Early stage NSCLC

RADIANT

Background:

- Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), improves overall survival (OS) of patients with advanced NSCLC after failure of ≥ 1 chemotherapy regimen and in the maintenance setting post induction with a platinum doublet.1,2

- The RADIANT trial was designed to evaluate the efficacy of adjuvant erlotinib in patients with resected stage IB to IIIA NSCLC. The primary endpoint was disease-free survival (DFS). Exploratory analysis of earlier studies found that high EGFR high protein expression by IHC or gene amplification detected by FISH predicted improved outcomes to erlotinib and, thus, enrollment to RADIANT was limited to these patients.3

- After enrollment began in September 2006, scientific and clinical data revealed that patients who harbour EGFR Del19 or L858R mutations (EGFR M+) confer sensitivity to EGFR TKIs and derive the greatest improved clinical benefit.4 Erlotinib significantly improved progression free survival (PFS) compared with first-line chemotherapy in patients with advanced EGFR M+ NSCLC.5

- The secondary endpoints of RADIANT were then later amended to DFS and OS in patients with EGFR M+ NSCLC.

- Limited data of EGFR TKIs in resected EGFR M+ NSCLC patients exist (BR19, included 15 patients with EGFR M+ treated with adjuvant gefitinib, also an EGFR TKI).6

New data:

- RADIANT was a randomized phase III trial of two years of erlotinib versus placebo in completely resected stage IB-IIIA NSCLC.7 Adjuvant chemotherapy was at discretion of the treating physician.

- The primary endpoint of DFS in the intent to treat population (n=973) was not improved with the addition of erlotinib, nor was OS.

- In the subset of patients with EGFR M+ (n=161) there was a non-significant 18-month improvement in DFS at two years with erlotinib (46.4 mos versus 28.5 mos, HR: 0.61, p=NS).8 There was no significant difference in DFS at four years and OS is still maturing. Baseline characteristics of patients in this subgroup analysis had major differences with more stage IIIA patients and patients with larger tumours in the placebo arm.

Implications for practice:

There is no clinical benefit to adjuvant erlotinib after resection of stage IB-IIIA NSCLC. Although the results of adjuvant therapy with erlotinib in the subset of EGFR M+ NSCLC patients are suggestive, there remains uncertainty on the clinical benefit and it cannot be recommended until confirmatory randomized controlled trials are conducted.

Advanced NSCLC—Squamous cell carcinoma

SQUIRE

Background:

- Squamous cell carcinoma subtype of NSCLC (sq-NSCLC) accounts for 25%–30% of NSCLC. Cisplatin/gemcitabine is currently standard first-line therapy for these patients with advanced NSCLC. Advances in NSCLC with targeted therapies have been limited to adenocarcinoma subtype (adeno-NSCLC).

- The FLEX trial reported a statistically significant improvement in OS with addition of cetuximab, a monoclonal antibody to EGFR, to platinum doublet in both advanced adenoc-NSCLC and sq-NSCLC. The uptake of cetuximab was limited by its modest improvement in OS of 1.2 mos (11.3 mos versus 10.1 mos, HR: 0.87, with a 5% improvement at 1 year) and its supportive study BMS099 showed no significant improvement in OS.9,10

- Subgroup analysis of FLEX revealed that sq-NSCLC patients and those patients who had an EGFR H-score of >200 derived the greatest benefit from cetuximab.

- Necitumumab is a humanized monoclonal antibody to EGFR.

- INSPIRE was a randomized phase III trial of necitumumab with cisplatin/pemetrexed versus cisplatin/pemetrexed alone in advanced non-squamous NSCLC, enrolment in this study was halted due to increased risk of thromboembolic events (TE) and sudden death.11

New data:

- SQUIRE is a phase III trial of gemcitabine/cisplatin +/- necitumumab, as first-line treatment of patients with advanced sq-NSCLC.12 Patients received up to six cycles of cisplatin/gemcitabine +/- necitumumab and in those patients in the necitumumab arm were continued on maintenance therapy until disease progression or unacceptable toxicity.

- This was the largest first-line clinical trial in patients with sq-NSCLC. 1,093 patients were enrolled and included patients with an ECOG 2.

- Primary endpoint of OS was improved with the addition of necitumumab to cisplatin/gemcitabine (median OS of 11.5 mos versus 9.9 mos, HR: 0.84, p=0.012 and a 5% improvement at 1 year).

- Progression free survival (PFS), although significant was marginally improved (5.7 mos versus 5.5 mos, HR: 0.85, p=0.02), with no difference in overall response rates (ORR).

- No biomarker was found. EGFR H-score was not predictive of improved outcomes.

- The rate of grade ≥ 3 arterial and venous TE was 8.9% versus 4.6% in the necitumumab and control arms, respectively and the rate of fatal TE was low and no different between the study arms. Toxicity profile was as expected for an anti-EGFR antibody, with less infusion reactions than reported with cetuximab.

Implications for practice:

Necitumumab is a new targeted treatment for sq-NSCLC. However, the improvement of OS when added to standard chemotherapy is modest (1.6 month absolute difference), which questions its clinical significance. The results are comparable to FLEX with cetuximab, although necitumumab may have increased uptake, as the clinical benefit is in the sq-NSCLC population where there are limited therapeutic options. In Canada, the use of necitumumab will also depend on its cost effectiveness.
Implications for practice:
Although this study met its primary endpoint, the addition of ramucirumab to docetaxel had a modest improvement in survival. The observed >20% response rate is almost double than expected with current approved second line therapies. Quality of life will strengthen these data and will be presented at a later meeting.

Advanced NSCLC—EGFR mutation positive
Pooled survival data with Afatinib

Background:
- Presence of EGFR activating mutations (M+) defines a distinct subtype of NSCLC, sensitive to EGFR TKIs. Exon 19 deletion (Del19) and missense mutation in exon 21 (L858R) account for 90% of EGFR activating mutations.18
- Standard of care for advanced EGFR M+ NSCLC patients is a first line EGFR TKI. Multiple randomized controlled trials have reported improved PFS and OS with upfront EGFR TKI with gefitinib or erlotinib in EGFR M+ patients compared to standard chemotherapy.25-26 However, among these trials, no difference in OS has been reported, most likely due to the high proportion of crossover from chemotherapy to EGFR TKIs after study completion (65%-95% crossover rates). The median OS reported in these trials ranges from 18.6 to 39 months, which is much longer than historical controls of chemotherapy trials (median OS of 8–10 months).2524
- LUX-Lung 3 and LUX-Lung 6 were two randomized controlled trials comparing second generation EGFR TKI afatinib to either cisplatin/pemetrexed or cisplatin/gemcitabine. Similar to first generation EGFR TKI trials, afatinib reported improved in PFS and ORR compared to chemotherapy, but no improvement in OS.25-26
- The preliminary analysis of OS in both studies included patients with rare EGFR activating mutations including exon 20 insertions and T790M mutations that are associated with resistance to EGFR TKIs.27

New data:
- A pooled analysis of LUX-Lung 3 and LUX-Lung 6 for OS was conducted and included only those patients with either Del19 and L858R EGFR mutations.28
- Patients treated with afatinib had a significant improvement in OS compared to chemotherapy (median OS of 27.3 mos versus 24.3 mos, HR: 0.81, p=0.037).
- The survival advantage was driven mainly by patients with Del19 mutation with an 11-month improvement in median OS with afatinib (31.7 mos versus 20.7 mos, HR 0.59, p=0.0001). There was no difference in OS in patients with L858R mutation.
- Rate of crossover was comparable in both LUX-Lung 3 and 6 compared to first generation EGFR TKI trials.

Implication for practice:
- This pooled analysis is the first study to show an improvement in OS in patients with advanced EGFR M+ NSCLC treated with an upfront EGFR TKI, which provides ongoing support that standard of care for these patients is a first-line EGFR TKI.
- The median OS seen in this pooled analysis was comparable to first generation EGFR TKI trials and an OS benefit may have been detected due to the large number of patients. The individual trials of both LUX-Lung 3 and LUX-Lung 6 the median OS of patients with common mutations was not statistically improved with afatinib although there was a trend in favour of afatinib similar to first generation EGFR TKI trials.
- As there is no direct comparison of afatinib to first generation EGFR TKIs, one EGFR TKI cannot be recommended over another, although afatinib may be the treatment of choice in those patients with Del19, although this needs to be balanced with the toxicity profile. More insight on this will be obtained from LUX-Lung 7, a head-to-head trial of gefitinib vs afatinib, which has recently completed enrolment.

New therapies—Immune checkpoint blockade
KEYNOTE-001

Background:
- Programmed death-1 (PD-1) is an immune checkpoint receptor expressed by activated T-cells, which downregulates T-cell activation upon interaction with its ligands PD-L1 and PD-L2. Tumour expression of PD-L1 can engage PD-1 of activated T-cells suppressing the immune response and protecting the tumour from T-cell attack.
- Data were presented from phase I trials of two anti PD-1 antibodies pembrolizumab and nivolumab in treatment-naïve and previously treated patients with advanced NSCLC. Also, phase I data with the anti-PD-L1 antibodies MEDI3746 and MPDL3280A in previously treated NSCLC were presented.
- KEYNOTE-001 is an ongoing phase I multi-cohort study of two doses of pembrolizumab as monotherapy in patients with advanced NSCLC. This study was selected for further discussion.29-30

New data:
- PD-L1 positivity was defined as ≥1% of tumour cells expressing PD-L1 detected by immunohistochemical staining. The rate of PD-L1 positivity in this trial was 62% of previously treated patients, and 78% of treatment-naïve patients, of which 78% were non-squamous histology and 87% were former or current smokers.
- ORR, disease control rate (DCR) and PFS with pembrolizumab according to line of therapy and PD-L1 staining are presented in Table 1.
- Responses by RECIST or immune response criteria (irRC) to pembrolizumab correlated with PD-L1 expression.
- Responses in treatment-naïve patients were durable with a median time on therapy of 218 days. 100% (11/11) of patients who responded by RECIST criteria and 90% (19/21) of patients who responded by irRC are ongoing.
- In the treatment-naïve cohort, 80% of patients experienced a drug-related adverse event (AE), usually grade 1-2 in severity. Most common AEs were fatigue (22%), pruritus (13%), hypothyroidism (9%), dermatitis acriform (7%), diarrhea (7%) and dyspnea (7%). One case of grade 3 pneumonitis led to discontinuation of drug. In previously treated patients the AE profile was similar, although 4 of 217 patients (1.8%) experienced grade 3 – 4 pneumonitis.

Implications for practice:
Pembrolizumab is well tolerated and has antitumor activity in the first-line setting in patients with advanced NSCLC who express PD-L1 and in previously treated patients. The phase I data with anti-PD-1/PD-L1 antibodies are encouraging and support these drugs as a potential new class of therapy for the treatment of advanced NSCLC. Confirmatory trials with anti-PD-1 and anti-PD-L1 inhibitors are underway, including trials in combination with targeted therapies, CTLA-4 inhibitors and in earlier stage NSCLC.

Table 1: Efficacy of pembrolizumab according to line of therapy and PD-L1 status

<table>
<thead>
<tr>
<th>Treatment Naïve PD-L1 Positive NSCLC</th>
<th>Previously Treated PD-L1 Positive NSCLC</th>
<th>Previously Treated PD-L1 Negative NSCLC</th>
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<tr>
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<tr>
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</table>

ORR, overall response rate; DCR, disease control rate; PFS, progression free survival; PD-L1, program death 1 ligand 1; NSCLC, non small cell lung cancer; irRC, immune response criteria.

REFERENCES

References are available upon request