Editorial

Osimertinib for *EGFR*-mutant non-small cell lung cancer: place in therapy and future perspectives

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In the last 20 years the clinical management of patients with advanced non-small cell lung cancer (NSCLC) has shifted form a histology-driven to a molecularly-based approach due to the identification of actionable genetic alterations and the subsequent development of highly efficacious targeted therapies. As result, genomic analysis has now become routine in clinical practice to identity the molecular predictors of targeted therapies efficacy, including somatic epidermal growth factor receptor (*EGFR*) mutations (1). Over the last decade, patients harboring a sensitizing *EGFR* mutation, typically exon 19 deletion and exon 21 L858R point mutation, have been preferentially treated with first- (gefitinib, erlotinib) or second-generation generation (afatinib) EGFR tyrosine kinase inhibitors (TKIs), which excelled chemotherapy in terms of objective response rate (ORR), progression-free survival (PFS) and quality of life (QoL) in large randomized clinical trials (2-9). Despite these drugs produce prolonged responses in the vast majority of patients harboring *EGFR* sensitizing mutations, relapse invariably occur after a median of 9–12 months due to the development of acquired resistance (10). Osimertinib mesylate is a novel pyrimidine-based irreversible, covalent third-generation EGFR-TKI and potent inhibitor of *EGFR* T790M mutation, the most common mechanism of acquired resistance to first-generation EGFR-TKIs. In the phase I, dose-expansion arms of AURA 1, osimertinib produced an ORR of 61% (95% CI, 52–70%), and a median PFS of 9.6 months in patients harboring the T790M mutation (11). These data have been further corroborated in the phase II AURA extension and the phase II AURA 2 trial where osimertinib produced ORRs of 62% (95% CI, 54–68%) and 70% (95% CI, 64–77%), respectively, and a median PFS of 12.3 and 9.9 months in heavily pretreated patients with T790M-positive NSCLC (12,13). More recently, in the randomized phase III AURA 3 trial osimertinib improved the ORR (71% versus 31%, P<0.001) and the median PFS (10.1 versus 4.4 months, HR: 0.30; 95% CI, 0.23–0.41; P<0.001) over cisplatin/pemetrexed chemotherapy as second-line treatment in patients who had progressed on or following first- or second-generation EGFR TKIs (14). The extended clinical benefit of the sequential treatment with a first-generation EGFR TKI followed by osimertinib observed in this study led to the approval of this compound for patients with NSCLC harboring the T790M mutation and disease progression after treatment with first- or second-generation EGFR TKIs. However, in the recent randomized phase III FLAURA trial osimertinib excelled standard of care gefitinib or erlotinib in treatment-naive NSCLC patients harboring *EGFR* exon 19 deletions and L858R point mutation, with a significantly improvement in median PFS compared to standard TKIs (18.9 versus 10.4 months, P<0.001) and a 54% reduction of risk of disease progression or death compared to standard of care (15).

As outlined by Jiang and colleagues in the consensus paper accompanying this Editorial (16), with the positive results of the AURA 3 and the FLAURA trials, osimertinib has become the standard of care for treatment-naive patients with *EGFR* activating mutations, or *EGFR* T790M mutation-positive NSCLC who progress on previous EGFR-TKI treatment. However, with the increasing

number of effective EGFR TKIs, and the emergence of resistance to novel agents, oncologists are faced with several questions that still need to be properly addressed.

First, should osimertinib to be considered the preferred first-line option in patients with metastatic *EGFR*-mutant NSCLC (exon 19 deletion, L858R) or should be used sequentially upon documentation of T790M resistance mutation? The traditional sequential approach has been the mainstay of treatment for a longer time compared to the up-front third generation TKIs strategy and is supported by solid data showing an unprecedented long-term survival. In support of this, a recent pooled analysis of the AURA 2 and AURA extension studies has shown a median OS of 26.8 months and a 2-year OS rate of 56% in T790M-mutant NSCLCs who received osimertinib after the failure of either first- or second-generation TKIs (17). Mature OS data form the AURA 3 and ASTRIS trials are still pending and are expected to provide an additional insight in the sequential management of *EGFR*-mutant NSCLCs harboring the T790M resistance mutation.

Nonetheless, this sequential strategy has been questioned by clinical evidence showing improved PFS and improved intracranial disease control when next- generation TKIs are used as up-front treatment in patients with actionable genetic alterations (15,18,19). With a nearly doubled median PFS, osimertinib is undoubtedly superior to first-generation TKIs as frontline therapy. In addition, although the OS data from the FALURA trial are still pending, the median time to second-line treatment or death was 23.5 months with osimertinib and 13.8 months with first-line EGFR TKI, while the median time to third-line treatment was not reached and 25.9 months, respectively, suggesting an extended clinical benefit for patients starting with up-front osimertinib. Favoring this approach is also the better tolerability of osimertinib, especially because these patients are expected to remain on treatment for a longer time compared to those treated with standard EGFR TKIs. Importantly, osimertinib has also been reported to exert higher activity against brain metastasis (BMs), allowing for a sustained control of intracranial disease, with the potential of delaying the use of brain radiotherapy and its cognitive side effects in a population of patients with a life expectancy now measured in years. In addition, starting with osimertinib would grant the totality of *EGFR*-mutant patients the benefit of receiving a third generation TKI during the course of their disease. By contrast, a considerable proportion of patients progressing on standard TKIs do not harbor the T790M secondary mutation (40%) and are not candidate for receiving osimertinib, with an expected median PFS shorter than the 18.9 months they might achieve with up-front osimertinib.

It should be highlighted that second-generation EGFR TKIs were excluded from the comparator arm in the FLAURA trial. Although a recent meta-analysis has shown no difference in efficacy among gefitinib, erlotinib and afatinib (20), the ARCHER 1050 study has demonstrated a clear advantage of the second-generation EGFR TKI dacomitinib over gefitinib in treatment-naïve NSLCs in terms of median PFS and OS (21,22), leaving unanswered the question whether starting with osimertinib would be superior to a sequential approached in which osimertinib is administered upon documentation of T790M-positive progression after dacomitinib. Of note, in the ARCHER trial only a minority of patients received subsequent third generation EGFR TKIs, because of the limited availability of these agents when the study was conducted. Whether in this scenario the baseline assessment of T790M status should be used to decide which patients might benefit from first-line osimertinib remains to be determined. In this context, future analyses of the FLAURA trial are expected to provide us relevant information about the activity of osimertinib in the subgroup of patients harboring *de novo* T790M mutations.

Another challenge that thoracic oncologists are facing is that we currently do not have an option that has been proven to be effective as a second-line targeted therapy after acquired resistance to osimertinib. However, emerging evidence is showing that, according to the molecular mechanism underlying the development of resistance to osimertinib, there may be a room for targeted approaches in selected patients who progress on osimertinib.

A recent multi-institutional retrospective analysis of 41 NSCLCs who underwent tumor next-generation sequencing after acquired resistance to osimertinib revealed that among 32% of patients with maintained T790M at the time of resistance, *EGFR* C797S occurred in 22% of cases. By contrast, in 28 individuals (68%) with loss of T790M, a range of competing resistance mechanisms was detected, including acquired *KRAS* mutations and targetable gene fusions (*RET*, *FGFR3*, and *BRAF* fusion) or *MET* amplification (23). Given that osimertinib was designed to covalently bind to the EGFR kinase-binding site C797, mutation occurring at this site abrogate the binding activity of osimertinib. However, a first-generation EGFR TKI can potentially be effective after osimertinib when C797 tertiary mutation occurs in trans with the T790M mutation (24,25). Similarly, patients with actionable

gene fusion or amplification may benefit from switching to a different targeted approach. Interestingly, a recent study demonstrated that *RET* fusions may mediate resistance to EGFR TKIs and that this bypass track can be effectively targeted with the combination of the selective RET inhibitor (BLU-667) with osimertinib (26). Unfortunately, other mechanisms of resistance such as small-cell transformation and epithelial to mesenchymal transition (EMT) are no susceptible to any targeted agents (24,26). In such cases a standard treatment is chemotherapy, and a consideration can be given to immunotherapy.

Another argument that should be considered is whether first-line osimertinib could modify the spectrum of resistance mutations that can potentially influence the long-term survival of *EGFR*-mutant NSCLC patients who progress on treatment. Detailed genomic analysis from the FLAURA trial upon disease progression have not been presented, therefore data regarding the possible shift of the mutational profile under the selective pressure of early osimertinib administration are currently unavailable. However, circulating tumor DNA (ctDNA) analysis from 19 patients treated with upfront osimertinib in the AURA1 trial, unveiled putative resistance mechanisms in 9 patients, including amplification of MET (n=1); amplification of *EGFR* and *KRAS* (n=1), *MEK1*, *KRAS*, or *PIK3CA* mutation (n = 1 each), EGFR C797S mutation (n=2), *JAK2* mutation (n=1), and *HER2* exon 20 insertion (n=1). Of note, acquired *EGFR* T790M was not detected. Genomic analysis from patients progressing on first-line osimertinib are necessary to further investigate the different mechanisms of osimertinib resistance between the use in first line setting and following the standard TKIs.

In conclusion, the question of the best treatment sequence in *EGFR*-mutant NSCLC has not been properly addressed yet. The phase II APPLE trial comparing upfront osimertinib versus gefitinib followed by osimertinib at disease progression is ongoing and will help us to better understand the optimal strategy to approach patients with *EGFR*-mutant NSCLC (27). While waiting for these results and the mature OS data from the FLAURA trial, in light the impressive efficacy and the higher intracranial activity showed as frontline therapy, osimertinib should be considered the best treatment option for all patients with newly diagnosed NSCLC harboring *EGFR* sensitizing mutations.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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