Editorial

Afatinib in the treatment of squamous non-small cell lung cancer: a new frontier or an old mistake?

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Abstract: Lung squamous cell carcinoma represents approximately 20% of all non-small cell lung cancer (NSCLC) and is associated with a very poor prognosis. In the randomized phase III LUX-Lung 8 trial afatinib showed a statistical significant efficacy advantage compared to erlotinib as second-line treatment of advanced/metastatic squamous NSCLC. Despite its well-built design and the statistical significant results, in our opinion the study is still far from being clinically relevant for this subset of patients. Moreover, during the last years other drugs have shown encouraging activity with low toxicity in pretreated lung squamous cell carcinomas. In particular, nivolumab in the treatment of platinum-pretreated squamous NSCLC has recently radically changed the treatment paradigms in this histology. Sure, LUX-Lung 8 trial achieved its primary endpoint progression-free survival showing some afatinib activity in one of the most difficult-to treat and genetically complex neoplasm but we haven't found the most active drug in this subset of patients yet. The purpose of this editorial is to discuss some of the most controversial aspects of the LUX-Lung 8 trial focusing especially on its rational and design.

Keywords: Afatinib; squamous histology; non-small cell lung cancer (NSCLC); LUX-Lung 8; erlotinib

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Lung squamous cell carcinoma represents approximately 20% of all non-small cell lung cancer (NSCLC) cases (1). It is associated with a very poor prognosis, with less than 5% of patients alive after 5 years (1). In non-squamous NSCLC the discovery of driver oncogenes, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations, has radically changed the treatment paradigm and patients' clinical outcome (2,3). In 2004, three groups at the same time, discovered the presence of EGFR activating mutations in those patients who dramatically responded to EGFR tyrosine kinase inhibitors (TKIs). Since then, several randomized trials unequivocally established the superiority of TKIs versus chemotherapy in EGFR mutated patients (2,3). EGFR mutations are present in approximately 10–15% of NSCLCs, but they are sporadic in squamous histology. For this reason EGFR molecular testing is not routinely done in the clinical practice for this patient subgroup (4).

Afatinib is a second generation TKI that irreversibly inhibits ErbB family tyrosine kinase receptors.

At present, it is approved by the Food and Drugs Administration (FDA) for the first line treatment of advanced/metastatic EGFR mutated NSCLC (2). Some preclinical data suggest that the lung squamous cell carcinoma pathobiology has a strong dependency from the ErbB family pathway. HER2 and HER3 are overexpressed in 20–30% of squamous cell carcinomas and they present genetic aberrations in almost 3% and 4% respectively. Furthermore several genetic alterations are present in various signaling molecules depending by the ErbB receptors (NF1 11%, KRAS 3%, HRAS 3%, RASA1 4% and BRAF 4%) (5,6). In these, the rationale relies. The LUX-Lung 8 study (7) authors postulated that afatinib, inactivating multiple ErbB dependent signaling pathways, was

a promising candidate to the treatment of squamous NSCLC independently by EGFR mutational status. Nevertheless frequently in the past the evidence of a pre-clinical or phase I clinical drug activity revealed a failure in more advanced study phases. So in our opinion few early positive results, are not sufficient to jump-start a phase III trial.

The LUX-Lung 8 study (7) is a large multi-national, phase III trial, specifically designed in a population where EGFR mutations are almost absent. The study randomized 795 advanced stage squamous NSCLCs who had progressed after a platinum based chemotherapy, to receive either afatinib or erlotinib. Results are positive from the statistical point of view, reporting an advantage both in the primary endpoint progression free survival (PFS) and in the secondary endpoint overall survival (OS), less than 1 month and 1.1 months, respectively. It is also reported a modest improvement in terms of disease control rate (DCR), disease-related symptoms control and patient-reported outcome. A detailed analysis, reveals a well-built design of the study. The large sample size and the centralized analysis are both important quality guarantees. Finally, the programmed bio-molecular analysis, even if still partially published, is certainly another strength of this study. However, the comparison between the toxicity profile of afatinib and erlotinib does not seem so favorable for afatinib. If we consider grade 3–4 adverse events there is a difference ranging from 16% for erlotinib and 25% for afatinib. Looking in more depth into the results, we can also observe that the diarrhea is almost doubled in the afatinib arm (69% *vs*. 33%) and that patients having a grade 3–4 diarrhea are fourfold in the afatinib (10%) than in the erlotinib arm (2,5%). We highlight that a grade 3 diarrhea requires hydration and grade 4 is life threatening. This means that 1 out of 10 patients require at least parenteral support.

At the time LUX-Lung 8 trial (7) was conceived, in squamous lung carcinoma limited therapeutic options existed, especially for patients progressed after first-line platinum based chemotherapy. Historically docetaxel became the gold standard second line therapy (3,8) and in 2005 also erlotinib was approved by FDA for second and third line therapy in all NSCLCs independently by EGFR mutational status (9). In 2012, when the first patient was enrolled into the trials, the two therapeutic options were considered equivalent in this setting, without any significant interaction between treatment and histology (9). The available literature data from three distinct studies (9-11) and the similar route of administration were the reasons given by the investigators to justify the choice of erlotinib as comparator arm. Some comments on these topics are needed.

In the meta-analysis by Li *et al.* (10) EGFR TKIs showed better tolerability and comparable OS in second line therapy compared to chemotherapy both in unselected and EGFR wild-type NSCLC patients. But really, according to the results of the same meta-analysis, chemotherapy compared with EGFR TKIs significantly prolongs PFS in EGFR wild type patients. Moreover, even in EGFR mutated patients, EGFR TKIs reported significant differences only in PFS and not in OS. Failure in detection of differences in OS between the two groups could be justified from cross-over as well as from other confounding factors.

In the discussion of LUX-Lung 8 study, authors affirm that in the subgroup analysis of the phase III BR.21 trial (9) erlotinib improves PFS and OS in patients with squamous NSCLC with results similar to docetaxel. They also underline that in the TAILOR trial (11) there is not a statistically significant difference in terms of OS between docetaxel and erlotinib in patients with squamous histology (HR 0.9, 95% CI: 0.49–1.65). Nevertheless in the BR.21 subgroup analysis erlotinib was compared to placebo, so the relevance of OS and PFS advantage is questionable. Then, the reported equivalence with docetaxel efficacy, derives from an indirect comparison between the BR.21 and Shepherd *et al.* trial data (12). Finally, the TAILOR study (11) clearly suggests that second-line docetaxel is superior to erlotinib in all patients with EGFR wild-type NSCLC, this trend is present also in patients with squamous histology and the lack of statistical significance is probably due to the small patients sample size and to the worse performance of docetaxel in squamous NSCLC than in adenocarcinoma. Finally, no interaction was found assessing a differential effect either for docetaxel or erlotinib for histology.

As regards the same oral route of administration, certainly this could be an additional parameter in terms of results quality and comparability but, in this context, it is evident the lack of a double-blind design. We think that it would have been possible and easily achievable and it would have been another warranty of impartial judgment and data reliability for the trial. Moreover, a double-blind design would have guaranteed a greater reliability on quality of life data.

The LUX-Lung 8 selected population and the exclusion of docetaxel as comparator arm are other hotspots. Patients with lung squamous cell carcinoma represent about one fourth of all lung cancers, so although this histology is diminishing, placing afatinib in this niche covers an

important unmet need. Erlotinib is the only already approved TKI for the second line therapy in squamous cell lung cancer, but this trial could be the springboard for afatinib approval by the FDA and by European Medicines Agency (EMA) in this setting. However today, in clinical practice, TKIs are not the first therapeutic choice after failure of first line therapy in squamous cell lung cancer. Unless an oral therapy is a specific patient request or there are contraindications to chemotherapy, the oncologists commonly use second line chemotherapy in these patients. So it would have been interesting to have a third chemotherapy arm in the study, for example a docetaxel treatment group. Moreover EGFR wild type squamous cell carcinoma patients are not certainly the most helpful population to be selected for such comparison. It is just well known the significant advantage of TKIs compared to chemotherapy in patients with EGFR mutated non squamous NSCLC. Therefore, a direct comparison between the three currently used inhibitors (gefitinib, erlotinib and afatinib) would have been much more helpful in this subset. In our opinion, data deriving from the ongoing phase II LUX-Lung 7 study (13), that compares afatinib versus gefitinib in EGFR mutated advanced adenocarcinoma, will be more interesting and of greater clinical importance.

Despite all these considerations, we have to highlight the relevance of the declared study purpose: to respond to the need of effective treatments for patients with advanced lung squamous cell carcinoma. Unfortunately, although the statistical significant results, we think that LUX-Lung 8 (7) is still far from the identification of a drug able to achieve this aim. The median PFS or OS remain globally, in both treatment groups, unsatisfactory: there is an advantage of just a month or a little over a month, at the cost of significant grade 3 or greater scale world health organization (WHO) toxicities with both TKIs.

Finally, over the last two years other drugs have shown encouraging activity in pretreated lung squamous cell carcinoma. Particularly, two distinct phase III trials, REVEL (14) and CheckMate-017 (15), have led to the ramucirumab and nivolumab FDA approval in platinum-pretreated NSCLC patients, the first both in squamous and non-squamous histology. The angiogenesis is one of the hallmarks of cancer. Formation and proliferation of blood vessels are inhibited by blockade of vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) signaling. Ramucirumab, a fully human IgG1 monoclonal antibody directed against the extracellular domain of VEGFR-2, binding to the receptor, prevents the interaction with all VEGF ligands and inhibits receptor activation (16). The phase III trial REVEL (14) compared the combination of docetaxel plus ramucirumab versus docetaxel alone, in patients with squamous and non-squamous platinum-pretreated NSCLC, showing a statistically significant even if modest improvement in OS (HR 0.86, 95% CI: 0.75–0.98; P=0.02) in the combination group. This improvement was maintained both for squamous and non-squamous histology. However the addition of ramucirumab to docetaxel was associated with a significant increase in toxicity. Much more relevant is the current clinical impact of immunotherapy (17). Newly developed immune checkpoint inhibitors, targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD1) receptor and programmed cell death 1 ligand (PD- L1) are changing current treatment paradigms in all NSCLCs, especially in squamous histology (15,17). Nivolumab, a human IgG4 anti-PD-1 monoclonal antibody, blocks PD-1 receptor on activated T cells causing an increase in the immune-mediate antitumor response. Recently, in the Check-Mate 017 study (15) nivolumab showed a significant advantage in OS compared to docetaxel in squamous NSCLC second line therapy, being able to reduce the risk of death by 41%, to extend the median OS of 3.2 months and to nearly double the survival rate at 1 year. In this study the early separation of the Kaplan-Meier curves suggests that the advantage given by nivolumab is evident from the first weeks of treatment. The benefit in OS (primary endpoint) is reinforced by the results of all the secondary efficacy endpoints (38% reduction in the risk of progression and an almost doubled response rate, with many long responses in the nivolumab group). As regard the safety profile, nivolumab showed to be significantly less toxic than docetaxel: in nivolumab group only 7% of patients had grade 3 or 4 events and no grade 5 event was recorded; in the docetaxel group, 86% patients had events of any grade, 55% had grade 3 or 4 events, and 2% had an event of grade 5. Typical immunological adverse events, including immune-mediated pneumonia, were generally rare. According with these data in March 2015, FDA granted the fast track designation for nivolumab in the treatment of platinum-pretreated squamous NSCLC.

By an indirect comparison between Check Mate 017 (15) and LUX-Lung 8 (7), considering the poor prognosis of lung squamous carcinoma after first line therapy, OS (primary end point of Check Mate 017) rather than PFS (primary endpoint of LUX-Lung 8) is the best parameter to assess the treatment value. Moreover docetaxel seems to us

a more valid comparator than erlotinib and the lower rate of grade 3 and 4 adverse events reported with nivolumab than afatinib is clinically encouraging. The preliminary data obtained with other immunological agents such as pembrolizumab and atezolizumab are moving in the same direction and other phase II and III trials, that could change the current therapeutic scenario, are ongoing (17). So is the era of targeted therapies in squamous NSCLC ended with immunotherapy? The answer is certainly no. In fact, LUX-Lung 8 (7) study provided *in vivo* the rationale that targeting EGFR in squamous cell carcinoma, although in a still unclear way, could be an useful therapeutic option. The trial achieved its efficacy endpoints showing some afatinib activity in one of the most difficult-to treat and genetically complex neoplasm. Several ErbB dependent signaling pathways are implicated in squamous NSCLC pathobiology (HER2, HER3 etc.). The afatinib role on the inactivation of these pathways and its potential cytotoxic activity are very interesting issues (5,6). Just for this reason we look forward the results of LUX-Lung 8 (7) programmed bio-molecular analysis. Furthermore, a new generation of targeted therapies are coming up, targeting FGFR1, DDR2, PI3K (5,6) and many phase II trials are quickly running.

In conclusion, in our opinion, today only those who present a specific gene alteration, can obtain significant therapeutic advantages from targeted and personalized therapies such as afatinib or other TKIs. In the majority of advanced NSCLC, including squamous cell carcinoma, there is still a long way to go for TKIs category alone. According with the available data, afatinib can not be considered a standard second line treatment in squamous NSCLC. To date, although in the absence of a direct comparison in randomized trials, nivolumab should be preferred to afatinib, in terms both of efficacy and toxicity and it should be considered the new standard second line therapy in this subset. However, the unexpected activity showed by afatinib in this setting deserves more research, not excluding proper trials in combinations with other agents in the future.

Only the identification of prognostic or predictive markers of response could help oncologists in choosing the most effective treatment (TKIs versus chemotherapy versus immunotherapy).

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Footnote

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References

1. Travis WD. Pathology of lung cancer. Clin Chest Med 2011;32:669-92.
2. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst 2013;105:595-605.
3. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii27-39.
4. Dearden S, Stevens J, Wu YL, et al. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol 2013;24:2371-6.
5. Drilon A, Rekhtman N, Ladanyi M, et al. Squamous-cell carcinomas of the lung: emerging biology, controversies, and the promise of targeted therapy. Lancet Oncol 2012;13:e418-26.
6. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519-25.
7. Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase III trial. Lancet Oncol 2015;16:897-907.
8. Scagliotti GV, Novello S, Rapetti S, et al. Current state-of-the-art therapy for advanced squamous cell lung cancer. Am Soc Clin Oncol Educ Book 2013:354-8.
9. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al.

Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
10. Li N, Yang L, Ou W, et al. Meta-analysis of EGFR tyrosine kinase inhibitors compared with chemotherapy as second-line treatment in pretreated advanced non-small cell lung cancer. PLoS One 2014;9:e102777.
11. Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013;14:981-8.
12. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
13. LUX-Lung 7: a phase IIb trial of afatinib (BIBW2992) versus gefitinib for the treatment of 1st line EGFR mutation positive adenocarcinoma of the lung. ClinicalTrials.Gov ID NCIO146666O.
14. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase III trial. Lancet 2014;384:665-73.
15. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
16. Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010;28:780-7.
17. Asmar R, Rizvi NA. Immunotherapy for Advanced Lung Cancer. Cancer J 2015;21:383-91.

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