Editorial Commentary

Erlotinib plus bevacizumab for EGFR-mutant advanced non-squamous non-small-cell lung cancer patients: ready for first-line?

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EGFR tyrosine kinase inhibitors (TKIs) represent the standard of care for first-line treatment for patients with advanced EGFR mutant non-small cell lung cancer (NSCLC) with superiority in overall response rate (ORR), progression free survival (PFS) and quality of life compared to platinum-based chemotherapy (ChT) (1).

The incidence of EGFR activating mutation varies from 10–15% for Caucasian to up to 35–50% in East Asians patients. A never or light smoking history, adenocarcinoma histology and female sex are associated with a higher mutation incidence (2,3). First-line EGFR-TKIs achieve ORR of 60–80% but ultimately all patients develop progressive disease. In almost two thirds of patients an acquired amino acid substitution at position 790 (T790M) of the EGFR exon 20 domain is the underlying mechanism of resistance conferring to reduced ATP competitive TKI-binding and loss of drug activity (4). Osimertinib, a third generation TKI, has proven to overcome T790M-induced resistance with improved PFS and ORR compared to ChT [PFS: 10.1 vs. 4.4 months, hazard ratio (HR) 0.3, P<0.001, ORR: 71% vs. 31%, odds ratio (OR) 5.39, P<0.001] (5) and has been licensed by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) in the first-line setting due to improved PFS (18.9 vs. 10.2 months, HR 0.46, P<0.001) and tolerability compared to the first-generation TKIs erlotinib and gefitinib (6).

The benefit of anti-PD-(L)1 checkpoint inhibitor (CPI) monotherapy in EGFR-mutant patients, even with tumors harboring a PD-L1 expression of ≥50%, is questionable and current licenses for the use of first-line CPI exclude patients with an EGFR sensitizing mutation or ALK gene rearrangement (7,8). At progression after EGFR-TKI treatment, prognosis is very poor and salvage ChT shows only limited benefit. Therefore, combination therapy to improve first line outcomes is an attractive option to explore.

The combination of erlotinib with bevacizumab has been investigated in two previous phase II clinical trials: BELIEF (9) and JO25567 (10). Bevacizumab, an anti-angiogenic monoclonal antibody, targets the VEGF signalling pathway and has been shown to prolong survival when combined with first-line platinum-based ChT in non-squamous NSCLC (11-13). In the BELIEF study (9), 109 patients were randomised to combination therapy vs. erlotinib alone and were excluded if they had T790M mutation at baseline. Again, PFS was longer in the...
erlotinib and bevacizumab arm (16.0 vs. 9.7 months, HR 0.54, 95% CI: 0.36–0.79; P=0.0015). Notably, the JO25567 study was not powered to assess overall survival (OS).

Contrary to these positive trials, results of a phase II randomised study evaluating erlotinib plus bevacizumab vs. erlotinib were recently published in *JAMA Oncology* (14). Eighty-eight patients were randomly assigned (1:1) to combination therapy vs. erlotinib. There was no improvement in PFS (17.9 vs. 13.5 months, HR 0.81; 95% CI: 0.50–1.31; P=0.39) or OS (32.4 vs. 50.6 months, HR 1.41; 95% CI: 0.71–2.81; P=0.33) for combination therapy and erlotinib arm, respectively. Study limitations include patient selection (85% were white), and the lack of blinded independent radiology review. OS data from this study should be interpreted with caution due to small number of events and limited access to subsequent therapies, which hindered analysis of post study therapies on OS results.

The interim analysis of NEJ026 was recently reported in *The Lancet Oncology* (15). In this phase III randomised, multicentre, open label, study across 69 centres in Japan, participants were assigned to receive erlotinib 150 mg OD with bevacizumab 15 mg/kg once every 21 days vs. erlotinib alone. Patients with asymptomatic brain metastasis were eligible for enrolment whilst patients whose tumours harboured T790M mutations at baseline or who had received previous ChT for advanced stage disease were excluded. Two hundred and twenty-eight patients were enrolled and randomly assigned. This interim analysis was performed at data cut off when 117 PFS (primary endpoint) events had occurred.

The baseline characteristics of both treatment groups were well balanced with similar incidence (32%) of brain metastasis in each treatment arm. With a median follow up of 12.4 months, median PFS was longer in the erlotinib plus bevacizumab group (16.9 vs. 13.3 months, HR 0.605, 95% CI: 0.417–0.878; P=0.016). In the post hoc subgroup analysis, erlotinib plus bevacizumab was superior in most subgroups, although this was not statistically significant. Median PFS was longer in those with Leu858Arg mutations in the combination group (17.4 vs. 13.7 months, HR 0.57, 95% CI: 0.33–0.97) however no difference was found in those with exon 19 deletions (16.6 vs. 12.4 months, HR 0.69, 95% CI: 0.41–1.16). Patients without CNS metastasis had improved PFS with combination erlotinib and bevacizumab (HR 0.56, 95% CI: 0.35–0.90) with no significant difference identified in those with CNS involvement (HR 0.78, 95% CI: 0.42–1.43).

Grade ≥3 toxicity was reported in 88% (98/112) of patients in the combination group and 46% (53/114) of patients in the erlotinib only group. The most common grade 3–4 adverse event was rash, 21% in both treatment arms, and serious adverse events occurred in 8% vs. 4% of patients enrolled in the combination group and erlotinib group, respectively. Twenty-nine percent (33/112) patients discontinued bevacizumab due to adverse events.

Study limitations include a small sample size and lack of power to assess PFS in subgroup analysis. Furthermore, the proportion of patients with ECOG PS of 0 was high (59%) as was the proportion of patients with post-operative recurrence (19%). These, combined with exclusion of patients harbouring *de novo* T790M mutation, may have led to longer PFS than reported in previous trials.

Notably, the NEJ026 trial was conducted to evaluate the impact on OS from erlotinib and bevacizumab combination as follow on from JO25567 study, yet PFS was used as primary outcome.

Results of NEJ026 (15) and sequencing of therapy does need to be considered alongside evidence from recent clinical trials including FLAURA (6), NEJ009 (16) and IMpower-150 (17). FLAURA demonstrated that first-line Osimertinib achieved a longer PFS (18.9 vs. 10.2 months, HR 0.46; 95% CI: 0.37–0.57; P<0.001) vs. erlotinib or gefitinib, regardless of baseline T790M status. Adverse events of grade 3 or higher were lower with osimertinib than standard TKI therapy (34% vs. 45%). OS (secondary endpoint) data is still immature (6). The NEJ009 evaluated combination gefitinib plus platinum doublet ChT vs. gefitinib alone demonstrating longer PFS for the combination (20.9 vs. 11.2 months, HR 0.493; 95% CI: 0.39–0.62 P<0.001) but no difference in PFS2 (16). IMpower-150 evaluated first-line carboplatin/paclitaxel/bevacizumab + atezolizumab (ABCv) vs. carboplatin/paclitaxel + bevacizumab (BCP). Patients with a sensitizing *EGFR* mutation were eligible, after TKI failure. In patients with sensitising EGFR mutations treated with ABCP (n=26) there was a longer OS (NE vs. 17.5 months, HR 0.31; 95% CI: 0.11–0.83) than patients who received BCP (n=32). Notably, in patients with EGFR sensitising mutations who previously received an EGFR-TKI (n=50), the only population to be allowed in the study as per protocol, there was a trend towards longer OS which was not statistically significant [NE vs. 17.5 months, HR 0.39 (0.14–1.07)] (17). This subgroup analysis needs to be interpreted with caution due to small sample sizes and confirmatory studies are needed.

With an increasing number of therapies being
investigated in *EGFR* mutant NSCLC the landscape of first-and later-line of therapy is becoming increasingly complex. To improve patient outcomes, it is of utmost importance to understand the mechanisms of TKI resistance such as upregulation of MET, HGF, HER2 mutations, HER3 overexpression, activation of IGF-1R or downregulation of PTEN (18). Furthermore, it is crucial to develop reliable biomarkers to early expose acquired TKI resistance.

With the caveat of cross-trial comparison, the PFS reported in NEJ026 (15) seems to be inferior to what reported in FLAURA (6) and it would be very important to see the updated OS data from FLAURA, when available. Without demonstrable OS improvement, PFS could be seen as an inadequate measure of benefit for the combination of two known active drugs. Until NEJ026 OS data is mature, we anticipate that the combination of erlotinib and bevacizumab will not be considered a standard first line option. Combination *EGFR-TKI* and bevacizumab therapy may have a role when access to osimertinib in the first line setting is limited but with increased toxicity and associated costs. Two phase II clinical trials evaluating the combination of osimertinib and bevacizumab in the 1st line setting are ongoing. The results of these studies may help shed more light on the most appropriate treatment strategies in *EGFR* mutant patients.

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**Footnote**

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