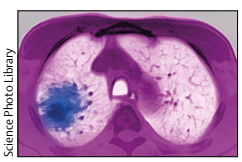
Bevacizumab in *EGFR*-positive NSCLC: time to change first-line treatment?



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The first-line treatment for patients with advanced non-small-cell lung cancer (NSCLC) with a common *EGFR* mutation is EGFR tyrosine kinase inhibitor (TKI) monotherapy. Once patients have disease progression and continuing treatment is deemed inappropriate, patients with *EGFR* Thr790Met resistance mutations are switched to osimertinib,[1] or to pemetrexed and cisplatin if osimertinib was the first-line treatment. Subsequent treatment after disease progression following second-line treatment is more complicated and should be personalised according to clinical manifestations and genomic tumour alterations. Recent clinical trials have shown that median overall survival for patients with *EGFR*-positive NSCLC ranges between 3 and 5 years.[2]

The results of recent randomised trials might alter first-line and second-line treatment options for patients with *EGFR*-positive NSCLC. The FLAURA study[3] showed that as a first-line treatment, osimertinib resulted in improved median progression-free survival compared with erlotinib monotherapy or gefitinib monotherapy (18·9 months [95% CI 15·2–21·4] *vs* 10·2 months [9·6–11·1]). Previous studies showed that dacomitinib was superior to gefitinib in terms of progression-free survival (14·7 months [95% CI 11·1–16·6] *vs* 9·2 months [9·1–11·0])[4] and overall survival (34·1 months [29·5–37·7] *vs* 26·8 months [23·7–32·1]).[5] In the NEJ009 study,[6] chemotherapy plus gefitinib was superior to gefitinib with regard to progression-free survival (20·9 months [95% CI 18·0–24·2] *vs* 11·2 months [9·0–13·4]) and overall survival (52·2 months *vs* 38·8 months). In the phase 2 JO25567 trial,[7] bevacizumab plus erlotinib prolonged progression-free survival compared with erlotinib alone. On the basis of this trial, the NEJ026 phase 3 study was done. The interim analysis by Haruhiro Saito and colleagues published in *The Lancet Oncology*,[8] suggests that bevacizumab improves progression-free survival in patients with common *EGFR* mutations when combined with erlotinib. The results of these studies increased the complexity of selecting first-line treatment for patients with *EGFR*-positive advanced stage NSCLC.

Cross-trial comparisons are not appropriate for the selection of optimum treatment for patients, but can be used as a reference before large-scale studies for such comparisons become available. Progression-free survival is affected by eligibility criteria and the characteristics of accrued patients in different studies. Additionally, treatment options after disease progression must be taken into consideration. In ARCHER 1050,[4] patients with brain metastases were excluded; in FLAURA,[3] chemotherapy was the only treatment option for patients following disease progression after treatment with osimertinib; and in NEJ009,[6] the use of platinum chemotherapy as a salvage treatment was not possible. The median progression-free survival durations of patients administered bevacizumab and erlotinib in JO25567[7] (16·0 months [95% CI 13·9–18·1]) and NEJ026[8] (16·9 months [14·2–21·0]) are promising. However, in NEJ026, patients had to fulfill criteria to use bevacizumab. The proportion of patients with an Eastern Cooperative Oncology Group performance status of 0 (around 60%) and recurrence after surgery (around 20%) were high. Furthermore, patients who had *EGFR* Thr790Met mutations detected in tissue samples were excluded.[8] These factors could have potentially contributed to longer progression-free survival than that observed in previous trials.

Comparison of the median overall survival in each trial could be used to select an optimum treatment strategy for patients with NSCLC. However, median overall survival is always confounded by subsequent treatment. A previous study[5] has suggested that irreversible EGFR TKIs might provide long-term benefit in overall survival. The negative overall survival benefit of combined treatment with bevacizumab and erlotinib versus erlotinib alone in JO25567 should be interpreted with caution, since an insufficient number of patients provided consent for follow-up.[7] Additionally, in most recent studies, overall survival estimates are not yet mature, making indirect comparisons impossible.

Chemotherapy or osimertinib is the standard second-line treatment for patients with disease progression after treatment with first-line EGFR TKIs. Programmed death receptor-1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors are the standard treatment for patients with wildtype *EGFR* lung cancer, but might not be suitable for patients with *EGFR* mutations. However,

a subgroup analysis of a phase 3 study in 64 patients with *EGFR* mutations showed improved progression-free survival and overall survival in those given bevacizumab and atezolizumab in combination with paclitaxel and carboplatin compared those treated with only paclitaxel and carboplatin.[9] These results needs to be confirmed by future randomised studies.

Bevacizumab improves the overall survival of patients with stage IV NSCLC who are treated with paclitaxel and carboplatin.[10] Although bevacizumab and chemotherapy are widely used in many cancers, the exact mechanism by which bevacizumab increases the anti-cancer effect of chemotherapy is unclear. This paucity of knowledge increases the difficulty of identifying biomarkers to select patients for bevacizumab treatment. The benefit of bevacizumab might extend to combination with osimertinib, which is currently being investigated in several trials (NCT02803203, NCT02971501, and NCT03133546).

In the NEJ026 study, *EGFR* activating mutations and Thr790Met cell-free DNA were detected in the patient's plasma,[8] and the results were provided to the researchers during the trial. This study also selected a large cohort of patients without de novo *EGFR* Th790Met mutations using sensitive detection methods. It will be interesting to assess the dynamic changes in cell-free DNA during treatment and the development of resistance in this cohort of patients.

The number of possible combinations and treatment sequences of EGFR TKIs, chemotherapy, bevacizumab, or anti-PD-1 and PD-L1 inhibitors complicate recommendations for first-line and second-line treatment in patients with NSCLC and *EGFR* mutations. At present, no biomarkers exist to enable the selection of the optimum treatment order for patients. Future studies might provide more evidence about treatment strategies.

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Fighting against the challenge of treating patients with late-line ovarian cancer: are we there yet?

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Treatment of subsequent relapses after the first recurrence of ovarian cancer remains challenging. Few studies have been designed in this patient setting, with varying inclusion and exclusion criteria and, as a result, outcomes remain poor and expectations are often unmet.

In *The Lancet Oncology*, Kathleen Moore and colleagues[1] present the results of the QUADRA study, which try to overcome these challenges. In this multicentre, single-arm, phase 2 trial, patients with relapsed high grade serous ovarian cancer, who had previously received three or four chemotherapy regimens were enrolled and treated with 300 mg once daily niraparib—one of the most investigated poly(ADP-ribose) polymerase (PARP) inhibitors in high grade serous ovarian cancer. Patients