

# Gefitinib with pemetrexed as first-line therapy in patients with advanced nonsquamous non-small cell lung cancer with activating epidermal growth factor receptor mutations

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*Comment on:* Cheng Y, Murakami H, Yang PC, *et al.* Randomized Phase II Trial of Gefitinib With and Without Pemetrexed as First-Line Therapy in Patients With Advanced Nonsquamous Non-Small-Cell Lung Cancer With Activating Epidermal Growth Factor Receptor Mutations. *J Clin Oncol* 2016;34:3258-66.

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While lung cancer is the most common cause of cancer death worldwide, epidermal growth factor receptor (EGFR) is the most common type of actionable mutation. Improved outcome with EGFR tyrosine kinase inhibitor (TKI) compared with conventional chemotherapy was the beginning of precision medicine for non-small cell lung cancer (NSCLC) (1). And the testing of EGFR became routine especially in adenocarcinoma of the lung. However, most patients will develop disease progression following successful treatment with EGFR TKIs. In the pooled analysis of 54 studies, gefitinib produced 9.4 months (95% CI, 9.0–9.8) of progression-free survival (PFS) (2). The most common mechanism of resistance is secondary mutation of T790M (3). So, improving PFS of patients with EGFR mutated tumor treated with EGFR TKI remains a critical therapeutic challenge.

There would be two strategies to improve the efficacy of the first generation EGFR TKI alone. One is employing more efficacious drug and another strategy would be EGFR TKI plus other drugs to delay the appearance of resistance clones. The Iressa follow up measures study (IFUM) showed objective response rate of 50% by central review and 70% by investigator assessment (4). Afatinib, a second generation irreversible EGFR TKI produced superior objective response rate with 70% compared with 56% in gefitinib arm ( $P=0.0083$ ) and showed a longer median duration

of response (10.1 *vs.* 8.4 months respectively) (5). Osimertinib which is a third generation EGFR TKI designed to target patients with T790M mutated tumor, which might enable patients to achieve more prolonged PFS than first generation EGFR TKI (6). Osimertinib also seems to have a higher central nervous system activity than other EGFR TKIs and it would further support the front-line treatment (7). Currently ongoing phase III FLAURA trial is exploring the osimertinib in the front-line treatment compared with gefitinib or erlotinib.

Because the mechanism is different, the combination of EGFR TKI and conventional chemotherapy is an attractive strategy to improve the efficacy of chemotherapy or EGFR TKI alone. There have been many trials of the combination treatment against chemotherapy alone in all-comers, but those were not such successful (8-10). FASTACT-II showed benefit of intercalated combination of chemotherapy [platinum (day 1), gemcitabine (day 1 and 8)] and erlotinib (day 15–28 of a 28-day cycle). But the benefit was contained mainly in the patients with EGFR mutated tumor and partially interpreted as due to erlotinib maintenance. Mean PFS was 16.8 months (11). In the second-line setting, pemetrexed (day 1) plus intercalated erlotinib (day 2–14 of a 21-day cycle) could improve its PFS in non-smoking and nonsquamous cell carcinoma patients compared with either erlotinib or pemetrexed alone (12). In the randomized phase

II trial of erlotinib alone or with carboplatin and paclitaxel (up to six cycles), the addition of chemotherapy could not prolong PFS (5.0 *vs.* 6.6 months,  $P=0.1988$ ) in patients who were never or light former smoker with advanced lung adenocarcinoma (CALGB 30406 trial) (13).

In the study led by Cheng *et al.* they added concomitant pemetrexed to gefitinib in the patients with EGFR mutated tumor and showed PFS of 15.8 months (95% CI, 12.6–18.3) compared with 10.9 months [95% CI, 9.7–13.8, adjusted hazard ratio 0.68 (95% CI, 0.48–0.96)] with gefitinib alone ( $P=0.14$ ) (14). The result was regardless of the mutational type (exon 19 deletion or L858R point mutation). This is the first report of successful concurrent pemetrexed plus EGFR TKI therapy against EGFR TKI alone in the patients with EGFR mutated tumor. Interestingly, two PFS curves run along initially then began to divert after more than 6 months later of treatment, which suggests that the PFS prolonging effect would be attributed to the suppression of resistant clones by the addition of concurrent pemetrexed. Continuous treatment with pemetrexed might have produced different results rather than combining up to six cycles of chemotherapy in CALGB 30406 trial (13,14).

In preclinical study, when PC9 and HCC827 cells were simultaneously exposed to gefitinib and pemetrexed, selection of resistant clones were not observed, suggesting that combined treatment prevented the appearance of EGFR TKI resistance (15). It was also known that the expression of thymidylate synthase was reduced with gefitinib treatment (15). So the enhancement of cytotoxicity when pemetrexed is added to gefitinib might suppress the small subpopulation of cells harboring T790M mutation or with the mesenchymal phenotype. Preclinical studies indicated there is cell cycle dependent synergism or antagonism when combining chemotherapy and EGFR TKI, however clinical data do not support it well (10–16).

Treatment with front-line combination of erlotinib and bevacizumab was highly effective in patients with EGFR mutated tumors. Although the response rate was similar (69% *vs.* 64%), median PFS was 16.0 months (95% CI, 13.9–18.1) in combination group compared with 9.7 months (95% CI, 5.7–11.1) with erlotinib alone (17). This finding suggests that the addition of bevacizumab to erlotinib might help maintain the tumor suppressing effect after reduction in tumor size. Improved drug delivery with bevacizumab could achieve higher intra-tumor concentration of erlotinib, which could delay the appearance of resistant cells. Or VEGF receptor blocking might contribute to delay the appearance of T790M mutation (18). In the

phase II BELIEF trial, the combination of bevacizumab and erlotinib resulted in a 1-year PFS of 72.4% (95% CI, 53.4–84.7) in patients with T790M (19). BEVERLY trial (erlotinib plus bevacizumab *vs.* erlotinib alone) and RELAY trial (erlotinib/ramucirumab *vs.* erlotinib/placebo) are ongoing. Other combination such as gefitinib plus durvalumab (PD-L1 inhibitor) trial was reported but PFS data are immature (20).

While there are many therapeutic options for patients with EGFR mutated tumor: first generation EGFR TKI, second generation EGFR TKI, third generation EGR TKI, immunotherapy and conventional chemotherapy, PFS for each therapy might not be a relevant surrogate to see the overall survival. Some patients progress rapidly during initial treatment and might not have the next opportunity to overcome resistance. So, initial decision of front-line therapy would be important for the patients. As the most prominent resistant mechanism after EGFR TKI is the appearance T790M or mesenchymal phenotype, those combination strategies to overcome the appearance of resistant clones during EGFR TKI treatment are encouraging. More data will be needed to accept such strategy as front-line therapy of patients with EGFR mutation.

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## Footnote

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

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