Editorial

Tracking and tackling the tumor dynamics clonal evolution: osimertinib rechallenge after interval therapy might be an effective treatment approach in *epidermal growth factor receptor* (*EGFR*)-mutant non-small cell lung cancer (NSCLC)

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Comment on: Song Y, Jia Z, Wang Y, *et al.* Potential treatment strategy for the rare osimertinib resistant mutation EGFR L718Q. J Thorac Dis 2020;12:2771-80.

Submitted Jan 22, 2022. Accepted for publication Mar 09, 2022.
doi: 10.21037/jtd-22-98
View this article at: https://dx.doi.org/10.21037/jtd-22-98

The FLAURA study comparing the 3rd-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (-TKI) osimertinib versus a 1st-generation EGFR-TKI such as gefitinib or erlotinib clearly demonstrated the superior efficacy of osimertinib in *EGFR*-mutated non-small cell lung cancer (NSCLC) patients (1,2). As a result, osimertinib has since then become the preferred first-line therapeutic option in this setting, at least for the patients who harbor a common *EGFR* exon 19 deletion or exon 21 L858R mutation. On the other hand, the optimal treatment approach to be offered at the time of acquired resistance to osimertinib remains unsettled. While continuing osimertinib beyond progression with or without the addition of local ablative therapy is an option for some patients with oligoprogressive disease (3,4), platinum-doublet chemotherapy should be offered in fit patients with rapid systemic progression (3,5). In regard to chemotherapy, a small retrospective study showed that chemotherapy administered at the time of acquired resistance to osimertinib was associated with a post-progression overall survival (OS) of 18.1 months, 12.9 months for those with rapidly progressive disease (3). However, little is known on the efficacy of subsequent systemic treatments administered after osimertinib followed by an interval therapy, and on whether osimertinib rechallenge may have a role in this context.

In theory, re-administration of osimertinib could be reasonable: while cytotoxic chemotherapy eradicates the cancer clones, responsible for resistance to the EGFR-TKI, new clones that may still be sensitive to the same target therapy could arise. Our group was among the first who documented the effectiveness of this approach in an *EGFR*-mutated NSCLC patient who progressed on the sequence osimertinib and platinum-doublet chemotherapy (6). Similarly, another work evaluating osimertinib rechallenge after interval therapy in 15 *EGFR*-mutated NSCLC patients showed that re-administration of the same target therapy provided a response rate of 33%, with a median progression-free survival (PFS) and OS of 4.1 and 9.0 months, respectively (7).

The development of new technologies, able to detect circulating tumor DNA (ctDNA) and to perform next-generation sequencing (NGS) analysis, has improved the capacity to monitor cancer evolution during the course of therapy. This approach might be helpful in order to further refine and direct personalized treatment decisions. Importantly, as compared to tissue biopsy, liquid biopsy has the convenience of reflecting intra-tumoral heterogeneity as well as allowing frequent assessments of tumor's mutational status (8). Of note, in *EGFR*-mutated

NSCLCs with acquired resistance to a 3rd-generation EGFR-TKIs, liquid biopsy has helped unveil a high intra- and inter-patient heterogeneity in terms of mechanisms of resistance. For instance, Chabon *et al.*, who analyzed ctDNA from serial plasma samples (using the ultrasensitive CAPP-Seq) of 43 NSCLC patients progressing on the 3rd-generation EGFR-TKI rociletinib, succeeded in detecting high intra-patient heterogeneity in 46% of patients featuring multiple resistance mechanisms (9). Similarly, another study showed that as much as 19% of patients who progress on osimertinib after prior TKI have more than one putative mechanism of resistance at plasma NGS analysis (Guardant360 assay) (10). On the other hand, 91 osimertinib-treated patients were evaluated through plasma sampling (Guardant360 assay or GuardantOMNI assay) from the FLAURA trial, which showed a large inter-patient variability in terms of on-target (*EGFR* resistance mutations such as C797S, L718Q, S768I) and off-target (e.g., *MET* or *HER2* amplifications, *PIK3CA*, *BRAF* or *KRAS* mutations) resistance mechanisms (11). In this complex scenario, it would seem reasonable to consider chemotherapy at progression on osimertinib in the absence of actionable resistance mutations, while monitoring the clonal evolution through liquid biopsy in order to offer re-challenge with osimertinib in case of persistent *EGFR* mutation clones.

Recently, a case report was published in 2020 in *Journal of Thoracic Disease* by Song *et al*. which best exemplified the latter concept (12). It reported on an *EGFR* exon 21 L858R-mutated patient who benefitted from osimertinib administered following the sequence of the EGFR-TKI icotinib and platinum-doublet chemotherapy. Importantly, osimertinib was not shown to be effective right after icotinib despite the detection of the osimertinib sensitive *EGFR* T790M mutation at liquid biopsy (QIAamp Circulating Nucleic Acid kit). In fact, resection of a metastatic lung nodule showed the concomitant presence of *EGFR*-mutated L858R tumor clones harboring a rare *EGFR* L718Q mutation as well as *EGFR* amplification, which was put forward as the reason behind the lack of response to osimertinib. That is because, the *EGFR* L718Q mutation affects the L718 residue of the EGFR TK domain, thus altering the binding of osimertinib to EGFR (13). However, administration of platinum-based chemotherapy was able to clear the resistant *EGFR* L718Q clones, thus leading to predominance of the *EGFR* T790M ones. As a consequence, osimertinib re-administration was now effective, resulting into partial response and a PFS of 4.7 months. This study underlines the potential and the limitation of liquid biopsy as this technique was not able to detect the *EGFR* L718Q at the time of resistance to icotinib. Such could be documented only by NGS performed on tumor tissue. Although several issues regarding liquid biopsy in NSCLC still need to be addressed (e.g., lack of standardized protocols for sample collection, processing, and interpretation) monitoring the evolution of cancer clones through ctDNA could be incorporated into routine oncology practice in the near future. This could certainly improve treatment strategies, especially in later lines. To back this concept up, Fuchs and colleagues used liquid biopsy (Guardant260) as a tool to determine whether an *EGFR*-mutated NSCLC patient pretreated with osimertinib could be rechallenged with the same target therapy after interval chemotherapy (14). At the time of acquired resistance on osimertinib the liquid biopsy identified the parental *EGFR* exon 19 deletion plus T790M and C797S mutations in a patient. At this time, they offered chemo-immunotherapy with carboplatin/pemetrexed/pembrolizumab and obtained a near complete response with clearance of ctDNA and of all the resistant *EGFR* mutations identified by liquid biopsy. However, at progression on chemo-immunotherapy, the liquid biopsy revealed only the appearance of a new *EGFR* V1097I mutation, and osimertinib was restarted. The patient continued osimertinib since then for approximately 7 months with a sustained partial response.

Currently, research is focusing on customizing post-osimertinib treatments for *EGFR*-mutated NSCLC patients based on the molecular mechanisms that underlie the acquired resistance to osimertinib. For instance, in the phase 1B 'TATTON' trial the combination of osimertinib plus the MET-inhibitor savolitinib has shown a response rate of 67% and a median duration of response of 12.4 months in *EGFR*-mutated patients with a MET amplification as assessed on tissue rebiopsy at the time of acquired resistance to first-line osimertinib (15). At the present time, the 'SAVANNAH' phase 2 trial (NCT03778229) is being conducted in order to assess continuation of osimertinib with the addition savolitinib in MET overexpressed/amplified *EGFR*-mutated NSCLCs that progress on osimertinib. 'ORCHARD' is an open-label, multicentre, biomarker-directed, phase 2 platform study (NCT03944772) evaluating the optimal treatment for individual patients with *EGFR*-mutated NSCLC depending on the underlying resistance mechanism at the time of acquired resistance to osimertinib. In this context, molecular characterization of the tumor at progression by means of either tissue or liquid biopsy is crucial to select

the right treatment. Importantly, a non-matched treatment such as chemotherapy or chemo-immunotherapy for patients without an unidentified/not actionable resistance mechanism is planned with the potential of resensitizing the tumor to osimertinib by getting rid of the resistant cancer clones.

To conclude, re-administration of osimertinib might be a viable option in select patients following an interval therapy administered in case of no clear mechanism of resistance to osimertinib and it could be considered when supported by serial monitoring of tumor dynamics at critical time points.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-98/coif). GM serves as an unpaid editorial board member of *Journal of Thoracic Disease* from February 2021 to January 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Metro G, Bonaiti A, Birocchi I, Marasciulo F, Ubaldi M, Metelli N, Minotti V, Addeo A. Tracking and tackling the tumor dynamics clonal evolution: osimertinib rechallenge after interval therapy might be an effective treatment approach in *epidermal growth factor receptor* (*EGFR*)-mutant non-small cell lung cancer (NSCLC). J Thorac Dis 2022;14(4):816-819. doi: 10.21037/jtd-22-98