Editorial

Necitumumab for first-line treatment of advanced, squamous, non-small-cell lung cancer: a relevant step forward?

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Squamous-cell lung carcinoma accounts for approximately 30-40% of the non-small-cell lung cancer (NSCLC) cases in our setting (1). Unfortunately, most of the recent advances in the treatment of metastatic NSCLC have been confined mainly to non-squamous histology. On the one hand, drugs included in currently used combination regimens in the first line setting such as bevacizumab and pemetrexed are restricted, because of toxicity and efficacy concerns, to non-squamous tumors (2). On the other hand, the success of precision oncology initiatives is almost exclusive to lung adenocarcinomas, since driver aberrations in *EGFR/ALK/ROS-1* are rarely found in squamous-cell tumors (1,3). Comprehensive genomic profiling of lung squamous carcinomas has also revealed potentially druggable genomic alterations (*PIK3CA*, *FGFR* or *DDR2* among others) in a non-negligible fraction of these tumors, but their clinical validation as potential predictive targets is yet to be demonstrated (1,4). Therefore, having platinum-based chemotherapy as the only first-line treatment option, there is a clear need to improve treatment outcomes in these patients. In this sense, the look for new targets and therapeutic options has been challenging in lung squamous-cell subsets. Among these targets *EGFR* has been one of the main focuses in recent years. It should be noted that while *EGFR* activating mutations are extremely rare in squamous-cell histologic subtype, EGFR overexpression is a common feature of these tumors (60–80%), some of which (7–10%) also demonstrate *EGFR* gene copy number alterations (3,5). Thus, EGFR seems to be a reliable target in squamous-cell lung cancer. A number of monoclonal IgG1 antibodies targeting EGFR have undergone clinical development, of which cetuximab and necitumumab have been more exhaustively studied in lung cancer. Both drugs block the ligand-binding site of EGFR (domain III) competitively with EGF. In addition, steric interactions following antibody binding impede the adoption of the extended conformation required for receptor dimerization (6). Alternatively, these drugs could also induce antibody-dependent immune cytotoxicity. Both strategies ultimately result in EGFR down-regulation and EGFR signaling inhibition (5).

The addition of cetuximab to cisplatin and vinorelbine improved response rates (RR) (36% *vs.* 29%, P=0.01) and overall survival (OS) (primary endpoint) in histologically unselected patients in the FLEX trial (11.3 *vs.* 10.1 months, HR 0.87; P=0.044) (7). These results could not be fully validated in a second phase III trial (BMS099), where cetuximab showed no benefit in OS, progression-free survival (PFS) or RR in combination with first-line carboplatin and paclitaxel (8). A meta-analysis including individual patient efficacy data of four randomized trials (n=2,018) confirmed a 1-month improvement in OS favoring cetuximab (HR 0.88, 95% CI: 0.79–0.97, P=0.009), with statistically but doubtful clinically significant improvement in PFS (4.7 *vs.* 4.5 months, HR 0.90, P=0.045). Of note, a subgroup analysis according to histology suggested a higher benefit for patients with squamous (HR 0.77, 95% CI: 0.64–0.93) as compared to non-squamous cancers (HR 0.94, 95% CI: 0.82–1.09) (9).

With regard to necitumumab, its efficacy and safety have been assessed separately in 2 histologically-selected randomized phase III trials (10,11). Thatcher *et al*. have recently published in The *Lancet Oncology* the results of the SQUIRE (squamous NSCLC treatment with the Inhibitor of EGF receptor) trial, where necitumumab plus cisplatin and gemcitabine was compared to cisplatin and gemcitabine alone for advanced, squamous-cell lung cancer patients. The SQUIRE trial is the largest and more robust study conducted to date in patients with squamous-cell lung cancer (n=1,093). The study met its primary end-point,

showing a statistically significant benefit it terms of OS favoring necitumumab (11.5 *vs.* 9.9 months; HR 0.84, 95% CI: 0.74-0.96; P=0.012). The PFS data were also consistent and similar to those reported in the cetuximab meta-analysis (HR 0.85, 95% CI: 0.74-0.98; P=0.02). This therapeutic benefit was maintained across most study subgroups except for those patients aged ≥70 y, although this subset was relatively small (n=205) to draw definitive conclusions (11). These results contrast with those in the in parallel conducted INSPIRE trial for the non-squamous NSCLC population, where necitumumab plus cisplatin and pemetrexed added no survival benefit over chemotherapy alone (10). With regard to toxicity, the adverse event profile of necitumumab in the SQUIRE trial resembled that of cetuximab, but remarkably less neutropenic fever (<1%) and hypersensitivity reactions (<1%) were reported (11). Thromboembolic events were pooled under adverse events of interest since clinical evidence suggests a potential additive increment in thromboembolic disease related to the combination of anti-EGFR monoclonal antibodies with chemotherapy. Actually, the incidence of fatal thromboembolic events associated with necitumumab raised major concerns in the INSPIRE trial, being one of the reasons, together with futility, leading to early trial discontinuation (10). Fortunately, while the incidence of venous thromboembolic events of any grade was slightly higher in the netitumumab arm (9%) compared to the control arm (5%), fatal events were rarely reported (<1% in both arms) (11).

Is the benefit of adding EGFR monoclonal antibodies to the fist line treatment of squamous-cell lung cancer of clinical relevance? Is it for all patients? Clinical data, together with mechanistic similarities, suggest a similar and moderate impact in efficacy outcomes for cetuximab and necitumumab. Associated toxicity is likely to adversely affect quality of life, and may somehow favor necitumumab over cetuximab. Overall, we believe that some patients, but not all, will benefit from the incremental survival gain with necitumumab, and potential pros and cons should be discussed with appropriate candidates (e.g., fit young patients). Overtly, we must admit that the lack of clearly defined predictive markers to optimize patient selection is one of the main limitations for the use of necitumumab. The utility of the most obvious potential predictive biomarker, EGFR overexpression, was first analyzed in the FLEX trial. EGFR overexpression was retrospectively assessed in prospectively collected tumor samples by means of an immunohistochemistry score on a continuous scale from 0-300 (H-score). Among patients with high EGFR expression (≥200), the median OS for those treated with chemotherapy plus cetuximab was 12 months, compared to 9.6 months for those treated with chemotherapy alone (HR 0.73, 95% CI: 0.53-0.93; P=0.011). Survival times were not different in the low expression subset (HR 0.99; P=0.9). Treatment interaction was statistically significant (P=0.044), suggesting a predictive effect of EGFR H-score for patients treated with cetuximab (12). These findings were not consistently validated in the SQUIRE trial. While there seemed to be a similar and potential treatment effect in terms of OS in those with high expression (HR 0.75, 95% CI: 0.60-0.94) compared to those with low expression (HR 0.90, 95% CI: 0.75-1.07), the test for interaction was statistically negative (P=0.24) (11). The results of the INSPIRE trial also failed to demonstrate its predictive power (10). On the other hand, the prognostic utility of EGFR H-score is also inconclusive. In the SQUIRE trial no significant prognostic association was found (P=0.67) (11) while, intriguingly, the data in the FLEX and INSPIRE studies seem to point out in opposite directions. Very high EGFR expression (≥250) seemed to be associated with poor prognosis for patients treated in the control arm in the FLEX trial (median OS 7.6 months as compared to 10.3 months for patients with <250 expression) (12). Contrary, survival was higher for patients with high EGFR expression in both arms in the INSPIRE trial (10). The most evident reason for these discrepancies regarding the predictive and/or prognostic utility of EGFR H-score is the poor robustness of the test, which limits its validity and clinical application. Alternatively, it is tempting to speculate that an imbalance in other markers potentially associated with EGFR overexpression (ex: amplification) might explain the differences between trials. High EGFR polysomy or amplification is found in approximately 7% of squamous-cell lung cancers and might be associated with treatment benefit of EGFR inhibitors (including tyrosine-kinase inhibitors or monoclonal antibodies) in these tumors (3,13), though this could not be validated in the FLEX trial (14).

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Footnote

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