Editorial

The continuing role of epidermal growth factor receptor tyrosine kinase inhibitors in advanced squamous cell carcinoma of the lung

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Abstract: Squamous cell carcinoma (SCC) of the lung represents about 20-30% of non-small cell lung cancers (NSCLC) and is associated with a poorer prognosis with limited treatment options. Erlotinib is an approved, standard second-line therapy in this setting, besides docetaxel. The LUX-Lung 8 study has shown superior overall survival (OS), progression-free survival (PFS), as well as disease control rates for treatment with afatinib compared to erlotinib in this head-to-head trial in patients with previously treated advanced SCC of the lung, with manageable side effect profile. This is the first and largest prospective phase III trial comparing two different tyrosine kinase inhibitors in patients with advanced SCC of the lung. Whether the results would be practice-changing remains to be seen, especially with the advent of novel immunotherapeutic agents such as nivolumab, which is recently approved for advanced lung SCC.

Keywords: Non-small cell lung cancer (NSCLC); squamous cell cancer; epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor

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Squamous cell carcinoma (SCC) is the second most common histology in non-small cell lung cancer (NSCLC), and account for 20-30% of NSCLC (1). Compared to advanced lung adenocarcinoma for which targeted therapeutics are available for those harbouring actionable mutations, including epidermal growth factor receptor (EGFR) mutations and ALK-rearrangement, treatment options for advanced lung SCC beyond first-line remain limited. Erlotinib and docetaxel were the only standard second-line treatment options for lung SCC (erlotinib being the only EGFR TKI approved for this setting), until the recent approval of ramucirumab (in combination with docetaxel) for NSCLC (2), and the PD-1 checkpoint inhibitor nivolumab (3).

Although EGFR mutations are rare (<5%) in lung SCC (4), EGFR overexpression and gene amplification tend to be common in these cancers and may play a role in their pathobiology (5). This is supported by phase III studies showing improved overall survival (OS) with the addition of anti-EGFR monoclonal antibodies to platinum doublet chemotherapy in NSCLC—cetuximab in the FLEX study (6), and necitumumab in the SQUIRE study (7). The higher proportion of high-level EGFR expression in lung SCC may also explain why erlotinib has shown efficacy and survival benefit in unselected non-small-cell lung carcinoma including SCC in the BR.21 trial (8,9).

Compared to erlotinib (a reversible EGFR TKI), afatinib is a second-generation EGFR TKI that is an oral, irreversible inhibitor of the ErbB family, blocking signalling from EGFR (ErbB1), HER2 (ErbB2) and HER4 (ErbB4). It has improved progression-free survival (PFS) compared to standard first-line platinum-based doublet chemotherapy in the two phase III LUX-Lung 3 and 6 studies for EGFR mutant NSCLC (10,11). LUX-Lung 8 is the largest phase III trial for second-line treatment of lung SCC comparing two established EGFR TKIs, afatinib and erlotinib, based on the hypothesis that afatinib would be superior to erlotinib in pre-treated lung SCC, due to its broader mechanism of action and favourable activity seen for squamous histology cancers (12).

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In LUX-Lung 8, Dr. Soria and colleagues looked at patients with pre-treated stage IIIB or IV lung SCC who had failed previous platinum-based chemotherapy, stratified by ethnic origin (eastern Asian *vs.* non-eastern Asian), and randomised to receive oral afatinib (40 mg per day) or erlotinib (150 mg per day), until disease progression (12). The patients were not pre-selected for presence of EGFR mutational status at baseline, as testing for EGFR is not standard practice for lung squamous cell cancers. The primary objective was PFS assessed by independent central review for intention-to-treat population, and the key secondary study endpoint being OS. The toxicity profiles were similar in each group (57% of at least grade 3 adverse events); most common adverse events were diarrhoea, rash or acne, fatigue, and stomatitis for afatinib; and rash or acne, diarrhoea, fatigue, and pruritus for erlotinib. There were more grade 3 diarrhoea and stomatitis for afatinib compared to erlotinib which caused more significant rash and acne than afatinib. Notably, there were fatal events from both groups: six treatment-related deaths from afatinib group *vs.* five cases from erlotinib group; causes include interstitial lung disease, pneumonia, pneumonitis, and acute renal failure.

This study had met its primary and secondary end-points. After a median follow-up period of 18.4 months at primary analysis of OS, treatment with afatinib demonstrated significantly longer PFS over erlotinib (median PFS 2.6 *vs.* 1.9 months, HR 0.81, P=0.0103); as well as longer OS (median OS 7.9 months for afatinib *vs.* 6.8 months for erlotinib, HR 0.81, P=0.0077). The effect of afatinib on OS was consistent across all the subgroups, but noted to be most significant and favourable for patients of Eastern Asian ethnicity. Afatinib also resulted in better disease control rate and objective response rate (ORR), as well as improved patient-reported outcomes and disease-related symptoms compared to erlotinib. A similar proportion of patients in both treatment groups went on to receive at least one line of subsequent treatment, docetaxel being the most common post-progression treatment, suggesting that the improvement in survival with afatinib was not due to difference in post-progression treatment.

Does the LUX-Lung 8 study establish EGFR TKI as standard second line therapy for patients with SCC of the lung? The use of erlotinib is still not widely practised for SCC in many institutions. Studies like TAILOR by Garassino *et al.* and DELTA by Kawaguchi *et al.* have not shown superiority of EGFR TKIs over chemotherapy in treatment of advanced NSCLC (unselected and EGFR wildtype) (13,14). In fact, docetaxel was more effective than erlotinib for EGFR wild type NSCLC in the TAILOR study, with slight improved PFS (2.9 *vs.* 2.4 months, HR 0.71, P=0.02); and median OS was 8.2 months for docetaxel *vs.* 5.4 months for erlotinib (HR 0.73, P=0.05). So perhaps it may have been preferable to compare using docetaxel as the control arm, instead of erlotinib. It is therefore uncertain whether the 1.1 month difference in OS in this head-to-head comparison of afatinib *vs.* erlotinib is clinically relevant and would translate into routine clinical practice.

Moreover, the advent of immunotherapeutic agents may possibly soften the appeal for TKIs. In the CheckMate 017 study, which led to the approval of nivolumab in advanced or metastatic squamous cell lung cancer by the FDA in March 2015, nivolumab demonstrated improved ORR, PFS and OS benefit (median OS 9.2 months) over docetaxel (median OS 6.0 months), with 41% lower risk of death with nivolumab than with docetaxel (3). However, there remain several unanswered questions on the use of immune checkpoint inhibitors, including the lack of a robust predictive biomarker, and uncertainty regarding the ideal schedule and duration of therapy (15).

Survival outcomes in patients with advanced SCC of the lung have largely plateaued in the last decade, in part due to the inability to identify actionable mutations that translate to new drug development. Recent data suggest that a detailed understanding of the possible targets in lung SCCs may identify targeted therapeutic approaches. The study on comprehensive genomic characterisation of lung SCC by The Cancer Genome Atlas (TCCA) Research Network has revealed the complex genomic landscape of lung SCC, with a higher mean somatic mutation rate [8.1 mutations per megabase (Mb)] than observed in other tumours including for acute myelogenous leukaemia (0.56 per Mb), breast carcinoma (1.0 per Mb) and colorectal carcinoma (3.2 per Mb) (16). A mean of 360 exonic mutations, 165 genomic rearrangements, and 323 segments of copy number alteration per tumour is found in lung SCC; and significantly altered pathways included NFE2L2 and KEAP1 (34%), squamous differentiation genes (44%), phosphatidylinositol-3-OH kinase pathway genes (47%), and CDKN2A and RB1 (72%) of the 178 advanced untreated lung SCC profiled in the same study (16). The several molecular alterations found in lung SCC can be classified by their respective therapeutic targets: those involving the membrane receptors (e.g., FGFR1, MET, ERBB2/Her2); the signalling pathways (EML4-ALK, PIK3CA, PTEN, BRAF); and the transcription factors

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(p53, SOX2) (17). Of these, agents that target FGFR1 and MET amplification appear promising, with several orally available FGFR1 TKIs (BGJ398, AZD4547, TKI258, and E-3810) as well as MET inhibitors (crizotinib, XL 184, MetMAb, and ARQ 197), being developed and investigated in clinical trials. Whether the discovery of all these potential therapeutic targets in lung SCC will translate into corresponding therapeutic success in clinical practice is yet to be established, but it certainly highlights the increasing importance of molecular testing in patients with lung SCC.

In summary, EGFR TKI will continue to play an important but limited role in the treatment of patients with advanced and metastatic SCC of the lung, in part due to its ease of oral administration and acceptable toxicity profile. There is a need to develop predictive and specific molecular biomarkers that might identify subgroups of patients with SCC of the lung that are most likely to benefit from EGFR TKI treatment. Finally, as more treatment options become available for patients, what would be most important is to tailor the various therapeutic options to the patient's own preferences, tolerability, as well as affordability, especially in the era of rising healthcare costs and longer lifespan of patients with advanced lung cancers.

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Footnote

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