Somatic mutations within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are the most reliable predictors of efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in patients with non-small cell lung cancer (NSCLC). In randomized phase III trials, EGFR-TKIs in patients with advanced EGFR mutant NSCLC were associated with longer progression-free survival (PFS) and higher radiographic response rates than the standard first-line platinum-based chemotherapy (1-7). Based on these results, three types of EGFR-TKIs, gefitinib, erlotinib and afatinib have been approved for treatment of advanced EGFR-mutant NSCLC as a first-line setting. Despite an initially marked response, almost all patients treated with EGFR-TKIs eventually acquire resistance to these drugs, with an average PFS of around 1 year. To improve these results, several combinations of EGFR-TKIs and other drugs, such as targeted drugs and chemotherapy, have been developed.

One of the candidates in combination with EGFR-TKIs is an antiangiogenic agent. The JO25567 trial is a randomized, open-label phase II study that compared the EGFR-TKI erlotinib monotherapy versus erlotinib plus bevacizumab, a monoclonal anti-vascular endothelial growth factor (VEGF) antibody, in patients with untreated EGFR-mutant advanced NSCLC. This study demonstrated a significant better PFS and tumor response for erlotinib plus bevacizumab compared with erlotinib monotherapy [median PFS of 16.0 vs. 9.7 months; hazard ratio (HR) =0.54, 95% confidence interval (CI): 0.36–0.79, P=0.0015; overall response rate (ORR) 69% vs. 64%] (8). Because of these favorable results, a randomized phase III study comparing erlotinib monotherapy and erlotinib plus bevacizumab is currently underway in Japan (UMIN000017069). Furthermore, another antiangiogenic agent, ramucirumab, a monoclonal antibody against anti-VEGF receptor 2, has been evaluated in combination with erlotinib in a global randomized phase III study (NCT02411448).

Another candidate is chemotherapy. Cheng et al. recently reported a multicenter, randomized, open-label, parallel-arm, phase II study comparing first-line pemetrexed plus gefitinib versus gefitinib monotherapy in untreated EGFR-mutant advanced NSCLC patients (9). Pemetrexed is one of the standard cytotoxic chemotherapy drugs for patients with locally advanced or metastatic non-squamous NSCLC. Preclinical and early clinical studies also indicate a potential synergy between pemetrexed and EGFR-TKIs (10-13). Based on these evidences, this clinical trial was conducted. The primary endpoint in this study was PFS.
Of 232 patients enrolled, 195 were randomly assigned to pemetrexed plus gefitinib (P+G: n=129) or gefitinib monotherapy (G: n=66). Of these, 191 patients received at least 1 dose of the study drug. As per efficacy, there was a statistically significant prolongation of PFS in the P+G arm (median PFS: 15.8 months; 95% CI: 12.6–18.3 months) compared with the G arm (median PFS of 15.8 vs. 10.9 months, adjusted HR =0.68, 95% CI: 0.48–0.96, one-sided P=0.014, two-sided P=0.029). Overall survival (OS) data is immature. Concerning safety, a significantly higher proportion of patients in the P+G arm compared with the G arm reported one or more possibly drug-related grade 3 or 4 treatment related adverse events (42% vs. 19%, P<0.001), reflecting the expected additional events for both study drugs. The most commonly reported grades 3–5 toxicities were alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase (ALT increased: 16% for P+G vs. 8% for G, and AST increased: 6% for P+G vs. 3% for G), which is consistent with the known safety profiles of both drugs. Despite the increase in toxicity with P+G, these toxicities were clinically manageable. This study demonstrated that EGFR-TKIs with pemetrexed are a new first-line option for patients with EGFR-mutated NSCLC.

There have been several clinical trials of combinations with EGFR-TKIs and chemotherapy in advanced NSCLC. Four previous phase III studies (INTACT-1, INTACT-2, TRIBUTE, and TALENT) that compared platinum doublet chemotherapy with or without EGFR-TKIs and were performed in patients with untreated advanced NSCLC regardless of their EGFR mutation status (14-17). These studies showed no additional survival benefit for the combination of chemotherapy and EGFR-TKIs. However, patients in these studies were not included accounting for the presence of EGFR mutation, which is the most reliable predictor of the efficacy of EGFR-TKIs. In fact, several phase II studies to evaluate the efficacy of chemotherapy/EGFR-TKIs combination in patients with advanced NSCLC harboring a sensitive EGFR mutation showed an encouraging PFS (around 18 months) and OS (32–48 months) (18-20). In addition, FASTACT-2, which is phase III trial comparing erlotinib intercalated with chemotherapy versus chemotherapy plus placebo in patients with advanced NSCLC, showed a significant benefit only in EGFR-mutant NSCLC (median PFS of 16.8 vs. 6.9 months; HR =0.25, 95% CI: 0.16–0.39, P=0.0001; median OS, of 31.4 vs. 20.6 months, HR =0.48, 95% CI: 0.27–0.84, P=0.0092). On the other hand, no difference was observed in the subgroup with EGFR wild-type NSCLC.
EGFR-TKIs acquired resistance mechanisms between EGFR-TKIs monotherapy and the combination treatment with both EGFR-TKIs and chemotherapy is important.

In conclusion, the Cheng et al. study showed that patients with advanced EGFR mutant NSCLC obtain clinical benefit from the addition of pemetrexed to EGFR-TKIs as a first-line setting. However, understanding the difference in resistance mechanisms between G and G+P, which include the emergence of EGFR T790M mutation, is also important.

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Footnote
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