0.74) p<0.0001	- HR: 0.37 (0.17-0.82) p:0.014
Surgical margins	Negative Positive	- 1.96 (1.01-3.83) p:0.048	- 2.33 (0.93-5.83) p:0.72
Mediastinal nodal involvement	No Yes	- 2.56 (1.14-5.77) p:0.023	- 2.10 (0.95-4.64) p:0.066

Conclusion: The presence of FOXP3-positive TILs is associated with improved outcome in surgically resected SCLCs.

Keywords: small cell lung cancer, tumor-infiltrating lymphocytes (TILs), PD-L1

PUB039 FDG-PET SCANNING HAS A LIMITED ROLE IN THE MANAGEMENT OF LOW AND INTERMEDIATE GRADE NEUROENDOCRINE TUMORS OF LUNG

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Background: Positron emission tomography (PET) provides information on staging, extent of disease and prognosis in lung cancer. Attempts to use PET in low grade (typical-TC) and intermediate grade (atypical-AC) pulmonary neuroendocrine tumors have led to conflicting results. We aim to assess the utilization of PET and its impact on the risk of recurrence and survival. **Method:** Retrospective review of 436 consecutive patients who underwent resection for primary TC and AC from 2000-2016 in 8 centers. Patients with and without PET were described. We compared 229 patients as PET positive (PET+) or negative (PET-), positive defined as SUV≥2.5. Factors influencing recurrence and survival were assessed by Cox regression analysis. **Result:** PET was obtained in 52.5% (229/436) of patients with 70.7% (162/229) positive (Table 1). Compared to those without a PET, TC patients with a PET were older with fewer central tumors and underwent more sublobar resections. AC patients were older with fewer central tumors and similar rates of anatomic resection. In 177 TC patients, more recurrences occurred in the PET+ group (6 vs 2, p=0.06). The disease free interval (DFI) was shorter in the PET+ group (20.0 vs 63.5 months, p=0.60). Overall survival was similar (42.4 vs 44.0 months, p=0.64). In 52 AC patients, all recurrences occurred in PET+ patients (10 vs 0, p=0.76). The DFI was shorter in the PET+ group (10.7 vs 30.3 months, p=0.49). Overall survival was similar (35.5 vs 33.8 months, p=0.07). After univariable analysis, a PET+ scan was not associated with survival (HR=-0.27, 95% CI=0.33-2.91, p=0.96) or recurrence (HR=0.55, 95% CI 0.62-4.81, p=0.29).

Table 1: Patient Characteristics by Typical and Atypical Carcinoids				
	PET + N=162 (37.2%)	PET- n=67 (15.4%)	p Values	PET null N=207 (47.5%)
Typical	118 (72.8%)	59 (88.1%)		180 (87.0%)
Age (median)	62	63		56
Sex (%F)	89 (75.4%)	37 (62.7%)	0.001	113 (63.8%)
Tumor size (median)	2.2	1.8	0.05	2.6
Central tumor	30 (24.4%)	13 (22.0%)	0.001	109 (63.7%)
Surgery				
Lobectomy	69 (58.5%)	28 (47.5%)	0.99	131 (72.8%)
Wedge resection	37 (31.4%)	28 (47.5%)	0.99	31 (17.2%)
Bilobectomy	6 (5.1%)	3 (5.1%)	0.99	15 (8.3%)
Pneumonectomy	6 (5.1%)	0	0.99	3 (1.7%)
Lymphadenectomy				
Sampling	55 (46.6%)	22 (37.3%)	0.66	80 (44.4%)
Complete	39 (21.4%)	17 (28.9%)	0.66	72 (40.0%)
Atypical	44 (27.2%)	8 (11.9%)		27 (13.0%)
Age (median)	61	61	0.84	58
Sex (%F)	29 (65.9%)	5 (62.5%)	0.08	18 (66.7%)
Tumor Size (median)	3	2.2	0.52	2.2
Central tumor	13 (29.6%)	2 (25.0%)	0.98	16 (59.2%)
Surgery				
Lobectomy	28 (63.6%)	5 (62.5%)	0.98	17 (63.0%)
Wedge resection	6 (13.6%)	2 (25.0%)	0.98	4 (14.8%)
bilobectomy	3 (6.8%)	0	0.98	3 (11.1%)
pneumonectomy	7 (15.9%)	1 (12.5%)	0.98	3 (11.1%)
Lymphadenectomy				
Sampling	21 (48.0%)	6 (75.0%)	0.15	15 (56.0%)
Complete	22 (50.0%)	2 (25.0%)	0.15	9 (33.0%)

Conclusion: The majority of tumors were PET+. PET was used in peripheral nodules and older patients. Central tumors were less likely to undergo PET. PET does not predict recurrence or survival but may predict a shorter DFI. The role of PET is limited in TC and AC.

Keywords: Positron emission testing imaging, Neuroendocrine tumor

PUB040 FORMULATION AND EVALUATION OF EMBELIN LOADED TRANSFERSOME FOR EFFECTIVE TREATMENT OF SKIN CANCER

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Background: Transdermal drug delivery has made an important contribution to medical practice, but has thus far to fully achieve its potential as an alternative to oral delivery and hypodermic injections. The object of the present study was to formulate and evaluate transfersomal vesicles of embelin a natural benzoquinone derivative as a transdermal drug delivery system. Embelin is obtained from dried fruit of *Embelia ribes* and widely used in potent Cancer, fungal, bacterial and viral infection. **Method:** It was investigated by incorporate the drug in various transfersomal formulations composed of various ratios (1:1, 1:2, 2:1) of different spans-80 and tween-80 prepared by thin film hydration method. The prepared formulations were characterized and optimized. **Result:** The vesicles were spherical in structure as confirmed by transmission electron microscopy. The best entrapment efficiency of embelin in the vesicles was in the 89.86% (F3). The result revealed that embelin in all of the formulations was successfully entrapped with uniform drug content. A transfersomal gel containing 2% of drug, carbopol 934 (1%, 2%, 3% and 4%) and propylene glycol was concluded as the optimized formulation (H3). **Conclusion:** This research suggests that embelin loaded transfersomes can be potentially used as a transdermal drug delivery system for treatment of skin cancer.

PUB041 POTENTIALLY OVERLOOKED BRANCHES OF THE LEFT PULMONARY ARTERY

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Background: During pulmonary resection, we sometimes encounter 'pitfall branches' of the pulmonary artery (PA) which could cause serious vessel injury. Current computed tomography (CT) instrument and computer processing technology can identify the PA along the peripheral bronchus, thereby revealing the true rates of the different PA branching patterns. Knowledge of these branching patterns allows safe and definitive surgery. **Method:** For 186 cases of left lung resection performed at our institution from January 2006 to September 2011, two general thoracic surgeons and one radiologist independently reviewed CT images and examined the branches of pulmonary artery arising from pars mediastinalis. **Result:** Branching patterns of lingular artery included17 cases with mediastinal origin (9.2%), 50 cases with interlobar and mediastinal origins (26.9%), and 119 cases with interlobar origin (63.9%). The two types of lingular artery of mediastinal origin, which were potentially overlooked during surgery, were observed in 36.1% of cases. This was a higher rate than previously reported. Moreover, mediastinal basal PA (A4+5+8+10 abnormal branching) was seen in 1 case. **Conclusion:** Potentially overlooked branches of the left PA arising from pars mediastinalis are much higher than we expected. It is crucial to understand the branching pattern of the PA by preoperative CT assessment.

Keywords: Pulmonary artery, Surgery, Computed Tomography

PUB042 THE DETECTION AND ANALYSIS OF RET GENE FUSION IN NON-SMALL LUNG CANCER INHIGH-THROUGHPUT SEQUENCING

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Background: The non-small lung cancer is one of the most malignant tumors threats to the human health. Moreover, the morbidity and mortality of non-small lung cancer have increased year by year, and is one of the major public health problems in China. In recent years, Lung cancer-driven genes provide a clear treatment for the non-small lung cancer, and the molecular targeted drugs can significantly improve the living quality for the non-small lung cancer patients. Therefore, it is important to detect and assessment of patient's mutation accurately is particularly important. RET protein is one kind of tyrosine kinase receptor and the RET proto-oncogene located in chromosome No. 10 chromosome q11.2 area. RET gene often fractures and re-combined with another gene, which have the function of self-phosphorylation and automatic signal transmission to escape the control of Ligand. **Method:** This study collected non-small lung cancer 380 cases in the Department of Pathology, Zhongnan Hospital of Wuhan University from June 2016 to June 2017. The descriptive epidemiology method was used in these cases to analyze the age's classification, WTO clinical stage, histological grade, lymph node metastasis and the gene mutation of the tumors. The high throuthput parallel sequencing methods were used to detected the gene mutation of EGFR, KRAS, NRAS, RAS,BRAF, PIK3CA, PTEN, AKT1 and HER2, and detected the gene fusion of ALK, ROS1and RET. **Result:** Then on the base of these cases, the gene mutation and gene fusion rate were screened and analyzed as well as the correlation research between the various types of genetic changes in non-mall lung cancer and the epidemiological studies. **Conclusion:** The purpose of this study was to reveal the screening rate, molecular genetic characteristics and pathogenesis of non-small lung cancer in the local region. Then, to establish and implement the ideal initial target genes detection in non-small lung on specific and sensitive.

Keywords: Non-small lung cancer; RET gene fusion; High-throughput sequencing

PUB043 SECOND HAND SMOKE "A THREAT TO CHILD'S HEALTH AND DEVELOPMENT"

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Background: According to the Global Youth Tobacco Survey 2008, 25.9% students in Lagos Nigeria currently live in homes where others smoke in their presence, 43.1% are around others who smoke in places outside their home, 14.6% of the students currently use any tobacco product. 38.9% think smoke from others is harmful to them, 5.0% have one or more parents who smoke while 2.4% have most or all friends who smoke. It is evident that second-hand smoke causes many of the same diseases as direct smoking, including cardiovascular diseases, lung cancer, and respiratory diseases. **Method:** A descriptive cross sectional study was carried out in Ibadan, involving students who doesn't attend schools regularly in 10 schools in Ibadan Oyo State, Nigeria. A multistage cluster random sampling was employed to select **300** students in the schools. Data was collected using structured questionnaires by trained interviewers. **Result:** The result revealed that 141 (47%) were within the age group 15 to 17 years, 110 (36.7%) were within the age group 12 to 14 years while 49 (16.3%) of the respondents were within the age group 18 to 20 years. Ninety one (30.3%) of the respondents live with both parents, 79 (26.3%) live with relatives, 66 (22%) live with father alone while 64 (21.3%) also live with mother alone. A majority, 149 (49.7%) have relatives, parents or siblings who smoke around them, 123 (41%) have experienced sicknesses related to pneumonia and 90 (30%) have experience asthma. The result further showed that about 268 (89.4%) students not attending school regularly are attributed to second hand smoking related illnesses. **Conclusion:** Since Second Hand Smoke affects a child's health, education and overall development in Ibadan, Oyo State Nigeria. The State government should intensify effort towards domestication of the National Tobacco Control Law in Oyo State.

Keywords: Tobacco Control, Second Hand Smoking, Tobacco Related Illnesses

PUB044 DIAGNOSTIC VALUE OF FR$^+$-CTCS DETECTED BY LT-PCR FOR LUNG CANCER IN SPN AND TUMOR INVASIVENESS IN ADENOCARCINOMA (T<<3CM)

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Background: To investigate the diagnostic value of folate receptor (FR)-positive circulating tumor cells (CTCs) detected by ligand-targeted polymerase chain reaction (LT-PCR) in distinguishing lung cancer from lung benign diseases in patients with solitary pulmonary nodules (SPN), and to identify the tumor invasiveness in lung adenocarcinomas of 3cm or smaller. **Method:** We enriched FR$^+$-CTCs by immunomagnetic depletion of leukocytes and labeling with a conjugate of a tumor specific ligand folic acid and a synthesized oligonucleotide. The bounded conjugates were then analyzed by quantitative PCR (qPCR). Blood samples were collected from 319 lung cancer patients (257 adenocarcinoma patients), 120 benign patients. Including 257 lung adenocarcinoma patients, 41 were adnocarcinoma in situ (AIS), 53 were microinvasive adnocarcinoma (MIA), and 163 were invasive adnocarcinoma (INV). The clinicopathological characteristics were analyzed from medical records. **Result:** Patients were randomly assigned to a training set and a validation set. FR$^+$-CTC levels of patients with lung cancer were significantly higher than patients with benign lung diseases (p=0.000). With a threshold of 8.74 CTC units, FR$^+$-CTC showed a markedly sensitivity (training set, 72.05%; validation set, 74.36%) and specificity (training set, 80.9%; validation set 77.42%) in the diagnosis of lung cancer. When compared with established clinical biomarkers including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), CA-125, squamous cell related antigen (SCC), and neuron-specific enolase (NSE), FR$^+$-CTC showed the highest area under the receiver operative characteristic curve (training set, 0.754; validation set 0.765). With a threshold of 9.051 CTC units, FR$^+$-CTC showed a comparable sensitivity (training set, 77.50%; validation set, 79.07%) and specificity (training set, 61.24%; validation set 60%) to CEA and CA-125 in distinguishing the AIS from INV. Notably, the combination of FR$^+$-CTC with established clinical biomarkers including CEA, CYFRA21-1, CA-125, SCC and NSE could significantly improve the diagnostic efficiency. **Conclusion:** LT-PCR based FR$^+$-CTC detection platform is reliable to be used as a biomarker for the diagnosis of lung cancer in patients with SPN, moreover, the FR$^+$-CTC level might be a promising biomarker to identify the tumor invasiveness in lung adenocarcinomas of 3cm or smaller.

Keywords: lung cancer;, Circulating tumor cells, Folate receptor

PUB045 ANTI-TUMOR EFFECT OF HONOKIOL IN LUNG SQUAMOUS CELL CARCINOMA

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Background: Patients with lung squamous cell carcinoma(SCC) still benefit few from new therapies of lung cancer, and seeking for potential effective therapies is imperative. Honokiol (HNK) is a natural compound isolated from the magnolia plant with numerous pharmacological activities and exerts anticancer activity, Here, we demonstrated that the effect of HNK in lung SCC cells in vitro and related signaling mechanisms. **Method:** Cell viability of human lung SCC cell lines NCI-H520 and SK-MES-1 exposed to HNK were measured by CCK-8. Flow cytometry was applied to identify the cellular apoptosis with HNK exposure of SCC cells compared to lung adenocarcinoma cells. Fibroblast growth factor(FGF)-2 expression of both SCC cells with HNK exposure were explored by quantitative real-time PCR. Furthermore, the effect of HNK on FGFR1 and signal pathways related to proliferation, apoptosis and cell cycle were detected by western blot. **Result:** In two subpopulations of human lung SCC cells, NCI-H520 and SK-MES-1, HNK exposure remarkably inhibited the cell proliferation in both time-and dose-dependent manners. Compared to A549 cells, a more significant cell apoptosis was observed in NCI-H520 cells after HNK incubation. Next, real-time PCR analysis indicated that HNK down-regulated the expression of FGF2 in both NCI-H520 cells and SK-MES-1 cells in dose dependence. Meanwhile, HNK also obviously inhibited FGFR1 in both cell lines. Moreover, HNK exposure activated PARP and caused caspase-3 cleavage, suppressed cyclineD1 and ERK expression. **Conclusion:** These results broaden our understanding of the mechanisms on HNK effects in lung SCC, and reinforce the possibility of its potential anticancer benefit on SCC patients.

Keywords: honokiol, Lung Squamous cell carcinoma, signal pathway

PUB046 SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES – A SINGLE TERTIARY CENTER EXPERIENCE

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Background: Brain metastases (BMs) are common in patients with small cell lung cancer (SCLC) and are usually fatal. The purpose of this analysis is to evaluate the outcomes of SCLC patients with BMs and explore the prognostic factors. **Method:** Pathological diagnosis of SCLC patients with radiologically confirmed BMs were enrolled except those who received surgery of primary lesion. Overall Survival (OS) was calculated from the date of diagnosis of BMs to the date of death from any cause, or the last follow-up. Univariate and multivariate analyses were performed by the log-rank and Cox's proportional hazard model test, respectively. **Result:** From January 2012 to October 2016, 116 patients were eligible for the study. The median follow-up time was 14 months (range 1-77). For the entire cohort, median OS was 9 months (95% CI, 7.6-10.4), 1- and 2- year OS rate were 31.2% and 7.7%, respectively. As expected, the OS of patients with oligmetastatic BMs (3) turned out to be significantly better compared to the survival of patients with non-oligmetastatic BMs (>3) (10 months vs 7 months, P<0.05). Similarly, median OS of patients with initial brain metastatic presentation was 11 months (95% CI, 9.4-12.6) while OS of patients with brain metastatic development during follow-up was 7 months (95% CI, 5.7-8.3), the difference was statistically significant (P<0.021). In addition, patients received radiation to brain or chemotherapy after diagnosis of BMs also had a significantly better survival rate (P<0.001). Multivariate analyses revealed sex, radiation to brain, number of BMs and chemotherapy after diagnosis of BMs were relevant parameters in predicting outcome of SCLC patients with BMs. **Conclusion:** In our investigated population, median OS of SCLC patients with BMs was 9 months. Therapy after diagnosis of BMs (radiation to brain or chemotherapy) could improve clinical outcomes. Meanwhile, sex and number of BMs were implicated to have an impact on survival and may provide stratification factors in predicting prognosis in future.

Keywords: brain metastases, SCLC

PUB047 EFFICACY OF EGFR-TKI FOR LUNG ADENOSQUAMOUS CELL CARCINOMA HARBORING EGFR MUTATION

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Background: Lung adenosquamous cell carcinoma (ASC) is a rare subtype of lung cancer. Little is known about the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) for lung ASC with EGFR mutation. **Method:** We retrospectively analyzed 44 patients with advanced or recurrent lung ASC harboring EGFR mutation who were treated with EGFR-TKI from two cancer centers to investigate the efficacy. Then a pooled analysis on the efficacy of EGFR-TKI was performed in 74 patients including 30 patients selected from 11 published reports. **Result:** In our bicenter study, for the ASC patients treated with EGFR-TKI, the objective response rate (ORR), the disease control rate (DCR), the median progression free survival (mPFS) and the median overall survival (mOS) were 54.5%, 79.5%, 8.8 months and 19.43 months, respectively. In pooled analysis, the ORR, DCR, mPFS and mOS of ASC patients were 63.4%, 85.9%, 10.00 months and 21.37 months, respectively. Similar PFS (11.0 vs. 10.0 months; P=0.771) and OS (23.67 vs. 20.33 months; P=0.973) were found in patients with deletion in exon 19 and exon 21 L858R mutation. The patients treated with erlotinib or gefitinib had a trend of better OS than those treated with icotinib. **Conclusion:** EGFR-TKI is an effective treatment for ASC harboring EGFR mutation, comparing with historical data, similar to EGFR-mutated adenocarcinoma (ADC). Further study is needed to identify the different role of the two components of ASC in EGFR treatment.

Keywords: EGFR mutation, EGFR-TKI, lung aenosquamous carcinoma

PUB048 DOWN-REGULATION OF SHISA3 IS ASSOCIATED WITH GEFITINIB RESISTANCE IN NON-SMALL CELL LUNG CANCER

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Background: The failure of targeted therapy due to the resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, is considered a major problem in the treatment of non-small cell lung cancer (NSCLC) patients. Shisa3, a novel tumor suppressor, is associated with prolonged survival through promoting β-catenin degradation in NSCLC. Nevertheless, the relationship between Shisa3 and EGFR-TKIs resistance has not been elucidated. **Method:** The correlation of shisa3 and EGFR-TKI resistance were determined by comparison of gene expression profiles in NSCLC patient tumor samples with different therapeutic benefits for EGFR-TKIs. The effect of Shisa3 on drug sensitivity, invasion, and migration in NSCLC cells and on tumor growth and drug susceptibility in mice models were examined by knockdown and overexpression of Shisa3. The underlying mechanism of Shisa3 was explored by microarray and pathway analysis. Finally, the correlation of Shisa3 expression and clinical effect for EGFR-TKIs was also calculated. **Result:** We identified that Shisa3 was highly expressed in the tumor tissues of patients with partial response(PR) in EGFR-TKIs treatment and is down-regulated in gefitinib-resistant (PC9-Gef, H1975, H1650) cells compared to gefitinib-sensitive (PC9, HCC827) cells. The down-regulation of Shisa3 could induce gefitinib resistance and enhance invasiveness through PI3K/AKT/mTOR signaling predicted by microarray analysis. Furthermore, The down-regulated expression of Shisa3 could inhibit the activation of autophagy. Rather, the up-regulaton of shisa3 could enhance gefitinib sensitivity by inhibit PI3K/AKT/mTOR signaling and the activation of autophagy. In addition, our data confirmed that Shisa3 was positively associated with clinical effect for EGFR-TKIs in 20 NSCLC patients. **Conclusion:** Our results reveal that the prospective role of Shisa3 as a novel biomarker for acquired gefitinib resistance and a potential target for NSCLC treatment.

Keywords: non-small cell lung cancer, gefitinib, Shisa3

PUB049 TRENDS IN FIRST-LINE CHEMOTHERAPY TREATMENT FOR ADVANCED NSCLC PATIENTS IN CHINA: A MULTICENTER 10-YEAR (2005-2014) RETROSPECTIVE STUDY

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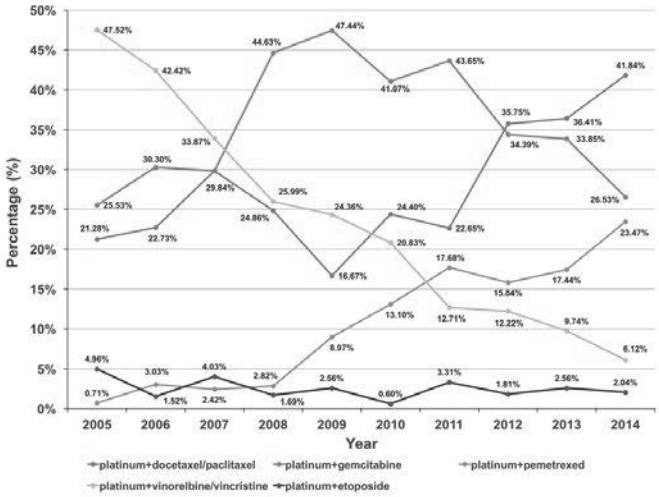
Background: The majority of patients have been at advanced stage with a poor prognosis when diagnosed as non-small cell lung cancer (NSCLC). Platinum-based doublet chemotherapies are the standard first-line treatment for patients without driver mutations. The purpose of this study is to describe trends in first-line platinum-based doublet chemotherapies and explore demographic and clinical factors that affect regimen selection in China. **Method:** This study was a hospital-based, multicenter, retrospective clinical and epidemiological survey. Primary lung cancer cases in eight provinces over a 10-year (2005-2014) interval were randomly selected via medical chart review. Descriptive statistical tests were used to illustrate trends of each first-line regimen. Chi-square tests and logistic regression analyses were used to assess the differences among regimens and determine the influential factors of regimen selection. **Result:** A total of 2736 advanced NSCLC patients were enrolled into the analyses. The rate of vinorelbine/vincristine doublets continuously reduced from 47.52% in 2005 to 6.12% in 2014 among the whole study population, while the rate of pemetrexed doublets increased from 2.08% in 2008 to 13.19% in 2009, and gradually ascended to 34.62% in 2014 among non-squamous patients. During 2010-2014, significantly more patients used pemetrexed doublets ($p < 0.001$), while fewer patients used vinorelbine/vincristine doublets ($p < 0.001$) in comparison with 2005-2009, and they both were influenced by pathological types. When controlling age, gender and pathological type, patients from provinces with inferior GDP level were less likely to use gemcitabine doublets, compared with docetaxel/paclitaxel doublets ($z = -2.670$, $p = 0.008$).



Conclusion: Vinorelbine/vincristine doublets reduced continuously during the entire study period among the whole study population, while pemetrexed doublets increased notably since 2009 among non-squamous NSCLC patients. Although there was no significant difference in the utilization between gemcitabine doublets and docetaxel/paclitaxel doublets, the financial advantage might attract more patients from provinces with inferior GDP level to use docetaxel/paclitaxel doublets.

Keywords: epidemiology, chemotherapy, non small cell lung cancer

PUB050 EPIGENETIC CHANGES OF G0S2 GENE IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: To evaluate the value of methylation levels and expression of G0S2 gene in early diagnosis and predicting prognosis of non-small cell lung cancer (NSCLC). **Method:** We used pyrosequencing to detect G0S2 methylation levels and Real-time PCR to detect its expression in the tissue of NSCLC patients. According to the G0S2 expression levels, patients were divided into high and low expression groups. We further analyzed the clinical characteristics and prognosis in these groups. **Result:** The hypermethylation rate of G0S2 gene in NSCLC patients was high (40%). And the expression of the gene in normal tissues was much higher than those in tumor tissues (P <0.001). There were no significant relationships between the level of expression of this gene and patients' age, sex, smoking history and tumor type cases (P> 0.05). Also we couldn't find any relationship between the prognosis and the level of G0S2 gene. **Conclusion:** The expression level of G0S2 gene has some value in the early diagnosis of NSCLC, while there is no obvious value in staging of NSCLC and predicting prognosis.

Keywords: non-small cell lung cancer, Gene Expression, early diagnosis

PUB051 TLR9 IS FUNCTIONAL MARKER FOR CANCER STEM CELL IN NON-SMALL CELL LUNG CANCER

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Background: Accumulating evidence has proposed a model that tumorigenesis is driven by cancer stem cells (CSCs). Those CSCs are capable of sustaining self-renewal, developing into phenotypically diverse cancer cell populations, proliferating extensively and being resistant to treatment.Toll-like receptor 9 (TLR9) has been described to trigger innate and adaptive immune responses that may promote an antitumor immune response against cancers. Our previous data show that activation of TLR9 by CpG-ODN could activate IKK/NF-kB, MAPK/AP-1 and PI3K/Akt signal pathways. We also demonstrated that increased expression of TLR9 results in promoted migration, invasion and metastasis in lung cancer cells. Thus, as a cancer progression associated factor, TLR9 might also be involved in stem-cell function in cancer. **Method:** We seperate CSCs from cell lines and lung cancer tissues by CSC marker CD133 and ALDH. Then we knock down the expression of TLR9 and then investigate biological changes of CSCs, including sphere formation, self-renewing ability, invasion, resistance to drugs, and in vivo tumor formation. **Result:** We found that toll-like receptor (TLR9) are constitutively overexpressed on cancer stem cells (CSCs) derived from lung cancer cell lines and patients' tissue when compared with non-stem cells. Knocking down of TLR9 in lung CSCs resulted in inhibited capacity for proliferation, invasion, tumorigenesis and resistance to chemotherapeutic drugs. Furthermore, cell cycle was arrested at G2/M stages and more apoptosis existed after TLR9 expression decreased. Further analysis indicated that TLR9 maintain the stemness of cancer cells by changing expression of other stem cell markers Gli1, Notch1 and beta-catenin, drug transporters ABCB1, ABCC1 and ABCG2 and anti-apoptotic factors BCL2 and Survivin. Of which, beta-catenin, was found to be most obviously related with TLR9 expression. Moreover, TLR9 expression was positively associated with tumor differentiation and inversely associated with lung cancer patient survival in clinic. **Conclusion:** Based on above data, TLR9 is crucial for marker and phenotype of lung CSC. It might work as a lung cancer stem cell maintainer.

PUB052 COMPUTER TOMOGRAPHY (CT) TEXTURE ANALYSIS AS PREDICTION FACTOR IN NON SMALL CELL LUNG CANCER PATIENTS UNDERGOING NIVOLUMAB TREATMENT

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Background: Nivolumab is a human mAb able to PD-1 receptor on activated CTL which is able to reignite a significant antitumor response. We evaluated the hypothesis that a baseline CT texture analysis (TA) may help in the identification of those patients with advanced NSCLC who will receive benefit by Nivolumab treatment. **Method:** We performed a retrospective analysis of 38 lung cancer patients undergoing salvage therapy with Nivolumab at our Hospital between January 2015 and May 2017. The gross tumor volume (GTV) of the primary tumor was contoured on CT sequences pre and post contrast performed before salvage therapy. The impact of variations on contouring was analysed performing two delineation on each patients, and the TA parameters were tested for reliability with Intraclass Coefficient Correlation method (ICC). All the analysis for this work have been done with LifeX Software ©. TA parameters included features of gray-level co-occurrence matrix (GLCM), neighbourhood gray-level dependence matrix (NGLDM), gray-level run length matrix (GLRLM), gray-level zone length matrix (GLZLM), sphericity and indices from the gray-level histogram. The development of new metastasis or death within 6 months after the beginning of immunotherapy was defined as the endpoint of early failure (eF). We performed a univariate analysis (Pearson Correlation) and a multivariate analysis (binary logistic regression) between all the significant TA parameters, the performance status, the tumor histology with the eF. **Result:** Thirty-eight patients (30 males, 8 females) were included, among them 12 patients (31,6%) developed new metastases or died within 6 months of the salvage therapy. The reliability analysis performed with ICC showed that the TA parameters that resulted significantly reproducible (ICC>0.70, single measure) were, respectively, 24 out of 39 for the post-contrast CT (61%), 29 out 39 (74%) for the pre contrast CT. TA parameters correlated with eF included post contrast GLCM contrast (p:0.009), GLCM dissimilarity (p:0.019), NGLDM Coarseness (p:0.004). ROC curve for the prediction of eF showed an AUC of 0.755 (95% CI: 0.630-0.879). **Conclusion:** GLCM Contrast and GLCM dissimilarity refer to the local variations in gray-level in voxel pairs, whereas NGLDM Coarseness refers to the spatial change in intensity. These parameters seem to be related to the aggressiveness of lung cancer and to the responsiveness to immunotherapy. Our results appear to be promising since the TA seems to improve the prediction of early failure, and may lead to a better selection of patients that may benefit from immunotherapy.

Keywords: Texture analysis, Immunotherapy, predictive factors

PUB053 SURGERY FOR NON-SMALL-CELL LUNG CANCER WITH MALIGNANT MINOR PLEURAL EFFUSION DETECTED ON THORACOTOMY

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Background: Surgery is usually not indicated for malignant pleural effusion due to its poor prognosis. However, malignant pleural effusion is first detected at thoracotomy (malignant minor pleural effusion), and it is difficult to judge an appropriate mode of resection. Several reports have demonstrated that the prognosis of patients with malignant pleural effusion first detected at thoracotomy is relatively favorable, aggressive surgical approaches may result in long-term survival. In some cases long-term survival is expected for malignant pleural disease unless the causal tumor is highly responsive to systemic chemotherapy. The aim of this study is to describe the results of surgical intervention in NSCLC patients with malignant minor pleural effusion. **Method:** We retrospectively studied 21 surgical patients with NSCLC and malignant minor pleural effusion that is found during thoracotomy, from January 1989 till March 2017. Surgical-pathological staging was carried out according the 7th edition of the TNM classification of lung cancer. We examined the clinicopathological features, the current status of therapy, and surgical outcomes in patients with malignant minor pleural effusion. **Result:** The median survival time and 5-year survival rate in the 21 patients were 16.9 months and 19.3%. Primary tumor resection was perfomed in 20 patinets(95.2%), pneumonectomy was 1 case, lobectomy was 14 cases, segmetectomy was 1 case and wedge resection was 4 cases. Of our 21 petients, 10 had malignant pleural nodule. The 5-year survival rate for 10 patients with malignant pleural nodule was 0%, whereas the 5-year survival rate for 11 patients without malignant pleural nodule was 30.0%. But there is no significant difference in survival between with or without malignant pleural nodule. Univariate analyses revealed that women, adenocarcinoma histology were associated with significant longer survival. 6 patients(28.6%) survive more than 3 years and 3 patients(14.3%) survive more than 5 years, all patients were adenocarcinoma, cN0. **Conclusion:** Tumor resection is beneficial for the survival of several patients with NSCLC who have a minor malignant pleural effusion. Our results warrant to the possible benefits of surgery in NSCLC patients, and to justify the inclusion of surgery in multimodality treatment of NSCLC patients with minor malignant pleural effusion.

Keywords: lung cancer, pleural effusion, Surgery

PUB054 PATHOLOGICAL DISCREPANCIES IN THE DIAGNOSIS OF THYMIC MALIGNANCIES: THE TALLINN-LYON EXPERIENCE

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Background: Thymic malignancies are rare thoracic tumors for which pathological diagnosis is complex due to multiple subtypes and variations in interobserver reproducibility. In this study, we aimed at analysing the consistency between initial diagnosis in the largest thoracic oncology center in Estonia, and one of the expert center for thymic pathology in France. **Method:** Hospital electronic database and pathology databases from the Tallinn North Estonia Medical Centre were searched for thymic and mediastinal tumors from 2010 to 2017. Pathology specimens were referred to the Pathology Department of the Lyon University hospital. **Result:**

Table 1. Demographic and baseline clinical characteristics of patients with thymic tumours and other mediastinal tumours included for central review.

Characteristic	N (%) 49
Gender	
F	27 (55)
M	22 (45)
Age at diagnosis (median, range)	61 (22 – 88)
Biopsy	29 (59)
Radical surgery	35 (71)
Tumour type	
Thymic	41 (84)
Other	8 (16)
Masaoka stage (1,2)	
I	11 (27)
II	12 (29)
III	10 (24)
IV	8 (20)
Autoimmune disease (1)	6 (15)
Radiotherapy (1)	6 (15)
Chemotherapy (1)	9 (22)
Median follow up in years from initial diagnosis (range)	4 (0 – 16)
Follow up status	
Dead	12 (25)
Disease free	32 (65)
Stable disease	5 (10)

(1) Only patients with thymic tumours
(2) Updated retrospectively based on medical records if not present in pathology report

55 tissue specimens from 49 patients were included (Table 1). The quality of pathology reports was assessed, with tumor size, diagnosis, and invasion mentioned in ≥80% of cases, while resection status and staging were assessed in 52% and 31% of cases, respectively. The initial diagnosis was consistent with that of the review in 60% of cases. Minor discrepancies - regarding thymoma subtype - were observed in 20% of cases. Three patients had normal thymus according to the reference centre, whereas thymoma B1 or B2 had been diagnosed locally, including one patient with severe myasthenia gravis. Three patients had implications for treatment due to the major differences in pathohistological diagnoses. **Conclusion:** Implementing structured pathology reports may help to decrease discrepancies in the diagnosis of thymic malignancies. The development of expert networks is an opportunity in this setting.

Keywords: thymic malignancies, interobserver variation, histological diagnoses

PUB055 NODAL STATUS BASED ON THE ANATOMICAL LOCATION OR THE NUMBER OF LYMPH NODES METASTASIS

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Background: The 8th edition of the TNM staging system for lung cancer has been published. In the new staging system, the N component remains the same as in the previous version. However, the number of involved nodal stations has been previously shown to be correlated with patient outcomes. In the present study, we retrospectively investigated the correlations between the anatomical location versus the total number of metastatic lymph nodes and the outcomes of patients with non-small cell lung cancer. **Method:** We retrospectively collected 237 samples (16.1%) from patients with pN1 and N2 primary lung cancer who underwent complete resection between 2004 and 2013. In those samples, we divided N1 samples into N1ss (single station N1) and N1ms (multiple station N1). We also divided samples into hilar N1 (#11, #10; N1h) and peripheral N1 (#14, 13, and #12; N1p) subgroups. pN2 lymph nodes were divided into "single station N2 with skip metastasis" (N2ss1), "single station N2 with N1 metastasis" (N2ss2), and N2ms. The clinicopathological factors and outcomes for each group were statistically analyzed. **Result:** In this study, per patient, a mean of 17.9 lymph nodes were dissected and the mean number of lymph node metastases was 3.9. The pN1 and pN2 groups consisted of 74 and 163 cases, and their 5-year survival rates were 74.7% and 54.8%, respectively (p = 0.021). The 5-year survival rates of the N1p and N1h groups were 74.7% and 63.6%, respectively. Although the N1h group showed a tendency towards poorer outcomes, no statistically significant difference between the groups was observed (p = 0.114). The 5-year survival rates of the N2ss1 and N2ss2 groups were 65.4% and 62.4%, respectively, and the N2ms group had poorer outcomes (45.0%, p = 0.010). In our cohort of patients with N1 and N2 lymph node metastasis, the number of metastatic lymph nodes was not correlated with patient outcomes. **Conclusion:** In the cases of pN1, patients with N1h had poorer outcomes than those with N1p. In the cases of pN2, patients with N2ms had poorer outcomes than those with other subsets of pN2. From a prognostic point of view, classification based on the anatomical location of metastatic lymph nodes may be important. Further accumulation and examination of cases will be necessary to confirm our findings.

Keywords: N factor, Metastatic lymph nodes, TNM Staging System

PUB056 SMOKING HISTORY AFFECTS THE PRODUCTION OF TUMOR ANTIGEN SPECIFIC ANTIBODIES NY-ESO-1 IN PATIENTS WITH LUNG CANCER

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Background: Lung cancer is the leading cause of cancer mortality worldwide therefore understanding the biological or clinical role of tumor associated antigens and autoantibodies is of an eminent interest for designing anti-tumor immunotherapeutic strategies. **Method:** Here we prospectively analyzed the serum frequencies of NY-ESO-1, Her2/*neu* and MAGE-A4 antibodies and corresponding antigens expression in tumors of 121 non-small cell lung cancer (NSCLC) patients undergoing surgery without prior neoadjuvant chemotherapy and compared them with 57 control age-matched patients with no history of a malignant disease, each with no sign of malignancy on chest X-ray. In addition to pulmonary X-ray, a panel of tumor markers (CEA, TPA, NSE, SCC, CYFRA 21-1) was used to compare the group of cancer patients and the group of control patients. The complete set of samples for NY-ESO-1 analyses which includes serum, tumoral and non-tumoral tissue was obtained only for 40 patients. RT-PCR analyses of HER2/*neu* and MAGE-A4 antigen expression was performed only in 42 and 57 patient's tumor samples, respectively. **Result:** We found that only antibodies specific for NY-ESO-1 (19.8%; n=24/121) were significantly elevated in NSCLC patient group over the controls. NY-ESO-1 seropositivity was significantly positively associated with active smoking history in NSCLC patients but not in smokers from the control group. In tumors, the frequency of NY-ESO-1 mRNA expression was 6.3% (4/64), Her2/*neu* 11.9% (5/42) and MAGE-A4 35.1% (20/57). MAGE-A4 expression in tumors correlated with a smoking status and male gender in NSCLC patients. Squamous cell carcinoma patients displayed higher expression of NY-ESO-1 and MAGE-A4 in tumors than patients with adenocarcinoma. On the other hand, 94.7% non-smoking patients in our study had adenocarcinoma out of which 73.7% were women. **Conclusion:** In summary we showed here for the first time that autoantibodies against CT antigen NY-ESO-1 correlate with smoking history in NSCLC patients which suggest that smoking-related chronic inflammation might induce the development of NY-ESO-1-specific immune responses. We also observed that tumor-associated expression of MAGE-A4 correlated with a smoking history which might suggest its role in early stages of NSCLC development. Since both the tumor-associated expression of NY-ESO-1 and MAGE-A4 were reported to be in an inverse correlation with survival in advanced stages of the disease the clinical relevance and the immunotherapeutical value of our findings remains to be determined.

Keywords: non-small cell lung cancer, smoking, NY-ESO-1

PUB057 NEUTROPHIL TO LYMPHOCYTE RATIO PREDICTS SURVIVAL IN ADVANCED NSCLC PATIENTS TREATED WITH SECOND-LINE PD-1 IMMUNE CHECKPOINT INHIBITORS

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Background: Baseline high neutrophil to lymphocyte ratio (NLR) has been associated with inferior overall survival in patients with stage III/IV non-small cell lung cancer (NSCLC). Inflammation and neutrophilic infiltrates in the tumor microenvironment appear to inhibit anti-tumor immune response. We suspect that NLR might reflect the level of inflammation in this microenvironment. The objectives of this study were to evaluate potential relationships between pretreatment NLR and progression free survivial (PFS) and overall survival (OS) in advanced NSCLC patients treated with second-line nivolumab or pembrolizumab. **Method:** Patients with stage IV NSCLC who received at least one cycle of nivolumab or pembrolizumab after first-line treatment with a platinum doublet between January 2015 and December 2016 were included. Patient demographics including NLR at baseline, date of starting immunotherapy, and date of progression were recorded. The association between NLR and duration of response was assessed using a Mann-Whitney-Wilcoxon test. A cutoff of NLR of 3.5 and 5.0 based on published data (ref) were analyzed for differences in median overall survival and progression free survival. **Result:** 113 patients were analyzed: median age

68, male/female 38.9%/61.1%, 15% never smoked. The median PFS for patients with NLR <5 was 4.14 months vs. 2.27 months in those with NLR > 5 (p = 0.031). Overall survival was also impacted by NLR. There were a total of 29 deaths in the cohort, 24 of these occurred in patients with NLR > 3.5 and 5 were in patients with NLR < 3.5. A lower NLR at baseline was significantly associated with improved overall survival (p = 0.036). **Conclusion:** A low baseline NLR is associated with superior progression free survival and overall survival in metastatic non-small cell lung cancer patients treated second line with nivolumab or pembrolizumab. These findings suggest that evaluating mediators of inflammation might help to identify potential therapeutic targets which could enhance effectiveness of PD-1 immune checkpoint inhibitors in advanced NSCLC.

Keywords: NLR, advanced NSCLC, Immunotherapy

PUB058 IS EFFICACY RESULT IN PHASE 2 TRIAL REPLICATED IN PHASE 3 TRIAL IN ADVANCED NSCLC: A META-ANALYSIS

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Background: Phase 3 trial has been mandatory to establish new treatment. However, molecular targeted agents were often approved based on phase 2 trials. There have not been fully investigated whether efficacy data in phase 2 would be replicated in phase 3. **Method:** We extracted phase 2 and 3 trials for advanced non-small cell lung cancer (NSCLC) using platinum doublet (Plt) or EGFR-tyrosine kinase inhibitor (TKI) monotherapy, published between 2005 and 2015. Overall response rate (ORR) and median progression-free survival (PFS) in each study were collected. We compared these data between phase 2 and 3. **Result:** 155 phase 2 trials and 13 phase 3 trials were adopted as Plt trials, while 21 phase 2 trials and 6 phase 3 trials were adopted as TKI trials. Plt trials had larger sample size (median number of patients: 47 in phase 2, and 203 in phase 3) than TKI trials (median number of patients: 29 in phase 2, and 101.5 in phase 3). In Plt trials, median ORR and median of median PFS were 31% and 5.2 months in phase 2, while 27% and 4.7 months in phase 3. There was statistically significant difference between phase 2 and phase 3 in ORR and mPFS (p = 0.03 and 0.03, respectively). In TKI trials, median ORR and median of median PFS were 64.0% and 9.7 months in phase 2, while 64.5% and 10.9 months in phase 3. There were not significant difference between phase 2 and phase 3 either in ORR and mPFS (p = 0.88 and 0.31, respectively). Among TKI trials, equivalence of efficacy data between phase 2 and phase 3 was also investigated in ORR and mPFS, but not proved (p = 0.30 and 0.45, respectively). **Conclusion:** Efficacy of TKI in phase 2 trial was well replicated in phase 3 trial.

Keywords: advanced NSCLC, EGFR-TKIs, platinum doublet

PUB059 GEFITINIB VERSUS PEMETREXED-PLATINUM THERAPY IN EGFR ACTIVATING MUTATED LUNG CANCER: IMPACT ON BRAIN METASTASIS

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Background: Brain metastasis is an important cause of death in NSCLC patients. EGFR mutated patients have a higher incidence of brain metastasis. The impact of gefitinib on existing brain metastasis and its role in the prevention of development of brain metastasis has rarely been reported in the literature. **Method:** This was a post hoc analysis of a randomized study done at our center in newly diagnosed EGFR mutated NSCLC patients between Gefitinib (250 mg once daily) and pemetrexed (500 mg/m2 intravenous) carboplatin (AUC-5) followed by maintenance pemetrexed. These patients were followed at regular interval till death. At progression in general patients in gefitinib arm were planned for intravenous chemotherapy while patients in other arm received gefitinib. R studio was used for this analysis. In patients with upfront brain metastasis, the progression free survival in brain was compared between the 2 regimens using log rank test. Progression free survival in brain (PFS_brain) was defined as time duration in months between date of randomization to date of progression in brain metastasis.Patients who had either not progressed or had progressed at other sites prior to brain were censored. In patients without brain metastasis the cumulative incidence of development of brain metastasis between gefitinib and pemetrexed-platinum was compared. A p value of 0.05 was considered as significant. **Result:** Among 290 patients, 45 patients (15.5%) had upfront brain metastasis. The median PFS_brain was not reached in gefitinib arm while it was 9.367 months in Pemetrexed-carboplatin arm (p-0.084) { figure 1}. The corresponding overall survival were 18.33 (95%CI 10.10-26.56 months) & 19.43 (95%CI 11.75-27.12) months in gefitinib and Pemetrexed- carboplatin arm respectively (p-0.907). In patients without brain metastasis the cumulative incidence of development of brain metastasis at first progression was similar between the 2 arms (18 % versus 12%, p-0.355). However in patients who had progressed post first line treatment, the cumulative incidence of development of brain metastasis at second progression was higher in patients who received intravenous chemotherapy as opposed to gefitinib (51.2% versus 14.5%, p-0.073). **Conclusion:** Gefitinib leads to a delay in progression of existing brain metastasis and it prevents the development of them in EGFR mutated NSCLC.

Keywords: EGFR mutation, Brain metastasis, NSCLC

PUB060 COMPARISON OF TUMOR MUTATIONAL BURDEN (TMB) DERIVED FROM WHOLE EXOME AND LARGE PANEL SEQUENCING IN LUNG CANCER

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Background: Several studies have shown that assessment of tumor mutational burden (TMB) could be helpful in clinical immunotherapy, which is promising to make TMB a more sensitive and efficient biomarker in prognostic practice. TMB is traditionally estimated by whole-exome-sequencing (WES) with relatively low depth and high cost, whereas estimating TMB from targeted cancer gene panels besides assessing mutational status is quite cost-effective. Here, we propose such an alternative for accurately estimating TMB based on targeted sequencing data, to show more opportunities of next-generation-sequencing (NGS) assay for cancer therapy. **Method:** TMB was calculated as the number of filtered variants per megabase. We have developed an approach to estimate TMB after targeted sequencing using Novogene 550-gene panel, which covers all coding and 21 non-coding regions of 550 genes associated with solid tumors. Variants were filtered successively by germline, driver mutation, intron, mutation frequency and repeat region. Then we compared the performance of TMB assessment between our targeted panel sequencing with WES by using two datasets from the TCGA and another 5 FFPE samples, which were sequenced both by WES and 550-gene panel. Finally, we applied our method to depict the primary TMB distribution in 262 Chinese patients with lung cancer by using 550-gene panel. **Result:** High correlations between our method and WES estimation of TMB were found among TCGA lung cancer datasets (514 adenocarcinomas: $R^2 = 0.91$; 492 squamous-cell-carcinomas: $R^2 = 0.83$), and in 5 FFPE samples ($R^2=0.99$). TMB estimation for each FFPE sample was replicated three times and robust estimates were found. TMB value among 262 Chinese patients ranges from 0 to 222.17, with mean and median being 22.80, 7.83 (mutation/MB) respectively. High/Low TMB threshold is determined by the following formula: median(TMB) + 2*IQR(TMB). Frequencies of high or low TMB tumors are not significantly different based on gender and age, but significantly different based on MMR, POLE mutation status (Fisher's exact test, P<0.001). **Conclusion:** Our analysis has shown that this NGS large panel-based method is a reliable alternative to traditional WES, and can be used to accurately estimate TMB from lung cancer tumors. TMB status was highly correlated with MMR and POLE status. The correlation between this threshold with clinical outcome will be tested in the future study.

Keywords: tumor mutational burden; immunotherapy; targeted sequencing

PUB061 CIRCULATING UPA AS A POTENTIAL PROGNOSTIC BIOMARKER FOR ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Background: Previous studies have demonstrated that the four genes of matrix metallopeptidase 9 (MMP9), cyto-keratin 20 (CK20), cyto-keratin 19 (CK19) and urokinase type plasminogen activator (uPA) are stably detectable in the peripheral blood. All the four genes have been proved to relate with tumor invasion and metastasis. However, whether their expression associated with clinicopathologic factors and the prognosis of patients in esophageal squamous cell carcinoma (ESCC) is remained unknown. **Method:** Expression levels of MMP-9, CK20, CK19 and uPA were evaluated by qRT-PCR in peripheral blood of 206 ESCC patients who received radical resection. Their impacts on clinicopathologic factors and survival were investigated. **Result:** The uPA expression positively correlated with vascular invasion (P=0.035), perineural invasion (P=0.045), smoking (P=0.047) and drinking history (P=0.046). Meanwhile, CK19 expression positively correlated with clinical stage (P=0.023), perineural invasion (P=0.033), age (P=0.038) and CK20 expression positively correlated with perineural invasion (P=0.025) and degrees of differentiation (P=0.031). However, the overexpression of MMP9 had no correlation with clinicopathologic factors. Among the selected genes, only uPA was a prognostic indicator for disease free survival and overall survival both in univariate analysis and multivariate analysis. **Conclusion:** This study suggests that uPA can serve as a potential unfavorable prognosis biomarker in ESCC.

Keywords: Peripheral blood testing, esophageal cancer, uPA

PUB062 SARCOPENIA IS A NOVEL PREDICTOR OF POOR PROGNOSIS IN MALE PATIENTS WITH PATHOLOGICAL STAGE I NON-SMALL CELL LUNG CANCER

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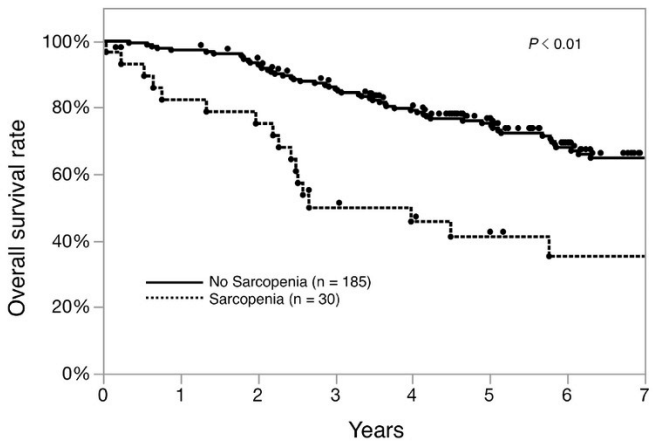
Background: Sarcopenia is the progressive loss of muscle mass and strength, and has a risk of adverse outcomes such as disability, poor quality of life and death. Depletion of skeletal muscle mass is the result of imbalance between pathways that favor protein synthesis and those favoring breakdown. As prognosis depends not only on disease aggressiveness, but also on a patient's physical condition, sarcopenia can predict survival in patients with various cancer types. However, its effects on postoperative prognosis in patients with localized non-small cell lung cancers (NSCLC) have never been reported. **Method:** We retrospectively investigated 215 male patients with pathological stage I NSCLC. L3 muscle index is defined as the cross-section area of muscle at the third lumbar vertebra level, normalized for height, and is a clinical measurement of sarcopenia. We then investigated the effect of preoperative sarcopenia on their postoperative prognosis. **Result:** Our 215 subjects included 30 patients with sarcopenia. Sarcopenia was significantly associated with body mass index, nutritional condition, serum CYFRA 21-1 level and pathological stage, but not with preoperative respiratory function or performance status. Frequency of postoperative complications, length of postoperative hospital stay, thoracic drainage period or causes of death were not correlated with the presence of sarcopenia. Their median follow-up period was 61 months. The sarcopenia group had a significantly shorter median overall survival (32 months) than the no-sarcopenia group. In univariate analysis, age ≥ 68 years, BMI < 18.5 kg/m^2, sarcopenia, serum CYFRA 21-1 > 3.5 ng/ml, and pathological stage were significant predictors of poor prognosis. In multivariate analysis age and sarcopenia were independent predictors.



Conclusion: Sarcopenia was a predictor of poor prognosis in male patients with Stage I NSCLC. As sarcopenic patients with NSCLC patients are at risk for significantly worse outcomes, their treatments require careful planning, even for those with stage I disease.

Keywords: non-small cell lung cancer, sarcopenia

PUB063 EPIDEMIOLOGIC AND RADIOMIC ANALYSIS OF HYPERPROGRESSERS OF LUNG CANCER PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Although checkpoint immunotherapy has revolutionized the field of cancer treatment, some patients unexpectedly show accelerated tumor growth, or hyperprogressive disease (HPD), characterized as rapid progression shortly after (<2 months) initiation of immunotherapy. To date, little is known about the clinical, genomic, or radiological factors that are associated with HPD among non-small cell lung cancer (NSCLC) patients treated with immunotherapy. Such analyses may reveal subsets of patients that are at an increased risk for HPD. In this work, we curated clinical information and high-dimensional quantitative imaging data ('*Radiomics*') among NSCLC patients who have received immunotherapy with the goal to predict patients at increased risk of HPD. **Method:** Clinical data and pre-treatment CT images were obtained on 214 patients from institutional immunotherapy clinical trials of NSCLC patients who received PD-1, PD-L1, or doublet checkpoint inhibitors. Radiomic features were extracted from largest RECIST lung target nodules present in baseline CT images consisting of size, shape, location, and texture information. Tumor growth rates (TGR) were calculated for pre- and post-immunotherapy ("Reference" and "Experimental") time intervals for RECIST 1.1 target lesions. Patients were defined as HPD if they had progressive disease by RECIST <2 months with a 2-fold increase in TGR between experimental and reference intervals. Fisher's exact test was used to compare HPD patients vs. non-HPD patients for clinical variables and logistic regression with backward elimination was used to identify radiomics features to discriminate HPD patients vs. non-HPD patients. **Result:** A total of 15 NSCLC patients (7%) were classified as HPD while 199 (93%) were classified as non-HPD. There were no significant differences between HPD patients vs. non-HPD patients by sex, disease stage, histology, checkpoint inhibitors, ECOG performance status, mutational status, smoking, and previous treatment history. However, age was found to be statistically significantly higher in HPD group vs. non-HPD patients (mean age = 67.1 vs 65.1, respectively; P = 0.018). We also identified a parsimonious model that included three radiomic features (*grey level size zone* variance, *neighborhood grey tone difference complexity, statistical maximum grey level*) that discriminated HPD patients vs. non-HPD patients (AUROC = 0.61). When we include age and histology to the model, the AUROC score increased to 0.70. **Conclusion:** These analyses revealed that histology of adenocarcinoma, increased age and radiomic features of the largest lung target nodules are associated with HPD among NSCLC patients treated with immunotherapy. Additional biomarkers are needed to identify lung cancer patients at increased risk for HPD.

Keywords: Radiomics, Immunotherapy, hyperprogression

PUB064 PROGNOSTIC IMPORTANCE OF TUMOR SPREAD THROUGH AIR SPACES IN LYMPH NODE NEGATIVE OPERATED ADENOCARCINOMA LUNG CANCERS

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Background: STAS (Spread through air spaces) defined as spreading of tumor cells to the adjacent pulmonary paranchyme by using air spaces, is a new invasion indicator adenocarcinoma lung cancers. In our study we aim to investigate relation between survey and lymph node existence as considering STAS **Method:** We evaluate the adenocarcinoma lung cancer patients had lobectomised or pneumonectomised in American Hospital and Koc University Hospital between 2000 -2016. Locally advanced cases and patients some may be prognostic positive factors other than STAS didn't considered. According to these criteria totally 171 patients counted in our study. STAS existence statistically analyzed in terms of lymph node metastasis and survey relation. In survey analysis we examined the data of patients had operrated before November 2011, owing to significance of follow up time **Result:** 103 of 171 patients were men (60,2%) and 68 of them were women (39,8%). Characteristic specialities and dermographic datas of them has demonstrated in 1st chart. Lymph node invasion (N1-N2) and alveolar spread togetherness was in statistically significant ratio comparing with the cases who hasn't alveolar spread (38.33% vs 24.32% p:0.05) When in last 5 years operated patients were excluded from study, 66 left. And 42 of them were men (63.6%) , 24 of them were women (36.4%) Mean age were 61.82/+-10.26 (36-84). Mean follow up time has detected as 58.98 months. Average survey was 71.47 months in patients has alveolar spread and 79.8 months at patients who hasn't. There weren't statistically significant difference between these two groups (p=0.66) When we analyzed survey of lymph node negative cases, we detected patients with alveolar spread had statistically worse survey (62.53 months versus 90.63 months , p=0.05) **Conclusion:** Instead of sublober rejections in lymph node negative patients with alveolar spread, low survey and high recurrence probability must be considered while to approach lober rejections. And in only STAS existence even if lymph nodes are negative, adjuvant therapy is recommended.

Keywords: lung cancer, STAS, survival, Prognosis

PUB065 TREATMENT AND PAIN MANAGEMENT OF LUNG CANCER: A PATIENT PERSPECTIVE

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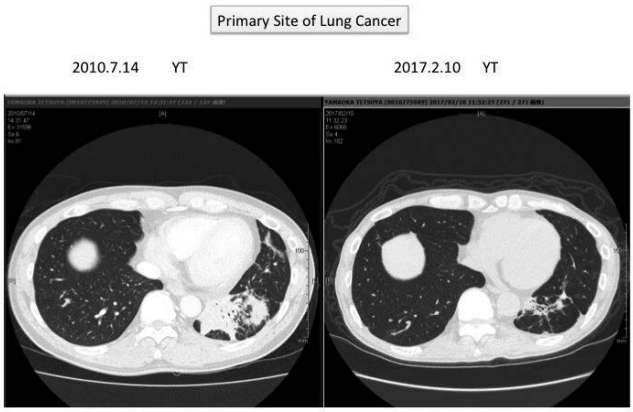
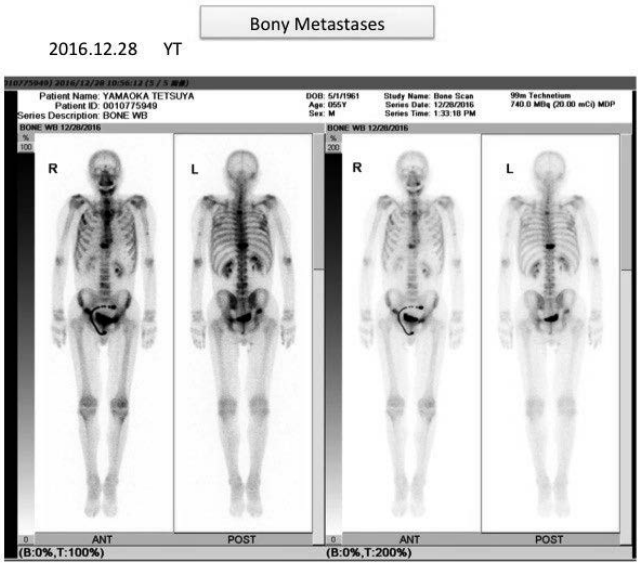
Background: Due to significant advances in the treatment of the lung cancer, the patient now could have longer period of treatment. The paper examines treatment and pain management experienced by a stage 4 NSCLC patient. **Method:** Case study of a 56-year old Japanese male patient diagnosed with pulmonary adenocarcinoma NSCLC (stage 4) metastases in July 2010. **Result:** The patient's treatment started with PTX CBDCA and Bev in July 2010. As EGFR was positive, Gefitinib was used for second and fourth line. The sixth line treatment was a clinical trial (1st Phase) of AZD9291 from Mar. 2014 to Jan. 2016. After a one-year interval, Osimertinib became again effective from Jan. 2017. Palliative care and cancer rehabilitation were also undertaken. The treatment options for pain were started with non-opioids, gradually shifted to codeine, oxycodone, and morphine. The rehabilitation was provided from cancer rehabilitation team and home health care team. The patient try his best to cope with his pain soonest, by acquiring breathing method, keeping regular workout for muscle training, walking by using cane and wheel chair.





Conclusion: Treatment and pain management influence the patient's QOLs. The patient centered multidisciplinary team approach helped to maximize fitness, reduce pains and symptoms, and increase treatment potential.

Keywords: treatment outcome, Multidisciplinary team, pain management

PUB066 ESOPHAGEAL STENOSIS OCCURRED DURING THE TREATMENT WITH NIVOLUMAB FOR METASTATIC SQUAMOS CELL LUNG CANCER

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Background: Lung cancer is one of the main causes of cancer-related death worldwide. Systemic immune checkpoint inhibitors are largely used in the treatment of metastatic non-small lung cancer. There are still unknown adverse events associated with this treatments. **Method:** This report presents three cases of patients with metastatic squamos cell lung carcinoma. Case 1 concerns a 60 year old man treated in the 4th line with Nivolumab (after 3 platinum containing lines of chemotherapy). He recived 11 cycles of Nivolumab. Case 2 concerns a 70 year old man treated in the 3th line with Nivolumab (after 1 platinum containing line of chemotherapy and 1line of taxane). He recived 8 cycles of Nivolumab. Case 3 concerns a 63 year old man treated in the 3th line with Nivolumab (after 1 platinum containing line of chemotherapy and 1line of taxane). He recived 11 cycles of Nivolumab. **Result:** The treatment was well tolerated by all this patients, until when they suddenly occurred partial dysphagia. The upper endoscopy and CT exam detected esophageal stenosis, without extrinsec compression. Unfortunately, we didn't proceed to biopsy at the time of endoscopy. Signs and symptoms were like in eosinophilic esophagitis: swallowing difficulty, food impaction, chest pain centrally located which does not respond to antacids, persistent heartburn, upper abdominal pain with no response to GERD medication, regurgitation. Eosinophilic esophagitis a chronic immune system disease characterized by a dense infiltrate with white blood cells of the eosinophil type into the epithelial lining of the esophagus. Neither of this patients had brain metastasis. All of them had history of platinum and docetaxel treatments. All of them had grade 1 or 2 of sensitive peripheric neuropathy. Two patients needed esophageal stent insertion. One of them (case 2) died during the stent insertion procedure (in eosinophilic esophagitis, because of inflammation of the esophagus, endoscopy can cause perforation or tears in the esophageal lining tissue). **Conclusion:** Esophageal stenosis and dysphagia may occur during the tratment with immune checkpoint inhibitors. This may be related with a imune-mediated mechanism like in eosinophilic esophagitis. Furher research is needed with biopsies at the time of endoscopy.

PUB067 MAXIMUM STANDARDIZED UPTAKE VALUE OF PRIMARY TUMOR PREDICTS LYMPH NODE METASTASIS IN NON-SMALL CELL LUNG CANCER

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Background: The study investigated the association between the maximum standardized uptake value (SUV_{max}) of primary tumor and lymph node metastasis in resectable non-small cell lung cancer (NSCLC). **Method:** A total of 189 patients with I-IIIA NSCLC were enrolled in the current study. All patients underwent radical surgical resection following preoperative FDG-PET/CT scanning from January 2009 to December 2015 at the department of Thoracic Surgery II, Peking University Cancer Hospital. Pearson's chi-squared test or Fisher's exact test was performed to assess the categorical variables. The association between clinicopathological variables and lymph node involvement was analyzed by multivariate analysis. 2×2 tables were used to compare the diagnosis accuracy. Receiver operating characteristic analysis was performed to identify cut-off value and compare diagnostic models. **Result:** 28.0% NSCLC patients were detected lymph node metastasis, medistinal lymph node metastasis accounted for 12.1%. The sensitivity and specificity of mediastinal lymph node SUV_{max} in predicting medistinal lymph node metastasis were 43.5% and 85.5%, respectively. In univariate analysis, lymph node involvement was associated with greater tumor size (P=0.009), tumor SUVmax (P<0.001), centrally located (P=0.003),solid nodule type (P=0.001)and visceral pleural invasion (P=0.015). Tumor SUVmax more than 4.5 was an independent risk factor for lymph node metastasis by multivariate analysis (OR 2.762 95%CI 1.108-6.885,P=0.029). Greater tumor size (P=0.005), tumor SUVmax >4.5 (P=0.016),solid nodule type (P=0.017)and visceral pleural invasion (P=0.036)were significantly associated with mediastinal lymph node involvement. Combination mediatinal lymph node SUVmax with tumor SUVmax would improve the accuracy diagnosis of mediastinal lymph node metastasis showed by ROC curves. **Conclusion:** Primary tumor maximum standardized uptake value (SUVmax) was a risk factor for lymph node metastasis in resectable NSCLC, combination mediastinal lymph node SUVmax with primary tumor SUVmax would improve the accuracy diagnosis of mediastinal lymph node metastasis.

Keywords: lymph node metastasis, NSCLC, Primary tumor SUVmax

PUB068 DIAGNOSTIC VALUE OF MICRORNAS DERIVED EXOSOMES FROM BRONCHOALVEOLAR LAVAGE FLUID IN EARLY STATE LUNG ADENOCARCINOMA: A PILOT STUDY

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Background: Low-dose computed tomography for lung screening is able to identify smaller nodules more often than can chest radiographs. However, complications of invasive diagnostic procedures of detected nodules are common in practice. Exosomes, membrane vesicles released from cells, contain a diverse array of biomolecules that closely reflect the biologic state of cell and tissue from which they are released. The aim of this study is to investigate diagnostic values in bronchoalveolar lavage (BAL) fluid exosomal micro (mi)RNA in early stage lung adenocarcinoma. **Method:** We chose candidate miRNAs (miR-7, miR-21, miR-126, Let-7a, miR-17, and miR-19) known as having a diagnostic value of lung adenocarcinoma. Exosomes were isolated from BAL fluid from control subjects (n = 15) and patients with lung adenocarcinoma (n = 13). Exosomal RNA was analyzed by using commercial kit containing probes for selected 6 miRNAs. Results were validated with quantitative RT-PCR. **Result:** The presence of miRNAs was confirmed in exosomes from BAL fluid of both lung adenocarcinoma patients and control subjects. MiR-126 (p<0.001) and Let-7a (p=0.015) were present in significantly higher levels in the BAL fluid of lung adenocarcinoma patients than in control subjects. The BAL fluid miRNA signature was confirmed using an independent set of paired adenocarcinoma and normal tissue samples (n = 4). Lung adenocarcinoma tissues showed increased expression of miR-126 (p=0.039) as compared to normal tissue samples. **Conclusion:** We identified that a close correlation between the BAL fluid exosomal miRNAs and tumor miRNAs. BAL fluid exosomal miRNAs obtained by noninvasive methods could serve as diagnostic biomarkers in early stage lung adenocarcinoma.

Keywords: lung adenocarcinoma, Exosome, MicroRNAs

PUB069 CIRCULAR RNAS: RESEARCH AND PROGRESS IN LUNG CANCER

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Background: Alterations of epigenetic information are important factors in tumorigenesis.Circular RNAs (circRNAs) which are recognized as competing endogenous RNAs (ceRNAs) play an increasingly important role in epigenetic regulation. It has been proved that circRNAs are associated with the development of diseases, they could participate in the regulation of tissue development, cell senescence and tumorigenesis. The discovery of circRNAs associated with lung cancer provides a new approach for diagnosis and treatment. **Method:** By reading the relevant literature on circRNAs, the formation mechanism, molecular characterization, biological function and related research of circRNAs in tumor are reviewed.The function of circRNAs in lung cancer and its role in pathway regulation are further described. **Result:** Circular RNAs are covalently closed circular molecules, which lack of the 5' caps and 3' polyadenylated tails,so they can resistant to RNA exonuclease with high stability. The formation mechanisms of circRNAs include intron-pairing-driven circularization and lariat-driven circularization. The inverted repeated Alu pairs and the RNA binding protein regulate the formation of the loop. CircRNAs can inhibit miRNAs through endogenous competition as miRNA sponges. Some of them could translate protein through their internal ribosome entry site elements and regulate genetic transcription. The multiple regulatory mechanisms of circRNAs indicate that they could participate in different nosogenesis. Their stability, tissue specificity and evolutionary conservatism show the advantages of being a biomarker for disease diagnosis. Circular RNAs can be excreted into the body fluid through exosomes, so the non-invasive examination is convenient to achieve. The expression of circRNAs between tumor tissues and adjacent normal tissues is different. In lung cancer ,the expression of *cir-ITCH* is decreased, so the adsorption of miR-7 and miR-214 is inhibited, and thus suppress the expression of ITCH. Finally, the Wnt/β catenin pathway is activated, and the proliferation of lung cancer cells is promoted. The lung cancer related gene translocation EML4/ALK1 can produce fusion-circRNAs, and the abnormal fusion -circRNAs is related to the occurrence of cancer. The expression of circRNA 100876 in lung cancer tissues is higher than that in adjacent normel tissues, and it is related to lymph node metastasis and tumor staging. **Conclusion:** Lung cancer is one of the most common malignant tumors. In the early stage, it has no obvious clinical symptoms and difficult to diagnose. CircRNAs participate in the regulation of tumor, and is expected to be a new biomarker for the diagnosis. With the research progress of circRNAs, the non-invasive examination of lung cancer is expected to be achieved.

Keywords: MicroRNA sponges, circular RNAs, lung cancer

PUB070 RARE ACTIONABLE MUTATIONS IN A LUNG ADENOCARCINOMA COHORT IN BRAZIL

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Background: The detection of driver mutations and targeted therapy have brought precision medicine into the treatment landscape of non-small cell lung cancer (NSCLC). EGFR mutations and ALK rearrangement were the first actionable driver alterations identified in lung adenocarcinomas. Further actionable mutations include ROS, BRAF, HER2, MET, and RET. These genes are less frequently mutated than EGFR/ALK, nevertheless, each of these mutations appear to be sensitive to clinically available targeted therapies. Brazil has a genetically admixed population and an emerging economy in which access to novel technologies may be limited. Our group have studied different aspects on the implementation of precision medicine to lung cancer patients in the country. Multiplex diagnosis platforms can optimize treatment decisions and we have recently shown it may be cost-effective in the Brazilian context. In this study, using Next Generation Sequencing (NGS), we describe the prevalence of oncogene rare mutations in a representative Brazilian cohort. **Method:** We included consecutive adenocarcinoma patients referred to a private reference center in Brazil from November-2015 to May-2017. DNA and RNA were extracted from paraffin-embedded tissue. NGS was performed for target regions using the Oncomine® Focus Assay on an Ion PGM platform. This panel evaluates 132 hotspot sites of driver mutations in 35 genes, copy number variations in 19 genes and 23 gene fusions. **Result:** To date 262-lung adenocarcinoma have been included. Genetic alterations were detected in 72% (189 of 262) of all patients. Corroborating previous data from different groups, including ours, the most common actionable alteration detected in this study were EGFR mutation (23%) and ALK rearrangement (7%). Oncogene rare mutations were detected in 68 patients. HER2 mutations were found in 4% and BRAF in 2% of tested patients. ROS were the second most common fusion (3%) followed by RET (2%) and MET exon 14 mutation in 1.5%. PIK3CA was seen 5% of patients. Other rare mutations such as MTOR, CTNNB1, FGFR2, JAK2, SMO, KIT, IDH1, GNA11, ERBB3, PGFRA, FGFR1 and MAP2K1 were detected each with less than 1%. **Conclusion:** In a representative Brazilian cohort, the percentage of rare mutations detected matches data published elsewhere. An extended cohort and health economics data will be presented during the meeting and will allow a better description of the rare mutations and the potential impact they may have in the landscape of lung adenocarcinoma treatment in Brazil. These data may support drug access decisions in the country.

Keywords: Rare mutations, next generation sequencing, Multiplex diagnosis platform

PUB071 CIRCULATING PROGRAMMED DEATH LIGAND-1 (PD-L1) IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The treatment landscape of Non Small Cell Lung Cancer (NSCLC) is rapidly changing with the introduction of immune-checkpoint inhibitors. Programmed death 1 (PD-1) is a key immune-checkpoint expressed in activated T cells, which mediates immunosuppression by binding its ligand, PD-L1. The predictive and prognostic value of PD-L1 is currently under investigation. The possibility to assess PD-L1 expression in plasma has been partially investigated and no data exist on the feasibility of such test in clinical setting as well as how levels of PD-L1 expression change during systemic therapy. Aim of the present study was to define feasibility of plasma PD-L1 testing and to assess how PD-L1 expression is modified by standard treatment. **Method:** PD-L1 expression was evaluated in plasma samples from patients with chemo-naïve NSCLC candidate for systemic first-line therapy, irrespective of histology or any other clinical or biological characteristic. A cohort of healthy volunteers (Healthy control Cohort-HC), individuals who are not affected by oncology, autoimmune, metabolic and infectious diseases, was also analyzed for plasma PD-L1 expression. PD-L1 in plasma samples was evaluated using the Human programmed death ligand-1 (PD-L1/CD274) ELISA kit (CUSABIO, MD, USA). **Result:** A total of 56 individuals with histologically confirmed stage IV NSCLC and 16 HC were included onto the study. Patients had a median age of 70 years (range 48-85), were predominantly male (67.9%) and former smokers (57.1%), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (67.8%). The majority of patients received chemotherapy as front line treatment (N=41, 73.2%), 3 (5.4%) immunotherapy and 12 (21.4%) targeted therapies (N EGFR inhibitors= 9, N ALK inhibitors= 3). PD-L1 plasma levels was first detected in the HC and then in NSCLC patients. In HCs median PD-L1 basal level was 37.81 pg/ml (range 9.73-90.21), while in NSCLC patients was 42.21 pg/ml (range 12.00-143.49). This difference was not statistically significant (p = 0.78). Interestingly, levels of PD-L1 plasma expression significantly increased during the first 3 months of systemic therapy (Wilcoxon test p=0.04). In addition, the 5 patients with high levels of plasma PD-L1 expression had significantly shorter progression free survival (PFS) and overall survival (OS) than individuals with low or no plasma PD-L1 expression (PFS: 1.2 versus 6.4 months, p=0.056; OS: 1.2 versus 9.7 months, p=0.003). **Conclusion:** Plasma PD-L1 expression is feasible in clinical practice. High levels of expression could correlate with worst prognosis. Additional studies exploring correlation between plasma and tumor tissue PD-L1 expression are needed.

Keywords: Immunotherapy, PD-L1, Non Small Cell Lung Cancer (NSCLC)

PUB072 SIGNIFICANCE OF PAK1/CREB PATHWAY IN LUNG ADENOCARCINOMA ONCOGENESIS

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Background: P21-activated kinase 1 (PAK1) is serine/threonine protein kinase that contributes to Ras-driven tumorigenesis in non-small cell lung cancer (NSCLC). Cyclic AMP-response element-binding protein (CREB) is the transcription factor that regulates tumor cell differentiation and proliferation. Several studies have shown that expression level of PAK1 and CREB is elevated in NSCLC, respectively. However, the association between PAK1 and CREB in the regulation of carcinogenesis has not been well known in NSCLC. Here, we identified that overexpression of PAK1 and CREB is more prevalent in lung adenocarcinoma compared to normal tissue and PAK1 expression is significantly associated with CREB expression. **Method:** Sixteen tumor tissues from patients with lung adenocarcinoma were collected to evaluate PAK1 and CREB expressions by immunostaining and western blot analysis. Knockdown of PAK1 by siRNA was performed to evaluate the association between PAK1 and CREB. **Result:** PAK1 and CREB expressions, which were evaluated by immunohistochemistry and western blot assay were significantly increased in lung adenocarcinoma compared to normal lung tissues. Kaplan-Meier survival analysis with a online database showed the prognostic significance of PAK1 and CREB in lung adenocarcinoma. Knockdown of PAK1 by siRNA significantly suppressed the expression of CREB. PAK1 expression level was linearly correlated with CREB expression level by regression analysis (p=0.013). **Conclusion:** We demonstrated that expression level of both PAK1 and CREB was elevated in lung adenocarcinoma and high expression predicted a poor prognosis. Our results suggest that PAK1 regulates carcinogenesis through CREB in lung adenocarcinoma.

Keywords: lung adenocarcinoma, PAK1, CREB

PUB073 LUNG CANCER SCREENING WITH LDCT – RESULTS OF A SMALL COHORT CONTINUAL MONITORING (PILOT SILESIAN STUDY)

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Background: Lung cancer still remains the leading cause of cancer deaths worldwide. Screening with low-dose computed tomography (LDCT) has been demonstrated to shift detected lesions towards lower stages, thus reducing lung cancer mortality. The aim of the study was to evaluate the results of a Pilot Silesian Study for Early Lung Cancer Detection with LDCT. **Method:** In total 602 asymptomatic volunteers over 50 years of age with a smoking history of at least 20 pack-years have been undergoing LDCT screening annually or in shorter intervals, if required. One patient was excluded from statistical analysis due to symptoms related to advanced lung cancer. Since 2010 to 2017 there were 1019 CT scans performed. Of the whole cohort 146 participants (24.3%) underwent more than one round of LDCT. Maximal number of rounds was 8. Per protocol the positive result was defined as a presence of solid or part-solid nodule equal to or larger than 5 mm or non-solid equal to or larger than 8 mm. For the subsequent rounds the positive result was defined as an enlargement of preexisting non-calcified nodules by more than 2 mm or apperance of a new nodule. **Result:** Lung nodules were detected in 265 individuals (44.1%). Lung cancer was diagnosed in 11 patients (1.8%) – 7 cases in the first round, 3 in the second and 1 in the third round . Stage I of non small cell lung cancer was detected in 8 patients (72.7%), stage II – 0 (0.0%), stage III -3 (27.3%). In pathology reports 5 squamous cell lung cancers, 3 adenocarcinomas, 1 large cell carcinoma were identified. One lesion had mixed pathology and in one individual co-occurred 2 adjacent lesions indicating the distinct neuroendocrine pathology, i.e. small cell and large cell lung cancer. The rate of positive results in the first round in our study was 219 (36.4%). Of 601 participants, the diagnostic assessment of positive results more often involved further CT scans in 87 individuals (14.5%) than invasive procedures as bronchoscopy/EBUS – 23 (3.8%), transthoracic biopsy – 11 (1.8%) or VATS – 1 (0.2%). Fifteen participants (2.5%) underwent surgical resection (10 because of malignant ; 5 benign lesions). **Conclusion:** The detection rate of lung cancer in our study is relatively low (1.8%). The majority of detected lung cancers were diagnosed at an early stage and were treated with curative intent. The results of our study were similar to large international studies such as NLST.

Keywords: lung cancer, LDCT, Screening

PUB074 PROGRAMMED DEATH LIGAND 1 (PD-L1) EXPRESSION IN SURGICALLY RESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Strategies against PD-1/PD-L1 have radically changed the therapeutic scenario of advanced NSCLC. PD-L1 status has shown predictive value for immunotherapy efficacy in first-line setting. In our study we sought to determine its potential prognostic role and correlation to clinical-pathological features in early stage surgically resected NSCLC. **Method:** PD-L1 expression was evaluated in a cohort of 289 surgically resected, stage IA-IIIA NSCLC samples by immunohistochemistry using the SP263 clone (Ventana). Tumors were considered PD-L1 positive (PD-L1+) if ≥50% of tumor cells expressed the ligand. PD-L1 status correlation to clinical characteristic and overall survival (OS) was studied with Chi Square, Fisher Exact Test and Kaplan Meier analysis. **Result:** Patients were mostly males (79%), former or current smokers (81%), with median age of 67 years, non-squamous histology (68%) and high-grade tumors (55%). PD-L1 staining was present in 39.4% (114/289) of tumors but only 18.7% (54/289) of them were positive according to the cut-off value of 50%. In this cohort no significant correlation with sex, age, smoking status and histology was seen. PD-L1 expression was mostly limited to grade 3 tumors (G1 vs G2 vs G3: 0 vs 13% vs 25%, p=0.005). There was a tendency to longer median OS for PD-L1+ patients although the difference was not statistically significant (PD-L1+ vs PD-L1-: 47.5 movs 32.2 mo, p=0.5). OS was not affected by PD-L1 status even when the survival analysis was restricted to grade 3 tumors. **Conclusion:** PD-L1 is mostly expressed in high grade NSCLC. High PD-L1 expression is not prognostic for OS although a tendency toward longer survival was observed for PD-L1+ patients. Further studies are needed to confirm PD-L1 correlation to grading in the metastatic setting and to evaluate whether grading could represent a surrogate biomarker for sensitivity to immunotherapy.

Keywords: NSCLC, Tumor grade, PD-L1

PUB075 DETECTION OF T790M MUTATION IN CIRCULATING FREE TUMOR DNA OF PATIENTS WITH EGFR-POSITIVE ADVANCED NON SMALL CELL LUNG CANCER

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Background: The identification of T790M mutation in EGFR exon 20 predicts sensitivity to third generation EGFR Tyrosine Kinases Inhibitors (TKIs) in patients (pts) with advanced non small cell lung cancer (aNSCLC). However, its detection as part of a complete molecular analysis may be hampered by limited amount of tumor tissue available both before and after treatment with first or second generation EGFR TKIs. Therefore, circulating free tumor DNA (cftDNA) may represent an alternative source to assess T790M mutation. **Method:** We considered as eligible patients with cytologically confirmed EGFR positive aNSCLC progressing after first or second generation TKIs. All patients were evaluated by a liquid biopsy assay to detect EGFR mutations in cftDNA. Plasma was analyzed by Real Time PCR (RT PCR). The degree of concordance between EGFR mutational analysis in blood and on tissue was evaluated. The T790M detection rate and the percentage of rebiopsy performed at disease progression following first line treatment were also reported. **Result:** Between April 2015 and May 2017, a consecutive series of 20 patient underwent liquid biopsies before and/or after treatment with EGFR TKIs (erlotinib, gefitinib or afatinib). All pts had a diagnosis of adenocarcinoma and stage IV disease, and the median age was 69 years; most of them were female (70%) and never smokers (80%). Before starting first line treatment, 16 pts underwent liquid biopsy: the concordance of cftDNA with tissue was 100% for negative T790M mutational status. After disease progression, 12 pts underwent liquid biopsy: T790M was positive in 7 pts (58.3%). A rebiopsy was performed only in 4 out of 12 pts (33.4%): contrary to plasma analysis, one of them was found positive for T790M on tissue. Therefore, sensitivity and specificity of cftDNA in detection of T790M were 87.5% and 100%, respectively. The overall frequency of T790M detection after first line treatment was 66.7%. The third generation TKI osimertinib was administered to seven of eight T790M positive pts (87.5%); the remaining patient received best supportive care due to poor performance status. **Conclusion:** Liquid biopsy confirmed to be a valid method to detect the T790M mutation in pts with aNSCLC, both before and after treatment with first and second generation EGFR TKIs. In particular, RT PCR showed high sensitivity and specificity in detection of T790M at disease progression, when T790M positive pts may be offered third generation TKIs treatment. Nevertheless, a rebiopsy need to be performed whenever possible to avoid T790M false negative at cftDNA analysis.

Keywords: non small cell lung cancer, circulating free tumor DNA, T790M

PUB076 PROGRAMMED CELL DEATH LIGAND 1 AND NEUTROPHIL TO LYMPHOCYTE RATIO TO PREDICT RESPONSE TO NIVOLUMAB IN NON SMALL CELL LUNG CANCER

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Background: Cost-effectiveness and viability of new predictive markers for immunotherapy limit their application in clinical practice. This retrospective study explores Programmed cell death ligand 1 (PD-L1) expression and Neutrophil to Lymphocyte Ratio (NLR) as an easy feasible panel to predict benefit to Nivolumab. **Method:** PD-L1 expression and baseline NLR were available for 86 out of 109 patients (pts) treated with nivolumab from August 2013 to March 2017. PD-L1 staining was performed with clone E1L3N or SP263. PD-L1 positivity was defined as expression on ≥ 1% of tumor cells, while NLR was considered as high (NLR≥3) or low (NLR<3). Kaplan Meyer method and Cox regression were used to define the combined predictive value of PD-L1/NLR for progression free survial (PFS) and response rate (RR) by RECIST 1.1 to Nivolumab. **Result:** Pts were mostly males (61%), smokers (85%), with advanced adenocarcinoma (76%); EGFR+ (11%), K-RAS+ (24%), PDL1+ (29%). Median PFS, OS and RR were 2.8 months (mo) (95% [CI] 1.9-4.73), NR (95% [CI] 3.38-NR) and 23%, respectively. While PFS was not affected by PD-L1 status, high NLR significantly predicted poorer PFS than low NLR (NLR>3: 2.3 mo, 95% [CI] 1.64-2.89 vs NLR<3: 3.5 mo, 95% [CI] 2.86-4.7,p<0.001). Patients were divided in two cohorts according to combined PD-L1/NLR (cohort1: PD-L1+/low NLR, cohort 2: PD-L1-/high NLR). In the multivariate analysis, PFS was significantly longer in cohort 1 (Cohort 1: 3.5mo, 95% [CI] 2.86-4.83 vs Cohort 2: 2.3 mo, 95% [CI] 1.64-3.15, p<0.05). Cohort 1 RR was 38% versus 14% of Cohort 2 [Table]. Median duration of response was longer in Cohort 1 than Cohort 2 (54 weeks vs 24 weeks, respectively). **Conclusion:** The current retrospective analysis supports the combined use of PD-L1/NLR to predict response to nivolumab. If validated, this panel could be routinely applied to select pts for immunotherapy avoiding more complex and expensive methods.

Keywords: NSCLC, PD-L1, Neutrophil to lymphocyte ratio

PUB077 THE ANTIMETASTATIC AND ANTITUMOR EFFECT OF TEICHOIC ACIDS FROM CELL WALL BIOPOLYMERS OF STAPHYLOCOCCUS AUREUS ON LEWIS LUNG CARCINOMA MODEL

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Background: In order to enhance the immunogenicity of vaccines ligands of Toll-like receptors are often used as adjuvants in therapy of lung cancer. Such ligands are cell wall biopolymers of gram-positive microorganisms *Staphylococcus aureus* – techoic acids (TAs). They play a significant role as immunomodulators. Previously we have shown increasing of apoptotic level and decreasing of cell population of proliferative pool after co-cultivation of macrophages from Lewis lung carcinoma (LLC)-bearing mice treated by TAs+PO244 with primary LLC culture. The aim of present study was to define antimetastatic and antitumor effect of above-mentioned agents on LLC model. **Method:** Administration of TAs from *Staphylococcus aureus* Wood 46 to the animals with metastatic LLC was intranasal in concentration 2 μg/kg of weight, whereas the bimetallic complex that consists of copper ions, cadmium and ethylenediamine (PO244) was carried out intraperitoneally at the total dose 0,8 mg/kg of body weight. Both TAs and PO244 was administrated on 8th day after tumor cell inoculation. Antimetastatic and antitumor effect was defined. The number of living cells was determined using MTT-colorimetric assay. **Result:** Administration of TAs+PO244 to LLC-bearing mice resulted in 64,3% tumor outcome in comparison with 85,7 % in control group. Under the condition of TAs+PO244 administration tumor weight decreased by 52,8% compared to control. Moreover, this pattern remains at different stages of tumor growth. Number of animals with metastases in control group was 78,6%, whereas number of metastases in lungs was 21,7%, TAs+PO244 influence led to decrease metastasis to 52,7% of animals with metastases and 9,3% had metastases in lungs. After the incubation primary LLC culture cells with above-mentioned agents during 24 hours distinct cytotoxic effect was showed (34,42% *vs.* control). **Conclusion:** On experimental model of metastatic LLC the application of combined therapy TAs with PO244 demonstrated significant both antitumor and antimetastatic influence in comparison with control.

Keywords: Immunotherapy, LLC

PUB078 LUNG CANCER IN THE ELDERLY - HISTOLOGY, LOCALIZATION AND GENDER DISTRIBUTION IN NORTH ROMANIA

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Background: Lung cancer remains one of the most challenging conditions due to its poor prognosis. Extensive data regarding changes in cancer histology, sex-specific incidence and tumor localization are available for developed countries in Europe and the US. However, for countries where there is no unified and comprehensive cancer registry, these data are scarce. Additionally, data from elderly individuals, that represent a significant proportion of all lung cancer patients, are insufficient. The aim of the study was to provide an analysis of lung tumor characteristics in elderly patients from North-East Romania. **Method:** We retrospectively analyzed all lung cancer cases admitted to the Regional Institute of Oncology (a territorial unit responsible for the diagnosis and treatment of cancer patients in Moldova) from 2012 to 2017. We then selected the elderly patients (aged over 75 at the time of diagnosis) and collected several types of data, such as sex, age, histology, stage, EGFR status and localization (right versus left lung). **Result:** We identified 201 patients over 75 years old at the time of diagnosis. Average age was 77.1±2.1, with a median of 77 and a maximum of 90 years. The male to female ratio was 3.27:1. Regarding histology, most cancers were adenocarcinomas (32.8%), followed by squamous cell carcinomas (30.8%) and atypical/undetermined histology (25.4% - carcinoid tumor, adenosquamous tumor or large-cell carcinoma). Females were more likely to have adenocarcinoma, while males were more likely to have squamous cell carcinoma. Most patients were diagnosed in stage IV (53.7%), with more males being diagnosed in earlier stages when compared to females. We found that a very large proportion of the adenocarcinoma patients was not tested for the EGFR mutation (25.4% of the stage III or IV adenocarcinomas). Of those tested for EGFR, 33% had a mutation present, all female. Right lung tumors were more frequent than left lung tumors (62.2% vs 37.8%) in both sexes. **Conclusion:** Elderly patients represent an important segment of the individuals affected by lung cancer. Most likely due to their age, they are diagnosed in advanced or metastatic stages and additional Immunohistochemical staining and/or EGFR testing are sometimes omitted. Our data for Romanian patients is mainly in accordance with available literature, although we found an unusually high percent of tumors with atypical histology in elderly patients.

Keywords: tumor localization, histology, elderly

PUB079 DETECTION OF THE EGFR P.(T790M) MUTATION BY DIFFERENT METHODS: A SMALL COMPARISON CASE STUDY

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Background: About 50-60% of non-small cell lung cancer (NSCLC) patients with a Tyrosine Kinase Inhibitor (TKI) sensitizing EGFR mutation can develop therapy resistance via the acquisition of the additional p.(T790M) mutation. The identification of this group of patients is important because they can be treated with a 3rd line TKI: Osimertinib. Analysis of plasma samples has become a minimally invasive alternative to repeat tissue biopsy for the detection of the *EGFR* p.(T790M) mutation. The mutation can be detected in plasma and tissue by various methods including the FDA approved Roche COBAS® EGFR v2 test, the EntroGen® EGFR test and digital droplet PCR (ddPCR). In this study, we compared the detection of the *EGFR* p.(T790M) mutation by ddPCR and COBAS in plasma specimens, and ddPCR and EntroGen in tissue specimens. **Method:** Blood from 14 NSCLC was collected in STRECK™ blood collection tubes. Plasma was prepared and circulating cell-free (ccf) DNA extracted with the COBAS and Qiagen method. DNA was analyzed for the presence of the EGFR TKI sensitizing and p.(T790M) mutation by COBAS, or the p.(T790M) mutation only by ddPCR on a Biorad QX200 platform. In addition, 26 biopsies from EGFR-positive patients who progressed on TKI, and which were tested p.(T790M) negative by Entrogen were re-analyzed by ddPCR. **Result:** Nine out of fourteen plasma samples were found to contain DNA with the sensitizing *EGFR* mutation by COBAS. The p.(T790M) mutation was found in four of these nine cases. ddPCR revealed one additional p.(T790M)-positive plasma sample that was tested negative by COBAS. ddPCR detected ten p.(T790M)-positive cases in the 26 EntroGen p.(T790M) negative samples, and suggests a 38% of false negative rate of the EntroGen method in this small cohort of samples. **Conclusion:** ddPCR for the detection of the *EGFR* p.(T790M) mutation in plasma and tissue appears to be associated with a higher sensitivity compared to the COBAS and EntroGen methods, respectively.

Keywords: EGFR T790M, ddPCR, COBAS

PUB080 A PHASE II STUDY OF BGB324 IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED LUNG ADENOCARCINOMA

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Background: The AXL receptor tyrosine kinase is associated with poor overall survival in NSCLC. AXL signalling is an important regulator of tumour plasticity related to epithelial-to-mesenchymal transition (EMT) and stem cell traits that drive metastasis and drug resistance. Up-regulation of AXL has been associated with reduced response to anti-PD-1. AXL is also a key suppressor of the anti-tumour innate immune response. Hence, AXL signalling contributes uniquely to both tumour cell intrinsic and microenvironmental anti-tumour immune suppression. AXL is required for EMT-mediated resistance to cytotoxic T cell and natural killer (NK)-cell mediated cell killing. In the syngeneic Lewis Lung mouse, blocking AXL signalling with BGB324, a selective clinical-stage small molecule AXL kinase inhibitor, enhanced the effect of immune checkpoint blockade. BGB324+anti-PD-1/anti-PD-L1 treated tumours displayed decreased tumour growth, a more epithelial phenotype, enhanced infiltration of cytotoxic T lymphocytes, NK and NKT cells and decreased infiltration of MDSCs. **Method:** BGBC008 (NCT03184571) is an open-label, phase II study designed to assess the antitumour activity of BGB324 in combination with pembrolizumab in patients with previously treated, advanced lung adenocarcinoma. Secondary objectives include safety and pharmacokinetics of BGB324 and pembrolizumab in combination. A single arm extension of Simon's 2-stage design is employed with an interim and final analysis. Up to 48 evaluable patients will be enrolled. Recruitment will be halted after 22 evaluable patients to determine the ORR. If 3 or fewer responses are observed, the trial will be terminated in favour of the null for futility. If 8 or more responses are observed, then the trial will be stopped in favour of the alternative for demonstration of activity. If 4 to 7 patients have an observed response, then a further 26 patients may be evaluated. This design provides an overall power of 80.1% to test the stated null and alternative hypothesis. BGB324 will be administered orally, once daily, in a fasted state. Days 1, 2, and 3 of BGB324 administration consist of a 'loading' dose of 400 mg followed by dose of 200 mg daily. A fixed dose of 200 mg pembrolizumab will be given by intravenous infusion over 30 minutes every 3 weeks. BGB324 and pembrolizumab will be given until disease progression, unacceptable dose toxicity, or until 106 weeks (35 cycles). Efficacy endpoints including ORR, Duration of Response, Progression Free Survival are based on tumour imaging evaluation by RECIST 1.1. Tumour specimens will be taken to assess AXL kinase and PD-L1 expression. **Result:** Section not applicable - Trial in progress **Conclusion:** Section not applicable - Trial in progress

Keywords: PD1, Axl, Keytruda

PUB081 EVALUATION OF TOXICITY PROFILE OF ALK INHIBITORS IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: ALK inhibitors showed promising clinical activity in patients with ALK-rearranged (ALK-positive) non-small-cell lung cancer (NSCLC). We aimed to evaluate the toxicity profile of four officially approved ALK inhibitors (crizotinib, ceritinib, brigatinib and alectinib) in advanced NSCLC patients. **Method:** Electronic literature search up to June 2017 was performed in MEDLINE and EMBASE for trials utilizing ALK inhibitors in NSCLC patients. Paired reviewers independently selected articles for inclusion and extracted safety data. A formal meta-analysis was conducted with Comprehensive Meta-Analysis software (Version 2.2). **Result:** Six-teen studies were eligible for the analysis. The total number of patients evaluated for toxicities were 2329 patients. The incidence of overall adverse events (AEs), grade 3-5 AEs, serious AEs (SAEs), treatment-related death (TRD), AEs leading to dose reduction, and AEs leading to drug discontinuation was 96.5%, 47.0%, 14.8%, 1.7%, 35.0%, and 7.7%, respectively. The most frequent AEs with ALK inhibitors was diarrhea (57.2%), nausea (46.8%), vomiting (33.1%), constipation (30.9%), and increased ALT (23.7%). Overall, alectinib seems to have superior efficacy and lower toxicity compared with other ALK inhibitors (see table).

	Drugs				total	p for difference
	crizotinib	ceritinib	brigatinib	alectinib		
Overall AEs	97.7	95.8	NA	96.9	96.5	0.467
Grade 3-5 AEs	40.8	54.2	NA	33.8	47	0.053
SAEs	18.6	13.2	NA	19.1	14.8	0.329
TRD	1.5	2	2.3	0.7	1.7	0.371
Dose reduction	12.3	61.2	20	15.9	35	<0.001
Drug discontiunation	6.2	7.7	7.9	8.3	7.7	0.901
Common AEs						
Diarrhea	54.9	81	39.5	10.8	57.2	<0.001
Nausea	55.1	75.4	46.5	14.2	46.8	<0.001
Vomitting	43.9	63.3	22.1	9	33.1	<0.001
Constipation	35.7	25	16.9	34.2	30.9	<0.001
Increased ALT	27.8	46.1	11.3	12.8	23.7	<0.001
Response rate	69	52.5	70	71.8	66.9	0.102

Conclusion: ALK inhibitors demonstrate unique toxicity profile. Early and appropriate management is strongly recommended to avoid unnecessary dose reductions and drug discontinuations. In-depth analysis with recreated individual patient data will be presented at the conference.

Keywords: Non-small-cell lung cancer, ALK Inhibitor, toxicity

PUB082 RADIOMIC FEATURES ON BASELINE CT ARE PREDICTIVE OF RECURRENCE IN EARLY STAGE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Surgery is the only potentially curative modality for early-stage non-small cell lung cancer (NSCLC) patients. However, 30% to 55% of patients develop recurrence. In this work, we explored the role of radiomic (computer extracted image) features from within and outside the lung nodule on baseline CT scans to predict risk of recurrence in early-stage NSCLC patients. **Method:** 110 patients with early-stage NSCLC were identified for the study. All patients underwent surgery with the primary tumor having recurred (relapsed) in 34 cases within 5 years of surgery. Tumor ROIs were contoured by an expert reader using the 3DSlicer program on chest CT scans. Radiomic texture features were extracted from within and outside the primary lung nodule on the same scans. Four rings of annular peri-tumoral regions were analyzed, each with a 5 mm increment leading upto maximum radius of 20 mm from the nodule center. Patients were randomly divided into training (N=60) and testing (N=50) cohorts and 5 most predictive radiomic features from out of a total pool of 2892 were selected from the training set via a feature selection algorithm and used to train a Random Forest (RF) classifier to predict risk of recurrence. The RF classifier was then evaluated on the test set via the area under the receiver operating characteristic curve (AUC). **Result:** The most predictive features were the Haralick entropy features within the 0-5mm and 5-10 mm annular rings outside the tumor (p-value <0.01). The RF classifier in conjunction with the 5 most predictive features yielded an AUC=0.77 in predicting recurrence vs non-recurrence in early stage NSCLC. **Conclusion:** Our results suggest that computer extracted texture features of the peri-tumoral region is predictive of disease recurrence in early-stage NSCLC. Additional independent, multi-site validation of these findings is warranted.

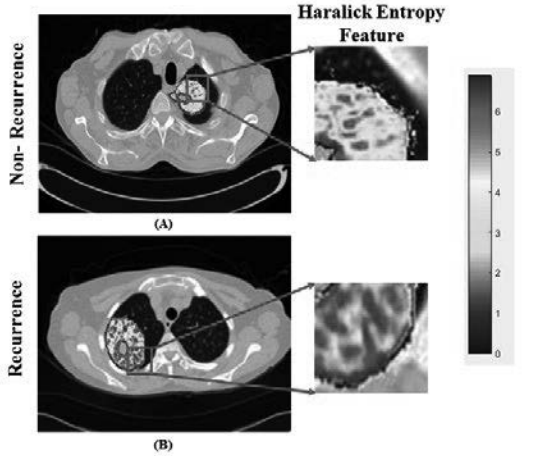

Figure: Chest CT scan corresponding to (A) Non-recurrent and (B) recurrent early stage NSCLC. The Haralick entropy texture feature is significantly overexpressed in the perinodular region of the lung nodule in the recurrent tumor compared to the non-recurrent tumor. These findings suggest that the microarchitecture of the peri-nodule region is significantly more chaotic and disordered in the recurrent tumors compared to the non-recurrent tumors.

Keywords: early stage NSCLC, recurrence, Radiomics

PUB083 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 a promising and minimally-invasive liquid biopsy sample for testing gene alterations and monitoring personalised treatment strategies. Because of its high expense, translation of sensitive and accurate method as next generation sequencing (NGS) into routine cancer care has been slow. **Method:** We retrospectively reviewed 36 advanced NSCLC pts who were performed gene test prior and after treatment using tissues 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 36 NSCLC pts, 22 were male, 22 were never-smokers, and 29 were adenocarcinoma. ctDNA profiling detected alterations in 31 pts (86%). TP53 (53%), EGFR (47%), KRAS (25%), MET (14%) were the commonest abnormalities detected. Additionally, PIK3CA (8%), HER2 (6%), ALK (3%) mutations were detected, respectively. Sensitizing mutations were detected in 13 pts (36%) prior to treatment using tissue by the method of ARMS, including 11 EGFR mutations and 2 ALK fusions, and all pts received tyrosine kinase inhibitor (TKI) as first-line therapy. Among 11 EGFR mutant pts, T790M mutation was detected in 6 pts (55%), KRAS mutation was detected in 3 pts (27%), and TP53 mutation was detected in 4 pts (36%), while MET amplification was found in 1 pt (9%). 1 KRAS mutation and 1 TP53 mutation were detected in 2 ALK –TKI resistant pts, respectively. 18 pts (78%) reported as tissue negative had a positive liquid biopsy, including 4 MET 14 exon skipping mutations, 1 EGFR 19 DEL and 1 EGFR L858R mutation. The mutation abundance is all below 1%, except EGFR 19 DEL (3%). All 6 pts received TKIs; 2 got parcial responses, 3 stable diseases and 1 progressive disease. **Conclusion:** ctDNA can be used as a 'liquid biopsy' for molecular profiling of advanced 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: liquid biopsy, lung caner, ctDNA

PUB084 UNUSUAL MORPHOLOGICAL VARIANTS OF LUNG TUMORS - A DIAGNOSTIC CHALLENGE: A SHORT SERIES FROM EASTERN INDIA

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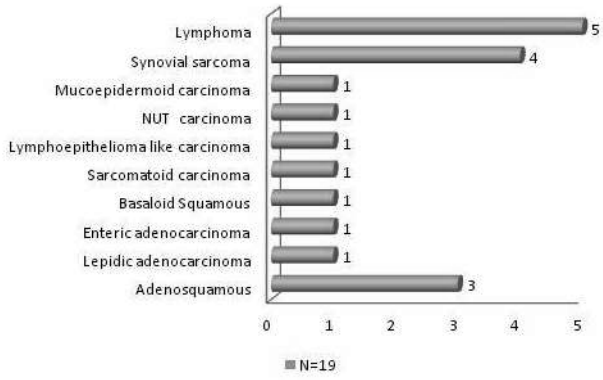
Background: Unusual variants of lung cancer are a cause of diagnostic dilemma. It is important to identify these entities because most of them are poorly differentiated, have an aggressive course, and worse survival **Method:** Over a period of 3 years (2014-2017) all cases of lung tumors were retrieved and the rare variants were analysed. Tumors were classified according to WHO 2015. Morphology & immunohistochemistry with a panel of antibodies were used to diagnose the rare variants. The antibodies used were TTF-1, P40, CK7, CK20, vimentin, napsin A, synaptophysin, chromogranin, CD20, CD3, ALK, CD30, CD10, BCL-2, BCL-6, CD34,

CD99 & NUT **Result:** 220 endobronchial biopsies were received. Unusual variants constitute 8.6% (19/220). Age ranged from 20-75 years with a median age of 35 years and male preponderance (M:F=3.75:1). The rare variants in the epithelial tumors were adenosquamous, lepidic adenocarcinoma, enteric adenocarcinoma, basaloid squamous cell carcinoma, sarcomatoid carcinoma, lymphoepithelioma- like carcinoma, NUT carcinoma and mucoepidemoid carcinoma. In the mesenchymal tumors, synovial sarcoma was commonly seen and in the lymphohistiocytic tumors lymphomas were the predominant ones. The most common lymphomas were diffuse large B cell lymphoma, ALK positive ALCL and peripheral T cell lymphoma NOS.



Conclusion: Unusual variants of lung tumors are difficult to diagnose. Immunohistochemistry is an important adjunct for proper diagnosis. Awareness of these rare entities is essential for appropriate molecular testing, targeted therapy, and treatment

PUB085 SURGERY OF PRIMARY NON-SMALL CELL LUNG CANCER WITH OLIGOMETASTASIS: ANALYSIS OF 172 CASES

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Background: Previous studies have demonstrated survival benefits for local treatment in solitary metastatic non-small cell lung cancer (NSCLC).This study aimed to investigate the effect of local surgery for NSCLC with oligometastasis. **Method:** This study included 172 patients of NSCLC with oligometastasis between January 2006 and December 2016, which were divided into two groups, group A (82 cases) for local surgery and group B (90 cases) for systematic chemotherapy and radiotherapy. The median survival time (MST) and 5-year survival rate between the two groups were compared and analyzed, as well as the impact in group A between different pathological types, surgical approach of primary tumor and Oligometastatic site. **Result:** The MST of group A and B were 48 months and 18 months, 5-year survival rates were 21.1% and 7.6% respectively ($p < 0.05$). Patients with adrenal oligometastasis obtained higher survival rate than those with brain, bone, liver or other oligometastases in group A ($p < 0.05$). There was no significant difference in survival rate between pathological types and surgical approach of primary tumor ($p > 0.05$). **Conclusion:** Local surgery significantly prolonged the overall survival time and 5-year survival rate of primary NSCLC with oligometastasis.

Keywords: Oligometastasis, Local surgery, non-small cell lung cancer

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FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Adriaan	Bokhoven	Grants/Research Support	NIH
John	Bomalaski	Employee	Polaris Pharma
Zeev	Bomzon	Employee	Novocure
Samuel	Bonacorsi	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Franck	Bonnetain	Grants/Research Support	Bayer, BMS, Chugai, Integragen, Janssen, Nestlé, Novartis, Roche, Amgen, Celgene, Ipsen, Merck Serono
Philip	Bonomi	Speakers or Advisory Board	AstraZeneca, Merck, Biodesics, Bristol-Myers Squibb, Pfizer, Roche Genetech, Celgene
Jennifer	Bordeaux	Employee	Navigate BioPharma Services
Rodolfo	Bordoni	Other	BMS, Incyte, Merck and Genentech
Hossein	Borghaei	Consultant	Bristol-Myers Squibb, Lilly, Celgene, Genentech, Pfizer, Boehringer Ingelheim, EMD Serono, Trovagene, Merck, Novartis, AstraZeneca
		Employee	Fox Chase Cancer Center
		Other	BMS, Lilly, Celgene, Genentech, Novartis, AstraZeneca, Trovagene, Merck, EMD-Serono, Prizer, Clovis Oncology, Fox Chase Cancer Center, Mellennium, University of Pennsylvania
		Grants/Research Support	Celgene, Merck, Mellennium
Andrea	Borondy Kitts	Employee	Prosumer Health
Diana	Borthwick	Speakers or Advisory Board	Boehringer Ingelheim
Joaquim	Bosch Barrera	Grants/Research Support	Boehringer Ingelheim
Jasper	Boschmans	Employee	Owlstone Medical Ltd
Johan	Botling	Speakers or Advisory Board	MSD, AstraZeneca
		Grants/Research Support	Roche
		Other	AstraZeneca, Roche, MSD
Mark	Bowling	Consultant	Medtronic
		Other	Medtronic
Michael	Boyer	Grants/Research Support	Peregrine Pharmaceuticals, Inc, Bristol-Myers Squibb, Merck Sharpe and Dohme, Genentech/Roche, AstraZeneca, Pfizer, Amgen, Novartis, Beigene
		Other	Merck Sharpe and Dohme, AstraZeneca, Bristol-Myers Squibb
Billy	Boyle	Other	Owlstone Medical Ltd
Julie	Brahmer	Consultant	Bristol-Myers Squibb, Celgene, Lilly, Merck
		Grants/Research Support	Bristol-Myers Squibb, Janssen, Medimmune/AstraZeneca, Merck
		Other	Bristol-Myers Squibb, Merck
Jeffrey	Bradley	Speakers or Advisory Board	Varian Proton Therapy, ViewRay Scientific
		Grants/Research Support	Mevion Medical Systems. ViewRay, Inc.
Julie	Brahmer	Consultant	BMS, Celgene, Eli Lilly, Merck, AstraZeneca
		Other	BMS (uncompensated), Celgene, Eli Lilly, Merck
		Grants/Research Support	BMS, MedImmune/AstraZeneca, Merck
Fadi	Braiteh	Consultant	Genentech
		Speakers Bureau	Genentech
Juergen	Braunger	Employee	Boehringer Ingelheim
Emilio	Bria	Speakers Bureau	Eli Lilly, Roche, Novartis, MSD, Helsinn
		Speakers or Advisory Board	AstraZeneca, Roche, MSD, BMS, Novartis, Helsinn, Celgene
		Grants/Research Support	Novartis, AstraZeneca, BMS
J. Michelle	Brockman	Employee	Genentech, Inc
Carol	Brooks	Employee	Guardant Health
Peter	Brossart	Other	Bristol-Myers Squibb, MSD, Roche-Peru
Kristine	Brovsky	Grants/Research Support	NIH
Helen	Brown	Employee	AstraZeneca
A	Bruynzeel	Speakers Bureau	ViewRay Inc.
Paolo	Bruzzi	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb
Lukas	Bubendorf	Speakers or Advisory Board	Roche, Pfizer, MSD, Boehringer Ingelheim, Novartis
		Stock Shareholder (directly purchased)	Roche, Novartis
Raphael	Bueno	Grants/Research Support	NIH, Siemens, Genetech, Verastem, Myriad Genetics, Gristone Oncology, HTG molecular
		Other	Roche / Imcore, Castle Biosciences, Myriad, Astrazeneca, Cleaveland Clinic, Aspen Lung Conference, Arthur Tuverson Law Office, Neil Leifer Attorney, Morrison Mahoney Law Office, David Weiss Law Office

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Khanh	Bui	Employee	AstraZeneca
Paul	Bunn, Jr.	Consultant	AZ, BMS, Genentech, Lilly, Pfizer, Merck, Novartis, Merrimack, Daiichi
		Other	AstraZeneca, Bristol-Myers Squibb, Genentech, Merck, Pfizer
Sjaak	Burgers	Consultant	AstraZeneca, Roche, Boehringer Ingelheim
Marco	Burgio	Other	BMS
Tom	Burke	Employee	Merck & Co., Inc.
Ronald	Burkes	Consultant	AstraZeneca
Christine	Burns	Employee	Foundation Medicine
Virginia	Burns	Other	Bristol-Myers Squibb
Charles	Butts	Speakers or Advisory Board	Pfizer, BMS, Merck, AstraZeneca
		Other	Boerhinger Ingelheim
Reinhard	Büttner	Other	Targos Molecular Pathology
Lauren	Byers	Consultant	Scientific Advisory Committee
Maria	Cabanillas	Other	LOXO
Jacques	Cadranel	Consultant	BMS, AZ, Roche
Laura	Caffrey	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Shay	Cahal	Employee	Novocure Ltd
Can	Cai	Stock Shareholder (directly purchased)	Novartis
		Employee	Novartis
Xuyu	Cai	Stock Shareholder (directly purchased)	AnchorDx Medical
Luana	Calabro	Consultant	BMS
Raffaele	Califano	Speakers or Advisory Board	Astrazeneca, Roche, BMS, MSD, Novartis, Pfizer, Lilly Oncology, and Boehringer ingelheim
		Other	AstraZeneca, Roche, BMS, MSD, Novartis, Pfizer, Lilly Oncology, and Boehringer Ingelheim
Emiliano	Calvo	Consultant	Novartis, GlaxoSmithKline, Astellas Pharma, Roche/Genentech, Lilly/ImClone, Nanobiotix, Pfizer
		Speakers Bureau	Novartis
		Grants/Research Support	Lilly, PsiOxus Therapeutics, Novartis, Roche/Genentech, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Oncology, Eisai, AbbVie, OncoMed, PharmaMar, Puma Biotechnology, Spectrum Pharmaceticals, Sanofi, Pfizer, Merck, Nektar, Millenium
		Other	Pierre Fabre, Bristol-Myers Squibb
D. Ross	Camidge	Other	Pfizer, Genoptix, Turning Point, ARIAD, Roche/Genentech, Takeda, Celgene, Array, AbbVie, Clovis, Novartis, Orion, Eli Lilly, G1 Therapeutics, Genoptix
		Grants/Research Support	ARIAD, Takeda
		Consultant	Roche/Genentech, Takeda, G1 Therapeutics, Novartis, Genoptix, Mersana Therapeutics,
Frederique	Cantero	Employee	Servier
Xiting	Cao	Employee	Merck
William	Capra	Employee	F. Hoffmann-La Roche Ltd
David	Carbone	Speakers Bureau	Merck, Bristol-Myers Squibb, Novartis, AstraZeneca, Genentech, Celgene, Pfizer
Andres	Cardona	Employee	F. Hoffmann-La Roche Ltd
Adrian	Cassidy	Employee	F. Hoffmann-La Roche Ltd
		Stock Shareholder (directly purchased)	F. Hoffmann-La Roche Ltd
Fabiola	Cecchi	Employee	NantOmics, LLC
Giovanni	Ceresoli	Grants/Research Support	Bayer
		Consultant	Bayer, BMS
Jeremy	Cetnar	Other	Novartis, Ipsen
Young Kwang	Chae	Consultant	Foundation Medicine, Biodesix, Guardant Health, Counsyl
Jamie	Chaft	Speakers or Advisory Board	BMS, AZ, Merck, Genetech
Allen	Chan	Consultant	Sanomics Limited Hong Kong
Faye	Chan-Diehl	Employee	Eli Lilly and Company
Jason	Chandler	Speakers Bureau	Janssen
		Consultant	BMS
		Other	Bristol-Myers Squibb
Sheenu	Chandwani	Employee	Merck & Co., Inc.

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Alex	Chang	Speakers' Bureau	Pfizer
		Speakers or Advisory Board	MSD
		Other	BMS
Joe	Chang	Grants/Research Support	Varian Medical System
		Stock Shareholder (directly purchased)	Global Oncology One
Shao-Chun	Chang	Employee	AstraZeneca
Bo	Chao	Employee	Eli Lilly and Company
Richard	Chao	Employee	Mirati Therapeutics, Inc.
Parneet	Cheema	Grants/Research Support	AstraZeneca, Boehringer Ingelheim, Hoffmann La Roche
		Consultant	AstraZeneca, Boehringer Ingelheim, Hoffmann La Roche, Pfizer, Novartis, Merck Canada, Bristol-Myers Squibb
		Other	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Roche
Kuan-Yu	Chen	Speakers Bureau	AstraZeneca
Peng	Chen	Employee	Celgene
Tianlei	Chen	Employee	Celgene Corporation
Zhengming	Chen	Grants/Research Support	NIH
Zhe	Chen	Employee	Novartis
Isan	Chen	Employee	Mirati Therapeutics, Inc.
Hui	Chen	Employee	OrigiMed
Lijuan	Chen	Employee	OrigiMed
Ying	Cheng	Other	BMS
Rebecca	Cheng	Employee	Eli Lilly and Company
Carol	Cheung	Consultant	Agilent Technologies, AstraZeneca Canada, Bristol-Myers-Squibb Canada, Merck Canada, Roche Canada
Alberto	Chiappori	Grants/Research Support	Novartis, Bristol - Myers Sqibb, ARIAD
		Speakers Bureau	Genetech, Merck, Takeda, Novartis, Pfizer, Celgene, Boehringer Ingelheim
Chun-Ru	Chien	Grants/Research Support	China Medical University Hospital
Barrett	Childs	Employee	Bayer HealthCare Pharmaceuticals Inc
Lucian	Chirieac	Grants/Research Support	NIH
Oana	Chirita	Employee	Bristol-Myers Squibb
Gung-Wei	Chirn	Employee	OrigiMed
Michael	Chisamore	Employee	Merck & Co., Inc
Chao-Hua	Chiu	Speakers Bureau	Ignyta
Marijana	Chlistalla	Employee	F. Hoffmann-La Roche Ltd
Byoung Chul	Cho	Speakers Bureau	Novartis
		Grants/Research Support	Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST
		Consultant	Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, Yuhan, Pfizer, Eli Lilly
		Other	Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, Yuhan, Pfizer, Eli Lilly
Daniel	Cho	Other	Bristol-Myers Squibb, Exelis, Genentech
		Consultant	Pfizer, Prometheus
Negar	Chooback	Grants/Research Support	AstraZeneca
Christos	Chouaid	Grants/Research Support	Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche, Lilly
Laura	Chow	Grants/Research Support	BMS, Merck, Pfizer, Incyte, Novartis, Medimmune/AstraZeneca, Genentech, GlaxoSmithKline (Inst), Incyte (Inst), VentiRx (Inst), Seattle Genetics
		Consultant	Amgen, Genentech, Emergent BioSolutions, Merck, Novartis
		Other	Amgen, Astellas Pharma, Emergent BioSolutions, Merck, Novartis, Merck, Novartis, Bristol-Myers Squibb
Vincent	Chow	Employee	Amgen
		Stock Shareholder (directly purchased)	Amgen
Edna	Chow-Maneval	Employee	Ignyta, Inc.
Hak	Choy	Grants/Research Support	Celgene
James	Christensen	Employee	Mirati Therapeutics, Inc.
Laura	Chu	Employee	Genentech/Roche
		Stock Shareholder (directly purchased)	Genentech/Roche

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Quincy	Chu	Other	Boehringer Ingelheim, Lilly, Merck, Novartis, Bristol-Myers Squibb
		Consultant	Boehringer Ingelheim, Lilly, Merck, Novartis
		Grants/Research Support	Boehringer Ingelheim
Michael	Chui	Grants/Research Support	NIH
Fortunato	Ciardiello	Consultant	Merck Serono, Bayer, Lilly, Roche, AstraZeneca, Astellas, Sanofi, Servier
Jill	Clancy	Employee	inVentiv Clinical
Jeffrey	Clarke	Other	Inivata
		Consultant	Premier, Inc
		Grants/Research Support	Medpacto, Genentech, AbbVie, Adaptimmune, Eli Lilly, Bayer, Bristol-Myers Squibb
Timothy	Clay	Other	MSD
Charles	Cleeland	Grants/Research Support	Bayer Healthcare
June	Clements	Employee	Ventana Medical Systems
Roger	Cohen	Consultant	Takeda, Zymeworks, Bristol-Myers Squibb
Shelley	Coleman	Employee	Genentech
		Stock Shareholder (directly purchased)	Genentech, Gilead Science, TEVA, Celgene, Johnson and Johnson
Paul	Conkling	Grants/Research Support	US Oncology Research Program
Maurizio	Conti	Employee	Siemens
Wendy	Cooper	Other	Pfizer
Karen	Copeland	Consultant	OncoCyte
Ryan	Corcoran	Consultant	Amgen, Avidity, Genentech, Merrimack, Taiho, Roche
Stefani	Corsi-Travali	Employee	Loxo Oncology
		Employee	Bristol-Myers Squibb
Diego	Cortinovis	Other	F. Hoffmann-La Roche
Alexis	Cortot	Grants/Research Support	AstraZeneca, Roche, Boehringer Ingelheim, Novartis, Pfizer, MSD
		Other	Pfizer, Novartis, Roche, AstraZeneca, Boehringer Ingelheim, BMS, MSD
Daniel	Costa	Consultant	Pfizer, Boehringer Ingelheim, ARIAD Pharmaceuticals, Pfizer, AstraZeneca
Mathieu	Coudert	Employee	Roche
Jeffrey	Crawford	Consultant	Celgene, AstraZeneca, Pfizer
		Other	Roche, Beyond Spring, G1 Therapeutics, Janssen, Merrimack, Mylan
		Grants/Research Support	Amgen, AstraZeneca, Bayer
Ben	Creelan	Speakers or Advisory Board	AZ, BMS, Takeda, AbbVie
		Grants/Research Support	Iovance, Prometheus, BI, BMS
Lucio	Crinò	Other	BMS
Agnieszka	Cseh	Employee	Boehringer Ingelheim RCV
Sinead	Cuffe	Other	Ipsen, BMS, Roche, Prizer, MSD
J. Jean	Cui	Employee	TP Therapeutics, Inc.
K. Michael	Cummings	Speakers or Advisory Board	Pfizer, Inc.
Lisa	Cupit	Employee	Bayer Healthcare Pharmaceuticals
Walter	Curran	Consultant	AZ, BMS
Richard	Cutler Jr.	Employee	Puma Biotechnology
Sanja	Dacic	Other	Bristol-Myers-Squibb
Ibiayi	Dagogo-Jack	Consultant	Boehringer Ingelheim
		Other	Foundation Medicine, Inc.
Naveen	Dakappagari	Employee	Navigate BioPharma Services
Tapashi	Dalvi	Employee	Astrazeneca
Thomas	D'Amico	Consultant	Scanlan
Kathleen	Danenberg	Employee	NantOmics
Peter	Danenberg	Employee	NantOmics
Mark	Danese	Consultant	BMS
		Other	BMS
Liz	Darlison	Grants/Research Support	Lilly Oncology, Bayer, Pierre Fabre, Asbestos Law Firms
Kaid	Darwiche	Grants/Research Support	Epigenomics AG
Marianne	Davies	Speakers' Bureau	Merck Pharmaceutical, Bristol Meyers Squibb, Genentech, AstraZeneca
Farshid	Dayyani	Employee	Roche Diagnostics
Flavia	De Angelis	Other	Bristol-Myers Squibb

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Javier	De Castro	Other	AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Pfizer, Roche
Harry	De Koning	Grants/Research Support	ZonMw, KWF Kankerbestrijding, RVVZ, Cancer Care Ontario, University of Zurich, Siemens AG, F. Hoffmann-La Roche Ltd
		Consultant	MD Anderson/Health Sciences
		Other	Siemens Germany, F. Hoffmann-La Roche Ltd
Joop	De Langen	Consultant	AstraZeneca, Bristol-Myers Squibb, Lilly, MSD
		Grants/Research Support	AstraZeneca, Bristol-Myers Squibb, MSD, Roche
Filippo	De Marinis	Consultant	Roche, Bristol-Myers Squibb, AstraZeneca
		Grants/Research Support	Boheringer Ingelheim
		Grants/Research Support	Merck MSD
		Other	AstraZeneca, BMS, Celgene, Novartis, Pfizer, Pierre-Fabre, Roche/Genentech, BI, MSD
Marc	De Perrot	Speakers or Advisory Board	Merck
Maike	De Wit	Speakers Bureau	AstraZeneca
Simon	Dearden	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Jerome	Declerck	Employee	Optellum Ltd
		Stock Shareholder (directly purchased)	Optellum Ltd
Todd	Demmy	Speakers or Advisory Board	Medtronic, Clinical Trial Reviewer
Wei	Deng	Employee	TP Therapeutics. Inc.
Philip	Dennis	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Charuhas	Deshpande	Speakers Bureau	Merck Sharpe & Dohme Corp
Darrin	Despain	Employee	Clovis Oncology Inc.
		Stock Shareholder (directly purchased)	Clovis Oncology Inc.
Ninad	Dewal	Employee	Foundation Medicine
Xavier	Dhalluin	Grants/Research Support	AstraZeneca
Anna Maria	Di Giacomo	Consultant	Bristol Meyer Squibb
Adi	Diab	Consultant	Celgene, CureVac, Nektar
		Grants/Research Support	Celgene, Idera, Nektar, Pfizer
		Other	Nektar
Marco	Dibonaventura	Employee	Pfizer
		Grants/Research Support	BMS, Teva, Genentech, Avanir, Orexigen
		Other	Bristol-Myers Squibb
Nicolas	Dickgreber	Consultant	Boehringer Ingelheim, Roche, Lilly, BMS
Maximilian	Diehn	Consultant	Roche
Lieming	Ding	Employee	Betta Pharmaceuticals Co, Ltd
		Stock Shareholder (directly purchased)	Betta Pharmaceuticals Co, Ltd
Daniel	Dix	Employee	Guardant Health
Robert	Doebele	Consultant	Pfizer, AstraZeneca, Ignyta, Takeda, Guardant, Spectrum, OncoMed, Trovagene, Green Peptide
		Other	Pfizer, AstraZeneca, ARIAD, Guardant Health, Abbott Molecular, GVKbio, Loxo
		Grants/Research Support	Ignyta, Mirati Therapeutics, Abbott Molecular, Loxo, Ignyta
Michael	Doherty	Employee	Foundation Medicine
Susan	Domchek	Other	AstraZeneca
Susan	Domchek	Grants/Research Support	AstraZeneca, Clovis, AbbVie
David	Donnelly	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Glenn	Dranoff	Employee	Novartis Institutes for Biomedical Research
Alexander	Drilon	Consultant	Pfizer
		Other	Loxo Oncology, Ignyta, TP Therapeutics, Roche/Genentech, ARIAD, AstraZeneca, Blueprint Medicines
Elizabeth	Dudnik	Other	Boehringer Ingelhem, Roche, AstraZeneca, Novartis, Phizer, MSD
		Speakers Bureau	Boehringer Ingelheim, Roche, MSD, AstraZeneca, Novartis, Phizer
Carter	Dufrane	Employee	Alliance Foundation
Gary	Dukart	Consultant	Xcovery Holding Company

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Addie	Dvir	Employee	Oncotest (subsidiary of Teva Pharmaceuticals)
Rafal	Dziadziuszko	Consultant	Roche, Pfizer, Boehringer Ingelheim, Clovis Oncology, Novartis, Astra Zeneca, Tesaro
		Speakers or Advisory Board	BMS
		Other	Novartis, Pfizer, Roche, Tesaro, Clovis, Boehringer Ingelheim, Ignyta, AstraZeneca, Pfizer
		Speakers Bureau	Pfizer
Juliann	Dziubinski	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Beth	Eaby-Sandy	Speakers Bureau	Merck
		Speakers or Advisory Board	Amgen, Helsinn, ARIAD, AstraZeneca, Takeda, AbbVie
Todd	Eary	Employee	Loxo Oncology
Kevin	Ebata	Employee	Loxo Oncology
Wilfried	Eberhardt	Consultant	BMS, Roche, AstraZeneca, Novartis, Boehringer Ingelheim, Merck, Pfizer, Celgene, Bayer, Daichii-Sankyo, Amgen, Lilly
		Grants/Research Support	BMS, Roche, AstraZeneca, Novartis, Boehringer Ingelheim, Merck, Pfizer, Celgene, Bayer, Daichii-Sankyo, Amgen, Lilly
		Other	Hexal
Martin	Edelman	Consultant	Genentech, Amgen, Clovis
		Grants/Research Support	Apexigen, Pfizer, Genentech, Lilly Oncology
		Other	Biomarker Strategies, Andarix
Melanie	Edwards	Speakers Bureau	American Society of Radiation Oncology
Coumaran	Egile	Employee	AstraZeneca
Eva	Ehrnrooth	Employee	Boehringer Ingelheim
Lawrence	Einhorn	Consultant	Celgene
		Stock Shareholder (directly purchased)	AMGEN, Biogen-idec
Timothy	Eisen	Employee	AstraZeneca UK
		Grants/Research Support	Bayer and Pfizer
Lars	Ek	Grants/Research Support	Sanofi Aventis
Cem	Elbi	Employee	Bayer HealthCare Pharmaceuticals Inc
Peter	Ellis	Other	Celgene, Mylan
Julia	Elvin	Employee	Foundation Medicine
		Other	Foundation Medicine, Inc.
		Stock Shareholder (directly purchased)	Foundation Medicine
Ryan	Emerson	Employee	Adaptive Biotechnologies
Jeffrey	Engelman	Employee	Novartis institute of Biomedical Research
		Stock Shareholder (directly purchased)	Novartis
Walburga	Engel-Riedel	Consultant	Boehringer Ingelheim, Roche, Roche, Pierre Fabre, MSD, Bristol-Myers Squibb
Achim	Escherich	Employee	Roche Diagnostics
David	Ettinger	Speakers or Advisory Board	AbbVie, Inc., BeyondSpring Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Corp., Eli Lilly & Co., EMD Serono, Genentech, Golden Biotech, Corp., Guardant Health, Inc., Helsinn Therapeutics (US), Inc., Herron Therapeutics, Regeneron Pharma, Trovagene, Inc.
William	Evans	Consultant	Roche, Lilly, Celgene, AstraZeneca, Astellas, Takeda, Boehringer Ingelheim, BMS
Elizabeth	Fabre	Other	BMS, Merck, AstraZeneca
Amir	Faghih	Other	Bristol-Myers Squibb
Stephen	Fairclough	Employee	Guardant Health, Inc
Corinne	Faivre-Finn	Grants/Research Support	Merck, AstraZeneca, Elektra, ESMO-ESO, MSD
		Other	ESMO-ESO, CRUK, eCancer, Pfizer, Merck, CERP
Lionel	Falchero	Grants/Research Support	Amgen, Boehringer Ingelheim, Chiesi, Novartis, Roche
Markus	Falk	Other	Pfizer
		Consultant	Boehringer Ingelheim, Roche, AstraZeneca
Jean	Fan	Employee	Boehringer Ingelheim
Jianbing	Fan	Stock Shareholder (directly purchased)	AnchorDx Medical
Anna	Farago	Other	Bristol-Myers Squibb, Foundation Medicine
		Consultant	Pharmamar, AbbVie, Merrimack, Tesaro
Ori	Farber	Employee	Novocure
Nicholas	Faris	Grants/Research Support	NIH

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Kyle	Fedorchak	Employee	foundation medicine inc
Carrie	Fehnel	Grants/Research Support	NIH
Mirjam	Feldkamp	Employee	Roche Sequencing Solutions
Josephine	Feliciano	Speakers or Advisory Board	Takeda
Enriqueta	Felip	Other	Eli Lilly, Pfizer, Boehringer Ingelheim, BMS, MSD, Roche
		Speakers Bureau	AstraZeneca, BMS, Novartis
		Consultant	Eli Lilly, Pfizer, Roche, Boehringer Ingelheim, MSD
Federico	Felizzi	Employee	F.Hoffmann-La Roche Ltd
Dean	Fennell	Consultant	AstraZeneca, BMS, Bayer, Boehringer Ingelheim, Clovis, Roche, Lilly, MSD
		Grants/Research Support	Astex, Boehringer Ingelheim, Bayer, Eli Lilly, Lab21, FujiBio
Julio	Fernandez-Banet	Employee	Pfizer
Hiran	Fernando	Other	Galil Medical
		Speakers Bureau	Medtronic
Carlos Gil	Ferreira	Stock Shareholder (directly purchased)	Progenetica Molecular Diagnosis
		Speakers or Advisory Board	Astrazeneca, Roche, BMS
Andrea	Feyereislova	Stock Shareholder (directly purchased)	F. Hoffmann-La Roche Ltd
		Employee	F. Hoffmann-La Roche Ltd.
Mary Jo	Fidler	Speakers' Bureau	Merck, AbbVie, AstraZeneca, Genentech, Celgene, Takeda
John	Field	Speakers or Advisory Board	VisionGate
Rainer	Fietkau	Speakers Bureau	Lilly, Roche Pharma, Roche Pharma, Roche Pharma, Fresenius Nutrition
		Consultant	Sennewald GmbH, Merck Oncology
Nicholas	Finn	Other	Bristol-Myers Squibb
Joseph	Fiore	Employee	Merck Sharp and Dohme
Jurgen	Fischer	Employee	Klinik Löwenstein
		Other	AstraZeneca, BMS, Celgene, Roche, MSD, Boehringer Ingelheim
		Consultant	Celgene
		Speakers Bureau	AstraZeneca, BMS, Celgene, Roche
Rieke	Fischer	Grants/Research Support	Bristol-Myers Squibb
		Consultant	MSD, Roche Pharma AG
Erik	Folch	Consultant	Medtronic, Boston Scientific, Olympus
		Other	Medtronic
Patrick	Forde	Grants/Research Support	Bristol Myers-Squibb
Stefan	Foser	Employee	F. Hoffmann-La Roche Ltd
Courtney	Foust	Grants/Research Support	PCORI
Tyler	Foutch	Employee	Ventana Medical Systems
Wilbur	Franklin	Grants/Research Support	NIH
Bruce	Freimark	Employee	Peregrine Pharmaceuticals, Inc.
Helano	Freitas	Consultant	MSD, Pfizer
		Other	AstraZeneca
Lyssa	Friedman	Stock Shareholder (directly purchased)	OncoCyte Corporation
Melanie	Frigault	Employee	Astraeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Richard	Fritz	Employee	Boehringer Ingelheim RCV
Sebastian	Froehler	Employee	Roche Sequencing Solutions
Martin	Früh	Grants/Research Support	BMS
Jon	Fryzek	Grants/Research Support	AstraZeneca
Daichi	Fujimoto	Speakers Bureau	Ono Pharmaceutical Co., Ltd
		Speakers Bureau	Bristol-Myers Squibb
Nobukazu	Fujimoto	Consultant	Bristol-Myers Squibb, KISSEI Co. Ltd.
		Grants/Research Support	Ono Pharmaceutical, Hisamitsu, Boehringer Ingelheim, MSD
Daichi	Fujimoto	Speakers Bureau	Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K.
Yuka	Fujita	Speakers Bureau	Boehringer Ingelheim, Kyowa Hakko Kirin, ARKRAY, Pfizer, Chugai Pharma, Taiho Pharmaceutical, Lilly
Taiki	Fujiwara	Speakers Bureau	Olympus

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Yutaka	Fujiwara	Grants/Research Support	AstraZeneca, Chugai Pharmaceutical, Daiichi-Sankyo, Eisai, Eli Lilly, MSD, Merck Serono, Novartis, Bristol-Myers Squibb, Incyte
		Speakers Bureau	Bristol-Myers Squibb, Ono Pharmaceutical
		Consultant	Bristol-Myers Squibb, Ono Pharmaceutical
Masahiro	Fukuoka	Other	Astellas
Andrew	Futreal	Consultant	Geneplus
Rabab	Gaafar	Consultant	Pfizer, Novartis
		Grants/Research Support	Roche, Eli Lilly
Christine	Gabarroca	Employee	Servier
Marta	Gabasa	Grants/Research Support	Boehringer Ingelheim Inc
Shirish	Gadgeel	Speakers Bureau	AstraZeneca, Genentech/Roche
		Consultant	AstraZeneca, ARIAD, Pfizer, Bristol Myers- Squibb, Genentech/Roche
		Other	AstraZeneca, ARIAD, Pfizer, Bristol-Myers Squibb, Genetech Roche, Boehringer Ingelheim, Novartis
Justin	Gainor	Consultant	Novartis, Bristol-Myers Squibb, Merck, Loxo Oncology, Genentech/Roche, Theravance, Pfizer, ARIAD, Incyte, Jounce, Kyowa Hakko Kirin
		Other	Novartis, ARIAD
Ajeet	Gajra	Consultant	Celgene, Helsinn Therapeutics (U.S.), Inc
Davina	Gale	Employee	Inivata Ltd.
David R.	Gandara	Grants/Research Support	Genentech, AstraZeneca, BMS, Roche Genentech, Johnson & Johnson, Lilly, Novartis, NIH
		Consultant	AstraZeneca, Boehringer Ingelheim, Celgene, Clovis, Roche Genentech, Guardant Health, Lilly, Merck, Novartis, Pfizer
Mayank	Gandhi	Employee	Genentech
Leena	Gandhi	Other	Genentech/Roche, Merck
		Grants/Research Support	BMS IION Foundation
Eric	Gandossi	Employee	Servier
Apar Kishor	Ganti	Grants/Research Support	Genentech, Pfizer, Newlink Gentics, AstraZeneca, Amgen, Merck
Yong	Gao	Other	Shandong Cancer Hospital Affiliated to Shandong University
Yangbin	Gao	Employee	AnchorDx Medical
Marina	Garassino	Other	BMS, Roche, AstraZeneca
		Speakers Bureau	BMS, MSD, Roche, AZ
		Consultant	CI
Judy	Garber	Grants/Research Support	AstraZeneca, Ambry Genetics, Myriad Genetics, Myriad Genetics
		Consultant	Helix Genetics, Novartis, GTx
Shafick	Gareeboo	Other	Pfizer, AstraZeneca
Edward	Garon	Grants/Research Support	AstraZeneca, BMS, Genentech, Lilly, Merck, Pfizer, Novartis, Boehringer Ingelheim, Mirati
		Other	Bristol-Myers Squibb, AstraZeneca, Genentech, Eli Lilly, Merck, Pfizer, Novartis, Boehringer Ingelheim, Mirati
Pilar	Garrido	Other	Roche, BMS, MSD, Novartis, Pfizer, AstraZeneca, BI, AbbVie
		Speakers Bureau	Roche, BMS, MSD, Novartis, Pfizer, Guardant, AstraZeneca, BI, AbbVie
		Consultant	Roche, BMS, MSD, Novartis, Pfizer, AstraZeneca, BI, AbbVie
Laurie	Gaspar	Other	AstraZeneca
Thomas	Gauler	Consultant	Roche, AstraZeneca, BMS, Boehringer Ingelheim, Merck Serono, Novartis, Pfizer
		Grants/Research Support	Merck
Sanja	Gauthier	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Laurie	Gay	Employee	Foundation Medicine, Inc.
		Other	Foundation Medicine, Inc.
		Stock Shareholder (directly purchased)	Foundation Medicine, Inc.
Adi	Gazdar	Speakers Bureau	Bristol-Myers Squibb, Genentech, HTG Molecular Diagnostics
Sarayut	Geater	Other	Novartis, Boehringer Ingelheim, Roche, AstraZeneca
		Grants/Research Support	Boehringer ingelheim, Novartis, Roche, AstraZeneca, Samsung
		Employee	Prince of Songkla University
William	Geese	Employee	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb

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Akihiko	Gemma	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Cyugai
		Grants/Research Support	Boehringer Ingelheim, AstraZeneca, Cyugai
		Speakers or Advisory Board	Ono, MSD, Astrazeneca, Boehringer Ingelheim
Carlo	Genova	Grants/Research Support	NIH
		Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb
Ryan	Gentzler	Other	Bristol-Myers Squibb, Takeda Oncology, Merck
		Grants/Research Support	Merck, Celgene, BMS
Ben	George	Consultant	Celgene Corporation
		Consultant	Cook Medical
David	Gerber	Grants/Research Support	Peregrine Pharmaceuticals, Inc.
		Other	Bristol-Myers Squibb, Lilly, ArQule, Oxford University Press, Clinical Decision Support-Oncology
		Stock Shareholder (directly purchased)	Gilead Sciences
		Grants/Research Support	Immunogen (inst), ArQule (inst), Synta (inst), Genentech (inst), Celgene (inst), ImClone Systems (inst), BerGenBio (inst)
Ivan	Gergel	Employee	Nektar Therapeutics
		Stock Shareholder (directly purchased)	Nektar Therapeutics
Radj	Gervais	Other	BMS
Scott	Gettinger	Consultant	ARIAD, BMS, Janssen, Alexion, Pfizer
		Grants/Research Support	ARIAD, AstraZeneca/MedImmune, BMS, Boehringer Ingelheim, Incyte, Pfizer, Roche/Genentech
		Other	BMS
		Grants/Research Support	Bristol-Myers Squibb (Inst), Genentech (Inst), Incyte (Inst), Pfizer (Inst)
		Other	Bristol-Myers Squibb
Smadar	Geva	Other	Guardant Health
		Grants/Research Support	GuardantHealth
Dana	Ghiorghiu	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Neil	Gibson	Employee	Boehringer Ingelheim
Moshe	Giladi	Employee	Novocure
Houston	Gilbert	Employee	Genentech
Colin	Gillespie	Speakers or Advisory Board	Americal College of Chest Physicians
David	Gilligan	Other	AstraZeneca, Pfizer, Boehringer Ingelheim
Monica	Giovannini	Employee	Novartis
Nicolas	Girard	Other	BMS, MSD, Roche, AstraZeneca, Boehringer Ingelheim, Pfizer, Lilly
Rachel	Gittelman	Employee	Adaptive Biotechnologies
Meredith	Giuliani	Grants/Research Support	Elekta, Inc
Michelle	Gleeson	Consultant	BMS
		Other	BMS
Fergus	Gleeson	Stock Shareholder (directly purchased)	Optellum Ltd
John	Goffin	Other	AstraZeneca
Sarah	Goldberg	Grants/Research Support	AstraZeneca
		Consultant	AstraZeneca
Michael	Goldberg	Employee	Foundation Medicine
		Stock Shareholder (directly purchased)	Foundation Medicine
Jonathan W.	Goldman	Consultant	AstraZeneca, Bristol-Myers-Squibb, Clovis Oncology, Genentech/Roche, Lilly, Trovagene, Vortex Biosciences
		Grants/Research Support	Lilly, Genetech/Roche, Astex Pharmaceuticals, Clovis Oncology, Bristol-Myers-Squibb, AstraZeneca/MedImmune, Threshold Pharmaceuticals, Array BioPharma, Celgene, AbbVie, Astellas Pharma, Corvus Pharmaceuticals
		Other	Bristol-Myers Squibb
Tony	Golsorkhi	Employee	Clovis Oncology Inc.
		Stock Shareholder (directly purchased)	Clovis Oncology Inc.
Gregoria	Gomez	Employee	Advantagene
Yuhua	Gong	Employee	Geneplus
Glenwood	Goss	Consultant	AstraZeneca, Boehringer Ingelheim, Bristol Myers-Squibb, Pfizer
		Other	AstraZeneca, Novartis, Boehringer Ingelheim, Pfizer, Celgene, Bristol-Myers Squibb, Chugai, Chugai, Taiho, Lilly

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Koichi	Goto	Grants/Research Support	Bristol-Myers Squibb, Pfizer, Kyowa Hakko Kirin, Daiichi Sankyo, Eli Lilly, Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, AstraZeneca, Sumitomo Dainippon Pharma, MSD, Astellas Pharma, Eisai, Novartis Pharma K.K., Takeda Pharmaceutical, Takeda Pharmaceutical, Merck Serono, OxOnc, AbbVie Stemcentrx, Ignyta, Boehringer Ingelheim
		Other	Eli Lilly, Pfizer, Kyowa Hakko Kirin, Bristol-Myers Squibb, Nippon Kayaku, Daiichi Sankyo, AstraZeneca, Quintiles, Novartis Pharma, BIOMEDIS International, Pfizer, Merck Serono, Life Technologies Japan, SRL, Riken Gemesis, Ono Pharmaceutical, Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly Japan, Boehringer Ingelheim Japan, Nippon Kayaku
Yasushi	Goto	Speakers Bureau	Chugai Pharmaceutical Co. Ltd.
		Grants/Research Support	Chugai Pharmaceutical Co. Ltd., Eli Lilly, Pfizer, Taiho Pharmaceutical, AbbVie
		Other	Eli Lilly, Pfizer, Taiho Pharmaceutical, AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb, Novartis, Boehringer Ingelheim
		Consultant	GlaxoSmithKline, Pfizer, Lilly, Boehringer Ingelheim, Taiho Pharmaceutical, GlaxoSmithKline
Ramaswamy	Govindan	Other	Merck, Baxalta, Roche, Boehringer Ingelheim, Novartis, Pfizer, Celgene, AstraZeneca, MSK, AbbVie, Inivata
		Consultant	Genentech, ARIAD, Astellas, BMS, INC Research, AbbVie, NIH,
Kyle	Gowen	Employee	Foundation Medicine
Richard	Gralla	Grants/Research Support	BMS
		Speakers or Advisory Board	Merck, Helsinn
Jhanelle	Gray	Grants/Research Support	Bristol-Myers Squibb, Boehringer Ingelheim, AstraZeneca, Genentech, Merck, Array, Epic Sciences, Eli Lilly, Clovis, Novartis, Array,
		Consultant	AstraZeneca, Celgene, Genentech
Matt	Green	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Laurent	Greillier	Other	Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Pfizer, AstraZeneca, Roche-Peru
		Grants/Research Support	Roche-Peru
Christopher	Gresty	Employee	AstraZeneca
Alastair	Greystoke	Consultant	BMS, MSD, Boehringer Ingelheim, AstraZeneca, Pfizer, Novartis
Frank	Griesinger	Consultant	ARIAD, AstraZeneca, Boehringer Ingelheim, Bristo-Myer-Squibb, Celgene, Clovis, Lilly, MSD, Novartis, Pfizer, Roche Pharma AG
		Other	Roche, AstraZeneca, Lilly, BMS, MSD, Celgene, Boehringer, Pfizer, Novartis, Clovis
		Grants/Research Support	Roche, AstraZeneca, Lilly, BMS, MSD, Celgene, Boehringer, Pfizer, Novartis
Harry	Groen	Consultant	AbbVie, BMS, Eli Lilly, MSD, Novartis, Pfizer, Roche/Genentech
		Grants/Research Support	Eli Lilly, Roche
Francesco	Grossi	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb
Federica	Grosso	Other	Boehringer Ingelheim
Freundliche	Grube	Speakers or Advisory Board	Boeringer; Celgene, Lilly, Roche, Pfizer, Novartis, BMS, Astrazeneca
Yanfang	Guan	Employee	Geneplus
Matthew	Gubens	Consultant	AbbVie, ARIAD, AstraZeneca, BMS, Mersana, Genentech/Roche, Novartis
		Grants/Research Support	Genentech Roche, Novartis, Celgene, Merck, OncoMed
		Other	AbbVie, ARIAD, AstraZeneca, BMS, Genentech/Roche, Mersana, Novartis
Maria	Guerin	Speakers or Advisory Board	BMS
Ferdinand	Guevara	Employee	Daiichi Sankyo
		Stock Shareholder (directly purchased)	Daiichi Sankyo
Scott	Gulbranson	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Vijay	Gunuganti	Speakers Bureau	BMS, Genentech, AstraZeneca
		Other	Bristol-Myers Squibb
Vincent	Haddad	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Koichi	Hagiwara	Speakers Bureau	Boehringer Ingelheim, AstraZeneca
		Consultant	AstraZeneca
		Other	LSI Medience
David	Halverson	Employee	Perthera
Balazs	Halmos	Grants/Research Support	Merck, Eli Lilly, AstraZeneca/Medimmune, BI, Mirati, Takeda, Novartis, Pfizer, Foundation One, Genoptix
Celeste	Hamilton	Employee	VisionGate

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Stephen	Hamilton-Dutoit	Grants/Research Support	AstraZeneca
Ji-Youn	Han	Speakers Bureau	Roche
		Grants/Research Support	Roche
		Stock Shareholder (directly purchased)	Novartis
		Consultant	Novartis
Amir	Handzel	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	Corbus Pharma, Crispr Therapeutics, Editas Medicine, Intuitive Surgical, Pangea Diagnostics
Valdimir	Hanes	Employee	Amgen
		Stock Shareholder (directly purchased)	Amgen
Amy	Hanlon Newell	Employee	Ventana Medical Systems
Christine	Hann	Other	AbbVie/StemCentrx, BMS
		Grants/Research Support	GSK
		Grants/Research Support	Merrimack pharmaceuticals
Karin	Hansen	Other	AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Roche, BMS, MSD, Pfizer,
		Consultant	AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Roche
Desiree	Hao	Grants/Research Support	AstraZeneca
		Other	AstraZeneca
Toshiyuki	Harada	Speakers Bureau	Chugai Pharma, Taiho Pharmaceutical, Ono Pharmaceutical, AstraZeneca KK, Novartis, Boehringer Ingelheim
Daijiro	Harada	Speakers Bureau	Ono Pharmaceutical, Bristol-Myers Squibb Company, Yakult Honsha Co.,Ltd., Yakult Honsha Co.,Ltd., Kyowa Hakko Kirin Co., Ltd.
Koji	Haratani	Speakers Bureau	Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd
Greg	Harlow	Employee	Ventana Medical Systems
David	Harpole	Grants/Research Support	NIH
Kimberly	Harrow	Employee	Xcovery Holding Company
		Stock Shareholder (directly purchased)	Xcovery Holding Company
Seiki	Hasegawa	Grants/Research Support	Taiho pharmaceutical company, ONO, Eli Lilly
Aaron	Hata	Grants/Research Support	Novartis, Amgen
Hiroto	Hatabu	Consultant	Toshiba Medical Systems
		Grants/Research Support	Canon Inc., Konica-Minolta, Toshiba Medical Systems
Osamu	Hataji	Speakers Bureau	Novartis Pharm, Boehringer Ingelheim
		Grants/Research Support	Novartis Pharm, Boehringer Ingelheim, Kyorin Pharm, Bayer Health Care, Diichi Sankyo, Glaxo Smith Kline
Ben	Hatano	Employee	Novartis Pharma KK
Hidetoshi	Hayashi	Consultant	AstraZeneca, Eli Lilly, Boehringer Ingelheim
		Speakers Bureau	Ono Pharmaceutical
Hidetoshi	Hayashi	Speakers Bureau	AstraZeneca, Eli Lilly, Boehringer Ingelheim, MSD, Chugai Pharmaceutical, Taiho Pharmaceutical, Bristol-Myers Squibb Co. Ltd., Ono Pharmaceutical Co. Ltd
		Grants/Research Support	Ono Pharmaceutical
		Other	AstraZeneca K.K., Bristol-Myers Squibb Company
		Consultant	AstraZeneca K.K.
Takashi	Hayashi	Employee	Median Technologies
Wendy	Hayes	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Cara	Haymaker	Grants/Research Support	Idera, Nektar
Shuang	He	Employee	Eli Lilly and Company
Yuting	He	Employee	Foundation Medicine
Jie	He	Employee	Foundation Medicine
Xian	He	Employee	Genentech
Shuang	He	Employee	Eli Lilly and Company
		Stock Shareholder (directly purchased)	Eli Lilly and Company
Pei	He	Employee	Roche/Genentech
Ying	He	Employee	Roche Diagnostics
Diane	Healey	Employee	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
Graham	Healey	Employee	Oncimmune PLC

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Elizabeth	Hedgeman	Grants/Research Support	AstraZeneca
Priti	Hegde	Employee	Genentech
Rebecca	Heist	Consultant	ARIAD
		Consultant	Boehringer Ingelheim
		Grants/Research Support	Roche, Novartis, Celgene, Mirati, Debiopharm, Millenium, Peregrine, Incyte, Exelixis, AbbVie, Genetech, Corvus, Takeda,
Matthew	Hellmann	Consultant	AstraZeneca/MedImmune, Janssen, Novartis, Third Rock Ventures, Bristol-Myers Squibb, Merck, Genentech, Alexion Pharmaceuticals, Inovio Pharmaceuticals
		Grants/Research Support	Bristol-Myers Squibb, Genentech/Roche
		Other	Bristol-Myers Squibb
Todd	Hembrough	Employee	NantOmics, LLC
Samantha	Henderson	Employee	Resolution Bioscience
Brian	Henick	Consultant	Boehringer Ingelheim
Claudia	Henschke	Other	Early Diagnosis and Treatment Research Foundation, Cornell Research Foundation
Pia	Herbolsheimer	Employee	AstraZeneca
Roy	Herbst	Consultant	AstraZeneca, Eli Lilly, Genetech/Roche, Merck, Pfizer
		Grants/Research Support	Genentech, Merck
Hadas	Hershkovich	Employee	Novocure
Felix	Herth	Grants/Research Support	Roche Diagnostics
Lyndal	Hesterberg	Stock Shareholder (directly purchased)	OncoCyte Corporation
John	Heymach	Grants/Research Support	AstraZeneca, GlaxoSmithKline, Bayer
		Other	Genentech, AstraZeneca, Novartis, GlaxoSmithKline, Lilly, Boehringer Ingelheim, Synta, Exelixis, EMD-Sereno, GuardantHealth
Toyoaki	Hida	Grants/Research Support	Novartis, Pfizer, AstraZeneca, Ono Pharmaceutical, Boeringher Ingelheim, Taiho, Astellas, Eli Lilly, Ignyta, Chugai Pharmaceutical, Nippon Boehringer Ingelheim, Bristol-Meyers Squibb, Clovis Oncology, Eisai, Takeda Bio, Dainippon Sumitomo Pharma, AbbVie, Merck Serono, MSD, Kyowa Hakko Kirin, Daiichi Sankyo
		Other	Ono Pharmaceutical, Bristol-Meyers Squibb, MSD, Merck Serono, Chugai Pharmaceutical, AstraZeneca
Karen	Higginbottom	Employee	Ipsos Healthcare
		Other	Bristol-Myers Squibb
Frank	Hilberg	Employee	Boehringer Ingelheim Inc.
John	Hilton	Consultant	AstraZeneca
Bernd	Hinzmann	Employee	Roche Sequencing Solutions
Fred R.	Hirsch	Consultant	BMS, Merck, Ventana/Roche/Genentech, Pfizer, lilly, AstraZeneca, Boehringer Ingelheim, ARIAD, HTG Molecular Diagnostics, AbbVie, Innovent Biologics
		Grants/Research Support	NIHm Genentech/Ventana/Roche, BMS, Lilly, Bayer, Amgen
Vera	Hirsh	Other	Bristol-Myers Squibb, Boehringer Ingelheim
		Consultant	Boehringer Ingelheim
Chao-Chi	Ho	Consultant	Boehringer Ingelheim, Eli Lilly, Roche/Genentech/Chugai, MSD, Pfizer, Novartis, BMS, Ono Pharmaceutical
		Grants/Research Support	AstraZeneca, Boehringer Ingelheim
		Other	AstraZeneca
Steffan	Ho	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
James Chung-man	Ho	Speakers' Bureau	AstraZeneca, Roche, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, MSD
		Speakers or Advisory Board	AstraZeneca, Roche, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, MSD
		Other	AstraZeneca, Roche, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, MSD
Ute	Hoch	Employee	Nektar Therapeutics
		Stock Shareholder (directly purchased)	Nektar Therapeutics
Rachel	Hodge	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
F. Stephen	Hodi	Other	Bristol-Myers Squibb, Merck, Genentech
		Consultant	Bristol-Myers Squibb, Novartis, Amgen, EMD Serono
Chris	Hodkinson	Employee	Owlstone Medical Ltd
Johanne	Højbjerg	Consultant	AstraZeneca A/S
Esther	Holgado	Other	BMS
ARIADna	Holynskyj	Employee	Bayer Healthcare Pharmaceuticals

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Andrew	Hope	Grants/Research Support	Elekta, Inc
Atsushi	Horiike	Speakers Bureau	Chugai Pharmaceutical, Eli Lily, Boehringer Ingelheim, AstraZeneca
		Other	Chugai Pharma, Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim
		Grants/Research Support	Chugai Pharma, Quintiles, MSD Oncology
Hidehito	Horinouchi	Grants/Research Support	Taiho, MSD, Merck Serono, Novartis, Astellas, Ono, Chugai
		Other	BMS, Kyowa-Kirin, Lilly, Taiho Pharmaceutical, Daiichi Sankyo, Kyowa Hakko Kirin, Merck SErono, Novatis, Astellas Pharma, MSD Oncology
Leora	Horn	Consultant	AbbVie, BMS, Genentech/Roche, Merck, Xovery Holding Company, BI, Lilly, Janssen
		Other	Bristol-Myers Squibb
Yukio	Hosomi	Speakers Bureau	AstraZeneca, Taiho Pharmaceutical, Lilly Japan, Chugai Pharma, Ono Pharmaceutical, Boehringer Ingelheim, Bristol-Myers Squibb Japan
Katsuyuki	Hotta	Grants/Research Support	Nippon Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly Japan, ONO Pharmaceutical, Astellas Pharma, Novartis Pharma, AstraZeneca, Bristol-Myers Squibb, MSD, Merck
		Speakers Bureau	AstraZeneca, Eli Lilly Japan, Daiichi-Sankyo Pharmaceutical, Boehringer Ingelheim, Nihon Kayaku, Taiho Pharmaceutical, Chugai Pharmaceutical, Sanofi-Aventis, Merck
		Other	AstraZeneca
Cheryl	Houston-Harris	Grants/Research Support	NIH
Karen	Howarth	Employee	INIVATA
Christopher	Hoyle	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Te-Chun	Hsia	Grants/Research Support	AstraZeneca
Wen Son	Hsieh	Consultant	Roche
Beibei	Hu	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Jinwei	Hu	Employee	OrigiMed
Hairui	Hua	Employee	Boehringer Ingelheim
Yong	Huang	Employee	Shandong Cancer Hospital Affiliated to Shandong University
Yu-Jing	Huang	Employee	Eli Lilly and Company
Zhongdong	Huang	Employee	TP Therapeutics. Inc.
Hui	Huang	Employee	ARIAD
		Other	ARIAD
Yifan	Huang	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Han-Yao	Huang	Employee	BMS
James	Huang	Grants/Research Support	Bristol-Myers Squibb
Rudolf	Huber	Other	ARIAD, AstraZeneca, BMS, Boehringer Ingelheim, Pfizer, Roche
		Consultant	BMS, Boehringer Ingelheim, Celgene, Clovis Oncology, Eli Lilly, Novartis, Roche
		Grants/Research Support	Pierre Fabre
Brett	Hughes	Other	Merck Sharp & Dohme, Bristol-Myers Squibb, Roche-Peru
		Consultant	Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, Roche, AstraZeneca
Rina	Hui	Other	MSD, BMS, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Roche
		Consultant	MSD, AstraZeneca, Prizer, Novartis
James	Hurley	Employee	Exosome Diagnostics Incorporation
Michael	Hurwitz	Consultant	Nektar Therapeutics
Hatim	Husain	Speakers' Bureau	Astrazeneca, Foundation Medicine, AbbVie, BMS, Merck, AstraZeneca
		Grants/Research Support	Pfizer
Maen	Hussein	Other	Bristol-Myers Squibb
David	Hwang	Consultant	Merck Canada, Pfizer Canada
Patrick	Hwu	Stock Shareholder (directly purchased)	Immatics; Lion Biotechnologies
		Consultant	Lion Biotechnologies
		Grants/Research Support	Genentech
Anthony	Iafrate	Stock Shareholder (directly purchased)	ArcherDx
		Consultant	Chugai

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Sai-Hong	Ignatius Ou	Grants/Research Support	Pfizer, Roche, AstraZeneca, ARID, Ignyta
		Other	Pfizer, Roche, AstraZeneca, ARIAD, Ignyta, Foundation Medicine
Atsuko	Ikeda	Employee	Ajinomoto Co., Inc.
Peter	Illei	Other	Genentech
		Consultant	Roche Diagnostics, AstraZeneca
		Grants/Research Support	Genentech
		Grants/Research Support	Bristol-Myers Squibb
Maya	Ilouze	Other	Pfizer, Roche, MSD
		Speakers Bureau	MSD, Pfizer, Roche
Fumio	Imamura	Speakers Bureau	AstraZeneca, Ono Pharmaceutical Co
		Grants/Research Support	AstraZeneca
Michael	Imperiale	Employee	Nektar Therapeutics
		Stock Shareholder (directly purchased)	Nektar Therapeutics
Saki	Inamura	Employee	Chugai Pharmaceutical
Akira	Inoue	Other	AstraZeneca, Boehringer Ingelheim, Chugai
		Speakers Bureau	Lilly, AstraZeneca
		Other	Chugai Pharmaceutical
Hiroshi	Isobe	Speakers Bureau	Bristol-Myers Squibb, Chugai Pharma
Yuichi	Ishikawa	Speakers Bureau	Novartis, Chugai, Ono-Pharm., BMS
Malinda	Itchins	Other	Pfizer
Aviran	Itzhaki	Employee	Novocure Ltd
Puneeth	Iyengar	Consultant	Helsinn Therapeutics
Iyare	Izevbaye	Consultant	AstraZeneca
Bianca	Jackson	Grants/Research Support	PCORI
Colin	Jacobs	Grants/Research Support	MeVis Medical Solutions AG.
Thierry	Jahan	Grants/Research Support	Acerta, Aduro, AstraZeneca, Bayer, Boehringer Ingellheim, Bristol-Myers Squibb, Eli Lilly, Epizyme, Golden Biotech, Kadmon
Mohammad	Jahanzeb	Speakers or Advisory Board	Novartis, Genentech, Lilly, AbbVie, Roche, ARIAD, Pfizer, BMS, Merck
Mark	Jakoovic	Speakers Bureau	Roche, AstraZeneca, Boehringer Ingelheim, Pfizer
Shadia	Jalal	Grants/Research Support	AstraZeneca
Leonard	James	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Pasi	Jänne	Consultant	AstraZeneca, Boehringer Ingelheim, Pfizer, Merrimack, Roche/Genentech, Chugai, Acea Biosciences, Ignyta, LOXO Oncology, ARIAD, Eli Lilly, Araxes
		Stock Shareholder (directly purchased)	Gatekeeper Pharmaceuticals
		Grants/Research Support	Astellas, AstraZeneca, Daiichi Sankyo, Eli Lilly, PUMA
Anthony	Jarkowski	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Jacek	Jassem	Speakers' Bureau	AstraZeneca, Roche, Pfizer, Boehringer, BMS, Celgene, G1 Therapeutics, Merck, Pierre Fabre
		Grants/Research Support	Roche, Boehringer
Suzanne	Jenkins	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
James	Jett	Employee	Oncimmune LLC
Jim	Jett	Other	Oncimmune LLC
		Consultant	Up-To-Date
		Employee	Oncimmune PLC
Haiyi	Jiang	Employee	AstraZeneca
		Other	AstraZeneca
John	Jiang	Employee	Roche Sequencing Solutions
Thomas	John	Other	AstraZeneca/MedImmune, Pfizer, Roche/Genentech, Boehringer Ingelheim, Lilly, Bristol-Myers Squibb
Adrienne	Johnson	Employee	Foundation Medicine
Bruce	Johnson	Other	DFCI
Ann	Johnson	Employee	Ignyta, Inc.

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Melissa	Johnson	Grants/Research Support	OncoMed, BerGenBio, Lilly, EMD Serono, Kadmon, Janssen, Mirati Therapeutics, GenMab, Pfizer, AstraZeneca, Genentech/Roche, Stemcentrix, Novartis, Checkpoint Therapeutics, Array Biopharma, Regeneron, Boehringer Ingelheim
		Consultant	Astellas, Otsuka Pharmaceuticals, Genentech/Roche, Celgene, Boehringer Ingelheim
Eric	Johnson	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Erica	Johnston	Employee	Eli Lilly and Company
Greg	Jones	Employee	INIVATA, INC, MDXHEALTH
		Stock Shareholder (directly purchased)	MDXHEALTH
		Consultant	MDXHEALTH
Karin	Jordan	Consultant	Helsinn Healthcare, Merck, MSD, Tesaro
		Other	MSD
Leif	Jørgensen	Consultant	BMS
Alaknanda	Joshi	Employee	Novartis
Marybeth	Joshi	Grants/Research Support	NIH
Robert	Jotte	Speakers Bureau	Bristol-Myers Squibb, Lilly
		Other	Bristol-Myers Squibb, Lilly
ARIADna	Juarez-Garcia	Employee	BMS
Rosalyn	Juergens	Consultant	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Amgen
		Speakers Bureau	Amgen
		Other	Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, BetaPharma, AstraZeneca/MedImmune, Roche Canada, Merck Sharp & Dohme, Lilly
		Grants/Research Support	AstraZeneca/MedImmune, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis
Timor	Kadir	Employee	Optellum Ltd
		Stock Shareholder (directly purchased)	Optellum Ltd
Hiroshi	Kagamu	Grants/Research Support	Boeringer-ingelheim Inc., Chugai Pharm. Inc., Ono Pharm. Inc.
Carmen	Kahatt	Employee	PharmaMar
Kyoichi	Kaira	Grants/Research Support	Ono Pharmaceutical Company, Bristol-Myers Company, Ono Pharmaceutical Company, Bristol-Myers Company
		Speakers Bureau	Ono Pharmaceutical Company, Bristol-Myers Company
Gregory	Kalemkerian	Grants/Research Support	Merck, OncoMed, Glaxo, Pfizer, Takeda
Nikoletta	Kallinteris	Employee	Peregrine Pharmaceuticals, Inc.
Suzanne	Kamel-Reid	Consultant	AstraZeneca
Nyam	Kamsu-Kom	Employee	Servier
Zhengyan	Kan	Employee	Pfizer
Shintaro	Kanda	Other	Ono Pharmaceutical, AstraZeneca, Taiho Pharmaceutical
		Grants/Research Support	Bristol-Myers Squibb Japan
Hiroyasu	Kaneda	Speakers Bureau	Chugai Pharma, Boehringer Ingelheim, AstraZeneca, Pfizer, Bristol-Myers Squibb, Novartis Pharm, Eli Lilly
Yuichiro	Kaneko	Other	Astellas
Jin-Hyoung	Kang	Other	Seoul St. Mary's Hospital
Steven	Kao	Other	Novaris, Pfizer, BMS, MSD, AstraZeneca
Thomas	Karagiannis	Stock Shareholder (directly purchased)	Genentech Inc
		Employee	Genentech Inc
Peter	Kasan	Consultant	Boehringer Ingelheim
		Speakers Bureau	MSD, Pfizer
Yuki	Kataoka	Grants/Research Support	Eli Lilly
Ryohei	Katayama	Grants/Research Support	Fujifilm, Taiho Pharmaceutical Co., Ltd.
Rahul	Katdare	Employee	VisionGate
Terufumi	Kato	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Eli Lilly, Roche, Kyowa Kirin, Merck Serono, Merck Sharp and Dohme, Novartis, Ono, Pfizer, Sumitomo Dainippon, Taiho
		Grants/Research Support	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Eli Lilly, Roche, Kyowa Kirin, Merck Serono, Merck Sharp and Dohme, Novartis, Ono, Pfizer, Sumitomo Dainippon, Taiho
Pardeep	Kaurah	Employee	Contextual Genomics
Brian	Kavanagh	Grants/Research Support	Janssen

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Tomoya	Kawaguchi	Grants/Research Support	Chugai Co., Eli Lilly, AstraZeneca, BMS, Ono Co., Kyowa Hakko Kirin, MSD, Taiho Co, Boehringer Ingelheim
Yuko	Kawano	Grants/Research Support	Taiho Pharmaceutical Co Ltd
Jun	Kawashima	Employee	Gilead Sciences Inc
Noa	Kaynan	Employee	Novocure Ltd
Jordan	Kazakov	Other	Medtronic
Karen	Kelly	Consultant	ARIAD, AstraZeneca, Boehringer Ingelheim, BMS, Clovis Oncology, G1 Therapeutics, Genentech/Roche, Lilly, Synta
		Other	UpToDate, Regeneron, Merck
		Grants/Research Support	AbbVie, Celgene, EMD Serono, Five Prime Therapeutics, Roche/Genentech, Gilead, Lilly, Millenium, Novartis, Transgene
		Other	UpToDate, Regeneron, Merck, Roche, Bristol-Myers Squibb
Ronan	Kelly	Speakers or Advisory Board	BMS, Astellas, END Serono, Eli Lilly, AstraZeneca, OncoMed, Novartis
William	Kelly	Consultant	Targeted Oncology
Leon	Kempen	Consultant	AstraZeneca
Hirotsugu	Kenmotsu	Speakers Bureau	Chugai Pharmaceutical Co. Ltd.
		Grants/Research Support	Chugai Pharmaceutical Co. Ltd.
Jens	Kern	Consultant	MSD, Pfizer, Roche Pharma AG, Lilly, Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca
		Other	Novartis
		Other	Roche-Peru
Ryan	Kern	Consultant	Olympus America Inc
Keith	Kerr	Consultant	AZ, BI, Eli Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche
David	Kerstein	Employee	ARIAD
		Other	ARIAD
Zanobia	Khan	Consultant	Merck Canada
Sandeep	Khandhar	Consultant	Medtronic
		Other	Medtronic
Mohsen	Khorshid	Stock Shareholder (directly purchased)	F. Hoffmann-La Roche, AG
		Employee	F. Hoffmann-La Roche, AG
Leslie	Kiedrowski	Employee	guardant Health
Flavia	Kiertsman	Employee	Novartis
		Stock Shareholder (directly purchased)	Novartis
Takashi	Kijima	Speakers Bureau	Daiichi-Sankyo Co.Ltd., AstraZeneca Co.Ltd., Asahi Kasei Pharmaceutical Co.Ltd., Pfizer Co.Ltd., Eli Lilly Co.Ltd., Novartis Pharmaceutical Co.Ltd., Teijin Pharmaceutical Co.Ltd
Shinya	Kikuchi	Employee	Ajinomoto Co., Inc.
Edward	Kim	Consultant	Celgene, Boehringer Ingelheim, Eli Lilly, AstraZeneca
		Other	AstraZeneca, Celgene, Eli Lilly
Young	Kim	Consultant	AstraZeneca, Chugai Pharmaceutical, Bristol-Myers Squibb, Taiho Pharma, Merck Sharp & Dohme, Eli Lilly Japan, Boehringer Ingelheim, Pfizer
		Speakers Bureau	Bristol-Myers Squibb K.K., Ono Pharmaceutical Co., Ltd.
		Grants/Research Support	Bristol-Myers Squibb K.K., Ono Pharmaceautical Co., Ltd.
Ju	Kim	Employee	Navigate BioPharma Services
Eun-Hae	Kim	Employee	Ventana Medical Systems
Jong Seok	Kim	Employee	Eli Lilly
Hedy Lee	Kindler	Consultant	Bayer, Aduro, AstraZeneca, Boehringer Ingelheim, Ipsen, Merck, BMS, Erytech
		Grants/Research Support	Lilly, GSK
Jennifer	King	Speakers or Advisory Board	AstraZeneca, GRAIL
Ichiro	Kinoshita	Speakers Bureau	AsaraZeneca, Taiho Pharmaceutical
Eilon	Kirson	Employee	Novocure
Kazuma	Kishi	Grants/Research Support	MSD, Chugai, Boehringer Ingelheim, Ono, Taiho
Simon	Kitchen	Employee	Owlstone Medical Ltd
Thomas	Kitzing	Employee	Boehringer Ingelheim

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Katsuyuki	Kiura	Other	Astellas, Chugai Pharmaceutical, Pfizer Japan Inc., Novartis Pharma K.K., Taiho Pharmaceutical Co, Ono Pharmaceutical, Eli Lilly Japan K.K., Bristol-Myers Squibb, MSD K.K., AstraZeneca, Boehringer Ingelheim
		Grants/Research Support	Boehringer Ingelheim, Daiichi Sankyo Co, Shionogi & Co., LTD, Nippon Kayaku Co., Ltd., Chugai Pharmaceutical, AstraZeneca K.K
		Speakers Bureau	AstraZeneca K.K., Eli Lilly and Company, Astellas, Boehringer Ingelheim, Chugai Pharmaceutical, MSD, Novartis, Pfizer, Taiho Pharmaceutical Co, Ono Pharmaceutical, Bristol-Myers Squibb, Nihon Kayaku, Daiichi-Sankyo Pharmaceuticals, Sanofi-Aventis
Samuel	Klempner	Speakers Bureau	Foundation Medicine
Roland	Knoblauch	Employee	Janssen R&D
		Stock Shareholder (directly purchased)	Johnson & Johnson
Jen-Chung	Ko	Other	AstraZeneca, Lilly Taiwan, Roche Taiwan, MSD
Kunihiko	Kobayashi	Speakers Bureau	Chugai Pharma, AstraZeneca
Thomas	Koenig	Employee	Epigenomics AG
Hartmut	Koeppen	Employee	Genentech
Yoshihito	Kogure	Other	AstraZeneca
Yasuhiro	Koh	Speakers Bureau	Bristol-Myers Squibb, Boehringer Ingelheim, RainDance Technologies
		Grants/Research Support	Boehringer ingelheim
Leslie	Kohman	Grants/Research Support	Carefusion
Michael	Koller	Grants/Research Support	EORTC
Christian	Kollmannsberger	Other	Pfizer, BMS, Astellas, Novartis
Philip	Komarnitsky	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Kartik	Konduri	Consultant	Celgene
Shengchun	Kong	Employee	Gilead Sciences, Inc
Hans-Georg	Kopp	Consultant	Sanofi, MSD, Bristol-Myers Squibb
		Other	Pfizer, LEO Pharma, GlaxoSmithKline, Novartis, Lilly, Novartis, AMtene
Beata	Korytowsky	Employee	BMS
		Other	Pfizer, BMS
Marcin	Kowanetz	Employee	Genentech
		Stock Shareholder (directly purchased)	Roche
David	Kozono	Consultant	Vertex
Toshiyuki	Kozuki	Speakers Bureau	Chugai Pharmaceutical Co.
Nicole	Krämer	Employee	Boehringer Ingelheim
Jenny	Kreahling	Employee	Nilogen Oncosystems
William	Krimsky	Employee	Medtronic
		Other	Medtronic
Mark	Kris	Consultant	AstraZeneca
Michael	Krouse	Employee	NanoString Technologies
Lee	Krug	Employee	BMS
Timothy	Kruser	Speakers or Advisory Board	AbbVie, Varian Medical Systems
Kaoru	Kubota	Grants/Research Support	Chugai, Daiichi-Sankyo, Boehringer Ingelheim, Eli Lilly, Taiho
Suzana	Kukulj	Speakers Bureau	Roche
Jun	Kumazawa	Employee	Boehringer Ingelheim
Hideo	Kunitoh	Grants/Research Support	Chugai Pharmaceutical, Mochida Pharmaceutical Co. Ltd., BMS, Kyowa Hakko Kirin, Nippon Kayaku, Johnson & Johnson, Taiho Pharmaceutical, Lilly Japan, Chugai Pharma, Daiichi Sankyo, Nippon Chemiphar, Nihon Medi-Physics, Kyorin, AstraZeneca, Boehringer Ingelheim
David	Kuo	Employee	Boehringer Ingelheim
Takayasu	Kurata	Speakers Bureau	Eli Lilly
Hiroshi	Kuriki	Employee	Chugai Pharmaceutical
		Stock Shareholder (directly purchased)	Chugai Pharmaceutical
Masahiko	Kusumoto	Consultant	Pfizer, MSD, Astrazeneka, Ono Pharmacy
Shoichi	Kuyama	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb Japan, Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co, Meiji Yakuhin Co. Ltd., Eli Lilly Japan
Jaroslaw	Kuzdal	Stock Shareholder (directly purchased)	Medycyna Praktyczna
Marc	Ladanyi	Grants/Research Support	NCCN / AstraZeneca & LOXO Oncology

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Frank	Lagerwaard	Speakers Bureau	ViewRay Inc.
Jennifer	Lai	Employee	Peregrine Pharmaceuticals, Inc.
Nehal	Lakhani	Other	Beigene USA, Livzon Biopharma
Alshad	Lalani	Employee	Puma Biotechnology
Peter	Lambert	Employee	Genentech, Inc
Joshua	Lang	Stock Shareholder (directly purchased)	Salus Discovery
Maria	Lange	Employee	Roche Sequencing Solutions
		Other	BMS, Eli Lilly/ImClone, Roche/Genentech
		Consultant	Abbott, ARIAD, Bayer/Onyx, BMS, Cancer Support Community, Celgene, Clarient, Clovis Oncology, Eli Lilly/ImClone, Merck, Roche/Genentech
		Grants/Research Support	Advantagene, ARIAD, Celgene, Clovis Oncology, GSK, Inovio, Merck, Roche/Genentech, Stem CentRx
		Other	BMS, Eli Lilly/ImClone, Roche/Genentech
		Consultant	Abbott
Corey	Langer	Consultant	ARIAD, Abbott, AstraZeneca, Helsinn, Bayer/Onyx, BMS, Cancer Support Community, Celgene, Clarient, Clovis Oncology, Eil Lilly/ImClone, Merck, Roche/Genentech
		Grants/Research Support	Advantagene, ARIAD, Celgene, Clovis Oncology, GlaxoSmithKline, Inovio, Merck, Roche/Genentech, Stem CentRx, Celgene, MSD
		Other	BMS, Eli Lilly/ImClone, Roche/Genentech, AstraZeneca, Clovis, AbbVie, Amgen, Lilly, Peregrine, SWOG, Synta
Richard	Lanman	Employee	Guardant Health
		Stock Shareholder (directly purchased)	Guardant Health, Inc
Corinna	Lanzarotti	Employee	Helsinn Healthcare
Janessa	Laskin	Grants/Research Support	AstraZeneca, Eli Lilly, Roche, BI
Yvonne Y.	Lau	Stock Shareholder (directly purchased)	Novartis
		Employee	Novartis
Steven	Lau	Employee	LabCorp
Scott	Laurie	Speakers Bureau	AstraZeneca
		Grants/Research Support	Boehringer Ingelheim (inst), Bristol-Myers Squibb (inst), AstraZeneca (inst) Novartis (inst)
		Other	Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, AstraZeneca
David	Lawrence	Employee	AstraZeneca
Andrew	Layton	Consultant	Thermo Fisher Scientific
Deborah	Layton	Consultant	BMS
Anh	Le	Other	Abbott Molecular
Yvan	Le Bruchec	Employee	Celgene International
Ticiana	Leal	Consultant	Takeda, Genentech
Dae Ho	Lee	Other	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, CJ Healthcare, Eli Lilly and Company, Merck, MSD, Mundipharma, Novartis, Ono, Pfizer, Roche, Samyany Biopharm, ST Cube
		Consultant	Ministry of Food and Drug Safety (MFDS), Korea, Health Insurance Review and Assessment Service (HIRA), Korea, National Evidence-based Collaborating Agency (NECA), Korea, National Cancer Control Planning Board, Korea
Pablo	Lee	Employee	Eli Lilly and Company
		Grants/Research Support	Eli Lilly and Company
Adrian	Lee	Other	Eisai, Sanofi Aventis
Ho-Jin	Lee	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Se-Hon	Lee	Speakers or Advisory Board	Pfizer, Novartis, BMS/Ono, AstraZeneca, Roche
Victor	Lee	Consultant	Eli Lilly
		Speakers Bureau	Eli Lilly, Roche, Novartis, Celgene
Michael	Lees	Employee	Bristol-Myers Squibb
Natasha	Leighl	Other	AstraZeneca, BMS, MSD, Pfizer
		Consultant	AstraZeneca
Gregory	Lemense	Consultant	Medtronic
		Other	Medtronic
Brian	Lentrichia	Employee	AstraZeneca
Bonnie	Leung	Speakers or Advisory Board	AstraZeneca

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Shay	Levi	Employee	Novocure
Benjamin	Levy	Consultant	Eli Lily, Genentech, Celgene, AstraZeneca, Bristol-Myers Squibb, Merck, Boehringer Ingelheim
		Stock Shareholder (directly purchased)	Pfizer
Conrad	Lewanski	Other	Eli Lilly
		Consultant	AstraZeneca, Roche, MSD
Bob	Li	Speakers or Advisory Board	Genentech, ThermoFisher Scientific, Mersana Therapeutics, Biosceptre Australia
Cheng	Li	Employee	Shandong Cancer Hospital Affiliated to Shandong University
Yali	Li	Employee	Foundation Medicine
Mark	Li	Employee	Resolution Bioscience
Bob	Li	Consultant	Thermo Fisher Scientific, Genentech, Mersana Therapeutics, Biosceptre Australia
Xiang	Li	Other	BMS
Yishan	Li	Employee	TP Therapeutics. Inc.
Ang	Li	Other	Bristol-Myers Squibb
		Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Xuemei	Li	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
Yulin	Li	Speakers Bureau	AstraZeneca, Roche, Eli Lilly, Pfizer, Sanofi
Sherry	Li	Employee	Pfizer
Jack	Li	Employee	Daiichi Sankyo
		Stock Shareholder (directly purchased)	Daiichi Sankyo
Chong-Kin	Liam	Speakers or Advisory Board	AstraZeneca, Roche, MSD
Chris	Liang	Employee	Xcovery Holding Company
		Stock Shareholder (directly purchased)	Tyrogenex
Zhongxing	Liao	Consultant	Geneplus, Varian medical Systems
Eric	Lim	Speakers' Bureau	Ethicon, Medtronic
Lee	Lim	Employee	Resolution Bioscience
John	Lim	Employee	TP Therapeutics. Inc.
Jessica	Lin	Consultant	Boehringer Ingelheim
Philip	Linden	Other	Medtronic
Rolf	Linke	Employee	SFJ Pharmaceuticals Group
Rolf	Linke	Employee	SFJ Pharmaceuticals Group
Doron	Lipson	Employee	Foundation Medicine
Maruja E	Lira	Employee	Pfizer
Geoffrey	Liu	Consultant	AstraZeneca
		Other	AstraZeneca
Ting	Liu	Employee	F. Hoffmann-La Roche Ltd
Yuan	Liu	Employee	Pfizer
Frank	Liu	Employee	Merck
Stephen	Liu	Consultant	Genentech, Pfizer, AstraZeneca, Lilly
Ting	Liu	Employee	F. Hoffmann-La Roche Ltd
Isabell	Loftin	Employee	F. Hoffmann-La Roche Ltd, Ventana Medical Systems
Gilberto	Lopes	Other	Pfizer, Merck Sharp and Done
Jose	Lopez-Vilariño	Employee	PharmaMar
James	Lorens	Employee	BerGenBio ASA
Matthew	Lorenzi	Employee	Janssen R&D
Alexander	Louie	Speakers Bureau	Varian Medical Systems
Christine	Lovly	Consultant	Foundation Medicine, ARIAD/Takeda, Pfizer, AstraZeneca, Novartis, Genoptix
hun	Lu	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Hutchison, MediPharma, Roche, Lilly
		Grants/Research Support	AstraZeneca, Boehringer Ingelheim, Hutchison, Roche
		Consultant	Hutchison, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Roche, Berry Genomics, MediPharma
		Other	BMS, Hutchison, Medipharm Limited

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Deborah	Lubeck	Consultant	BMS
		Other	BMS
David	Lueng	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Jun	Luo	Employee	Foundation Medicine
Stephanie	Lustgarten	Employee	ARIAD
		Other	ARIAD
Zarnie	Lwin	Consultant	AbbVie
Charlotte	Lybeck Lind	Employee	Boehringer Ingelheim
Gustavo	Lyons	Speakers' Bureau	Johnson & Johnson
Isabel	Macdonald	Employee	Oncimmune PLC
Philip	Mack	Consultant	Apton Biosystems, Guardant Health, Celgene, AstraZeneca
		Grants/Research Support	Boehringer Ingelheim
		Speakers Bureau	Guardant Health
David	MacPherson	Grants/Research Support	Roche
Subha	Madhavan	Employee	Perthera
Makoto	Maemondo	Other	AstraZeneca, Chugai Pharmaceutical, Ono, BMS, Lilly, Pfizer
		Speakers Bureau	AstraZeneca, Chugai
		Grants/Research Support	Chugai, Boehringer
Paul	Mainwaring	Other	Celgene, Pfizer, Janssen
Michele	Maio	Consultant	Bristol Meyer Squibb, Roche, Genentech, AstraZeneca
Isabelle	Malet	Employee	Novartis
Melinda	Manley Daumont	Employee	BMS
Helen	Mann	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Melissa	Manoogian	Employee	Ventana Medical Systems
Aaron	Mansfield	Consultant	Genentech Advisory Board
Andrea	Manzanera	Stock Shareholder (directly purchased)	Advantagene
Robert	Markelewicz	Employee	Celgene
Aleksandra	Markovets	Stock Shareholder (directly purchased)	AstraZeneca
		Employee	AstraZeneca
Lawrence	Marks	Grants/Research Support	Elekta, Morphormics, Accuray
		Other	Varian
Richard	Markus	Employee	Amgen
		Stock Shareholder (directly purchased)	Amgen
Edith	Marom	Grants/Research Support	BMS
Marcelo	Marotti	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Katerine	Marquis	Other	Bristol-Myers Squibb
Norbert	Marschner	Grants/Research Support	Celgene, Lilly, Pfizer, MSD, Novartis
		Consultant	Lilly, MSD, Novartis, Celgene
Angela	Märten	Employee	Boehringer Ingelheim
Jean-Francois	Martini	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Afshin	Mashadi-Hossein	Employee	NanoString Technologies
Robert	Mason	Other	Bristol-Myers Squibb
Kimberly	Mason	Employee	Perthera
Dan	Massey	Employee	Boehringer Ingelheim
Elizabeth	Masters	Stock Shareholder (directly purchased)	Pfizer Inc.
		Employee	Pfizer Inc.
Christina	Matheny	Employee	Roche/Genentech
		Stock Shareholder (directly purchased)	Roche/Genentech
		Other	Roche/Genentech, Stanford University
Michael	Mathisen	Employee	Genentech
Tracy	May	Employee	Roche Molecular Systems

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Julien	Mazieres	Other	Novartis, Pfizer, BMS, MSD, Toulouse University Hospital, Roche
		Grants/Research Support	Roche, AZ, BMS, Puma
Mark	McCleland	Employee	Genentech
Tracey	McCulloch	Stock Shareholder (directly purchased)	Novartis
		Employee	Novartis
Fiona	McDonald	Speakers Bureau	Elektra
		Other	AstraZeneca, MSD
		Consultant	Pfizer
Joseph	McGill	Employee	Daiichi Sankyo
		Stock Shareholder (directly purchased)	Daiichi Sankyo
Margaret	McGrath	Consultant	Bristol-Myers Squibb, MSD
		Other	Bristol-Myers Squibb
Mark	McKee	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Philip	McQuary	Stock Shareholder (directly purchased)	OncoCyte
Melanie	Mediavilla-Varela	Employee	Nilogen Oncosystems
Ranee	Mehra	Grants/Research Support	Genentech
		Consultant	BMS, Genentech
Minesh	Mehta	Grants/Research Support	Novocure
Peter	Meldgaard	Grants/Research Support	Roche Molecular Systems
Barbara	Melosky	Other	AstraZeneca, Boehringer Ingelheim
Melody	Mendenhall	Other	Merck
Javier A.	Menendez	Grants/Research Support	Boehringer Ingelheim
Xue	Meng	Other	Shandong Cancer Hospital Affiliated to Shandong University
Gavin	Meredith	Employee	NanoString Technologies
Daniel	Merrick	Grants/Research Support	NIH
Matthew	Meyerson	Grants/Research Support	Bayer Pharmaceuticals
		Other	LabCorp
Gu	Mi	Employee	Eli Lilly and Company
Epstein	Michael	Employee	INIVATA
Sebastian	Michels	Grants/Research Support	Pfizer, Novartis
David	Micklem	Employee	BerGenBio ASA
Maria Rita	Migliorino	Grants/Research Support	MSD, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Pfizer
		Consultant	MSD, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, MSD
		Other	Boehringer Ingelheim, MSD, Bristol-Myers Squibb, AstraZeneca
Coren	Milbury	Employee	Foundation Medicine
Kathryn	Mileham	Other	AstraZeneca, Boehringer Ingelheim
		Speakers Bureau	Merck
		Grants/Research Support	Celgene
Vincent	Miller	Employee	Foundation Medicine, Inc.
		Other	Foundation Medicine, Inc.
		Stock Shareholder (directly purchased)	Foundation Medicine, Inc.
Alvin	Milner	Employee	AstraZeneca
Yuko	Minami	Speakers or Advisory Board	Bristol-Myers Squibb, Daiichi Sankyo Co.,Ltd., Chugai Pharmaceutical Co., Ltd., MSD
Koichi	Minato	Grants/Research Support	Chugai Pharma, Ono Pharmaceutical
Mari	Mino-Kenudson	Consultant	Merrimack Pharmaceutical, ACD, Roche, H3 Biomedicine,
Doug	Minnich	Other	Medtronic
Paul	Mitchell	Consultant	Merck, Roche, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, AstraZeneca
Tetsuya	Mitsudomi	Speakers Bureau	AstraZeneca, Pfizer, Boehringer Ingelheim, Chugai, Taiho, MSD, ONO, Bristol-Myers Squibb, Roche
		Grants/Research Support	Pfizer, Boehringer Ingelheim, Chugai, Taiho, Ono, Bristol-Myers Squibb
		Consultant	Novartis, Pfizer, Chugai, AstraZeneca, MSD, ONO, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Roche
Masaya	Mizushima	Employee	Boehringer Ingelheim
Simonetta	Mocci	Employee	Genentech

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Mehdi	Moezi	Other	Bristol-Myers Squibb
Sanae	Moizumi	Employee	Novartis Pharma KK
Tony	Mok	Stock Shareholder (directly purchased)	Sanomics Limited Hong Kong
		Grants/Research Support	AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, SFJ, Roche, MSD, Clovis Oncology, Bristol-Myers Squibb, Eisai, Taiho,
		Speakers Bureau	AstraZeneca, Roche, Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, MSD, Novartis, Bristol-Myers Squibb, Taiho, Amgen, Janssen, Clovis Oncology, GSK, Prime Oncology
		Consultant	AstraZeneca, Roche, Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Clovis Oncology, Merck Serono, MSD, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Vertex Pharmaceauticals, BMS, geneDecode Co., Ltd., OncoGenex Technologies Inc, Celgene, Ignyta Inc, Cirina, Berry Genomics, Janssen, BioMarin, GSK, AVEO & Biodesix, Prime Oncology, Amgem
		Employee	The Chinese University of Hong Kong
		Other	AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, BI, Clovis Oncology, Merck Serono, MSD, Janssen, BioMarin, GSK, Taiho, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Inc., Vertex Pharmaceuticals, BMS, geneDecode Co., Ltd., OncoGenex Technologies Inc., Celgene, Ignyta, Inc. Cirina, IASLC, Chinese Lung Cancer Research Foundation Ltd, Chinese Society of Clinical Oncology (CSCO), Hong Kong Cancer Therapy Society (HKCTS), Aveo & Biodesix, Prime Oncology, Amgen
		Stock Shareholder (directly purchased)	Sanomics Limited
Alex	Molassiotis	Speakers' Bureau	Merck, Helsinn, Tesaro, Acacia Pharma
Olivier	Molinier	Consultant	BMS
Isabelle	Monnet	Other	BMS
Alessandro	Morabito	Other	Roche, AstraZeneca, Boehringer Ingelheim, Bayer, Pfizer
Shethah	Morgan	Employee	AstraZeneca
Daniel	Morgensztern	Other	Celgene Corporation
		Speakers Bureau	Boehringer
		Consultant	Bristol-Myers Squibb, Celgene, AbbVie
Paul	Morin	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Satoshi	Morita	Other	Astellas
		Speakers Bureau	AstraZeneca
Denis	Moro-Sibilot	Consultant	Roche, MSD, Pfizer, Novartis, BMS< AstraZeneca, Lilly
		Other	Eli Lilly, Roche, Pfizer, ARIAD, Boehringer, AstraZeneca, Novartis, MSD, BMS
David	Morris	Stock Shareholder (directly purchased)	St. Louis Cyberknife, LLC
Nassim	Morsli	Employee	Boehringer Ingelheim
Noriko	Motoi	Speakers Bureau	Novartis Pharma K.K., Taiho Pharmaceutical Co., Chugai Pharmaceutical Co., Ltd., Leica Microsystems Co., LTD., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co., AstraZeneca K.K., MSD Co., Agilent Technologies Japan, Ltd.
		Other	SRL Inc.
Monica	Motwani	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Shuo	Mu	Employee	OrigiMed
Tariq	Mughal	Employee	Foundation Medicine, Inc
		Stock Shareholder (directly purchased)	Foundation Medicine, Inc
Thomas	Muley	Grants/Research Support	Roche Diagnostics
		Speakers Bureau	Roche Diagnostics GmbH
Pratik	Multani	Employee	Ignyta, Inc.
Mijal	Munster	Employee	Novocure Ltd
Haruyasu	Murakami	Other	Chugai Pharmaceutical
Sadayuki	Murayama	Grants/Research Support	Toshiba Medical Systems
Boris	Murillo	Other	Medtronic
Danielle	Murphy	Employee	Pfizer
Andrea	Murray	Employee	Oncimmune PLC
Lina	Musallam	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
Faith	Mutale	Speakers Bureau	Merck

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Kristiaan	Nackaerts	Consultant	Boehringer Ingelheim, Novartis, Eli Lilly
Ernest	Nadal	Other	Eli Lilly and Company
Takeshi	Nagashima	Employee	SRL Inc
Rebecca	Nagy	Employee	Guardant Health, Inc
		Stock Shareholder (directly purchased)	Guardant Health, Inc
Jarushka	Naidoo	Consultant	AstraZeneca, Bristol-Myers Squibb
		Other	Bristol Myers-Squibb, AstraZeneca
		Grants/Research Support	Kyowa Kirin, Merck, AstraZeneca
Kazuhiko	Nakagawa	Other	Astellas, AstraZeneca, EPS, Ono Pharmaceutical, Kyowa Hakko Kirin, Showa Yakuhin Kako, SymBio Pharmaceuticals, Daiichi Sankyo, Chugai Pharmaceutical, Boehringer Ingelheim, Eli Lilly, Pfizer, Bristol-Myers Squibb, Novartis Pharma, Kissei Pharmaceutical, Quintiles Inc., Ayumi Pharmaceutical, Novartis Pharma K.K., MSD, Nippon, Taiho Pharmaceutical Co.,Ltd., AYUMI Pharmaceutical Corporation
		Grants/Research Support	Ono Pharmaceutical, Chugai Pharmaceutical, MSD, EPS, Daiichi Sankyo, Japan Clinical Research Operations, Eisai, Pfizer, PPD-SNBL, Takeda, Boehringer Ingelheim, Taiho Pharmaceutical, Bristol-Myers Squibb, GlaxoSmithKline, AstraZeneca, Kyowa Hakko Kirin, AbbVie, Novartis Pharma, Eli Lilly, Yakult, PAREXEL, Otsuka Pharmaceutical, Astellas, AC Medical, Merck Serono, Quintiles, Nippon,
		Speakers Bureau	Astellas Pharma Inc., AstraZeneca K.K., Kissei Pharmaceutical Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., MSD K.K., Chugai Pharmaceutical Co.,Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co.,Ltd., Nippon Boehringer Ingelheim Co.,Ltd., Bristol-Myers Squibb Company, Taiho Pharmaceutical Co.,Ltd., Ayumi Pharmaceutical Corporation
		Consultant	Astellas Pharma Inc., Ono Pharmaceutical Co.,Ltd., Eli Lilly Japan K.K., Astellas Pharma Inc., Ono Pharmaceutical Co.,Ltd., Eli Lilly Japan K.K., Astellas Pharma Inc., Ono Pharmaceutical Co.,Ltd., Eli Lilly Japan K.K.
Tomoki	Nakagawa	Grants/Research Support	Glaxo SmithKline KK, AstraZeneca, Kyowa Hakko Kirin Co, Pfizer Japan, AbbVie Inc., Novartis Pharma K.K., Nippon Boehringer Ingelheim, Daiichi Sankyo Co, Eli Lilly Japan, MSD KK, Quintiles Inc, Ono Pharma, Yakult Honsha Co, Parexel International Corp, Otsuka Pharmaceutical, Astellas Pharma Inc, AC Medical Inc, Taiho Pharmaceutical, Merck Serono Co, EPS International Co, Covance Inc., Chugai Pharmaceutical Co, Bristol-Myers Squibb, Eisei Co, Ayumi Pharmaceutical
		Other	Kissei Pharmaceutical
Yoshiro	Nakahara	Other	Lilly, AstraZeneca KK, Chugai Pharma, Taiho Pharmaceutical, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Ono, BMS, MSD, Pfizer
		Consultant	Meiji Seika Kaisha
		Speakers Bureau	Olympus, Chugai Pharmaceutical Co. Ltd., AstraZeneca
		Grants/Research Support	Chugai Pharmaceutical Co. Ltd., SRL, Inc., Taiho, Ono
Takahiro	Nakajima	Other	Olympus Medical Systems
Yoichi	Nakanishi	Other	Taiho, Chugai, Pfizer, MSD, Ono, BMS, Boehringer Ingelheim, AstraZeneca, Eli Lilly
		Grants/Research Support	Chugai
Ronald	Natale	Other	AstraZeneca, AbbVie, BMS, Pfizer
		Employee	AstraZeneca
		Grants/Research Support	AbbieVie, AstraZeneca, Bristol-Myers, Pfizer
Louie	Naumovski	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Keith	Naunheim	Speakers Bureau	St Louis Lung Cancer Alliance, New England Deaconness BI
		Other	Society of Thoracic Surgeons
Ariel	Naveh	Employee	Novocure
		Other	Medtronic
Joel	Neal	Consultant	Clovis Oncology, Boehringer Ingelheim, ARMO BioSciences, Arqule, Roche, ARIAD/Takeda, Eli Lilly, AstraZeneca, Medtronic
		Grants/Research Support	Genentech/Roche, Merck, Novartis, Boehringer Ingelheim, Nektar Therapeutics
Hovav	Nechushtan	Other	AstraZeneca
Maria	Netchaeva	Other	Roche, AstraZeneca, BMS
		Consultant	Boehringer Ingelheim
		Grants/Research Support	Celgene, Amgen, Pharma Mar
Judith	Neukirchen	Other	Bristol-Myers Squibb, Celgene, Janssen Corp
Saskia	Neuteboom	Employee	Mirati Therapeutics, Inc.
Michelle	Nguyen	Employee	Loxo Oncology

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Andrew	Nicholson	Speakers or Advisory Board	Eli Lilly, Pfizer, Roche, Merck, Novartis, AZ, BMS, Novartis,
		Stock Shareholder (directly purchased)	Merck
Dana	Nickens	Employee	Pfizer Inc
Seiji	Niho	Speakers Bureau	Taiho, Eli Lilly
		Grants/Research Support	Eli Lilly, BMS, AstraZeneca
		Other	AstraZeneca
Takashi	Ninomiya	Speakers Bureau	Chugai Pharmaceutical Co., Nippon Boehringer Ingelheim Co., Merck Serono
Mizuki	Nishino	Consultant	Worldcare clinical, Toshiba medical systems
		Grants/Research Support	Merck, Toshiba medical systems
		Other	Bayer Yakuhin
Makoto	Nishio	Grants/Research Support	Novartis, Astellas Pharma, Ono Pharmaceutical, Chugai Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, Eli Lilly, Pfizer, AstraZeneca
		Other	Pfizer, Bristol-Myers Squibb, ONO Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca
		Speakers Bureau	Pfizer, Bristol-Myers Squibb, ONO Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca
		Consultant	Novartis, Ono Pharmaceutical, Chugai Pharma, Taiho Pharmaceutical, Pfizer, Bristol-Myers Squibb Japan, Daiichi Sankyo, Lilly Japan
Makoto	Nishio	Consultant	Pfizer, AstraZeneca
Masahiko	Nishiyama	Grants/Research Support	Yakult Honsha Co., Ltd., Taiho Pharmaceutical Co., Ltd.
Takashi	Niwa	Other	Boehringer Ingelheim, Eli Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical
Johannes	Noe	Employee	F. Hoffmann-La Roche Ltd, Genentech
Naoyuki	Nogami	Grants/Research Support	Chugai Pharmaceutical Co.
		Speakers Bureau	Chugai Pharmaceutical Co.
		Other	Meiji Seika Pharma Co., Ltd., Boehringer Ingelheim, AstraZeneca, Pfizer Inc., Bristol-Myers Squibb, Ono Pharmaceutical, Kyowa Hakko Kirin, Taiho Phamaceutical, Chugai Pharmaceutical, Eli Lilly Japan
Lucia	Nogova	Other	Novartis, Pfizer, Celgene, Boehringer Ingelheim, Roche Pharma AG
Hiroshi	Nokihara	Grants/Research Support	Astellas Pharma, Pfizer, Taiho Pharmaceutical, Chugai Pharma, Eli Lilly, Novartis, Daiichi Sankyo, Quintiles, AstraZeneca, Boehringer Ingelheim, Ono Pharmaceutical, Eisai, GlaxoSmithKline, Yakult
		Other	Bristol-Myers Squibb, Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, AstraZeneca, Ono Pharmaceutical,
		Consultant	Lilly, Taiho Pharmaceutical
Kim	Norris	Speakers or Advisory Board	ARIAD Pharmacueticals
Silvia	Novello	Speakers Bureau	AstraZeneca, MSD, Bristol-Myers Squibb, Roche, Pfizer, Eli Lilly
Anna	Nowak	Other	Roche Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca
		Grants/Research Support	Astra Zeneca, Boehringer Ingelheim
		Consultant	Trizell, Aduro Biotech, Boehringer Ingelheim, Bayer, AstraZeneca, Sellas, Epizyme, Roche
Eveline	Nueesch	Employee	F. Hoffmann-La Roche Ltd
Toshihiro	Nukiwa	Consultant	Boehringer Ingelheim
		Speakers Bureau	Boehringer Ingelheim
Silpa	Nuthalapati	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Patrick	O'Donnell	Employee	Roche Molecular Systems
Mary	O'Brien	Consultant	Pfizer, Merck/MSD, AbbVie, Pierre Fabre, Bristol-Myers Squibb
		Other	BMS
		Grants/Research Support	Bristol-Myer Squibb
Kenneth	O'Byrne	Speakers Bureau	BMS, MSD, Boehringer Ingelheim, Lilly Oncology, Astrazeneca, Roche, Pfizer, Novartis,
		Consultant	BMS, Novartis, MSD, Boehringer Ingelheim, Lilly Oncology, Astrazeneca, Roche, Teva, Pfizer
		Stock Shareholder (directly purchased)	CARP Pharmaceuticals
		Other	MSD, Roche, Astrazeneca, Pfizer, Boehringer Ingelheim, BMS, Lilly Oncology, Novartis
Radka	Obermannová	Speakers Bureau	Amgen, BMS, Servier
		Grants/Research Support	Merck
		Consultant	Merck, BMS, SERVIER
Mary	O'Brien	Other	MSD, Abbvie, Pierre Fabre

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Peter	O'Dwyer	Grants/Research Support	Celgene Corporation
		Consultant	BMS
Vance	Oertel	Employee	Xcovery Holding Company
Filiz	Oezkan	Grants/Research Support	Epigenomics AG
Tetsuya	Oguri	Grants/Research Support	Ono Pharmaceutical
Kadoaki	Ohashi	Grants/Research Support	Nippon Boehringer Ingelheim Co ., Ltd., Novartis International AG, Eli Lilly and Company
		Speakers Bureau	AstraZeneca K.K., Chugai, ONO, Novartis Pharmaceuticals
		Consultant	AstraZeneca, Chugai, ONO
Yasuo	Ohashi	Employee	Public Health Research Foundation, Statcom
		Other	Chugai Pharmaceutical, Shionogi, Daiichi-Sankyo, Sanofi
		Grants/Research Support	Eisai
Yuichiro	Ohe	Grants/Research Support	Chugai, Lilly, ONO, BMS, Kyorin, Dainippon-Sumitomo, Pfizer, Taiho, Novartis, AstraZeneca
		Other	AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Kayaku, Boehringer Ingelheim, Pfizer, MSD, Taiho Pharmaceutical, Bayer, Clovis Oncology, Sanofi
		Consultant	AstraZeneca, Chugai Pharma, Lilly Japan, Ono Pharmaceutical, Novartis
Yoshiharu	Ohno	Grants/Research Support	Toshiba Medical Systems Corporation, Philips Electronics Japan, Bayer Pharma, Daiichi-Sankyo, Co., Ltd, Eizai, Co., Ltd, Guerbet, Smoking Research Foundation
Fumiyoshi	Ohyanagi	Speakers Bureau	Boehringer Ingelheim
Satoshi	Oizumi	Speakers Bureau	AstraZeneca, Eli Lilly
Philip	Ojeabulu	Grants/Research Support	NIH
Morihito	Okada	Grants/Research Support	Ono Pharmaceutical Co.,Ltd.
Isamu	Okamoto	Speakers Bureau	Chugai Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co Ltd, Boehringer ingelheim
		Consultant	AstraZeneca
		Grants/Research Support	Boehringer ingelheim, Merck Serono, MSD, Bristol-Myers Squibb, Taiho, AstraZeneza, Astellas Pharma, Chugai, Eli Lilly, Ono, Parexel International
Teng Jin	Ong	Employee	Celgene
		Other	Celgene Corporation, Taiho Pharmaceutical, Chugai Pharmaceutical
		Consultant	MSD, BMS, AstraZenca
		Grants/Research Support	Taiho Pharmaceutical, Takeda
		Speakers Bureau	Taiho, Chugai, Boehringer Ingelheim
Christine-Elke	Ortmann	Employee	Novartis
Raymond	Osarogiagbon	Grants/Research Support	NIH, PCORI
		Ownership Interest	Eli Lilly, Pfizer, Genentech, Foundation Medicine
		Other	Patent
Stacy	Osbaugh	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Karen	Osborne	Employee	Novartis
		Other	Novartis
Helene	Ostojic	Employee	Eli Lilly and Company
Gyula	Ostoros	Speakers or Advisory Board	MSD, BMS, Roche, Boehringer Ingelheim,Pfizer
Christian	Ottensmeier	Consultant	Bristol-Myers Squibb
		Grants/Research Support	Bristol-Myers Squibb
Gregory	Otterson	Grants/Research Support	BMS, Merck, Pfizer, Celgene, Boston Biomedical, Genentech, Novartis,
		Consultant	Genentech, Amgen, Novartis
Geoff	Otto	Employee	Foundation Medicine
		Consultant	Roche/Genentech, ARIAD, Novartis, Astra Zeneca, Pfizer
		Speakers Bureau	Roche/Genentech, ARIAD, Astra Zeneca, Genentech, Takeda
		Grants/Research Support	Pfizer, Roche/Genentech, Astra Zeneca, ARIAD, Ignyta
		Other	Pfizer, Roche, Astra Zeneca, ARIAD, Ignyta, Foundation Medicine, Inc.
Tobias	Overbeck	Consultant	Bristol-Myers Squibb, Boehringer Ingelheim, Medac, Roche Pharma AG, MSD, Novartis
Scott	Owen	Other	AstraZeneca
Taofeek	Owonikoko	Grants/Research Support	AbbVie, BMS, Astra Zeneca
		Consultant	AbbVie

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Geoffrey	Oxnard	Consultant	Sysmex, Guardant, Inivata, Bio-Rad, AstraZeneca, Novartis, ARIAD/Takeda, Chugai, Ignyta, LOXO
		Honoraria	BioRad, Chugai, Guardant, Sysmex
		Other	AstraZeneca, ARIAD/Takeda, Inivata, Novartis, Sysmex, LOXO
Yuko	Oya	Grants/Research Support	Nippon Boehringer Ingelheim
Sukhmani	Padda	Speakers or Advisory Board	G1 Therapeutics, Janssen Pharmaceuticals, AstraZeneca
		Supported/Contracted Research/Grant	Forty Seven, Inc, EpicentRx
Damian	Page	Employee	F. Hoffmann-La Roche Ltd, Novartis, Nilogen Oncosystems
		Stock Shareholder (directly purchased)	F. Hoffmann-La Roche Ltd, Novartis
Paul	Paik	Grants/Research Support	Celgene, EMD Serono
		Consultant	Lilly, Celgene, BMS
Miguel	Palacios	Speakers Bureau	ViewRay Inc.
John	Palma	Employee	Roche Sequencing Solutions
Michael	Palmer	Grants/Research Support	AstraZeneca, Boehringer Ingelheim
		Stock Shareholder (directly purchased)	AstraZeneca
		Other	AstraZeneca
Yoram	Palti	Consultant	Novocure Ltd
		Stock Shareholder (directly purchased)	Novocure Ltd
Jean	Pan	Employee	Amgen
		Stock Shareholder (directly purchased)	Amgen
Kaimin	Pang	Employee	Boehringer Ingelheim
Jens	Panse	Speakers Bureau	Bristol-Myers Squibb, Alexion Pharmaceuticals
		Consultant	MSD, Boehringer Ingelheim, Celgene
		Speakers Bureau	Novartis
Vassiliki	Papadimitrakopoulou	Employee	MD Anderson Cancer Center
		Other	Bristol-Myers Squibb, AstraZeneca, Celgene, Janssen, Merck, OncLive, Genentech, Merck and Co, Araxes Pharma, LLC, Nektar Therapeutics, Takeda Pharmaceuticals, Eli Lilly and Co
		Speakers Bureau	Creative Educational Concepts (CEC Oncology)
		Grants/Research Support	Merck & Co., NIH/NCI, Bristol-Myers Squibb, Oregon Health Science University, Cancer Prevention & Research Institute of Texas (CPRIT), American Association for Cancer Research (AACR)
		Consultant	Bristol-Myers Squibb, Roche/Genentech, AstraZeneca, Merck
Keunchil	Park	Grants/Research Support	AstraZeneca
		Other	Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Clovis, Eli Lilly and Company, Hanmi, Helsinn, KHK, Novartis, ONO, Roche, Sumitomo
		Consultant	Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Clovis, Eli Lilly, GSK, Hanmi, Helsinn, Kyowa Hakko Kirin, MSD, Novartis, ONO Pharm, Roche Research Fund
		Speakers Bureau	Boehringer Ingelheim
Russell	Parris	Employee	Owlstone Medical Ltd
Celine	Parsy-Kowalska	Employee	Oncimmune PLC
Harvey	Pass	Speakers' Bureau	Genentech
		Supported/Contracted Research/Grant	SomaLogic
Vanessa Q	Passos	Employee	Novartis
		Other	Novartis
Jyoti	Patel	Other	AbbVie, ARIAD
		Grants/Research Support	ARIAD, AbbVie
		Speakers or Advisory Board	AbbVie
Amita	Patnaik	Grants/Research Support	Merck
Thirupathi	Pattipaka	Grants/Research Support	F. Hoffmann-La Roche
Pallavi	Patwardhan	Employee	Merck
Edward	Patz	Ownership Interest	Grid Therapeutics
		Salary	Grid Therapeutics
		Employee	Grid Therapeutics
		Royalty, Receipt of Intellectual Property Rights/Patent Holder	Grid Therapeutics

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Sarah	Paul	Employee	Genentech
		Stock Shareholder (directly purchased)	Roche
		Other	Genentech
Nick	Pavlakis	Other	Specialised Therapeutics, Pfizer, Boehringer Ingelheim, Merck Serono, Bayer, AstraZeneca, Novartis Pharma KK, Roche-Peru, AMtene, Sanofi, Amgen
		Consultant	Specialized Therapeutics, Pfizer, Novartis, Amgen, Bayer, Boehringer Ingelheim, Roche, Merck-Serono, AstraZeneca, Sanofi-Aventis
Dean	Pavlick	Employee	Foundation Medicine
Cloud	Paweletz	Consultant	Digital Bioanalytics
		Other	BioRad, Clovis, AstraZeneca
Luis	Paz-Ares	Other	Eli Lilly and Company, Roche, MSD, BMS, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Clovis, Amgen, Bayer, PharmaMar, Servier
		Consultant	AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Merck, MSD, Novartis, Roche, Amgem, Clovis Oncology, Pfizer
		Speakers Bureau	BMS, MSD, Lilly, Roche, Novartis, AstraZeneca, Pfizer, Merck
Laura	Peek	Employee	Oncimmune PLC
Tobias	Peikert	Royalty, Receipt of Intellectual Property Rights/Patent Holder	CANARY software, Imbio
Nir	Peled	Consultant	AZ, NovellusDX, BI, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, MSI
		Other	AstraZeneca, BI, BMS, Lilly , MSD, Novartis, Pfizer, Roche, FMI, NovellusDx, Gaurdant360, Takeda
		Grants/Research Support	AstraZeneca, Bristol-Myers Squibb, MSD, Roche
		Speakers Bureau	Boehringer Ingelheim, AstraZeneca, BMS, MSD, Pfizer, Novartis, Lilly, Roche, Foundation Medicine, Guardant Health
Gerson	Peltz	Employee	Pfizer
Sylvie	Pennaforte	Employee	Servier
Nathan	Pennell	Consultant	Boehringer Ingelheim, AstraZeneca, Eli Lilly
		Grants/Research Support	Genentech, Newlink Genetics, Clovis Oncology, Astex Pharmaceuticals, Celgene, AstraZeneca, Pfizer, Merck
		Grants/Research Support	
John	Penrod	Employee	BMS
		Stock Shareholder (directly purchased)	BMS
		Other	BMS
Marta	Pereira	Employee	BMS
Maurice	Pérol	Speakers or Advisory Board	Roche, Genentech, Eli Lilly, Pfizer, Boehringer Ingelheim, Clovis Oncology, MSD, Bristol-Myers Squibb, Novartis, Pierre Fabre, AstraZeneca
		Grants/Research Support	AstraZeneca
		Honoraria	Eli Lilly, Roche, AstraZeneca, Pfizer, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb
Solange	Peters	Consultant	Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, Merck Serono, Novartis Pfizer,
		Other	Amgen AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, Merck Serono, Pfizer, Regeneron, Takeda
		Grants/Research Support	Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, and Merck Serono, Pfizer, Regeneron, Takeda
Eric	Peters	Employee	Genentech
Emanuel	Petricoin	Stock Shareholder (directly purchased)	Perthera
		Consultant	Perthera
Kelly	Phan	Supported/Contracted Research/Grant	Novartis, Ipsen
		Consultant	Novartis, Ipsen
Lyndsey	Pickup	Employee	Optellum Ltd
		Stock Shareholder (directly purchased)	Optellum Ltd
M Catherine	Pietanza	Employee	Merck
		Ownership Interest	Merck
		Salary	Merck
Anne	Pieters	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
Kerstin	Pietzko	Employee	Boehringer Ingelheim

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Rathi	Pillai	Consultant	Natera
		Other	Genentech/Roche, Takeda, Novartis, Clovis Oncology
Zofia	Piotrowska	Consultant	AstraZeneca, ARIAD
		Grants/Research Support	GuardantHealth
Bilal	Piperdi	Employee	Merck
		Stock Shareholder (directly purchased)	Merck
Robert	Pirker	Speakers Bureau	Boehringer Ingelheim
		Consultant	Boehringer Ingelheim, Eli Lilly, MSD, Genmab
David	Planchard	Other	Astrazeneca, BMS, MSD, Boehringer, Pfizer, Roche, Novartis, Lilly, Clovis Oncology, Sanofi
		Consultant	MSD, Pfizer, Roche, Novartis, AstraZeneca, Bristol-Myers Squibb, Boheringer, Lilly, Chugal
		Grants/Research Support	Novartis Pharma KK
Sanja	Plestina	Speakers Bureau	Roche, AstraZeneca
		Consultant	AstraZeneca, Merck, Novartis
		Other	Molecular MD
		Grants/Research Support	AstraZeneca, Roche, Koltan
Sanjay	Popat	Consultant	AstraZeneca, Boehringer Ingelheim, Guardant Health, Pfizer, Roche, MSD, Lilly, Novartis Pharma KK, Clovis Oncology Inc.
		Other	Pfizer, MSD, Boehringer Ingelheim, Lilly, AstraZeneca, Novartis Pharma KK, Roche-Peru, Bristol-Myers Squibb
		Grants/Research Support	Boehringer Ingelheim, Epizyme, Bristol-Myers Squibb, Clovis Oncology, Lilly, Roche-Peru
Pieter E.	Postmus	Other	Celgene, AstraZeneca, Roche, BMI, BS, Janssen, MSD, Clovis
		Consultant	BMS, Roche, AZ, Boehringer Ingelheim, Janssen, MSD
Danielle	Potter	Employee	AstraZeneca
Steven	Powell	Grants/Research Support	Merck, Bristol-Myers Squibb, Incyte, Genentech, Novartis, Pfizer
Aleix	Prat	Grants/Research Support	Nanostring Technologies
		Consultant	Nanostring Technologies
Michael	Pritchett	Consultant	Medtronic
		Other	Medtronic
Joe	Putnam	Speakers or Advisory Board	Merck & Co.
Igor	Puzanov	Consultant	Amgen; Bristol-Myers Squibb; Roche/Genentech
		Other	Amgen; Merck
Jiaheng	Qiu	Employee	Genentech
		Stock Shareholder (directly purchased)	Genentech
		Other	Genentech
Elisabeth	Quoix	Other	BMS, Boehringer Ingelheim
		Speakers or Advisory Board	Boehringer Ingelheim
Shahrooz	Rabizadeh	Employee	Nantomics
Luis	Raez	Grants/Research Support	Liquid Genomics, Guardant Health, BMS, Roche, Novartis, Pfizer, Merck, Syndax, Liquid Genomics, Genetech, AstraZeneca, LOXO, Mirati
Harry	Raftopoulos	Employee	Merck
Suresh	Ramalingam	Consultant	Amgen, AbbVie, BMS, Celgene, Lilly, Genentech, Novartis, Boehringer, Merck, AstraZeneca, ARIAD, Janssen
		Other	AstraZeneca, BMS, AbbVie, Boehringer Ingelheim, Celgene, Novartis, Lilly, Genetech, Merck, Amgen, Janssen Corp
Shakti	Ramkissoon	Employee	Foundation Medicine, Inc.
		Other	Foundation Medicine, Inc.
Suman	Rao	Other	Merck
Meredith	Ray	Grants/Research Support	NIH, PCORI
Chris	Raymond	Employee	Resolution Bioscience
Victoria	Raymond	Employee	Guardant Health
Neal	Ready	Consultant	BMS, Pfizer, Merck, AstraZeneca, Novartis
		Speakers or Advisory Board	BMS, Merck, Novartis, AbbVie, ARIAD, Celgene, AstraZeneca
		Other	BMS, ARIAD
		Supported/Contracted Research/Grant	BMS, Merck, ARIAD, Celgene, AstraZeneca

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Martin	Reck	Speakers Bureau	Roche/Genentech, Lilly, BMS, MSD, Merck, AstraZeneca, Pfizer, Boehringer Ingelheim, Celgene, Novartis,
		Consultant	Lilly, F. Hoffmann-La Roche, BI, BMS, MSD, AstraZeneca, Merck, Novartis, Pfizer, Celgene
		Other	Boehringer Ingelheim, Proacta, Bristol-Myers Squibb, MSD
Martin	Reck	Other	Pfizer, Lilly, AstraZeneca, Merck Inc., Celgene, Novartis Pharma KK, Roche-Peru,
		Grants/Research Support	Boehringer Ingelheim
Karen	Reckamp	Consultant	Amgen, Astellas, ARIAD
		Grants/Research Support	Adaptimmune, Xcovery, ARIAD, BMS, Clovis Oncology, Eisai, Gilead Sciences, Novartis, Pfizer, Roche/Genentech
Karen	Reckamp	Consultant	Amgen, ARIAD, Astellas, Gilead Sciences, Inc.
		Grants/Research Support	Adaptimmune, Xcovery, ARIAD, BMS, Clovis Oncology, Eisai, Gilead Sciences, Novartis, Pfizer, Roche/Genentech
Sandeep	Reddy	Employee	NantHealth
Anthony	Reeves	Other	Cornell Research Foundation, General Electric
		Ownership Interest	D4Vision Inc., VisionGate Inc.
		Grants/Research Support	Cornell Research Foundation, D4Vision Inc., VisionGate Inc.
		Royalty, Receipt of Intellectual Property Rights/Patent Holder	Cornell Research Foundation
Noemi	Reguart	Grants/Research Support	Boehringer Ingelheim Inc.
William	Reichmann	Employee	ARIAD
		Other	ARIAD
Mary	Reid	Honoraria	Delta Pharmaceuticals
		Grants/Research Support	Jannson Oncology
Arlene	Reisman	Employee	Pfizer
Antonio	Riccio	Employee	Merck & Co
David	Rice	Honoraria	Intuitive Surgical Inc., Pacira Pharmaceuticals Inc.
Donald	Richards	Other	Bristol-Myers Squibb
William	Richards	Grants/Research Support	NIH
Bill	Richardson	Employee	Ventana Medical Systems
Kristin	Richeimer	Speakers' Bureau	IASLC
		Speakers or Advisory Board	IASLC
		Ownership Interest	IASLC
		Salary	IASLC
		Employee	IASLC
		Honoraria	IASLC
		Financial support from tobacco company(ies)	IASLC
		Grants/Research Support	IASLC
		Royalty, Receipt of Intellectual Property Rights/Patent Holder	IASLC
Otis	Rickman	Grants/Research Support	Medtronic
		Consultant	Medtronic
		Other	Medtronic
Richard	Riedel	Other	Lilly, Boehringer Ingelheim
Todd	Riehl	Employee	Genentech
		Stock Shareholder (directly purchased)	Roche
Gregory	Riely	Grants/Research Support	Pfizer, Novartis, Takeda, Roche, ARIAD
		Consultant	Genentech/Roche, Novartis, AstraZeneca
Jonathan	Riess	Consultant	ARIAD, Medtronic, AbbVie, Celgene
		Grants/Research Support	Merck, Millenium, AstraZeneca, Novartis
		Consultant	Clovis
James	Rigas	Employee	AstraZeneca
Erika	Rijavec	Speakers Bureau	AstraZeneca, Bristol-Myers-Squibb

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David	Rimm	Grants/Research Support	Navigate BioPharma Services, AstraZeneca, Cepheid, Novartis, Gilead Sciences, Pierre Fabre, Perkin Elmer
		Speakers or Advisory Board	AstraZeneca, Agendia, Agilent, Bethyl Labs, Biocept, BMS, Cell Signaling Technology, Merck, OptraScan, Perkin Elmer, Ultivue
		Honoraria	AstraZeneca, Agendia, Agilent, Bethyl Labs, Biocept, BMS, Cell Signaling Technology, Merck, OptraScan, Perkin Elmer, Ultivue
		Ownership Interest	Metamark Genetics
Andreas	Rimner	Grants/Research Support	Boehringer Ingelheim, Pfizer, AstraZeneca, Merck
		Other	Boehringer Ingelheim, Pfizer, AstraZeneca, Merck
Achim	Rittmeyer	Consultant	Eli Lilly and Company, AstraZeneca, BMS, Boehringer Ingelheim, Pfizer, Roche Genentech
		Other	Roche/Genentec, Eli Lilly, BMS, Pfizer, AstraZeneca, Boehringer Ingelheim
		Grants/Research Support	AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Pfizer and Roche Genentech
Christopher	Rivard	Grants/Research Support	NIH
Naiyer	Rizvi	Speakers or Advisory Board	BMS, Merck, Roche, AZ, Pfizer, Lilly, Novartis, AbbVie BMS, Merck, Roche, AZ, Pfizer, Lilly, Novartis, AbbVie, Nillogen Oncosystems
		Ownership Interest	Gritstone Oncology
Harlan	Robins	Employee	Adaptive Biotechnologies
Andrew	Robinson	Other	Merck
		Grants/Research Support	AstraZeneca, Merck, Bristol-Myers Squibb, Roche Canada
Julia	Rockberg	Consultant	BMS
Steve	Roels	Employee	Foundation Medicine
Evan	Rogers	Employee	TP Therapeutics. Inc.
Kimberly	Rohan	Speakers Bureau	Genetech, Merck, BMS
		Speakers or Advisory Board	Genetech
Laila	Roisman	Other	Pfizer, MSD, Roche
		Speakers Bureau	Roche, Pfizer, MSD
Lindsey	Rolfe	Employee	Clovis Oncology Inc.
		Stock Shareholder (directly purchased)	Clovis Oncology Inc.
Christian Diego	Rolfo	Speakers' Bureau	Novartis, MSD, Boeringher
		Speakers or Advisory Board	Mylan, Oncompass
		Grants/Research Support	Sanofi, Novartis
Vinzent	Rolny	Employee	Roche Diagnostics
Stefan	Rose-John	Stock Shareholder (directly purchased)	CONARIS Research Institute
Nitzan	Rosenfeld	Stock Shareholder (directly purchased)	Inivata Ltd.
Mats	Rosenlund	Consultant	BMS
André	Rosenthal	Employee	Roche Sequencing Solutions, AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Kenneth	Rosenzweig	Other	Varian, Elekta
P. Martin	Ross	Employee	NanoString Technologies
Jeffrey	Ross	Employee	Foundation Medicine
		Other	Foundation Medicine, Inc.
		Stock Shareholder (directly purchased)	Foundation Medicine
D.	Ross Camidge	Other	Pfizer, Genoptix, Bristol-Myers Squibb, Roche Genetech, Celgene, Array, AbbVie, ARIAD, Clovis, Novartis, Orion, Eli Lilly, G1 Therapeutics
Stephen	Rothenberg	Employee	Loxo Oncology
Jeffrey	Rothenstein	Consultant	AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Roche
		Other	AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Roche
Sacha	Rothschild	Grants/Research Support	AstraZeneca
Charles	Rudin	Consultant	Bristol-Myers Squibb, Celgene, G1 Therapeutics, Harpoon Therapeutics, Medivation, Novartis, Chugai
		Other	AbbVie, Novartis, Harpoon, Araxes, BMS, Celgene, G1 Therapeutics
Fedoria	Rugless	Grants/Research Support	PCORI
Prudence	Russell	Speakers or Advisory Board	Bristol-Myers Squibb
Yuri	Rukazenkov	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Anna	Rydén	Employee	AstraZeneca

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Adrian	Sacher	Speakers or Advisory Board	AstraZeneca, Gritstone Oncology
		Honoraria	AstraZeneca
		Other	AstraZeneca, Genentech-Roche, Pfizer
Sandra	Sackmann	Consultant	Boehringer Ingelheim, BMS
Behbood	Sadrolhefazi	Employee	Boehringer Ingelheim
Tomohito	Saito	Grants/Research Support	Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb
Yuichi	Sakairi	Speakers Bureau	Olympus
Joseph	Salama	Consultant	BMS
		Grants/Research Support	Merck, BMS, AbbVie, Immunocore, Celldex, Reata Pharmaceuticals
Alexey	Salnikov	Employee	Boehringer Ingelheim
Miroslav	Samarzija	Speakers Bureau	Roche, Pfizer, AstraZeneca, MSD
Carl	Samuelsen	Employee	Boehringer Ingelheim
Rachel	Sanborn	Other	AstraZeneca, Seattle Genetics, Peregrine Pharmaceuticals, Inc, ARIAD, Genentech/Roche, Celldex
		Grants/Research Support	Merck, Bristol Meyer Squibb, MedImmune
Martin	Sandelin	Other	BMS
Rickard	Sandin	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Alan	Sandler	Employee	Genentech
		Stock Shareholder (directly purchased)	Genentech, Roche
		Speakers Bureau	Roche
Alexandra	Sanford	Employee	Celgene
Randeep	Sangha	Other	Roche, BI, AZ, Lilly, BMS, Merck, Novartis, Pfizer, Lundbeck, Lilly,
Antonio	Santo	Grants/Research Support	AstraZeneca, Boehringer Ingelheim
		Consultant	AstraZeneca, Boehringer Ingelheim
Eric	Santoni-Rugiu	Speakers Bureau	Roche, Pfizer, Novartis,
		Grants/Research Support	Pfizer, Roche
Edgardo	Santos	Speakers Bureau	Celgene, Genentech, Merck, AstraZeneca, Takeda, Novartis, Boehringer Ingelheim
Sanatan	Saraf	Employee	Merck
Medha	Sasane	Ownership Interest	Novartis Oncology
		Employee	Novartis Oncology
Andreas	Sashegyi	Employee	Eli Lilly and Company
Kohta	Satake	Other	CureApp, Inc.
Miyako	Satouchi	Grants/Research Support	Chugai, Ono, MSD, Bristol-Myers Squibb, AstraZeneca, Pfizer, Eli Lilly Japan, Astellas, Boehringer Ingelheim, Novartis
		Speakers Bureau	Chugai, Taiho , Eli Lilly Japan, Pfizer Japan, AstraZeneca, Boehringer Ingelheim,Bristol-Myers Squibb,Ono, Novartis ,MSD
		Other	Chugai, Taiho, MSD, Eli Lilly Japan, Pfizer Japan, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Ono, Novartis
Delia	Sauciuc	Other	Bristol-Myers Squibb
Spasenija	Savic Prince	Speakers or Advisory Board	MSD, Roche, Pfizer, AstraZeneca, Boehringer Ingelheim
		Honoraria	Roche, AstraZeneca, BMS, MSD
Hideyuki	Saya	Grants/Research Support	Daiichi-Sankyo Inc., Eisai Co., Ltd., Nihon Noyaku Co. Ltd., AQUA Therapeutics Co., Ltd.
Eric	Sbar	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Giorgio	Scagliotti	Other	Eli Lilly, Pfizer, AstraZeneca, Roche, Bayer, MSD,
		Consultant	Eli Lilly
		Speakers Bureau	Eli Lilly, MSD
Stephan	Schäfer	Consultant	Bristol-Myers Squibb, Boehringer Ingelheim,
		Other	Menarini
Kurt	Schalper	Grants/Research Support	Navigate BioPharma Services, Tesaro, Takeda, Navigate biopharma, Surface Oncology, Onkaido, Tioma,
		Consultant	Celgene, Foundation Medicine
Andreas	Scheel	Consultant	Bristol-Myers Squibb, MSD, Roche Pharma AG,
		Other	QuIP GmbH, NordiQC
Matthias	Scheffler	Consultant	Novartis, Boehringer Ingelheim, Bristol-Myers Squibb

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Anne	Schlegel	Employee	Epigenomics AG
Erica	Schleifman	Employee	Genentech
		Stock Shareholder (directly purchased)	Roche
Luciene	Schluckebier	Grants/Research Support	AstraZeneca
Sabine	Schmid	Grants/Research Support	BMS
Sebastian	Schmidt	Employee	Siemens Healthcare GmbH
Rosa	Schneiderman	Employee	Novocure Ltd
Roland	Schott	Grants/Research Support	Pierre Fabre, Roche, AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Hospira, BMS
Lea	Schotten	Grants/Research Support	Epigenomics AG
Alexa	Schrock	Employee	Foundation Medicine, Inc.
		Other	Foundation Medicine, Inc.
		Stock Shareholder (directly purchased)	Foundation Medicine
Martin	Schuler	Consultant	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Novartis, Roche, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Alexion, MSD
		Other	Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, MSD, Novartis, Universität Duisburg-Essen, University Hospital Essen
		Grants/Research Support	Boehringer Ingelheim, Bristol-Myers Squibb, Novartis
		Employee	University Duisburg-Essen, University Hospital Essen
Katja	Schulze	Employee	Genentech/Roche
		Stock Shareholder (directly purchased)	Genentech/Roche
Sylvie	Schulze	Employee	Roche Sequencing Solutions
Sarit	Schwartz	Employee	NantOmics, LLC
Jeffrey	Scott	Employee	Novartis
Martin	Sebastian	Other	MSD, Bristol-Myers Squibb, Boehringer Ingelheim, Roche Pharma AG, Pfizer, Lilly, Novartis, AstraZeneca
		Consultant	Boehringer Ingelheim, BMS, MSD, Roche, Novartis, AstraZeneca, Celgene, Lilly, Pfizer
M.-C.	Secouard-Faure	Employee	Servier
Ravi	Seethamraju	Employee	Siemens
Masahiro	Seike	Speakers Bureau	Chugai Pharmaceutical Co. Ltd.
Ikuo	Sekine	Honoraria	Ono Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Company, Limited, Mochida Pharmaceutical Co., Ltd, Nippon Boehringer Ingelheim Co ., Ltd, Taiho Pharmaceutical Co., Ltd ,Novartis Pharma K.K, Pfizer Japan Inc., AstraZeneca K.K.
		Grants/Research Support	Nippon Boehringer Ingelheim Co ., Ltd., Kyowa Hakko Kirin Company, Limited, Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Mochida Pharmaceutical Co., Ltd
Shankar	Sellappan	Employee	NantOmics, LLC
Giovanni	Selvaggi	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
Suresh	Senan	Grants/Research Support	Varian Medical Systems
		Speakers or Advisory Board	Varian Medical Systems, Lilly Oncology
Lecia	Sequist	Other	AstraZeneca, Bristol-Myers Squibb, Genentech, Boehringer Ingelheim, Novartis, Clovis, Genentech, Merrimack, ARIAD, Aviad
		Consultant	AZ, BMS, Genentech, BI, Merrimack, Novartis, Pfizer, Clovis, Merrimack
		Grants/Research Support	Clovis, Novartis, BI, Merrimack, Merck, AstraZeneca
Monika	Serke	Consultant	Roche Pharma AG, Bristol-Myers Squibb, MSD, Lilly, Pfizer, Boehringer Ingelheim
Takashi	Seto	Other	AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kissei Pharmaceutical, Kyowa Hakko Kirin, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer Japan, Roche Singapore, Taiho Pharmaceutical, YakultHonsha
		Speakers Bureau	AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kissei Pharmaceutical, Kyowa Hakko Kirin, MSD, Nippon Boehringer Ingelheim, Nippon Kayaku, Ono Pharmaceutical, Pfizer Japan, Roche Singapore, Taiho Pharmaceutical, YakultHonsha
		Grants/Research Support	Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly Japan, Merck Serono, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan
		Consultant	AstraZeneca, BMS, Chugai, Lilly, Kissei, Kyowa Hakko Kirin, Boehringer Ingelheim, Nippon Kayaku, ONO, Pfizer, Roche, Taiho

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Lesley	Seymour	Grants/Research Support	AstraZeneca
		Other	AstraZeneca
Manan	Shah	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Riyaz	Shah	Consultant	Boehringer Ingelheim, Lilly, AstraZeneca
Neil	Shah	Other	Targated Oncology
Manisha	Shah	Grants/Research Support	Eisai, LOXO, BMS, Merck
		Employee	Eisai, LOXO
Mona	Shahbazian	Ownership Interest	OncoCyte
		Employee	OncoCyte
David	Shames	Employee	Genentech
		Stock Shareholder (directly purchased)	Roche
Joseph	Shan	Employee	Peregrine Pharmaceuticals, Inc.
Yang W.	Shao	Stock Shareholder (directly purchased)	Geneseeq Technology Inc.
Geoffrey	Shapiro	Grants/Research Support	Pfizer, Lilly
		Consultant	Pfizer, Lilly, Vertex Pharmaceuticals, Roche, G1 Therapeutics
Alice	Shaw	Consultant	Pfizer, KSQ Therapeutics, Novartis, Genentech/Roche, ARIAD, Ignyta, Blueprint Medicines, Foundation Medicine, Taiho, Daiichi-Sankyo, EMD Serono, Loxo
		Other	Genentech/Roche, Pfizer, Novartis, ARIAD, Ignyta, Daiichi-Sankyo, Blueprint Medicines, Loxo, Taiho, KSQ Therapeutics, Foundation Medicine, EMD Serono
Liji	Shen	Employee	Merck
Frances	Shepherd	Stock Shareholder (directly purchased)	Eli Lilly, AstraZeneca
		Other	Merck, BMS, Lilly, AstraZeneca, Roche, Boehringer Ingelheim
		Consultant	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Recombio, Synta, Merck
		Grants/Research Support	Boehringer Ingelheim (Inst), NIH
Eric	Sherman	Other	Loxo Oncology
Ashwini	Shewade	Employee	Genentech, Inc
Junping	Shi	Employee	OrigiMed
Takuo	Shibayama	Grants/Research Support	ONO PHARMACEUTICAL CO., LTD
		Speakers Bureau	ONO PHARMACEUTICAL CO., LTD. Merck Sharp & Dohme K.K., Meiji Seika Pharma Co., Ltd
Jin-Yuan	Shih	Consultant	AstraZeneca, Roche, Boehringer Ingelheim, MSD Oncology, Chugai Pharmaceutical,
		Other	Pfizer, BMS, Novartis
Danny	Shih	Employee	Clovis Oncology Inc.
		Stock Shareholder (directly purchased)	Clovis Oncology Inc.
Tadashi	Shimada	Employee	Chugai Pharmaceutical
Masashi	Shimazaki	Employee	Astellas
Nicole	Shipitofsky	Employee	Daiichi Sankyo
		Stock Shareholder (directly purchased)	Daiichi Sankyo
Norah	Shire	Employee	AstraZeneca
Lynette	Sholl	Consultant	Research to Practice
Anna	Shteingauz	Other	Novocure Ltd
Jonathan	Siegel	Employee	Bayer HealthCare Pharmaceuticals Inc
Sandra	Siemann	Employee	Roche Sequencing Solutions
Alan	Sihoe	Grants/Research Support	Medela AG (Baar, Switzerland)
George	Simon	Grants/Research Support	Merck, Eli Lilly ; Boeringer Ingelheim
		Speakers' Bureau	Celgene
		Speakers or Advisory Board	Takeda, Merck, Eli Lilly, Celgene, Genprex, RefleXion
Jasmeet	Singh	Stock Shareholder (directly purchased)	Daiichi Sankyo
		Employee	Daiichi Sankyo
Taryn	Sisserson	Employee	vent
Johan	Skog	Employee	Exosome Diagnostics Incorporation
Joel	Skoletsky	Employee	Foundation Medicine
Berend	Slotman	Grants/Research Support	Varian Medical Systems
		Speakers Bureau	ViewRay Inc.

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Matthew	Smeltzer	Grants/Research Support	NIH
Egbert	Smit	Consultant	Eli Lilly
		Grants/Research Support	AstraZeneca, Bayer, Boehringer Ingelheim, Roche/Genentech
Margie	Smith	Employee	Ventana Medical Systems
Ralph	Smith	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Rob	Smith	Employee	Owlstone Medical Ltd
Vlatka	Smoljanovic	Stock Shareholder (directly purchased)	F. Hoffmann-La Roche Ltd
		Employee	F. Hoffmann-La Roche Ltd
Mark	Socinski	Other	Genentech
		Grants/Research Support	Pfizer
Flavio	Solca	Employee	Boehringer Ingelheim
Ben	Solomon	Consultant	Pfizer, Novartis, Roche-Genentech, Bristol-Myers Squibb, Merck, AstraZeneca
Ross	Soo	Other	Pfizer, Roche, Novartis
		Speakers or Advisory Board	AstraZeneca, BMS, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche, Taiho
		Grants/Research Support	AstraZeneca
Patrick	Soon-Shiong	Employee	NantHealth
Jens Benn	Sørensen	Other	Lilly, Boehringer Ingelheim, Merck Inc., Roche-Peru
		Speakers Bureau	Pfizer
Boe	Sørensen	Grants/Research Support	Roche Molecular Systems
Jean-Charles	Soria	Consultant	AstraZeneca, Astex, GSK, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar, Pierre Farbe, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda, Clovis
		Honoraria	AstraZeneca, Astex, Covagen, Clovis, GSK, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Takeda
		Other	AstraZeneca, Astex, Covagen, Pierre Fabre, Sanofi, Servier, Takeda
Hector	Soto Parra	Other	AstraZeneca, Lilly MSD, BMS
Arturo	Soto-Matos	Employee	PharmaMar
Pierre-Jean	Souquet	Grants/Research Support	Amgen, Astellas, AstraZeneca, BMS, Chugai, Lilly, Pfizer, Roche, Boehringer Ingelheim
Lior	Soussan-Gutman	Employee	Oncotest (subsidiary of Teva pharmaceuticals)
Alan	Spatz	Consultant	AstraZeneca
James	Spicer	Consultant	Bayer, Pfizer
		Honoraria	Pfizer
David	Spigel	Consultant	Genentech/Roche, Celgene, Brystel-Myers Squibb, Lilly, AstraZeneca, Pfizer, Clovis Oncology, Novartis, Boehringer Ingelheim
		Grants/Research Support	Genentech/Roche, Novartis, Celgene, Bristol-Myers Squibb, Lilly, AstraZeneca, Pfizer, Clovis Oncology, Boehringer Ingelheim, Peregrine Pharmaceuticals, Oncogenex, OncoMed, Amgen, Verastem, Daiichi Sankyo, University of Texas Southwestern Medical Center- Simmons Cancer Center, Merck
		Other	Bristol-Myers Squibb
Avrum	Spria	Ownership Interest	Veracyte Inc
		Consultant	Janssen Pharmaceuticals, Veracyte Inc.
Andrea	Sporchia	Employee	Bayer - Italy
Thomas	Sporn	Grants/Research Support	NIH
Virote	Sriuranpong	Grants/Research Support	AstraZeneca, Novartis, Roche, Pfizer, Sanofi, Boehringer, Eisai, Taiho, Lilly, BMS
		Consultant	AstraZeneca, MSD, Novartis, Pfizer, Roche, Eisai, Merck
Rolf	Stahel	Speakers or Advisory Board	AbbVie, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Pfizer, Roche
		Honoraria	Astellas, AstraZeneca, Lilly, MSD, Novartis, Roche
Nicola	Steele	Consultant	Merck Sharp & Dohme, Boehringer Ingelheim, Bristol-Myers Squibb
		Other	Pfizer, MSD Oncology, Boehringer Ingelheim, Novartis
		Grants/Research Support	Merck Serono, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Roche
Philip J.	Stephens	Employee	Foundation Medicine
		Other	Foundation Medicine, Inc.
		Stock Shareholder (directly purchased)	Foundation Medicine
James	Stevenson	Grants/Research Support	Merck, Bristol-Myers Squibb, Bayer Healthcare

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
David	Stewart	Grants/Research Support	Celgene Corporation, Boehringer Ingelheim, AstraZeneca, Novartis, Bristol-Myers Squibb
		Other	Roche Canada, Pfizer Canada, Boehringer Ingelheim Canada, Amgen, Novartis Canada,
Thomas	Stinchcombe	Consultant	AbbVie, Boehringer Ingelheim, ARIAD
		Grants/Research Support	Genentech/Roche, EMD Serono, Bristol-Meyers Squibb
John	Strickler	Consultant	Amgen, Bayer, Boehringer Ingelheim, Celgene, Genentech
		Grants/Research Support	AbbVie, Bayer, Exelixis, Gilead Sciences, MedImmune, Oncomed, Regeneron, Sanofi
Chipman	Stroud	Speakers' Bureau	Genentech
Xiaoxing	Su	Employee	Berry Genomics
Vivek	Subbiah	Grants/Research Support	Novartis, Bayer, GSK, AbbVie, Loxo, Nanocarrier
Deepa	Subramaniam	Other	Bristol-Myers Squibb, Takeda Oncology,
Shunichi	Sugawara	Speakers Bureau	Chugai Pharma, Boehringer Ingelheim, AstraZeneca
James	Suh	Employee	Foundation Medicine, Inc.
		Other	Foundation Medicine, Inc.
Xin	Sun	Employee	Shandong Cancer Hospital Affiliated to Shandong University
James	Sun	Employee	Foundation Medicine
Fuming	Sun	Employee	Berry Genomics
Yun	Sun	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Fuming	Sun	Employee	Berry Genomics
Jenny	Svärd	Consultant	BMS
Scott	Swanson	Honoraria	Ethicon
Peter	Szlosarek	Grants/Research Support	Polaris Pharma
Mario	Sznol	Stock Shareholder (directly purchased)	Adaptive Biotechnologies; Amphivena; Intensity Therapeutics
		Consultant	Adaptimmune; Agonox; Alexion Pharmaceuticals; Amgen; Anaeropharma; Astellas Pharma; AstraZeneca/MedImmune; Biodesix; Bristol-Myers Squibb; Genentech/Roche; Immune Design; Immune Design; Inovio Pharmaceuticals; Janssen Oncology; Kyowa Hakko Kirin; Lilly;
		Other	Academic CME; Clinical Care Options; DAVAOncology; Haymarket Media; Imedex; Physician Education Resource; Prime Oncology; Research to Practice; TRM Oncology; Vindico
Eric	Sztejman	Other	Medtronic
Vasisht	Tadigotla	Employee	Exosome Diagnostics Incorporation
Mary	Tagliaferri	Employee	Nektar Therapeutics
		Stock Shareholder (directly purchased)	Nektar Therapeutics
Toshiaki	Takahashi	Speakers Bureau	AstraZeneca, Eli Lilly, Chugai, ONO
		Grants/Research Support	AstraZeneca , Eli Lilly, Chugai, Pfizer, MSD
Yuichiro	Takeda	Grants/Research Support	Taiho Pharmaceutical, Nippon, Boehringer Ingelheim, Chugai Pharmaceutical, Kyowa Hakko Kirin
Koji	Takeda	Grants/Research Support	AbbVie, Astellas, AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Merck Serono, Ono Pharmaceutical, Pfizer
Mitsuhiro	Takenoyama	Other	AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Ono Pharmaceutical, Taiho Pharmaceutical
		Grants/Research Support	Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Novartis Pharma, Ono Pharmaceutical
Mitsuhiro	Takenoyama	Grants/Research Support	Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Boehringer Ingelheim, Novartis Pharma, Ono Pharmaceutical
Kengo	Takeuchi	Other	Nichirei, Chugai Pharmaceutical
		Consultant	Nichirei
Nagio	Takigawa	Speakers Bureau	Chugai Pharma, Pfizer, Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Eli-Lilly Japan
		Grants/Research Support	Boehringer Ingelheim, Chugai Pharma, Pfizer, AstraZeneca, Taiho Pharmaceutical, Kyowa-Hakko Kirin, Nihonkayaku, Ono Pharmaceutical
Yuichi	Takiguchi	Honoraria	AstraZeneca, Ono Pharmaceutical Co., Bristol-Myers Squib, Lilly, Chugai Pharmaceutical Co., Pfizer, Boehringer Ingelheim
		Grants/Research Support	Ono Pharmaceutical Co., Eizai, Pfizer, Boehringer Ingelheim, Lilly, Kyowa-Hkko Kirin, Chugai Pharmaceutical Co., Bristol Meyers Squib
Orna	Tal Yitzhaki	Employee	Novocure Ltd
Denis	Talbot	Other	Boehringer Ingelheim, Lilly, pfiyer, Roche
Martin	Tammemägi	Consultant	Brock University

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Tomohide	Tamura	Other	Ono Pharmaceutical, Chugai Pharmaceutical
Kazuo	Tamura	Speakers Bureau	Ono, Eli Lilly, Kyowa-Kirin, Boehringer Ingelheim
Daniel	Tan	Consultant	Novartis, Bayer, Boeringher Ingelheim, Celgene, AstraZeneca, Eli-Lilly, Loxo
		Honoraria	Novartis, Bayer, Boeringher Ingelheim, Celgene, AstraZeneca, Eli-Lilly, Loxo
		Grants/Research Support	Novartis, AstraZeneca, GlaxoSmithKline, Bayer
		Other	Merck, Pfizer, Novartis, Boehringer Ingelheim
Weiwei	Tan	Employee	Pfizer Inc
Fenlai	Tan	Employee	Betta Pharmaceuticals Co, Ltd, Xcovery Holding Company
		Stock Shareholder (directly purchased)	Betta Pharmaceuticals Co, Ltd
		Other	Xcovery Holding Company
Hiroshi	Tanaka	Other	AstraZeneca, Ono Pharmaceutical, Chugai Pharmaceutical
		Consultant	AstraZeneca
		Grants/Research Support	AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Astellas, Takeda, MSD, Boehringer Ingelheim, Eli Lilly
		Speakers Bureau	Ono Pharma Chugai Pharma
Fumihiro	Tanaka	Speakers Bureau	Chugai Pharmaceutical Co.LTD
Min	Tang	Employee	Peregrine Pharmaceuticals, Inc.
Wenbo	Tang	Employee	Boehringer Ingelhiem
Nizar	Tannir	Consultant	Nektar Therapeutics
Poonam	Tanwani	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Janis	Taube	Grants/Research Support	Bristol-Myers Squibb
		Consultant	Bristol-Myers Squibb, Merck, AstraZeneca
Fiona	Taylor	Employee	Adelphi Values
		Grants/Research Support	Adelphi Values
		Other	Adelphi Values, Bristol-Myers Squibb
Catalina	Teba	Other	Medtronic
Jennifer	Temel	Grants/Research Support	Pfizer
Ricardo	Terra	Speakers or Advisory Board	Johnson & Johnson, Medtronic, Pfizer, Boehringer, H.Strattner/Intuitive
		Employee	Bayer
Meena	Thayu	Employee	Janssen
		Stock Shareholder (directly purchased)	Janssen
Charles	Theuer	Employee	TRACON Pharmaceuticals
Michael	Thomas	Consultant	MSD, BMS, Lilly, AstraZeneca, Roche, Pfizer, Celgene, Novartis
Roman	Thomas	Speakers or Advisory Board	New Oncology
		Ownership Interest	New Oncology
		Honoraria	AstraZeneca, Merck, Clovis, Puma, Daiichi-Sankyo, J&J, Sanofi-Aventis, Roche, Boehringer Ingelheim, MSD, Lilly, Bayer
		Grants/Research Support	AstraZeneca, EOS, Merck
Erik	Thunnissen	Speakers or Advisory Board	Visiongate, SD, Pfizer, AstraZeneca
		Honoraria	Pfizer
		Grants/Research Support	Pfizer
Kenneth	Thress	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Holger	Thurm	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Yuan	Tian	Employee	NantOmics, LLC
Markus	Tiemann	Consultant	Novartis, Boehringer Ingelheim, Roche, AstraZeneca
Nalin	Tikoo	Employee	Roche Sequencing Solutions
Christopher	Tipton	Employee	Adaptive Biotechnologies
Marcello	Tiseo	Consultant	AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Novartis, Otsuka, Pierre Farbe
		Grants/Research Support	ARIAD
Kota	Tokushige	Employee	Novartis Pharma KK
Keisuke	Tomii	Speakers Bureau	Behringer-Ingelheim
Jing	Tong	Employee	Foundation Medicine

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Emina	Torlakovic	Consultant	Janssen Canada, Merck Canada, Bristol-Myers Squibb Canada, Pfizer Canada, Leica Biosystems Global, Roche Canada, Cell Marque, AstraZeneca Canada
Christopher	Towe	Other	Medtronic
Alison	Tradonsky	Consultant	Thermo Fisher Scientific
Quan	Tran	Other	Bristol-Myers Squibb
Alain	Tremblay	Consultant	Carefusion Inc.
		Consultant	Olympus America
		Consultant	BD inc
John	Truesdell	Employee	Foundation Medicine
Matt	Truman	Consultant	F. Hoffmann-La Roche Ltd
		Stock Shareholder (directly purchased)	F. Hoffmann-La Roche Ltd
Nataliya	Trunova	Employee	Celgene Corporation
Chung-Ming	Tsai	Speakers Bureau	Roche, Eli Lilly, AstraZeneca, MSD, Bristol-Myers Squibb, Pfizer, Novartis, Sanofi, Chugai
Ming	Tsao	Consultant	Merck, AstraZeneca, BMS, Ventana/Roche, Pfizer Canada
		Grants/Research Support	AstraZeneca, NIH, Merck, Pfizer Canada
Anne	Tsao	Consultant	Genentech, Roche, BMS, Boehringer Ingelheim, Merck, AstraZeneca, Arias
		Grants/Research Support	MedImmune, Eli Lilly, Millenium, Genentech, NIH/NCI, Boehringer Ingelheim, ARIAD,AstraZeneca, Novartis, Bayer, Seattle Genetics, Merck
Ann	Tsuji	Employee	Foundation Medicine
Fumito	Tsuji	Employee	SFJ Pharma Japan K.K.
Junji	Tsurutani	Other	AstraZeneca K.K.
Brian	Tuch	Employee	Loxo Oncology
		Stock Shareholder (directly purchased)	Loxo Oncology
Tal	Twito	Employee	Oncotest (subsidiary of Teva pharmaceuticals)
Scott	Tykodi	Other	Nektar Therapeutics, Jounce Therapeutics, Pfizer, Bristol-Myers Squibb, Bristol-Myers Squibb, Merck, Genentech, Prometheus Laboratories, ARGOS Therapeutics, Peloton Therapeutics
Jane	Ung	Employee	TP Therapeutics. Inc.
Patrick	Urban	Employee	Novartis
Edyta	Urbanska	Consultant	Pfizer
		Grants/Research Support	Roche
Noa	Urman	Employee	Novocure
Tiziana	Usari	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Joshua	Usher	Employee	NantOmics
Eric	Vallieres	Consultant	Spiration/ Olympus, Uptake Medical, Genentech, Regeneron, AbbVie, Myriad
		Other	Regeneron, AbbVie
		Speakers Bureau	Synthes
Erik (H.F.M.)	van der Heijden	Speakers or Advisory Board	Mediglobe Corporation, MSD
		Grants/Research Support	AstraZeneca, Pentax Medical
Marc	Van Der Schee	Employee	Owlstone Medical Ltd
		Ownership Interest	Owlstone Medical Ltd
		Consultant	Owlstone Medical Ltd
Jan	Van Meerbeeck	Consultant	Bayer
		Speakers Bureau	Roche-Genentech
		Other	Merck, Bristol-Myers Squibb
Paul	Vanderlaan	Consultant	Gala Therapeutics
Johan	Vansteenkiste	Consultant	AstraZeneca, Novartis, GSK Bio, Boehringer Ingelheim, Eli-Lilly, MSD
Rocio	Varea	Employee	Eli Lilly and Company
Marileila	Varella-Garcia	Grants/Research Support	Abbott Molecular
		Other	Clovis, Biocept, Pfizer
Maria	Vehreschild	Consultant	Berlin Chemie, MSD/Merck, Astellas Pharma, Baselia, Gilead Science, Organobalance, Pfizer, 3M, DaVolterra, Seres Therapeutics
Karen	Velastegui	Employee	Mirati
Vamsidhar	Velcheti	Grants/Research Support	Navigate BioPharma, Novartis, Bayer, GSK, AbbVie, LOXO, Nanocarrier, NantOmics
		Consultant	Merck, BMS, Genentech, AstraZeneca, Celegene, Foundation Medicine, Amgen

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Galina	Velikova	Consultant	Roche, Eisai, Novartis
Jo-Anne	Vergilio	Employee	Foundation Medicine, Inc.
		Other	Foundation Medicine, Inc.
Giulia	Veronesi	Grants/Research Support	LILT, INAIL
		Consultant	Medtronic, Ethicon, Intuitive surgical, Abmedica
Christine	Vietz	Employee	Foundation Medicine
Michele	Vigliotti	Stock Shareholder (directly purchased)	Daiichi Sankyo
		Employee	Daiichi Sankyo, Adaptive Biotechnologies
Santiago	Viteri	Speakers Bureau	Bristol Meyer Squibb, Boeringher Ingelheim
		Consultant	Roche, Clovis Oncology, Promega Biotech
Nicholas	Vogelzang	Other	Boehringer Ingelheim
Everett	Vokes	Consultant	AbbVie, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Genentech, Leidos, Merck, Regeneron, Serono, Takeda, VentiRx
Tali	Voloshin	Employee	Novocure Ltd
Joachim	Von Pawel	Other	AbbVie, Pfizer, Bristol-Myers Squibb, Novartis
		Consultant	Daiichi, AbbVie, Pfizer, Novartis
Momen	Wahidi	Honoraria	Olympus, Boston Scientific, Medtronics
Heather	Wakelee	Grants/Research Support	Clovis Oncology Inc., Roche/Genentech, Xcovery, AstraZeneca, BMS, Celgene, Exelixis, Novartis, Lilly, Pharmacyclis, Regeneron, Pfizer, Gilead Sciences, Inc.
		Other	International Thymic Malignancies Interest Group
		Consultant	Helsinn, Genentech, Peregrine, Acea, Pfizer
		Employee	Stanford University Medical Center
Jill	Walker	Employee	Astrazenca
Paul	Walker	Speakers' Bureau	Biodesix, Genentech
		Speakers or Advisory Board	Biodesix
Annette	Walter	Employee	Bayer AG
Jie	Wang	Other	BMS
		Consultant	Berry Genomics
Changli	Wang	Other	BMS
Mengzhao	Wang	Other	BMS
Tao	Wang	Stock Shareholder (directly purchased)	Pfizer
		Employee	Pfizer
Lisa	Wang	Employee	Genentech, Inc
Yin	Wang	Employee	Berry Genomics
Tianyang,	Wang	Employee	Berry Genomics
Lien Tu	Wang	Employee	Berry Genomics
Lu	Wang	Employee	AstraZeneca
Sherry	Wang	Employee	Pfizer Inc.
Aodi	Wang	Employee	OrigiMed
Kai	Wang	Employee	OrigiMed
Weifeng	Wang	Employee	OrigiMed
Yin	Wang	Consultant	Berry Genomics
Tianyang	Wang	Consultant	Berry Genomics
Lien Tu	Wang	Employee	Berry Genomics
Arne	Warth	Grants/Research Support	Roche Diagnostics
Satoshi	Watanabe	Speakers Bureau	AstraZeneca
David	Waterhouse	Consultant	BMS, Eli Lilly
		Speakers Bureau	BMS, Celgene, Eli Lilly, Genentech/Roche
		Other	Bristol-Myers Squibb
Mark	Watson	Grants/Research Support	NIH
Patricia	Watson	Employee	Janssen, Merck
Jerry	Weaver	Employee	Celgene Corporation
Birgit	Wehnl	Employee	Roche Diagnostics
Uri	Weinberg	Employee	Novocure
Jared	Weiss	Grants/Research Support	AZ, Astellas, Celgene, Merck, Pfizer, Novartis

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		Consultant	Biodesix, AstraZeneca, Eli Lilly, EMD Serono, Genentech, Clovis Oncology, Inivata, BioMarck Pharmaceuticals, OncoPlex Diagnostics
Tobias	Welte	Other	AstraZeneca, GSK, Bayer, Novartis, Pfizer, Boehringer Ingelheim, MSD
Howard	West	Consultant	AbbVie, ARIAD, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Merck, PharmaMar, Roche/Genentech, Spectrum, Takeda
		Speakers Bureau	ARIAD, BMS, Roche/Genentech
		Consultant	Novartis, Guardant Health
Virginie	Westeel	Consultant	Roche, BMS, AstraZeneca, MSD, Boehringer Ingelheim, Merk
		Other	BMS, Roche, Novartis, AstraZeneca
		Speaker's Bureau	BMS, Lilly, MSD, Boehringer Ingelheim, AstraZeneca
Kenneth	Westover	Grants/Research Support	Astellas
Paul	Wheatley-Price	Consultant	AstraZeneca
		Other	AstraZeneca
Jared	White	Employee	Foundation Medicine
Jane Liang	White	Employee	Pfizer
Jeffrey	Whitten	Employee	TP Therapeutics. Inc.
Ryan	Widau	Employee	Eli Lilly and Company
		Stock Shareholder (directly purchased)	Eli Lilly and Company
Rainer	Wiewrodt	Consultant	Boehringer Ingelheim, Bristol-Myers Squibb, Grifols, Lilly, Roche Pharma AG, Pfizer, Novartis
		Speakers Bureau	Bayer, Boehringer Ingelheim, GlaxoSmithKline, MSD, Talecris
		Grants/Research Support	Roche
		Other	AstraZeneca
Sharon	Wilks	Other	Bristol-Myers Squibb
Loretta	Williams	Grants/Research Support	Bayer Healthcare, Merck & Co., Inc.
Crystal	Williams	Employee	F. Hoffmann-La Roche Ltd
Keith	Wilner	Employee	Pfizer Inc
		Stock Shareholder (directly purchased)	Pfizer
Linda	Wilson	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Katherine	Winfree	Employee	Eli Lilly and Company
Lori	Wirth	Other	Blueprint, LOXO, Eisai
Ignacio	Wistuba	Speakers or Advisory Board	Genentech/Roche, Bristol-Myers Squibb, Boehringer Ingelheim, Medscape, AstraZeneca/Medimmune, Pfizer, ARIAD, HTG Molecular, Asuragen, Merck
		Grants/Research Support	Genentech, Oncoplex, HTG Molecular, DepArray, Merck, NCCN/ Bristol-Myers Squibb, Medimmune, Adaptive, Adaptimmune, EMD Serono, Pfizer
Corinna	Woestmann	Employee	Roche Sequencing Solutions
Jürgen	Wolf	Grants/Research Support	Novartis, Pfizer, Bristol-Myers Squibb, MSD, Roche Pharma AG
		Consultant	AstraZeneca, BMS, Boehringer Ingelheim, Chugai, Lilly, MSD, Novartis, Pfizer, Roche, Clovis Oncology
		Other	AstraZeneca, BMS, Boehringer Ingelheim, Clovis, Lilly
Katharina	Wolff	Employee	Eli Lilly and Company
Marianne	Wolfsteiner	Employee	Celgene Corporation
		Consultant	Celgene Corporation
Kwok Kin	Wong	Ownership Interest	G1 Therapeutics, Janssen Pharmaceuitcals, AZ Pharmaceuticals, Array Pharmaceuticals
		Grants/Research Support	G1 Therapeutics, Janssen Pharmaceuitcals, AZ Pharmaceuticals, Array Pharmaceuticals
Shekman	Wong	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
William	Wong	Employee	Genentech
		Stock Shareholder (directly purchased)	Genentech/Roche
David	Wong	Consultant	GlaxoSmithKline, Wrigley, Colgate Palmolive, PeriRx LLC
		Grants/Research Support	Delta Dental
		Stock Shareholder (directly purchased)	RNAmeTRIX
Douglas	Wood	Speakers or Advisory Board	Spiration, Inc., GRAIL
		Grants/Research Support	Spiration, Inc., GRAIL
Robert	Wood	Employee	Adelphi Real World

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Samuel	Woodhouse	Employee	INIVATA
Yi-Long	Wu	Speakers Bureau	AstraZeneca, Roche, Eli Lilly, Sanofi, Pfizer
		Other	AstraZeneca, Roche, Eli Lilly, Pfizer, Sanofi, BMS
		Consultant	Sanomics ltd
		Speakers or Advisory Board	AstraZeneca, Roche, Eli Lilly, Pfizer, Boehringer Ingelheim
		Honoraria	AstraZeneca, Roche, Eli Lilly, Pfizer, Boehringer Ingelheim
		Grants/Research Support	AstraZeneca, Roche, Eli Lilly, Pfizer, Boehringer Ingelheim
Charlie	Wu	Employee	Genentech
Qiong	Wu	Other	BMS
Xiaoling	Wu	Employee	Celgene Corporation
Ning	Wu	Employee	Genentech/Roche
		Grants/Research Support	Genentech/Roche
		Stock Shareholder (directly purchased)	Genentech/Roche
Bor-Wen	Wu	Employee	Polaris Pharma
Fan	Xia	Employee	Roche
		Stock Shareholder (directly purchased)	Roche
		Other	Roche
Xuefeng	Xia	Employee	Geneplus
Yan	Xin	Employee	Gilead Sciences, Inc
Weihong	Xu	Employee	AnchorDx Medical
Shanchao	Xu	Employee	Nanjing Geneseeq Technology Inc.
Tu	Xu	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Nobuyuki	Yamamoto	Other	Chugai Pharmaceutical
		Consultant	Chugai Pharmaceutical, Boehringer Ingelheim
		Grants/Research Support	Chugai Pharmaceutical, Boehringer Ingelheim
		Speakers Bureau	Chugai Pharmaceutical Co. Ltd., Boehringer Ingelheim, Ono Pharmatheutical Company
Hiroshi	Yamamoto	Employee	Ajinomoto Co., Inc.
Noboru	Yamamoto	Speakers Bureau	Bristol-Myers Squibb, Pfizer, AstraZeneca, Eli Lilly, Ono Pharmaceutical, Chugai Pharmaceutical
		Grants/Research Support	Quintiles, Astellas Pharma, Chugai Pharmaceutical, Esai, Taiho Pharmaceutical, Bristol-Myers Squibb, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim , Kyowa-Hakko Kirin, Takeda Pharmaceutical
Noboru	Yamamoto	Grants/Research Support	Quintiles, Astellas, Chugai, Eisai, Taiho, BMS, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO, Lilly Japan
		Speakers Bureau	BMS, Pfizer, AstraZeneca, Eli Lilly, ONO, Chugai
		Consultant	Eisai, Takeda, OncoTherapy Science
		Other	AstraZeneca, Pfizer, Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Lilly Japan
Takanori	Yamamoto	Employee	Ono Pharmaceutical
Takeharu	Yamanaka	Grants/Research Support	Taiho, Takeda
		Other	Taiho, Eli Lilly, Takeda, Chugai, Boehringer
Michiko	Yamato	Employee	Daiichi-sankyo Co., Ltd.
Noriko	Yanagitani	Consultant	Chugai Pharma
James Chih-Hsin	Yang	Speakers or Advisory Board	Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Clovis Oncology, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono pharmaceutical Daiichi Sankyo and AstraZeneca, Hansoh Pharmaceuticals
		Honoraria	Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Clovis Oncology, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono pharmaceutical Daiichi Sankyo and AstraZeneca, Hansoh Pharmaceuticals
Liu	Yang	Employee	AstraZeneca
Jing	Yang	Employee	Merck
		Stock Shareholder (directly purchased)	Merck
Ling	Yang	Employee	Geneplus
Zane	Yang	Employee	Spectrum Pharmaceuticals

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David	Yankelevitz	Royalty, Receipt of Intellectual Property Rights/Patent Holder	General Electric
		Stock Shareholder (directly purchased)	Accumetra LLC
		Speakers or Advisory Board	Grail
		Other	Cornell Research Foundation (CRF)
Seiji	Yano	Speakers' Bureau	Chugai, AstraZeneca, Eisai, BoelingerIngelheim
		Grants/Research Support	Chugai, AstraZeneca, Eisai, BoelingerIngelheim,Taiho
Lijing	Yao	Employee	Roche Sequencing Solutions
Ming	Yao	Employee	OrigiMed
James	Yao	Speakers or Advisory Board	Novartis, Ipsen
		Grants/Research Support	Novartis, Ipsen
Jicheng	Yao	Employee	OrigiMed
Kazuhiro	Yasufuku	Grants/Research Support	Olympus Corporation, Veran Medical, Simens, Concordia
		Consultant	Olympus
Stephanie	Yaung	Employee	Roche Sequencing Solutions
Xin	Ye	Employee	AstraZeneca
		Stock Shareholder (directly purchased)	AstraZeneca
Beow	Yeap	Consultant	Abcodia, Inc.
Ofir	Yesharim	Employee	Novocure
Yuting	Yi	Employee	Geneplus
Xin	Yi	Employee	Geneplus
Wai-ki	Yip	Employee	Foundation Medicine
Sue	Yom	Honoraria	AstraZeneca
		Supported/Contracted Research/Grant	Bristol-Myers Squibb, Merck, Genentech
		Royalty, Receipt of Intellectual Property Rights/Patent Holder	Springer, UpToDate, DSMB, BioMimetix
		Consultant	BioMimetix
Kimio	Yonesaka	Grants/Research Support	Daiichi Sankyo Co., Ltd.
Ichiro	Yoshino	Honoraria	Ethicon, Medtronic, Taiho, Chugai, Shionogi, MSD, Pfizer, Eli Lily, Boehringer Ingelheim, CSL Boehring
		Supported/Contracted Research/Grant	Taiho, Pfyzer, Chugai, Shionogi
Hiroshige	Yoshioka	Other	Eli Lilly, Chugai Pharma, Boehringer Ingelheim, Taiho Pharmaceutical, Pfizer, AstraZeneca, Bristol-Myers Squibb, Ono Pharmaceutical, Takeda
		Speakers Bureau	Lilly, Chugai Pharmaceutical, Boehringer Ingelheim, Taiho Pharmaceutical, Pfizer, AstraZeneca, Bristol-Myers Squibb, Ono Pharmaceutical
		Consultant	Takeda
		Grants/Research Support	Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K.
Tina	Young	Employee	Bristol-Myers Squibb
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb
Jinming	Yu	Other	Shandong Cancer Hospital Affiliated to Shandong University
Tiffany	Yu	Consultant	Thermo Fisher Scientific
Helena	Yu	Grants/Research Support	AstraZeneca, Novartis, Astellas, Eli Lilly and Company
		Consultant	AstraZeneca
Wei	Yu	Employee	Genentech
Hui	Yu	Grants/Research Support	NIH
Helena	Yu	Grants/Research Support	AstraZeneca, Lilly, Astellas
Channing	Yu	Employee	Daiichi Sankyo
		Stock Shareholder (directly purchased)	Daiichi Sankyo
Helena	Yu	Grants/Research Support	AstraZeneca, Lilly, Astellas
Yong	Yuan	Employee	BMS
		Other	BMS
		Stock Shareholder (directly purchased)	Bristol-Myers Squibb
Huibin	Yue	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Murray	Yule	Employee	BerGenBio ASA
John	Yun	Other	Bristol-Myers Squibb

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Tony	Yung	Other	Sanomics Limited Hong Kong
		Employee	Sanomics Limited Hong Kong
Renee	Yura	Employee	Novartis
Erik	Yusko	Employee	Adaptive Biotechnologies
Timothy	Zagar	Grants/Research Support	Accuray, Vision RT
		Consultant	Accuray, Vision RT
Jonathan	Zalevsky	Employee	Nektar Therapeutics
		Stock Shareholder (directly purchased)	Nektar Therapeutics
Ali	Zeaiter	Employee	F. Hoffmann-La Roche Ltd
Einav	Zeevi	Employee	Novocure Ltd
Christoph	Zielinski	Speakers or Advisory Board	Roche, Novartis, MSD, BMS, Merck KgA, ARIAD, Boehringer Ingelheim, Imugene, Fibrogen, AstraZeneca
Dayong	Zhai	Employee	TP Therapeutics. Inc.
Xiao	Zhang	Employee	Shandong Cancer Hospital Affiliated to Shandong University
Li	Zhang	Consultant	BI, BMS, MSD, Pfizer
		Grants/Research Support	BMS, Pfizer, Lilly, MSD, Helsinn Healthcare
Fan	Zhang	Employee	AbbVie
		Stock Shareholder (directly purchased)	AbbVie
Xin	Zhang	Employee	TP Therapeutics. Inc.
Han	Zhang	Employee	TP Therapeutics. Inc.
Hui	Zhang	Stock Shareholder (directly purchased)	Pfizer
Li	Zhang	Grants/Research Support	Bristol-Myers Squibb, Eli Lilly, Pfizer
Yue	Zhao	Employee	AnchorDx Medical
Caicun	Zhou	Grants/Research Support	BI, Pfizer
		Consultant	BI, Roche, Eli Lilly
		Other	Eli Lilly, AstraZeneca, Roche, Pfizer, Merck, Sanofi, Boehringer Ingelheim, Henrui
Wei	Zou	Employee	Genentech
		Grants/Research Support	Roche
Enrique	Zudaire	Employee	Janssen R&D
Javier Joseph	Zulueta	Ownership Interest	VisionGate, Inc.
		Employee	VisionGate, Inc.
Yunxia	Zuo	Employee	Roche

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