

# Necitumumab: a new therapeutic option for squamous cell lung cancer?

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Squamous cell carcinoma (SqCC) accounts for 25% to 30% of all non-small lung carcinoma (NSCLC) diagnosed worldwide. Therapeutic advances for squamous cell lung carcinoma have remained stagnant. This is in stark comparison to adenocarcinoma of the lung, which has benefited from the development of therapies such as bevacizumab and pemetrexed, as well as targeted therapies for specific molecular subsets with epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements. Recent genomic characterization of SqCC by The Cancer Genome Atlas has identified mutations/amplifications in receptor tyrosine kinase pathways *PI3K*, *AKT*, and *FGFR*, which may yield potentially druggable targets for therapy in the future (1). At the present time, patients with SqCC desperately need better treatment options.

Cetuximab, a monoclonal antibody against *EGFR*, has limited activity as monotherapy in NSCLC, but has been demonstrated to improve survival when combined with platinum-based chemotherapy (2). The relatively modest survival benefit [hazard ratio (HR) =0.87], combined with the absence of predictive biomarkers has essentially limited the clinical utilization of cetuximab. It remains as the only drug in NSCLC that improved survival, but did not gain approval by the US Food and Drug Administration. In a related set of developments, the use of *EGFR* inhibitors in NSCLC has increasingly been confined to patients with an activating mutation. For all of these reasons, the results of the recently reported phase III study with necitumumab, a humanized IgG1 monoclonal antibody against the *EGFR*, assume significance.

Dr. Thatcher and colleagues presented the results of the SQUIRE trial at the annual meeting of the American

Society of Clinical Oncology (ASCO) this year. This is the largest study to date for patients with SqCC of the lung (3). A total of 1,093 patients with metastatic SqCC of the lung were randomized to treatment with gemcitabine/cisplatin combination given with or without necitumumab 800 mg intravenously on days 1 and 8 of a 21-day cycle. Patients could receive up to six cycles of combination therapy and then continue on maintenance necitumumab if they achieved clinical benefit. The primary endpoint was overall survival (OS), with a pre-planned exploratory endpoint of the use of *EGFR* protein expression as measured by H-score as a predictive biomarker.

The study population consisted of over 90% smokers, with a higher representation of men and Caucasians. Over half of the patients had more than two sites of metastatic disease. Overall there was good treatment exposure, with a median of six cycles of gemcitabine/cisplatin administered in the necitumumab arm compared to five in the chemotherapy alone arm; 51% patients received continuation maintenance therapy with necitumumab, for a median of 4 (range, 1-41) cycles. The study achieved its primary endpoint and demonstrated a statistically significant improvement in overall survival with the addition of necitumumab to chemotherapy (11.5 vs. 9.9 months; HR =0.84; 95% CI, 0.74-0.96; P=0.012). The PFS differences reached statistical significance despite a relatively small numerical difference at the median (5.7 vs. 5.5 m; HR =0.85; 95% CI, 0.74-0.98; P=0.020). However, the addition of necitumumab did not improve the response rate (28.8% gemcitabine/cisplatin vs. 31.2% necitumumab; P=0.4). Combination therapy with necitumumab was generally well tolerated, with an increase in the incidence of grade 3/4 rash (7.1% vs. 0.4%), hypomagnesemia

(9.3% *vs.* 1.1%), and venous thromboembolic events (5% *vs.* 2.6%), which have been previously reported with EGFR antagonists.

In a post-hoc analysis of the FLEX trial, only patients with increased EGFR expression, defined as H-score of 200 or greater, derived a survival benefit with the addition of cetuximab (4). It was anticipated that the H-score might help select patients for therapy with necitumumab, given the close mechanistic similarity between the two agents. However, the SQUIRE failed to demonstrate a consistent association between H-score and OS and PFS. This calls into question the utility of the H-score as a biomarker for EGFR blockade in lung cancer.

In contrast with the results of the SQUIRE study, another randomized study of necitumumab in combination with cisplatin and pemetrexed for patients with non-squamous histology failed to demonstrate an improvement in survival over chemotherapy alone (5). The Independent Data and Safety Monitoring Committee closed the study prematurely due to an excess of thromboembolic events in the necitumumab arm. A slightly higher incidence of thromboembolic events was also noted on the experimental arm of the SQUIRE study. In the past, it was widely assumed that the efficacy of targeted agents with one chemotherapy was sufficient for its use with others. However, given that the toxicity was higher when necitumumab was combined with pemetrexed, it will be important to evaluate combinations with taxanes in prospective clinical trials.

While the positive results of the SQUIRE trial provide a new option for treatment of patients with squamous cell NSCLC, it has also prompted a healthy debate about the clinical significance of the therapeutic benefit with necitumumab. A statistically significant hazard ratio of 0.84 for overall survival observed with necitumumab is not much different from the extent of benefit based on which other oncology drugs have been approved and adopted for use. However, the rising costs of healthcare in the United States, and in other countries, have brought about a greater focus on financial burden associated with cancer therapies.

We view the ability to improve survival of patients with SqCC with necitumumab as a positive step forward. The treatment of squamous cell cancer based on genomic background of tumors is still at a rudimentary phase. Until those efforts come to fruition, even modest benefits in this patient population are not to be taken lightly. It is our opinion that further research conducted on the potential cost-benefit ratio of necitumumab, effect on symptoms

and quality of life, and biomarker discovery will provide more clarity about the role of this agent in the routine care of patients with squamous cell histology. We can also put an end to further evaluation of EGFR expression as a predictive marker for EGFR monoclonal antibodies in NSCLC.

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