Non-small cell lung cancer update

Dr. Parneet K. Cheema, BSc, MD, MBiotech, FRCPC, Department of Medical Oncology, Sunnybrook Odette Cancer Centre

Early stage

Background
• Adjuvant cisplatin-based chemotherapy for completely resected early stage NSCLC provides an OS benefit of 5.4%.1
• Bevacizumab in addition to carboplatin/ paclitaxel as first-line therapy in advanced NSCLC improved PFS and OS (E4599), whereas its addition to cisplatin/gemcitabine had no significant benefit (AVAiL).2,3

New data
• Randomized Phase III Trial of Adjuvant Chemotherapy with or without Bevacizumab in Resected Non-Small Cell Lung Cancer (NSCLC): Results of E1505
• Study design: Randomized, phase III trial, resected stage IB (≥4 cm) to IIIA NSCLC, all histologies (squamous NSCLC eligible as safety concerns with resected disease expected to be low), platinum doublet (with vinorelbine, pemetrexed, gemcitabine, or docetaxel) x 4 cycles +/- bevacizumab 15 mg/kg IV q 3 weekly x 1 yr. Primary endpoint: OS.
• Results: N=1501 enrolled, after 41 months of follow-up, independent DSMC advised to release results due to futility. Chemotherapy was prespecified and, thus, well balanced, 25% of patients received cisplatin/vinorelbine, 20% cisplatin/gemcitabine. 1/3 of patients were squamous cell carcinoma.
• OS: HR: 0.99, p=0.93 and DFS: HR: 0.98, p=0.75
• Safety: Significant increased neutropenia, hypertension and grade 3-5 adverse events with bevacizumab. No unexpected adverse events.
• Conclusion: The addition of bevacizumab to adjuvant chemotherapy did not improve survival. Data according to platinum doublet is not yet available.

Impact on practice
Negative trial. As bevacizumab is rarely used in Canada for advanced stage NSCLC mainly due to the negative results of the AVAiL trial, this trial will have little impact on clinical practice.

Locally advanced NSCLC

Background
• 30% of patients present with stage III disease of which half are elderly patients (≥70)
• The benefit of concurrent chemoradiation (CRT) in elderly population remains unclear.

New data (Canadian content)
• CRT versus Radiotherapy Alone in Elderly Patients with Stage III NSCLC: A Systematic Review.
• Study design: Systematic review. Four reports of three studies (n=407 elderly patients).
• Results: OS in elderly patients was superior in those treated with CRT compared to RT alone (HR 0.66, p=0.0099). PFS was also improved with CRT (HR 0.67, p=0.001).
• Safety: Treatment-related death: 5% CRT, 4% RT. Increased hematologic toxicity (neutropenia and thrombocytopenia) with CRT. Rate of febrile neutropenia with CRT was low (2.5%).

Impact on practice
This provides support to consider CRT for fit elderly patients. Determining what chemotherapy to give patients would also need to be considered. Carboplatin-based chemotherapy concurrent with RT has shown to improve survival compared to RT alone, including randomized data in elderly patients and may be a consideration if a patient cannot tolerate cisplatin.4,5

Advanced NSCLC

Advanced NSCLC – ImmunoOncology

First-line

Background
• Phase II and III trials targeting the PD1/ PD-L1 pathway in advanced NSCLC improved survival over standard chemotherapies, however responses were low.2-5
• Cytotoxic chemotherapy has an immune-modulatory effect.2 Thus, combining PD1/ PD-L1 with cytotoxic chemotherapy could increase immune response by increasing number of antigens presented to T-cells and changing tumour microenvironment.
• Combination of the anti-PD1 nivolumab with ipilimumab, an anti-CTLA4 antibody (dual immune checkpoint inhibition) has activity across multiple tumour types including phase III data in advanced melanoma, and has a manageable safety profile.6
• Initial data of nivolumab/ipilimumab combination in metastatic NSCLC at doses used in melanoma yielded high adverse events and moderate responses, thus the dosing and scheduling needed to be optimized.7

New data – Atezolizumab
• Atezolizumab and Chemotherapy Phase 1b: Atezolizumab (MPDL3280A) Combined with Platinum-based Chemotherapy in NSCLC: A Phase 1b Safety and Efficacy Update
• Study design: Phase 1b, treatment naïve, 3 cohorts: atezolizumab 15 mg/kg IV q 3 weeks + carboplatin/paclitaxel or carboplatin/pemetrexed or carboplatin/nab-paclitaxel x 4–6 cycles. All histologies, not limited to PD-L1 positive patients. Primary endpoint: safety. Enrollment not yet complete.
• Results: ORR:
  - All cohorts (n=41): 63%
  - Carboplatin/paclitaxel cohort (n=8): 50%
  - Carboplatin/pemetrexed cohort (n=17): 77%
  - Carboplatin/nab paclitaxel (n=16): 56%
• Characteristics of responses: durable, complete responses were noted and no unconventional immune related responses were reported.
• Toxicity: Grade 3/4 AE 69%. The profile did not appear to be markedly different to what would be expected without the PD-L1 inhibitor. Interestingly, no grade 3/4 immune-related adverse events (irAE) were noted, data regarding grade 1/2 irAE were not presented.
• Conclusions: This combination has impressive high response rates with a well tolerated safety profile.

New data – Nivolumab and Ipilimumab
• Safety and Efficacy of First-line Nivolumab and Ipilimumab in NSCLC (CheckMate 012)
• Study design: Phase 1, four cohorts of various doses and scheduling of nivolumab and ipilimumab (that differed from the phase 3 data in melanoma), treatment naïve advanced NSCLC. All histologies, irrespective of PD-L1, including EGFR+ patients. Primary endpoints: safety and ORR.
• Results: ORR: 13%–39% and unconventional responses were seen. Combinations that contained nivolumab given at its approved dose of 3 mg/kg IV q 2 weeks yielded the highest response rates. No complete responses were reported. PFS 4.9–10.6 months, but immature.
• PD-L1 as a biomarker: Activity in both PD-L1 positive (≥1%) and negative. PD-L1+: ORR 8% to 48%; PD-L1-: ORR 0% to 22 %.
• Toxicity: Grade 3/4 AEs were 29–35%. AEs leading to discontinuation were low 3–10%. No treatment-related deaths.
• Conclusions: Although small numbers, this combination is active and the change in dose/scheduling resulted in acceptable adverse event profile comparable to what would be expected with nivolumab alone. The best responses were reported with combinations of nivolumab containing its standard dose of 3 mg/kg q 2 weeks, which may support maintaining nivolumab dose intensity with this combination.

Impact on practice
Provocative data, confirmatory trials required to change practice. Phase III trials of atezolizumab with various combinations of chemotherapy are currently underway, as is a phase III trial (CheckMate 227) of nivolumab versus nivolumab/ipilimumab versus standard platinum doublet in first-line setting.

Advanced NSCLC – EGFR positive
First-line 3rd generation EGFR TKI
• EGFR TKIs are recommended first-line therapy for advanced EGFR mutated NSCLC.
• AZD9291 is an oral irreversible EGFR TKI that is selective for EGFR sensitizing mutations (Del19 and L858R) in addition to the resistance mutation T790M.

New data
• AZD9291 in Treatment-Naive EGFRm Advanced NSCLC: AURA First-Line Cohort.
• Study design: Phase 1, treatment-naïve cohort, AZD9291 80 mg or 160 mg po OD, EGFR mutated (included mutations other than Del19 and L858R).
• Results: N=160, ORR 67%, 83% and DCR 93%, 100% for 80 mg and 160mg respectively. Maximum duration of response and PFS were 18 and 19.2 months respectively (medians not yet mature).
• Toxicity: Most common were rash, diarrhea. Any grade 3 AE 17%. 5% of drug-related AE led to discontinuation. ILD rate was low. Hyperglycemia 5%.
• Conclusion: AZD9291 has encouraging activity in treatment-naïve advanced NSCLC patients and is well tolerated with low rates of hyperglycemia, which is more commonly seen with another third generation EGFR TKI rociletinib.

Impact on practice
The phase III trial FLAURA (NCT02296125) is comparing AZD9291 80 mg po OD versus standard of care EGFR TKI in treatment-naïve patients with advanced EGFR mutated NSCLC. Sites within Canada, including Sunnybrook Odette Cancer Centre, are currently enrolling patients. At this meeting, preclinical data were also presented showing high brain-to-plasma drug concentrations of AZD9291 compared to gefitinib. Patients with asymptomatic untreated brain metastases are included in FLAURA.

Uncommon EGFR mutations
• Standard first-line therapy for advanced NSCLC harbouring the common activating EGFR mutations (Del19, L858R) is an EGFR TKI where PFS range from 9 to 13 months. Less is known about the management of patients harbouring the 10% of EGFR mutations that are uncommon.
• Pivotal phase II/III trials (Lux Lung 2/3/6) with afatinib in treatment-naïve population included patients with uncommon mutations. Post hoc analysis found that uncommon mutations G719X in exon 18, S768I and L861Q in exon 21 appeared to be sensitive to afatinib. Exon 18 mutations PFS 13.6 months and OS of 26.4 months. De novo T790M and exon 20 insertions did not derive benefit from afatinib.11
• Multiple retrospective analyses of local or national databases were presented to gain insight into management of these mutations.

New data (combination of retrospective database studies)
Brazilian National Cancer Institute Database
• Domingues P. Clinical Outcomes in Patients with NSCLC, Harboring Rare EGFR Mutations

Supplement to Hot Spot, the newsletter of the Rapid Response Radiotherapy Program of the Odette Cancer Centre – November 2015
Preclinical data: IC90 ratio of EGFR

- Exon 18 G719X (n=21): ORR 18%, OS 10.9 mos., PFS 8.6 mos.
- Exon 20 (n=7): ORR 14%, OS 8.6 mos., PFS 2.6 mos.

Conclusion: Similar to previous reports, exon 18 mutations are less responsive to first-generation EGFR TKIs compared to common mutations, and exon 20 show resistance to EGFR TKIs.

Japanese databases (Aichi Cancer Centre & COSMIC), >16,000 patients

- EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Sensitivity to Afatinib or Neratinib but Not to Other EGFR-TKIs.

Results:
- Frequency of exon 18 mutations: 3% of all mutations in EGFR mutations. Most common: G709X, G719X, and Del18.
- Pre clinical data: IC90 ratio of EGFR TKIs were studied and compared to IC90 for common mutation Del 19. The IC90 were the lowest for second-generation EGFR TKI with afatinib or neratinib compared to first-generation TKIs (erlotinib and gefitinib) and third-generation (AZD9291 and CO1686).
- Conclusion: This data was consistent with retrospective data that exon 18 mutations are less responsive to first-generation EGFR TKIs. Afatinib may be the best therapeutic option for exon 18 mutations based on Lux Lung 2/3/6 pooled prospective data and supported by this in vitro data.

Impact on practice

- Indiscriminate use of EGFR TKIs when an EGFR mutation is found should not be standard practice. First-generation EGFR TKIs appear to be less effective in exon 18 G719X and both first generation and second generation are not effective for exon 20 insertions. A practical approach to first-line systemic therapy with currently available retrospective and prospective data could be as follows: exon 20 mutations clinical trial or chemotherapy, de novo T790M mutation third-generation EGFR TKI (AZD9291 or rociletinib) ideally through a clinical trial or chemotherapy, exon 21 L861Q and exon 18 G719X would favour afatinib based on prospective and preclinical data with close monitoring to detect early progression (in the scenario of G719C/S possibly having resistance to EGFR TKIs).

Impact on practice

- Continuation of EGFR TKI upon progression with chemotherapy may have a role in T790M- patients, although OS data are still immature and prospective analysis will be required to change practice.

New data – TIGER X

- Rociletinib in NSCLC Patients with Negative Central Testing for T790M in TIGER-X.
- Study design: Phase I/II study of T790M+ and - patients. Phase II component required central testing for T790M. Key endpoints ORR and safety.
- Results:
  - T790M- by central testing (n=37): ORR 35%, DCR 65%.
  - T790M- by central testing, T790M+ local testing (n=28): ORR 36%, DCR 64%.
  - T790M- by central testing, T790M- local testing or not available (n=9): ORR: 33%, DCR 67%.
- Hypothesis on why T790M- patients responded to rociletinib:
  - Tumour heterogeneity: may explain discordant results
  - Testing method: COBAS testing, THERASCREEN detection were discordant. Thus different testing method would not have picked up missed T790M mutations.
- Study design: 261/265 patients had plasma samples at baseline for T790M analysis, cDNA analysis by BEAMing.
- Results:
  - T790M+ (40%): PFS 4.6 mos. with gefitinib (n=81) vs. 5.3 mos. (n=61) with placebo, HR: 0.97, p=0.88.
  - T790M- (54%): PFS 6.7 mos. with gefitinib (n=46) vs. 5.4 mos. (n=59) with placebo, HR: 0.67, p=0.07.
- OS not mature. However, continuation of gefitinib in T790M+ patients appeared harmful, HR 2.16; p=0.017, although OS trended in favour of gefitinib in T790M negative patients HR was 0.83, p=0.66 with only 21% maturity.

Implications for practice

- Current data suggest that both T790M+ and - patients derive benefit from rociletinib. 35% responses in pretreated NSCLC that are T790M- is impressive compared to currently available second-line options. Interestingly, AZD9291 another third-generation EGFR TKI that targets T790M also reported responses in 21% of T790M-patients. To further explore these findings of rociletinib, the open-label TIGER-2 (NCT02147990) and the randomized Phase 3 TIGER-3 (NCT02322281) studies include T790M- patients. If benefit is confirmed in both T790M+ and - patients, the value of T790M prior to rociletinib will need to be clarified.

Practical Implementation of Biomarker Testing (Canadian content)

- IASCL guidelines recommend EGFR and ALK testing for patients with a diagnosis of advanced non-squamous NSCLC and results should guide treatment decisions. Testing at an earlier stage is also encouraged to allow for rapid initiation of systemic therapy upon disease recurrence.
- A recent international survey of medical oncologists found that in North America 24% of patients with advanced NSCLC do not have EGFR testing.
- One major barrier for biomarker testing and implementing personalized medicine
for advanced NSCLC patients is oncologists having to wait for biomarker results while running the risk of patients clinically deteriorating without therapy.

- Reflex testing for EGFR/ALK has been adopted by a few centres to expedite biomarker results for the treating medical oncologist. The definition of reflex testing is pathologists requesting EGFR and ALK at time of diagnosis of non-squamous NSCLC irrespective of clinical stage. This is opposed to the practice of routine testing where the medical oncologist requests EGFR/ALK at time of first visit with a patient with a diagnosis of advanced NSCLC.

**New Data**

- Impact of Reflex EGFR/ALK Testing on Time-To-Treatment and Integration of Personalized Medicine in Advanced NSCLC Patients
- Study design: Retrospective, centre analysis of Sunnybrook Health Sciences Centre. Compared data from time periods pre and post implementation of reflex testing.
- Results: With the implementation of reflex testing, there was a significant improvement in time to optimal first-line therapy according to biomarker status, 36 days versus 24 days, p=0.036. Reflex testing impacted quality of testing with significantly fewer tests requested being unsuccessful due to insufficient tissue, inappropriate tissue or tissue not sent from holding lab to the testing lab. Number of unsuccessful tests for EGFR 14% versus 4%, p=0.039, and for ALK 17% versus 3%, p=0.037. During the time period of reflex testing there was a significant increase in EGFR and ALK testing across all stages and in patients with advanced stage disease and there was a significant increase in biomarkers available to medical oncologists at patient’s first consultation.

- Conclusion: Reflex testing for EGFR/ALK by pathologists at time of diagnosis of non-squamous NSCLC irrespective of a patient’s clinical stage appeared to improve quality outcomes, including faster time to optimal systemic therapy and less unsuccessful test requests.

**Implications for practice**

Centres may consider implementing reflex testing as a mechanism to reduce barriers encountered with implementing personalized medicine in advanced NSCLC. Ideally this could be coordinated at a national level.

**Advanced NSCLC – Brain metastases**

**Background**

- A third of patients with advanced NSCLC will, at some point, develop CNS metastases.
- The central nervous system (CNS) is a frequent site of progression in ALK+ NSCLC patients treated with crizotinib.

**New data – ALK positive**

- Pooled Analysis of CNS Response to Alectinib in Two Studies of Pre-Treated ALK+ NSCLC
- Study design: Pooled analysis of two phase II trials (NCT01871805 and NCT01801111), single-arm, multicentre studies enrolled ALK+ NSCLC patients previously treated with crizotinib. Alectinib 600 mg po BID. Secondary endpoints CNS ORR and CNS duration of response (DOR)
- Results: N=225
  - Measurable disease at baseline (n=50): ORR 64%, CR 22%, DCR 90%. Median disease control was 10.8 mos.
  - Measurable or non-measurable CNS metastases at baseline (n=136):
    - ORR 47%, CR 37%, DCR 85% and median disease control 11.1 mos.
  - Prior radiation (n=95): ORR 36%, DCR 86%
  - No prior radiation (n=41): ORR 59%, DCR 83%
  - CNS site of progression:
    - No CNS metastases at baseline: 8%
    - Overall: 17%
  - Safety: There was no difference between pooled population with or without brain metastases.
- Conclusion: Alectinib has CNS activity in ALK+ NSCLC patients that was independent of previous radiation. Duration of CNS response seemed to be similar to that of systemic response. Phase III trial ALEX (NCT02075840), a study of alectinib versus crizotinib as first-line therapy for advanced ALK+ NSCLC, will provide further information on CNS efficacy, as CNS endpoints have been incorporated.

**New data – Immunotherapy**

- A Phase II Trial of Pembrolizumab for Untreated Brain Metastases from Non-Small Cell Lung Cancer.
- Study design: Phase II trial, advanced NSCLC or melanoma with at least one untreated brain metastases, treated with pembrolizumab 10 mg/kg q2weeks IV. If progressive disease patients could have RT or surgery and continue pembrolizumab.
- Results: N=18 advanced NSCLC patients; ORR in CNS was 33%, equivalent to systemic ORR of 33%. All patients with a systemic response had a CNS response, except one patient who transiently responded then progressed. Ongoing durable responses.
- Safety: Neurologic adverse events regardless if study drug-related or not were all grade 1.
- Conclusion: Small study, but suggests that pembrolizumab has durable activity on CNS metastases and may be correlated with systemic response.

**REFERENCES**

13. Mok TS. ESMO 2014 Congress. Abstract LBA2_PR.