Editorial

EGFR tyrosine kinase inhibitors as first-line therapy in advanced EGFR mutation-positive non-small cell lung cancer: strategies to improve clinical outcome

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The epidermal growth factor receptor (EGFR) has been established as a clinically relevant target for the treatment of patients with advanced non-small cell lung cancer (NSCLC) (1). EGFR blockade can be achieved by either monoclonal antibodies directed against the surface of the receptor or tyrosine kinase inhibitors directed against the intracellular domain of the receptor (1,2). Monoclonal antibodies such as cetuximab and necitumumab improved outcome including overall survival, particularly in patients with squamous cell NSCLC and/or high EGFR expression or EGFR fluorescence *in situ* positivity (3-7). EGFR tyrosine kinase inhibitors (TKIs) have also been established for the treatment of patients with advanced NSCLC (1). While these TKIs show efficacy in non-oncogene-driven NSCLC, they have much higher efficacy in patients who harbour EGFR mutations in their tumours. EGFR mutations occur in tumours of about 40% of Asian patients and 15% of Caucasian patients with advanced NSCLC (8). Based on the results from several randomized phase 3 trials, EGFR TKIs have been established as first-line therapy in patients with advanced EGFR mutation-positive NSCLC (1).

After a median treatment duration of 8–13 months, patients will develop resistance to EGFR TKIs and clinically progress. In approximately 50–60% of the resistant patients, resistance is due to the emergence of the T790M mutation (9). In order to improve outcome in these patients, third-generation EGFR TKIs have been developed (10). They include osimertinib, rociletinib and olmutinib. These drugs target both EGFR mutations and the T790M resistance mutation, while they spare wild-type EGFR. These properties should result in enhanced clinical efficacy at lower toxicity in comparison to first- and second-generation TKIs. Osimertinib was evaluated in phase 3 trials but the clinical development of the other two agents was halted because of insufficient efficacy or enhanced toxicity. The AURA3 phase 3 trial demonstrated the benefit of osimertinib over chemotherapy in patients with T790M-mediated resistance (11). Osimertinib improved progression-free survival compared to chemotherapy with platinum plus pemetrexed in patients who have acquired T790M-mediated resistance during treatment with EGFR TKIs. Data on overall survival were immature at the time of analysis. Based on these results, osimertinib has become the standard treatment of patients with advanced EGFR mutation-positive NSCLC who have developed T790M-mediated resistance during treatment with EGFR TKIs.

Several strategies have been investigated to improve outcome of first-line treatment with EGFR TKIs in patients with advanced EGFR mutation-positive NSCLC. These include EGFR TKIs combined with either bevacizumab or immunotherapy, and osimertinib as a third-generation EGFR TKI.

EGFR TKIs in combination with bevacizumab have been studied as first-line therapy in patients with EGFR

mutation-positive NSCLC. The rationale for combining both drugs is two-fold. Firstly, bevacizumab was shown to improve outcome when added to first-line chemotherapy in patients with advanced non-squamous cell NSCLC. Bevacizumab combined with carboplatin plus paclitaxel increased progression-free survival and overall survival, and bevacizumab added to cisplatin plus gemcitabine improved progression-free survival but did not increase overall survival compared to chemotherapy alone (12,13). Secondly, treatment with EGFR TKIs may lead to up-regulation of the expression of vascular endothelial growth factor (14,15). Both reasons led to clinical studies of EGFR TKIs plus bevacizumab in patients with advanced EGFR mutation-positive NSCLC.

The BELIEF trial was a single-arm, phase 2 trial done in 29 European countries (16). The trial evaluated oral erlotinib 150 mg per day plus intravenous bevacizumab 15 mg/kg every 21 days in 109 patients with stage IIIB or stage IV mutation-positive adenocarcinomas of the lung. The trial also tested whether outcome differs between patients with co-existing T790M mutations and those without T790M mutations. Therefore, patients were stratified according to the presence of the T790M mutation in the tumours. The primary endpoint of the trial was progression-free survival. T790M mutations were detected in 34% of the patients. Median progression-free survival was 13.2 months for the total population, 16 months for patients with co-existing T790M mutation and 10.5 months for those without T790M mutation. Median survival was 28 months but survival data were still immature at the time of analysis. Toxicity was considerable with 29% of patients experiencing a serious adverse event. Five grade 4 events (acute coronary syndrome, biliary tract infection, colon perforation, and other neoplasm) and one treatment-related death due to sepsis were observed. The authors concluded that the combined treatment benefits patients.

Japanese investigators have also evaluated erlotinib plus bevacizumab in patients with advanced EGFR mutation-positive NSCLC. In contrast to the BELIEF study, the Japanese study was a randomized phase 2 trial (17). A total of 154 patients were enrolled and randomized in a 1:1 ratio to oral erlotinib 150 mg per day plus intravenous bevacizumab 15 mg/kg every three weeks or to erlotinib alone. Treatment was continued until disease progression or unacceptable toxicity. Progression-free survival as the primary endpoint was prolonged with the combined treatment. The hazard ratio was 0.54 (95% CI, 0.36–0.79; P=0.0015) and median progression-free survival times were 16 and 9.7 months, respectively. Overall survival data were immature at the time of analysis. Serious adverse events occurred at similar rates among both groups (24% and 25%, respectively). However, grade 3 or worse adverse events were more frequently seen with erlotinib plus bevacizumab than with erlotinib (91% and 53%, respectively). Hypertension, haemorrhagic events and proteinuria were more frequent in the bevacizumab group.

The BELIEF study and the Japanese study indicated good efficacy of erlotinib plus bevacizumab in terms of progression-free survival but at the expense of increased toxicity. Based on these results, erlotinib plus bevacizumab has been approved by the European Medicines Agency (EMA) for the first-line treatment of patients with advanced EGFR mutation-positive NSCLC. However, a randomized phase 3 trial is required in order to definitively prove the clinical benefit of this combined treatment in these patients, particularly also in terms of overall survival. Until such a trial confirms the survival benefit, we believe that erlotinib plus bevacizumab can be considered as a treatment option for selected patients with advanced EGFR mutation-positive NSCLC but not as standard treatment.

EGFR TKIs in combination with immune checkpoint inhibitors have been studied as another strategy to improve outcome of first-line treatment with EGFR TKIs. Based on initial clinical trials, however, these combinations resulted in unexpected high toxicity, in particular interstitial lung disease (18). Therefore, further clinical evaluation of these combinations has been halted. In this context it should be noted that immune checkpoint inhibitors appear to have less efficacy in patients with oncogene-driven cancers than in those with non-oncogene-driven cancers. This difference in efficacy may be explained by a much higher tumour mutational burden in smoking-related cancers than in EGFR mutation-positive driven cancers. Thus, the clinical value of immune checkpoint inhibitors in patients with advanced EGFR mutation-positive NSCLC remains yet to be proven.

The most promising strategy to improve outcome of first-line treatment of patients with advanced EGFR mutation-positive NSCLC focussed on third-generation EGFR TKIs. Recently, the FLAURA trial demonstrated the superiority of osimertinib over first-generation EGFR TKIs in the first-line treatment of TKI-naive patients with advanced EGFR mutation-positive NSCLC (19). Osimertinib increased progression-free survival compared to erlotinib or gefitinib. The hazard ratio was 0.30 (95% CI, 0.23–0.41), and median progression-free survival times

were 10.1 and 4.4 months, respectively. Response rates were 71% with osimertinib and 31% with chemotherapy. Quality of life was also improved with osimertinib, in particular in terms of cough, chest pain, dyspnea, fatigue, and appetite loss. Overall survival data were not reported and are eagerly awaited.

In conclusion, adding bevacizumab to first-line treatment with EGFR TKIs in patients with advanced EGFR mutation-positive NSCLC may improve clinical outcome but, in our opinion, requires further proof of its clinical efficacy in a randomized phase 3 trial before its wide-spread use should be recommended. Combinations of EGFR TKIs with immune checkpoint inhibitors outside of clinical trials are not recommended at this time because of their increased toxicity in early clinical trials. However, osimertinib can be considered as a new standard in the first-line treatment of patients with advanced EGFR mutation-positive NSCLC.

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Footnote

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