Editorial

First line osimertinib for the treatment of patients with advanced EGFR-mutant NSCLC

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Background

Molecular profiling in patients with newly diagnosed advanced non-small cell lung cancer (NSCLC) has become routine in clinical practice, allowing us to provide the most effective treatment to individuals harboring actionable genetic alterations. Activating epidermal growth factor receptor (*EGFR*) mutations are present in approximately 10–15% of Caucasian patients and 35–40% East Asian patients with NSCLC (1). Together, in frame deletions in exon 19 at the LeuArgGluAla sequence (E746-A750), and the exon 21-point mutation Leu858Arg (L858R), account for nearly 85–90% of all *EGFR* mutations in NSCLC, and predict exquisite sensitivity to EGFR tyrosine kinase inhibitors (TKIs) (1). On the other hand, 10–18% of all *EGFR* mutations primarily consist of exon 20 insertions, exon 18 point mutations and complex mutations. Although improved detection techniques have enlarged the spectrum of genetic alteration within the 'uncommon group' their predictive role is variable and not yet fully enlighten (2).

Following the identification of such actionable genetic variants and the subsequent development of specifically designed targeted therapies, the overall survival of patients harboring *EGFR* mutations has dramatically increased over last decades, from a median of 7.9 months in 2001 to 27.3 months in 2015 (3,4).

Currently, first- and second-generation (gefitinib, erlotinib, afatinib) EGFR TKIs are recommended as up-front therapy in *EGFR*-mutant NSCLC patients, having definitely shown superior efficacy in terms of progression-free survival (PFS), objective response rate (ORR) and quality of life (QoL) as compared to chemotherapy (5). Unfortunately, although such patients usually experience rapid and durable responses, virtually all of them develop resistance to treatment within 9–12 months, which reflects either a pharmacodynamic resistance or a pharmacokinetic failure, as case of central nervous system (CNS) progression. Among the mechanisms of pharmacodynamics resistance, the emergence of the somatic *EGFR* T790M gatekeeper mutation represents the most common, and is responsible for approximately 60% of cases of acquired resistance to first- and second-generation EGFR TKIs (6). Osimertinib is a third-generation EGFR TKI that binds covalently to EGFR isoforms (del19, L858R and double mutants containing T790M mutation) via cysteine residue at codon 797 (C797) and has minimal activity against wild type *EGFR*, which minimizes skin and gastrointestinal toxicities (7). Although different third generation EGFR TKIs have been developed so far, osimertinib is the only agent approved for the treatment of T790M-positive *EGFR*-mutant NSCLC patients who experience disease progression to up-front first- or second-generation EGFR TKIs, based on the astounding results of the phase I/II AURA, phase II AURA2 and phase III AURA3 study. In the phase I part of the AURA study, which enrolled patients with advanced NSCLC that had progressed after treatment with EGFR TKIs, the ORR for osimertinib was

61%, with a median PFS of 9.6 months among patients who had centrally confirmed *EGFR* T790M mutation (8). These encouraging results were further corroborated in the phase II AURA extension, where the ORR was 62% and median PFS reached 12.3 months in patients with EGFR TKI-pretreated T790M-positive NSCLC (9). Consistently, 140 out of 210 (67%) of EGFR TKIs pretreated patients enrolled in the AURA2 study experienced an objective response, with a median PFS of 9.9 months (10). This data has been further validated in the confirmatory randomized, controlled, phase III AURA3 study. In this trial patients were randomized to osimertinib or platinum/pemetrexed doublet as second-line treatment for *EGFR*-mutant and T790M-positive NSCLC patients who had progressed on or following up-front standard EGFR TKIs. The median PFS was significantly longer in the osimertinib arm as compared to chemotherapy (10.1 versus 4.4 months, HR: 0.30; 95% CI, 0.23 to 0.41; P<0.001). Accordingly, osimertinib was also associated with a better ORR compared to platinum/pemetrexed (71% versus 31%, P<0.001) (11).

Notably, a predefined subgroup analysis conducted in patients with measurable baseline central nervous system (CNS) lesions, confirmed a greater intracranial efficacy of osimertinib compared to chemotherapy, with an intracranial ORR (IORR) of 70% and 31%, respectively (P=0.015). Of note, blind independent review committee (BIRC)-assessed CNS PFS was significantly longer with osimertinib than platinum-pemetrexed (11.7 *vs.* 5.6 months; P=0.004) (11). Consistently, a recent pooled analysis from two phase II trials (AURA extension and AURA2) has shown a clinical meaningful activity of osimertinib against brain metastasis in pretreated *EGFR*-mutant NSCLC patients, with confirmed CNS ORR and DCR of 54% and 92%, respectively (12).

Against this background, in November 2017, Soria and colleagues reported in the *New England Journal of Medicine* the eagerly awaited results of the FLAURA phase III trial, which has been designed to answer the question whether up-front osimertinib is superior to standard first-line EGFR TKIs in patients with advanced NSCLC harboring *EGFR* del19 or L858R genotype.

Strengthening the frontline treatment in EGFR-mutant NSCLC: the FLAURA trial

FLAURA trial is a phase III randomized, double-blind study that enrolled 556 patients with *EGFR*-mutant advanced NSCLC. Patients were stratified according to tumor genotype (del19 and L858R), race (Asian or non-Asian) and were randomly assigned to osimertinib (80 mg once daily) or standard EGFR TKIs (gefitinib or erlotinib at the dose of 250 and 150 mg once daily, respectively). At a median follow-up of 15 months, the study met its primary end-point showing a statistically and clinically significant improvement in PFS with osimertinib as compared to standard TKIs (18.9 versus 10.4 months, HR: 0.46 for PFS and death; 95% CI, 0.37 to 0.57; P<0.001) resulting in a 54% reduction of risk of disease progression or death compared to standard TKIs. The response rate was equally high in both the experimental and control arms (80% and 76%, respectively) (13). Intriguingly, a pre-specified subgroup analysis showed that osimertinib exerted better activity against brain metastasis as compared to gefitinib and erlotinib (ORR: 57% versus 40%, P=0.053), with a median CNS PFS not reached in the osimertinib arm versus 13.9 months of standard of care (HR: 0.48; 95% CI, 0.26 to 0.86; P=0.014) (14).

Preliminary OS data also favored osimertinib with a 37% reduction in the risk of death [HR 0.63; 95% CI, 0.45 to 0.88; P=0.007 (not significant)] at the interim OS analysis (25% maturity).

Although survival data were still immature at data cut-off, a higher percentage of patients in the osimertinib arm than in the standard EGFR TKIs group were alive at 12 months (89% versus 82%) and 18 months (83% versus 71%), despite crossover (13). However, this data is preliminary and still largely unstable.

When it comes to the safety profile, the range of toxicities was similar in both arms. In patients treated with osimertinib, the most common adverse events (AEs) were diarrhea [58% (2% grade ≥3)] and dry skin [32% (<1% grade ≥3)]. In the comparator arm, the most common AEs were diarrhea [57% (3% grade ≥3)] and dermatitis acneiform [48% (5% grade ≥3)].

Nonetheless, the frequency of grade ≥3 AEs was lower with osimertinib (34% versus 45%), despite the longer median duration of exposure with osimertinib. Consistently, osimertinib was also associated with a lower rate of AEs leading to discontinuation as compared to standard TKIs (13% versus 18%) (13).

Discussion

Results from the FLAURA trial provide evidence for the use of osimertinib as first-line treatment for patients with locally advanced or metastatic *EGFR*-mutant NSCLC. This study showed a nearly doubled PFS with osimertinib

as compared to currently approved first line EGFR TKIs erlotinib or gefitinib. Moreover, FLAURA safety data are in line with those reported in previous studies and no new safety concerns emerged. Previously, Ramalingam and colleagues have reported preliminary data from two cohorts of treatment-naive patients of the phase I AURA trial and investigated the safety and efficacy of osimertinib monotherapy as up-front therapy for *EGFR*-mutated NSCLC. At data cut-off, the median follow-up was 19.1 months, the confirmed ORR was 67% in the 80-mg cohort and 87% in the 160-mg cohort while DCR was 93% in the 80 mg once daily cohort and 100% in the 160-mg cohort. The median PFS was 22.1 and 19.3 months in the 80- and 160-mg cohort, respectively (15). In the context of the available literature, the FLAURA trial strengthens the rationale for the use of osimertinib as first-line therapy in *EGFR*-mutated NSCLC patients by providing the first head to head comparison between a third generation EGFR TKI and standard inhibitors.

The FLAURA trial met its primary end-point, however some considerations should be carried out.

The principal question that this study raises is whether osimertinib should be considered the best first-line option for patients with del19 or L858R *EGFR* genotype or should be used on relapse upon documentation of T790M resistance mutation. In patients with NSCLC harboring actionable mutations, the OS is now measured in years and represents a fundamental end-point in patients with driver mutations. Although osimertinib is undoubtedly superior to standard TKIs in terms of PFS and tolerability, OS data from FLAURA trial are immature. Still pending are also the final OS results from the AURA 3 study, which are expected to further contribute in shining light on the optimal treatment sequence in *EGFR*-mutant NSCLC. Therefore, at the present time, this question remains unanswered. An argument in favor of starting with up-front osimertinib rather than first and second-generation EGFR TKIs is certainly the better tolerability of osimertinib, as these patients are expected to remain on treatment for a prolonged time. In addition, osimertinib has increasingly been reported to exert higher activity against brain metastasis, which can allow for a prolonged control of intracranial disease, potentially delaying the use of radiotherapy and consequently its cognitive side effect. This aspect is of primary significance in light of the life expectancy of *EGFR*-mutant NSCLC patients treated with EGFR TKIs. More importantly, starting with upfront osimertinib would mean that the totality of *EGFR*-mutant patients will get the benefit of receiving a third generation TKI during the course of their life. Differently, approximately 40% of patients progressing on standard TKIs do not harbor the T790M secondary mutation and are not eligible for treatment with osimertinib, with a median PFS that is clearly less than the 18.9 months experienced by patients treated with first-line osimertinib. On the other hand, the exclusion of second-generation EGFR TKIs from the comparator arm may represents a limitation of the study, as at time of FLAURA trial initiation afatinib was not widely used as standard of care, while dacomitinib was exclusively investigational. However, the clinical impact of afatinib in patients with EGFR-mutant NSCLC is now well known, and a recent meta-analysis has concluded there is no difference in efficacy among gefitinib, erlotinib and afatinib (16).

Differently, in the ARCHER 1050 trial dacomitinib showed improved PFS compared to gefitinib (14.7 versus 9.2 months, HR: 0.59; 95% CI, 0.47 to 0.74; P<0.0001) in first-line setting, thus leaving unanswered the question whether second-generation EGFR TKIs followed by osimertinib may be superior in term of OS to up-front osimertinib (17). In this scenario, whether baseline T790M status should be assessed to decide which patients might benefit from first-line osimertinib remains to be determined. Another limitation of the FLAURA study relies in the fact that magnetic resonance imaging (MRI) of the brain was not mandatory. In light of the high incidence of asymptomatic brain metastasis in this subset of patients, this limitation will also bias the evaluation of intracranial activity of osimertinib.

Lastly, the mechanisms of resistance to osimertinib in first-line setting and their potential impact on survival are poorly understood. The only available data derives from two expansion cohorts of treatment-naïve patients enrolled in AURA trial. Among nineteen out of 38 patients with post-progression plasma sample, the presumed mechanism of resistance identified with next-generation sequencing (NGS) using a 56-gene panel (AstraZeneca, Cambridge, United Kingdom) and a 73-gene panel (Guardant Health, Redwood City, CA, USA), included *MET*, *EGFR* and *KRAS* amplification, somatic mutations in *MEK1*, *KRAS*, *PIK3CA* and *JAK2*, *EGFR C797S* mutation and *HER2* exon 20 insertion (15). Of note, tissue rebiopsy was not performed, thus hindering the possibility to recognize different molecular determinants of resistance. Further studies are required to verify whether such mechanisms impact on the use of osimertinib as first-line treatment.

Conclusions

With a doubled median PFS and an encouraging trend towards an improvement in OS, first-line osimertinib should be considered a new standard of care for first-line therapy of *EGFR*-mutant NSCLC. However, mature data from ongoing clinical trials are eagerly awaited to shine further light on the correct treatment sequence for patients with *EGFR*-mutant NSCLC.

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Footnote

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

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