

# The continued EGFR-TKI with cytotoxic chemotherapy at progression—poison or medicine?

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*Comment on:* Mok TSK, Kim SW, Wu YL, *et al.* Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): overall survival and biomarker analyses. *J Clin Oncol* 2017;35:4027-34.

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EGFR tyrosine kinase inhibitors (TKI) have shown the efficacy in treatment of lung cancer patients with EGFR sensitizing mutations, and their use has led to a doubling of progression-free survival (PFS) and a lengthening of overall survival (OS) by more than 2 years. However, the emergence of resistance is inevitable, which creates new challenges for the management of patients with EGFR-mutant lung cancer (1). As several approaches after the development of resistance have been suggested, one of them is the continuation of EGFR-TKI with local therapy to aggravated lesions if necessary (2). This recommendation is based on some studies which showed the survival benefits by the continuation of EGFR-TKI compared with switching to cytotoxic chemotherapy (3,4). It implies that EGFR-TKI still has a role on the control of the EGFR-mutant lung cancer despite acquired resistance to EGFR-TKI. This phenomenon may be contributed by the capability of EGFR-TKI-sensitive clones to grow fast if EGFR-TKI removed and the relatively slow growth rate of resistant clones (5).

Then, can the addition of cytotoxic chemotherapy to continued EGFR-TKI give more benefits to patients with EGFR-TKI-resistance? Mok *et al.* addressed this issue by a prospective, randomized, phase III study (IMPRESS study) investigating the efficacy of the continuation of an EGFR-TKI in combination with cisplatin and pemetrexed at progression after first-line gefitinib (6). They found that

it was detrimental to OS when compared with placebo plus cisplatin and pemetrexed [hazard ratio (HR), 1.44; 95% CI, 1.07 to 1.94;  $P=0.016$ ; median OS, 13.4 *vs.* 19.5 months]. The detriment was statistically significant in patients with T790M-positive plasma samples (HR, 1.49; 95% CI, 1.02 to 2.21) while statistical significance was not reached in T790M-negative patients (HR, 1.15; 95% CI, 0.68 to 1.94). PFS in T790M-positive patients was similar in both, and the difference observed in T790M-negative patients did not reach statistical significance (HR, 0.67; 95% CI, 0.43 to 1.03;  $P=0.0745$ ). They concluded that the finding is sufficient to warn physicians against the continuation of treatment with first-generation EGFR-TKIs when a decision is taken to initiate standard chemotherapy on the basis of radiologic disease progression (6).

There have been several studies investigating the efficacy of the combination of EGFR-TKI and cytotoxic chemotherapy with conflicting results (7-9). Those discordant results might be caused by heterogeneous study population, different line of treatment, different combined drug and drug delivery method. Although it's one of still controversial issues, more results seem to show favorable outcomes by the addition of cytotoxic chemotherapy. In 2016, a meta-analysis of 15 randomized controlled trials showed the combined regimen had a significant benefit on PFS (HR, 0.80; 95% CI, 0.71 to 0.90;  $P<0.001$ ), not on OS (HR, 0.96; 95% CI, 0.90 to 1.03;  $P=0.25$ ). The OS

benefit was shown in EGFR mutation-positive patients by subgroup analysis (10). Cheng *et al.* also demonstrated that the addition of pemetrexed to gefitinib in first-line treatment improved PFS compared with gefitinib alone in East Asian patients with advanced EGFR-mutant lung cancer (HR, 0.68; 95% CI, 0.48 to 0.96; one-sided P=0.014; two-sided P=0.029) (11). How to interpret the detrimental effect on OS in the IMPRESS study? As authors indicated, more patients in the placebo group were exposed to EGFR-TKI (30% in the placebo and 20% in the gefitinib group) including osimertinib and to doublet chemotherapy. Further, more patients had brain metastases of unfavorable outcome in the gefitinib group (12). Therefore, it's too early to draw a conclusion on the harmful effect of the continued EGFR-TKI with chemotherapy because these imbalances seem to be enough to result in the difference of OS. Otherwise, we can assume that the presence of T790M may have a real negative impact on the survival although we still don't know the exact mechanism because one of the striking differences between them is the status of T790M.

The recent emergence of osimertinib makes the significance of this study less meaningful. Osimertinib proved its efficacy in T790M+ EGFR mutant-lung cancer after 1<sup>st</sup>-line EGFR-TKI (13) and became the standard treatment. Therefore, there is no way to use the combined treatment with EGFR-TKI and cytotoxic chemotherapeutic drugs in wake of T790M-positive lung cancer instead of osimertinib at present. Unfortunately, the eventual development of resistance to osimertinib is also unavoidable requiring the optimal subsequent treatment. Several articles about the resistant mechanisms to osimertinib and overcoming strategies have been published (14-16). However, some researchers may want to try the continued osimertinib with the addition of cytotoxic agents in case of osimertinib-resistance because there are no other proven treatment options for osimertinib-resistance than conventional chemotherapy until now. Then, could the IMPRESS study be a guidance to discourage such trial? Given that osimertinib is active against T790M as well as sensitizing mutations unlike 1<sup>st</sup> or 2<sup>nd</sup> generation EGFR-TKIs (1), the combination of osimertinib and cytotoxic agents could show the different result in patients with T790M-positive lung cancer on the assumption that T790M is behind the detrimental effect of the combined treatment on OS.

The IMPRESS study suggests the potential detrimental effect of the combination of EGFR-TKI and cytotoxic chemotherapy in T790M-positive lung cancer. However,

even though it is true, we don't know how it works and whether the combination with osimertinib instead of gefitinib could lead to the different result, which should be pursued by following studies.

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## Footnote

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

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