Editorial

Moving osimertinib to first-line: the right "strategy" in the chessboard of epidermal growth factor receptor-mutated non-small cell lung cancer?

Francesco Passiglia[1], Luis E. Raez[2], Christian Rolfo[3]

[1]Department of Surgical, Oncological and Stomatologic Disciplines, University of Palermo, Palermo, Italy; [2]Thoracic Oncology Program, Memorial Cancer Institute, Memorial Health Care System, Florida International University, Miami, FL, USA; [3]Phase I-Early Clinical Trials Unit, Department of Oncology, Antwerp University Hospital and Center for Oncological Research, Antwerp University, Edegem, Antwerp, Belgium

Correspondence to: Christian Rolfo, MD, PhD, MBA. Phase I-Early Clinical Trials Unit, Department of Oncology, Antwerp University Hospital and Center for Oncological Research, Antwerp University, Wilrijkstraat 10, 2650, Edegem, Belgium. Email: christian.rolfo@uza.be.

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In the *N Engl J Med*, Soria and colleagues have recently reported the results of the phase III randomized FLAURA trial (1), comparing osimertinib with first generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) gefitinib or erlotinib in treatment-naive patients with advanced non-small cell lung cancer (NSCLC) and activating *EGFR*-mutations. The study met its primary end-point showing a significant longer median progression-free survival (PFS) in favor of osimertinib compared with the first-generation EGFR-TKIs (18.9 *vs.* 10.2 months; HR: 0.46; 95% CI: 0.37–0.57; P<0.001). The significant improvement in PFS was confirmed across all predefined subgroups, including specific types of *EGFR* mutations (exon 19 deletion and exon 21 L858R point mutation) and the presence or absence of baseline brain metastases. Despite the fact that the objective response rate (ORR) was similar between the two treatment arms (80% *vs.* 76%), the duration of response was significantly longer with osimertinib (17.2 months) than the other EGFR-TKIs (8.5 months). Overall survival (OS) data were not mature at the time of interim analysis, showing a not significant trend toward a longer OS in favor of osimertinib (HR: 0.63; 95% CI: 0.45–0.88; P=0.007). Both treatments were well tolerated with the majority of adverse events (AEs) being grade 1 or 2 and a similar low frequency of dose-reductions and dose-interruptions due to AEs. Interestingly the percentage of patients who reported grade 3–4 AEs was somewhat lower with osimertinib (34%) than the other EGFR-TKIs (45%). All these data suggested that osimertinib is more effective and better tolerated than first-generation TKIs, emerging as new standard of care for first-line treatment of EGFR-positive advanced NSCLC. EGFR-activating mutations have been reported in about 50% of Asian (2,3), 15% of Caucasian (4,5), and 30% of Latin-American (6) patients, thus representing a significant subgroup of the overall NSCLC population. The discovery of EGFR as oncogene driver in 2004 has led to the development of the first class of targeted agents which were able to selectively binding and inhibiting the EGFR-signaling pathway in lung cancer cells, known as EGFR-TKIs (7). The IPASS trial (8) was the first randomized study showing that the EGFR-TKI gefitinib was more effective and better tolerated than the standard first-line platinum-chemotherapy in the subgroup of patients with advanced NSCLC harboring EGFR-activating mutations, introducing the new concept of "personalized therapy". After that, several other randomized studies (9-14) consistently demonstrated a significant superiority of EGFR-TKIs over standard platinum-chemotherapy, in terms of ORR, PFS, tolerability and quality of life (QoL),

leading to the sequential approval by regulatory authorities of gefitinib, erlotinib and afatinib as first line treatment for EGFR-mutated NSCLC patients. Mutational analysis of tumor samples at the time of diagnosis is now recommended in all the patients with advanced disease since molecular selection has led to a significant increase of median OS reaching a plateau ranging from 21 to 30 months after the advent of EGFR-TKI in first-line (15). Unfortunately acquired resistance inevitably develops within the first year of therapy, leading to clinical disease progression, thus limiting the potential benefit of targeted drugs (16). In the last few years different alternative strategies have been investigated in clinical trials to overcome innate and acquired resistance to EGFR-TKI and ultimately improve the survival outcomes of EGFR-mutated NSCLC patients (16). The addition of either anti-angiogenic agent bevacizumab (17), or chemotherapy (18) in first-line seem to raise the effectiveness of single agent EGFR-TKI, likely thanks to the synergistic activity against *de novo* resistance alterations, but the results observed in Asian populations need to be confirmed in prospective phase III studies including Caucasian patients before to accept the increased toxicities and costs of potential upfront combinations. Besides the low benefit observed with immune checkpoint inhibitors (ICIs) in pre-treated, EGFR-positive NSCLC patients (19), several studies are currently combining ICIs and targeted therapies in first-line, and the results are expected. Second-generation pan-Her TKIs, afatinib and dacomitinib have been both compared with gefitinib as first-line treatment in advanced EGFR-mutated NSCLC. Particularly the phase IIb Lux-Lung 7 study (20) showed that afatinib was associated with increased ORR and longer PFS and time to treatment failure (TTF) than gefitinib without any significant differences in OS. Similarly, the phase III ARCHER 1050 trial (21) has recently demonstrated that dacomitinib significantly prolonged PFS and duration of response over gefitinib, while the OS data were not mature yet at the time of data analysis. Overall these studies suggested that second-generation EGFR-TKIs were more effective than first-generation TKIs as first line therapy of EGFR-positive NSCLC. However, the analysis of safety data emerging from these studies revealed that both afatinib and dacomitinib were more toxic than gefitinib, resulting in a significant higher incidence of severe AEs and dose-reductions due to AEs (20,21). In addition, there are not clinical evidences to support the activity of second-generation TKIs in patients with brain metastasis. Conversely, the randomized phase III FLAURA trial (1) demonstrated that the third-generation EGFR-TKI osimertinib is more effective and better tolerated than first-generation TKIs in untreated patients with advanced EGFR-positive NSCLC, including also 20% with brain metastasis at study entry. The activity of osimertinib in the brain is due to its peculiar structure which confers the ability to cross the blood brain barrier (BBB) (22), resulting in a lower incidence of central nervous system (CNS) progression than erlotinib/gefitinib (6% *vs.* 15%) (1), and confirming the meaningful clinical efficacy observed in previous studies including T790M-positive NSCLC patients with brain metastasis (23). Osimertinib is a third-generation TKI selectively targeting both EGFR-activating and resistant T790M mutation. The exon 20 T790M mutation is the leading cause of acquired resistance occurring in about 50–60% of tumors progressing to first-generation TKIs (16). The percentage of T790M-positive clones coexisting with EGFR-activating mutations in TKI-naïve patients is reported to range from 8% in the AURA1 trial (24) to 65% in EURTAC trial (25), depending on the detection method used. Thus, the ability of osimertinib to early target both *de-novo* and acquired 790M mutations could provide the biological rational to support its greater efficacy over other TKIs. The preliminary data coming from the first-line cohort of the AURA1 trial (24) showed that six of seven patients with *de-novo* T790M mutations had a partial response (PR), with duration of response ranging from 6.9 to 27.7 months. A subsequent analysis of the FLAURA trial will inform us about the activity of osimertinib in a larger subgroup of patients harboring *de-novo* T790M mutations. Recently osimertinib has been approved as standard treatment for EGFR-mutated NSCLC patients who progressed to first-generation TKIs and were T790M-positive on tumor re-biopsy. The phase III randomized AURA3 trial (26) revealed that osimertinib significantly improved ORR, PFS, and QoL as compared to platinum-chemotherapy becoming the new standard of care in this subgroup of patients who were T790M-positive on either tumor tissue or circulating tumor DNA (ctDNA) analysis and leading to the clinical use of ctDNA as routinely screening test for tumor-genotyping (15). Until FLAURA was presented it remained unclear whether the upfront use of osimertinib would result into a greater and more durable survival benefit as compared to the current sequential approach. If we look at the overall sequence of first/second-generation TKIs followed by osimertinib of the AURA3 trial (26), it

seems to offer longer survival outcomes as compared to upfront osimertinib. Similarly, the median OS was 48.3 months for gefitinib followed by osimertinib (1) and it was not reached yet for afatinib followed by osimertinib in the small subgroup of EGFR-positive patients who received sequential TKIs in the LUX-Lung 7 trial (27), suggesting that using osimertinib after second-generation TKI may further improve OS. The mature OS data from both AURA3 and FLAURA trials will be crucial to further investigate the optimal sequence, even if the cross-over to osimertinib allowed in the FLAURA trial will likely reduce the clinical relevance of final OS results. In addition, resistance mechanisms to upfront osimertinib, as well as potential options post-osimertinib and their effect on final OS data remain still unknown. Preliminary data from ctDNA analysis on 38 patients included in the first-line cohort of AURA1 trial (24) with post-progression plasma samples available, showed a heterogeneous scenario, including MET, EGFR and KRAS amplification, KRAS or PIK3CA mutations, HER2 exon 20 insertion, JAK2 V617F variants, and the EGFR C797S mutation. The combination of brigatinib with anti-EGFR monoclonal antibody has recently shown to overcome C797S/T790M-mediated resistance to osimertinib in NSCLC (28). However further analysis in larger cohorts of patients are urgently needed and, in this context, the FLAURA will represent a great source of information. The question of the best treatment strategy has been properly addressed by the ongoing randomized phase II APPLE trial (29) comparing upfront osimertinib *vs.* gefitinib followed by osimertinib at disease progression, with PFS rate at 18 months as primary endpoint. Waiting for these results, we should also consider that approximately half of the initial EGFR-positive population who do not harbor the T790M at the time of disease progression will never receive osimertinib in the natural course of their disease. Another subgroup of patients will not be eligible to second-line therapy because of rapid disease progression and clinical deterioration during first-line treatment. In addition, false T790M-negative results associated with ctDNA analysis and pre-existing conditions precluding tumor re-biopsy at the TTP will further increase the percentage of EGFR-positive patients who could potentially benefit from osimertinib but will never receive it. The results of the FLAURA trial (1) clearly demonstrated that upfront osimertinib nearly doubled median PFS and duration of response, is less toxic and has intracranial activity against brain metastasis that is superior than all other TKIs, emerging as the most effective and better tolerated EGFR-TKI currently available for clinical treatment of EGFR-positive NSCLC patients. Thus, we should offer this new TKI to the majority of patients with a newly diagnosed advanced NSCLC harboring EGFR mutations. The impressive and durable efficacy observed with upfront osimertinib in the FLAURA trial together with all the aforementioned clinical issue ultimately suggest that moving osimertinib to first-line is a right strategy in the chessboard of EGFR-positive NSCLC.

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Footnote

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