Editorial

Time to give a rest to cetuximab in the treatment of advanced non-small cell lung carcinoma?

Elisabeth Quoix[1], Virginie Westeel[2]

[1]Department of Pneumology, Nouvel Hôpital Civil, University Hospital, Strasbourg, France; [2]Department of Pneumology, University Hospital Jean Minjoz, INSERM UMR 1098, Université de Bourgogne Franche Comté, Besançon, France

Correspondence to: Elisabeth Quoix. Department of Pneumology, Nouvel Hôpital Civil, University Hospital, 1 Place de l'Hôpital, 67091 Strasbourg, France. Email: elisabeth.quoix@chru-strasbourg.fr; Virginie Westeel. Department of Pneumology, University Hospital Jean Minjoz, 3 Boulevard Alexandre Fleming, 25000 Besançon, France. Email: virginie.westeel@univ-fcomte.fr.

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Chemotherapy with a platinum-based doublet has long been the cornerstone of the treatment for advanced non-small cell lung carcinoma (NSCLC) (1). Since the early 2000s, several driver gene mutations and translocations have been discovered, giving rise to the possibilities of targeted therapies (2-4). Epidermal growth factor receptor (EGFR) which is expressed in about 85% of NSCLC, is the first largely studied of a now longer list of therapeutic targets (5). EGFR is a member of the ERbB transmembrane tyrosine kinase receptors. Activation of its extracellular part by its ligands (EGF and transforming growth factor alpha) results in a dimerization of the receptor, and as a consequence an activation of the intracellular tyrosine kinase, with a cascade of events leading to cell proliferation, invasion, metastasis development and angiogenesis (5). EGFR blockade, either its extracellular part by monoclonal antibodies or its intracellular part by tyrosine kinase inhibitors (TKI) has been investigated. With the discovery of *EGFR* activating mutations, we entered a new era in the treatment of NSCLC. First- and second-generation EGFR TKIs have dramatically improved outcomes in EGFR mutated NSCLC, with median survival times (MST) as high as 28 months (6) compared to 8–12 months with chemotherapy (7,8). Monoclonal antibodies, the most investigated in the treatment of NSCLC being cetuximab and necitumumab, not only block the signal by binding to the extracellular domain of EGFR, but also exert immunological effects through antibody-dependent cellular cytotoxicity, which might generate interest with the actual development of immuno-oncology (5). Cetuximab is a chimeric human-murine monoclonal IgG1 antibody.

In January 2018, Herbst *et al.* (9) published in the *Lancet Oncology*, the third phase III trial devoted to cetuximab in metastatic NSCLC. A total of 1,313 patients received carboplatin-paclitaxel (and bevacizumab for eligible patients), with or without cetuximab. Randomisation was stratified on smoking status (current or ever smoker *vs.* never smoker), bevacizumab use (yes or no) and the stage of the disease (M1a *vs.* M1b). Progression-free survival (PFS) in the *EGFR*-fluorescence in situ hybridization (FISH) positive population and overall survival (OS) in the entire study population, were the two co-primary objectives. The study was negative for both co-primary endpoints, with superimposable PFS curves in *EGFR*-FISH positive patients (HR 0.92; 95% CI, 0.75–1.12, P=0.40) and OS curves in the whole population (HR 0.93; 95% CI, 0.83–1.04, P=0.22). *EGFR*-FISH status was available in 76% of patients in the control group and in 73% in the cetuximab group. *EGFR*-FISH was positive in 31% and 30% of the tested specimens, respectively, which was lower than expected. This high proportion of unknown *EGFR* FISH status and this low *EGFR* FISH positivity rate cannot explain the negative

results of the trial, the protocol having been amended to include 400 EGFR FISH-positive patients for a maintained power of 80%.

There was no benefit either from adding cetuximab in patients treated with bevacizumab in terms of PFS, and response rate which were secondary endpoints whatever the *EGFR*-FISH expression. The only significant survival benefit in favour of cetuximab was observed in the subgroup of 101 patients with *EGFR*-FISH-positive squamous cell carcinoma (HR 0.58; 95% CI, 0.39–0.86, P=0.0071). This analysis was prespecified but only before data analysis, 11 months after the last inclusion and these positive results in a small subgroup of patients are insufficient to justify the use of cetuximab as first-line treatment for NSCLC, especially with significantly increased toxicity. The most common grade 3–4 adverse event was decreased neutrophil count (37% in the cetuximab group *vs.* 25% in the control group). As expected, acne-like rash was far more frequent in the Cetuximab group, and 6% of treatment-related deaths were reported in the cetuximab group versus 2% in the control group. Toxicity was even worse in patients receiving the four-drug carboplatin-paclitaxel-bevacizumab-cetuximab combination.

The first randomized trial which evaluated the addition of cetuximab to standard first-line chemotherapy was the FLEX study (10). A total of 1,125 patients with advanced NSCLC and EGFR expression defined as at least one stained cell by immunohistochemistry (IHC), received the cisplatin-vinorelbine combination with or without cetuximab. This trial reached its statistical endpoint with a significant benefit from the addition of cetuximab (HR 0.871; 95% CI, 0.762–0.996, P=0.044). MST was 11.3 months (95% CI, 9.4–12.4) in the cetuximab arm and 10.1 months (95% CI, 9.1–10.9) in the control group. The one-year survival rate was 47% and 42%, respectively. Response rate was significantly higher in the cetuximab arm (36% *vs.* 29%, P=0.01). PFS was 4.8 months in both arms (HR 0.943, P=0.39). In a preplanned subgroup analysis according to EGFR expression, OS was significantly longer in the cetuximab arm when the IHC score was over the not prespecified threshold of 200 (MST: 12 *vs.* 9.6 months; HR 0.73, P=0.011), whereas there was no significant difference between the two arms when the IHC score was ≤200 (11). Response rate was significantly higher in the cetuximab group, and PFS did not differ between arms, whatever the IHC score.

The second randomised phase III trial was the BMS099 study (12). The addition of cetuximab to the carboplatin and paclitaxel doublet did not improve PFS, which was the primary objective (median PFS: 4.4 months in the cetuximab arm versus 4.2 months in the chemotherapy alone arm). This study included 676 patients unselected for EGFR expression. Primary endpoint was PFS and there was no significant difference between the two arms (HR 0.902; 95% CI, 0.761–1.069; P=0.236). Response rate was higher in the cetuximab arm than in the CT only arm (27% *vs.* 17%, P=0.007). The trial was not sized for OS comparisons (HR 0.89; 95% CI, 0.754–1.051; P=0.169). Despite their methodological differences, both these trials demonstrated a consistent modest survival benefit, with a very close HR.

Two other phase III randomized trials evaluated necitumumab, another anti EGFR monoclonal antibody, in advanced NSCLC. Necitumumab is a recombinant human anti EGFR monoclonal antibody with a similar structure to cetuximab but with no murine component. The first randomized trial (INSPIRE) was devoted to non-squamous cell carcinoma and compared cisplatin-pemetrexed plus necitumumab to the same chemotherapy doublet alone without EGFR expression requirements (13). Six hundred and thirty-three patients were included. The study was negative regarding its primary endpoint with no significant difference in OS between treatment groups, (HR 1.01; 95% CI, 0.84–1.21, P=0.96). Serious adverse events were significantly more frequent in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group (51% *vs.* 41% patients).

The second trial (SQUIRE) (14) evaluated the addition of necitumumab to cisplatin-gemcitabine in squamous cell carcinoma in 1,093 patients. There was an improvement in OS in the necitumumab arm, with a HR for OS of 0.79 (95% CI, 0.69–0.92, P=0.002) and for PFS of 0.84 (95% CI, 0.72–0.97, P=0.018). In both trials there was a significant excess of grade 3 or worse adverse events especially hypomagnesaemia, rash, and thromboembolic events. In the first trial, there was also an excess of treatment-related deaths.

A meta-analysis of the randomised trials comparing chemotherapy plus cetuximab to the same chemotherapy alone was performed on the individual data of 2,018 patients and published in 2014 (15). It included 2 randomised phase 2 studies (16,17) and the 2 randomised phase 3 studies available at this time (10,12). It demonstrated that the addition of cetuximab to chemotherapy significantly improved OS (HR 0.88, P=0.009, median 10.3 *vs.* 9.4 months), PFS (HR 0.90, P=0.045, median 4.7 *vs.* 4.5 months) and response (odds ratio 1.46, P<0.001, overall response rate 32.2% *vs.* 24.4%).

However, the clinical meaningfulness of a 0.9 months improvement in OS is questionable. A systematic review of the Cochrane Library (18) showed a comparable benefit from the addition of cetuximab to standard chemotherapy (HR 0.87; 95% CI, 0.79–0.96, P=0.004).

Although there may be a benefit from targeting EGFR using monoclonal antibodies in addition to chemotherapy in the first-line treatment of advanced NSCLC, especially in squamous cell carcinoma with overexpression of EGFR (IHC or *FISH*), the magnitude of the benefit is insufficient for implementation in daily practice. According to the ESMO magnitude of benefit scale (19), the HR for OS with a consistent lower CI limit >0.65 are not considered as clinically meaningful. As a matter of fact, cetuximab was not approved neither in Europe nor in the US.

Further search for biomarkers more predictive of the effect of cetuximab might eventually lead to find some place for cetuximab in the treatment of NSCLC (20). However, survival benefits from strategies including immune checkpoint inhibitors are of such greater magnitude that, to our opinion, time for the cetuximab-chemotherapy combination is over. There is perhaps a biological rationale for the association of cetuximab with immunologic agents, which may be worth being studied.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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