Editorial

Osimertinib in first line setting: preventive or delayed T790M occurrence?

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Provenance: This is an invited Editorial commissioned by the Section Editor Dawei Yang (Zhongshan Hospital, Fudan University, Shanghai Respiratory Research Institution, Chinese Alliance against Lung Cancer, Shanghai, China).

Comment on: Soria JC, Ohe Y, Vansteenkiste J, *et al.* Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.

Submitted Apr 05, 2018. Accepted for publication Apr 16, 2018.
doi: 10.21037/tlcr.2018.04.16
View this article at: http://dx.doi.org/10.21037/tlcr.2018.04.16

The FLAURA clinical trial conducted by Soria *et al.* are recently reported in the *New England Journal of Medicine*, this trail was designed to test the efficacy of osimertinib as first-line treatment for none-small-cell lung cancer (NSCLC) patients. 556 previously untreated advanced NSCLC patients with EGFR mutation-positive (exon 19 deletion or L858R) are enrolled and 279 of which are assigned to the osimertinib group. The FLAURA set median progression-free survival (PFS) as the primary endpoint, which is significantly longer in the osimertinib group compared with patients taking standard EGFR-TKIs [18.9 *vs.* 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval (CI), 0.37 to 0.57; P<0.001]. Based on these remarkable outcomes of FLAURA, Soria *et al.* come to a promising conclusion that osimertinib is superior to standard EGFR-TKIs (gefitinib or erlotinib) as first line treatment for advanced NSCLC (1). However, a long way is still needed to go before osimertinib become standard first-line therapy. And the true value of this clinical trial is that it revealed the possible capacity of osimertinib in preventing T790M development, and the rearrangement of TKIs for advanced NSCLC should be further contemplated around this new position.

Osimertinib is an irreversible epidermal growth factor receptor tyrosine kinase inhibitor (2) (EGFR-TKI) targeted EGFR-TKI sensitizing (exon 19 deletion or 21L858R mutation etc.) and T790M mutations, which accounts for the majority of resistance events (50–60%) during the treatment of first generation TKIs (3,4). AURA3 trial has fully established the supremacy of osimertinib compared with platinum-doublet chemotherapy (PFS, 10.1 *vs.* 4.4 months), which set up the standard application of osimertinib as following treatment to first generation TKIs when T790M associated resistance was developed (5). However, the Phase I component of the AURA trial demonstrate that osimertinib might bring significant clinical benefits as first-line therapy for advanced NSCLC with EGFR mutations, and this trail present a challenge to the traditional arrangements of TKIs. Based on the DNA analysis of post-progression plasma samples (19 of 38), this trail also primarily revealed that no acquired EGFR T790M was detected after osimertinib treatment. The prevention of T790M by early intervention of osimertinib further explained the longer PFS compared with standard TKIs in FLAURA trail (6).

Then here comes the first argument, even though T790M mutation accounts for the majority resistance (60%) events in progressed NSCLC patients who might benefit from the prevention of second T790M mutation by osimertinib, how to manage therapy schedule for the rest 40% patients (7)? The throughout application of osimertinib from the first line may limit the clinical benefits among such groups, and cannot generate a longer PFS than standard TKIs due to the specific mutation resistance mechanisms

involving multiple genes with HER2 accounting for 33% of patients, followed by containing amplification of HER2, MET, and MAPK1; mutation of PIK3CA and BRAF; and small-cell transformation (8). MET amplification was proved to participate in acquired resistance to EGFR-TKIs of patients harboring EGFR-mutation, and a 33% response rate to crizotinib was reported in the phase 1 clinical trial included 12 MET-amplified NSCLC patients (9,10). A sequential treatment of first generation TKI and crizotinib may bring more clinical benefits compared with taking osimertinib as first line therapy among such group.

FLAURA and AURA have demonstrate the prevention on T790M mutation caused by early intervention of osimertinib, which result in the benefits of PFS in osimertinib group. But the overall survival data from FLAURA is not available, and the long-term survival status are still not fully evaluated (1). Then another issue need to be figured out is whether first line osimertinib therapy could change the resistance mutation spectrum, which would influence the long-term clinical benefits among progressed NSCLC patients. As the FLAURA did not present the genomic information after disease progression, a further investigation into the potential shift of mutation spectrum under the treatment pressure of early osimertinib intervention is not available. Based on the circulating tumor DNA (ctDNA) analysis conducted by phase 1 AURA, one patient was found harboring C797s (1/9) mutation without T790M co-occurring (6). As gefitinib have been shown to be effective in blocking C797S when T790M is absent, the following treatment of TKIs after first line osimertinib application may further expand the clinical benefits (11,12). Future analyses of resistance associated mutation based on the gene landscape drawn by FLAURA will be necessary for investigating the different mechanism of osimertinib resistance between the application in first line application and following the standard TKIs.

As the osimertinib may fail to generate more benefits among patients without a tendency to T790M mutation and the mutation spectrum after progression is essential for further treatment, a dynamic monitor of DNA status would help to consummate the first line application strategy of osimertinib. But how to arrangement the EGFR mutation detection and catch the potential T790M mutation trend if possible? Limited by the invasive operation and associated complications, dynamic monitor based on repeatedly biopsy are nearly impossible. As the sensitivity and specificity about detection with ctDNA have been evaluated by serials studies, ctDNA mutation status was proved to be a predictor for EGFR-TKI efficacy in patients with EGFR-mutant NSCLC (13-15). But the analysis based on pair matched tumor tissue and plasma samples from patients in AURA and AURA2 studies established a lower positive rate for T790M mutation in plasma samples, which suggest that the negative T790M result generated by plasma samples may need further confirmed with a tissue test (14). Nowadays, even though the technology is still far from perfection which cannot afford the mutation monitor function for the duration of TKI therapy, the detection of T790M mutation is still the standard instruction for osimertinib application. How to arrangement the detection within existing methods would be a tough challenge and an even harder task is to catch the trend towards T790M mutation.

The findings of FLAURA revealed several issues around the application of osimertinib as first line therapy for EGFR-mutation NSCLC. The most discussed dubiousness is how to determine the sequence of TKIs for a more significant clinical benefit. But the prevention in T790M mutation is another notable point which could lead to a whole new strategy for the TKIs schedule management. The further analyses based on gene mutation landscape drawn by FLAURA will be consequential for investigating the different mechanism of osimertinib resistance caused by first-line application of osimertinib or the standard TKIs. The next study should also focus on how to generate a more practicable T790M detection strategy which would help to catch the T790M mutation trend and serve for the arrangement of system TKIs therapy (*Figure 1*).

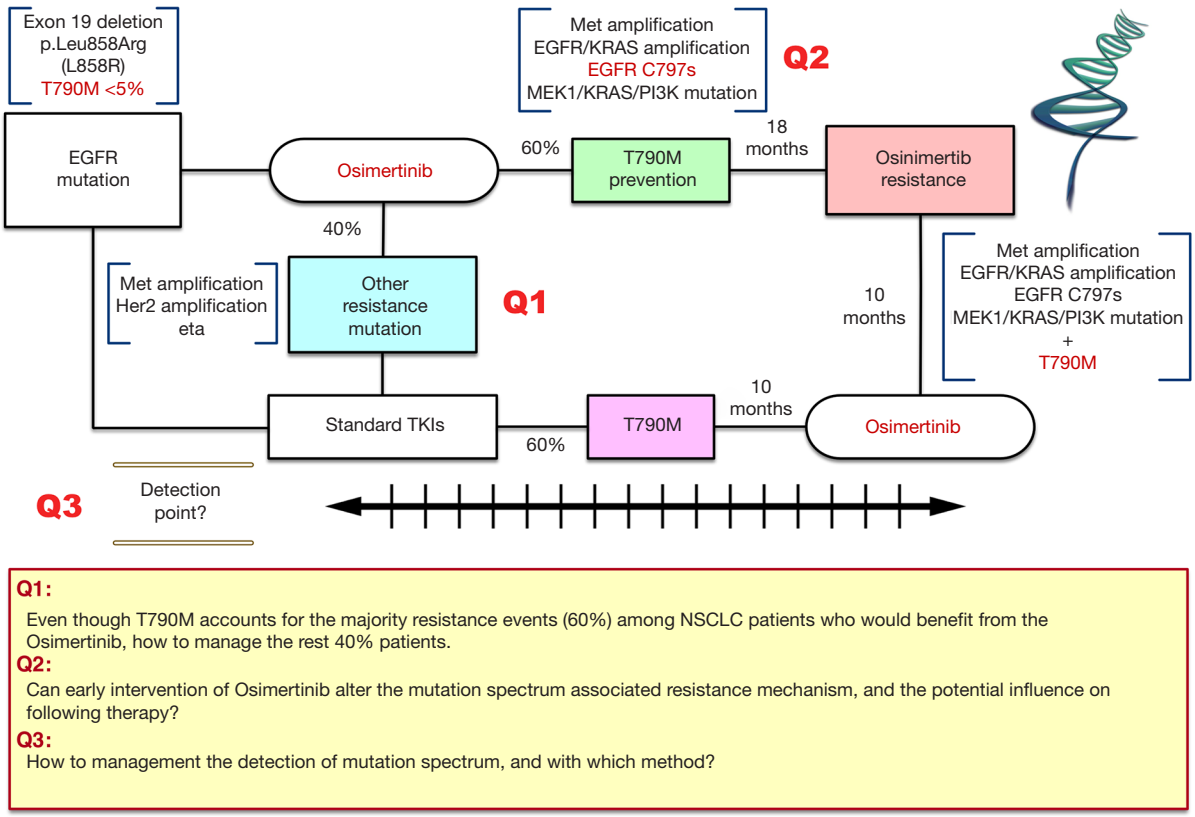

Figure 1 Further questions regarding to the application of osimertinib. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Acknowledgements

None.

Footnote

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

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Cite this article as: Sun H, Wu Y. Osimertinib in first line setting: preventive or delayed T790M occurrence? Transl Lung Cancer Res 2018;7(Suppl 3):S187-S190. doi: 10.21037/tlcr.2018.04.16

