Discontinuing epidermal growth factor receptor-tyrosine kinase inhibitor during second-line chemotherapy: is the evidence strong enough?

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Dr. Soria *et al*. reported an important randomized controlled trial showing that continuation of gefitinib after radiological disease progression on first-line gefitinib did not prolong progression-free survival (PFS) in patients who received pemetrexed plus cisplatin chemotherapy as subsequent line of treatment (1). This study clarified some previous controversies on the management strategy of patients who progressed after epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment. However, some concerns remain.

Firstly, the regimen of the treatment arm is the combination of pemetrexed, cisplatin and gefitinib. Four previous randomized trials and *in vitro* experiments suggested that EGFR-TKI is antagonistic to cytotoxic agents especially cisplatin (2). However, intercalated regimen of erlotinib plus platinum-based chemotherapy in the FASTACT2 study was superior to chemotherapy alone (3). In addition, a current study showed that gefitinib in combination with single agent pemetrexed contributed a relatively longer PFS of 18 months compared to historical controls (4). The conclusion derived from IMPRESS study might be different if either a regimen of gefitinib in combination with pemetrexed alone, or the intercalated administration strategy was employed.

Secondly, although there was no statistically significant difference in PFS between the two arms, the trends did potentially favor continuing gefitinib as the survival curve of the treatment arm was consistently superior to that of the control arm. We would argue that the estimation of the benefit of continuing gefitinib was over-optimistic given that no enrichment of a specific population (e.g., patients experiencing slow progression or oligo-site progression as the authors mentioned in the discussion) was proposed. Over-estimation of the benefit could reduce the sample size, declining the power to detect the difference. In the IMPRESS study, an over-estimated PFS of 9.5 months in the experimental arm is equivalent to the actual median overall survival of concurrent chemotherapy and EGFR-TKI in the first line setting (range, 8.7-10.6 months) (5). Notably, the four previous trials (5) enrolled patients with unknown EGFR mutation status; this is actually similar in the IMPRESS study as they tested the EGFR mutation at the first line but not at the second line when the mutation status might be altered.

Thirdly, in the subgroup analyses we observed that patients with stable disease in the first line gefitinib treatment benefited much more from continuing gefitinib in the second line chemothera.py (HR: 0.59; 95% CI, 0.35-1.02) than those who experienced initial tumor remission in receiving front-line gefitinib (HR: 0.97; 95% CI, 0.70-1.34). The benefit of continuation of gefitinib is considerable in that the upper limit of the 95% CI is close to the significance margin; thus, interaction tests of the subgroups might help to determine whether or not there is a beneficial subpopulation. If indeed there is a difference between the benefits of these two subpopulations, a correlated subgroup analysis stratified by progression mode of previous

EGFR-TKI treatment is warranted.

There are still many unanswered questions on this complex issue. It would be highly appreciated if the authors could address these events.

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Footnote

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

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