

# A reflection on the actual place of osimertinib in the treatment algorithm of EGFR-positive non-small cell lung cancer patients

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## Introduction

We read with interest the results of the TREM study, recently published by Eide *et al.* (1). The TREM was a multi-center, independent, single arm study, enrolling epidermal growth factor receptor (*EGFR*) mutant, stage IV, non-small cell lung cancer (NSCLC) patients who progressed to at least one previous treatment line with first/second-generation *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs), such as gefitinib, erlotinib and afatinib. Every patient received osimertinib (a third-generation *EGFR*-TKI) at the dose of 80 mg once a day, regardless of the T790M mutational status. The primary end-point was the objective response rate (ORR) in the overall population, even if a formal power calculation was not performed. Being a non-comparative study, no conclusive considerations are allowed; however, the subgroup analyses according to the T790M mutational status raises some interesting questions regarding the evolving therapeutic scenario of *EGFR*-positive NSCLC patients.

Outcomes reliability was supported by comparison with the AURA trial, which enrolled also T790M negative patients (2). Despite some meaningful differences, such as the dose escalation from 20 mg in the first 31 patients, or patients with performance status (PS)  $\geq 2$  not eligible, the AURA trial represents the best comparison for the study of Eide and colleagues. The ORR for the overall population of the two studies was indeed aligned (48%

*vs.* 51%). Moreover, in both the AURA and TREM trials patients received at least one prior *EGFR*-TKI and the percentage of T790M positive patients were similar between (28% *vs.* 26%), as like the percentage of baseline non-L858R point mutations/non-exon 19 deletions (5% both). On the other hand, comparing the clinical outcomes of the two trials according to the T790M mutational status, some intriguing differences emerge. The T790M positive subgroups displayed similar ORR (60% *vs.* 61%) and progression-free survival (PFS) (10.8 *vs.* 9.6 months), but the T790M-negative patients of the TREM study (1) showed a slightly higher ORR (28% *vs.* 21%) and a prolonged PFS (5.1 *vs.* 2.8 months). According to the AURA 3 study results, osimertinib should be considered the standard second line treatment only for NSCLC patients who develop a T790M-driven disease progression to first/second-generation *EGFR*-TKIs (3), whilst the finding of a certain clinical benefit with second line osimertinib in T790M negative patients, might again raise some questions. From this point of view, the TREM study results might suggest that all the patients who received front line first/second-generation *EGFR*-TKI (including those who develop T790M negative disease progression) could benefit from second line osimertinib, reinforcing the theory that all the *EGFR*-positive NSCLC patients should be treated with an *EGFR*-TKIs sequencing across treatment lines. Nevertheless, the recently updated

**Table 1** summary of the rate of patients who received post-progression systemic treatments in clinical trials with EGFR-TKIs

Study	EGFR-TKI	Post-progression treatment*, %
IPASS, Fukuoka <i>et al.</i> , J Clin Oncol 2011	Gefitinib	76
NEJ002, Inoue <i>et al.</i> , Ann Oncol 2013	Gefitinib	72
WJTOG 3405, Yoshioka <i>et al.</i> , Ann Oncol 2019	Gefitinib	86
EURTAC, Rosell <i>et al.</i> , Lancet Oncol 2012	Erlotinib	68
OPTIMAL, Zhou <i>et al.</i> , Ann Oncol 2015	Erlotinib	63
LUX-LUNG 3, Yang <i>et al.</i> , Lancet Oncol 2015	Afatinib	71
LUX-LUNG 6, Yang <i>et al.</i> , Lancet Oncol 2015	Afatinib	57
LUX-LUNG 7, Paz-Ares <i>et al.</i> , Ann Oncol 2017	Afatinib	73
FLAURA, Ramalingam <i>et al.</i> , N Engl J Med 2020	Gefitinib	77
	Osimertinib	60
	Erlotinib/gefitinib	68

\*, After discontinuation of study treatment, excludes patients remaining on assigned treatment at data cut-off, pre-progression treatment and death. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

FLAURA study confirmed that first line osimertinib lead to a significantly prolonged overall survival (OS) compared to first-generation EGFR-TKIs in NSCLC with common sensitizing mutations (4), refuting, at least partially, the EGFR-TKIs sequencing therapeutic approach.

### The EGFR-TKIs sequencing approach

EGFR-TKIs sequencing is a treatment strategy which provides a sequential use of first/second-generation EGFR-TKI as first line treatment, followed by osimertinib as second line in case of T790M-driven disease progression. This strategy has of course some positive aspects. A recent real-world analysis of 576 T790M positive patients who received first/second-generation TKIs followed by osimertinib, reported a 36-month OS rate of 51% (5). Careful interest was addressed to the sequence afatinib/osimertinib: a subgroup analysis of an observational prospective registry, although with an extremely small sample size (29 patients), reported a 24-month OS rate of 89.3% for T790M positive patients who received both drugs (6). Similarly, another retrospective real-life study highlighted a median OS of 41.3 months for the overall study population, and of 45.7 months for patients with exon 19 deletion (7). The greatest flaw of the sequential approach is due to not every patients are used to developing T790M driven disease progression, and therefore can benefit from second line osimertinib. Intriguingly, the quite good

efficacy reported by the TREM study for T790M negative patients (ORR of 28% and the PFS of 5.1 months), could make us believe this limitation overcome, supporting the sequencing approach for all. Ideal sequential approach should be offered to each patients; unfortunately, not every patients developed T790M driven disease progression, and therefore cannot benefit from second line osimertinib. However, to proper evaluate our considerations, several aspects must be taken into account. First, we analyzed the rate of patients who usually reach a second line treatment. Disease progression of metastatic NSCLC could be life-threatening, and a not negligible percentage of patients dies at each treatment line. *Table 1* summarized the rate of patients who received post-progression systemic treatments in clinical trials with EGFR-TKI (range: 60–86%). Also, the T790M test availability might be considered a limit to overcome. A recent analysis (8) reported that: (I) 23% of patients receiving first/second-generation EGFR-TKIs did not received a second line treatment; (II) 25% of the progressors were not tested for T790M mutation; (III) 41% of the progressors finally received second line osimertinib. Similarly, Shah *et al.* (9) reported that 21% of the progressors to first/second-generation EGFR-TKIs did not received a second line treatment, 26% of the progressors were not tested for T790M mutation and only 28.2% of the progressors received second line osimertinib. Therefore, the T790M detection rate at disease progression should always be taken into account. Eide *et al.* (1) showed 60% of T790M

patients which was higher than what reported in some real-life studies (10,11), but aligned to others (12). The updated FLAURA trial (4) experienced a median OS of 38.6 months for the experimental arm by first line osimertinib and a median follow-up of 39 months, which seems shorter than the OS (since the starting of the first line) reported for T790M positive patients receiving sequential first/second-generation TKIs and osimertinib. Nevertheless, we must to consider some selection bias. Patients developing T790M driven disease progression have a better prognosis, regardless of the treatment with second line osimertinib. A meta-analysis on the impact of acquired EGFR T790M mutation, which included studies where no patients had ever received third-generation EGFR-TKIs, displayed a significantly longer post-PFS, OS and PFS since the first line in T790M positive patients (13). Oxnard *et al.* (14), in a prospective re-biopsy protocol performed many years before the introduction into clinical practice of third-generation EGFR-TKIs, noticed that T790M positive *vs.* negative patients had a longer post-PFS and a longer time to new metastases. The TREM study (1) revealed a higher T790M detection rate for patients with previous exon 19 deletion (53%), compared to patients with exon 21-point mutation (26%), as already reported (15). Moreover, Eide *et al.* (1) showed, among the T790M negative patients, a prolonged PFS and OS if there were no central nervous system (CNS) metastases compared to CNS involvement. These results assume that a sequencing approach could be considered for patients with baseline exon 19 deletion and without CNS metastases. TREM study (1) enrolled also patients with uncommon mutations, and to date, the only category for whom EGFR-TKIs sequencing should to be considered upfront, is represented by patients with uncommon *EGFR* mutations (excluding exon 20 mutation). Indeed, the FLAURA study (4) enrolled only patients with common *EGFR* mutations, and despite some intriguing results have already reported in a phase II study (16), there are not reliable data for such indication yet. Instead, quite good results with afatinib have highlighted across the Lux-Lung trials (17).

### The evolving scenario of EGFR positive NSCLC

Recently, dacomitinib (second-generation EGFR-TKI) have considered in the first line scenario. Despite some major limitations such as the hierarchical order of the endpoints, the failure to enroll patients with CNS metastases and a not negligible toxicity profile, the phase III ARCHER 1050

study (18) showed an improvement of PFS and OS for first line dacomitinib compared to gefitinib. Even if the T790M detection rate among the progressors to dacomitinib is still not available, only 9.7% of the patients in the experimental arm received a third-generation TKI as second line treatment at the data cut-off. Combination of first-generation EGFR-TKI with anti-angiogenic monoclonal antibodies has proven effective. The phase III studies in treatment of EGFR positive NSCLC patients, comparing erlotinib alone with either erlotinib plus bevacizumab (19) or erlotinib plus ramucirumab (20), have both displayed interesting results in terms of efficacy. However, the same principles and flaws of the sequential approach already discussed, may be applied to this setting. In fact, the T790M detection rate reported among the progressors of the experimental arm of the RELAY study was 43% (19). Even the combination of gefitinib with platinum-based chemotherapy showed OS significant benefit over gefitinib alone (21), and might be taken into consideration in those countries where first-line osimertinib is not reimbursed. Currently, a phase III study of upfront combination of osimertinib with platinum-based chemotherapy is underway (22). While in the clinical practice of western countries the osimertinib indication is moving forward to the first-line setting, it might think that the avoidance of sequential approach could results in a lack of therapeutic options at disease progression. In our opinion, an early monitoring during treatment with quantitative and qualitative liquid biopsy techniques should be carried out when available, in order to early detect progressors with actionable biomarkers (23). In case of oligoprogression, when it occurs without actionable biomarkers emergence, osimertinib has already proved its feasibility eventually combined with local ablative treatments (24). The combination of carboplatin/paclitaxel with both bevacizumab and atezolizumab (an anti-programmed death-ligand 1 checkpoint inhibitor) (ABCP) is another therapeutic option to disease progression. The IMpower 150 study (25), enrolling also pre-treated oncogene addicted patients excluded from the primary analysis, revealed impressive efficacy outcomes for the subgroup of EGFR mutation-positive patients. However, the applicability of the ABCP combination in the setting of disease progression during first line osimertinib, is heavily flawed by the previous treatment with first/second-generation EGFR-TKI in the IMpower 150 experience (25). Moreover, the T790M status was not available and the sample size was also too low in order to make definitive considerations.

## Conclusions

In order to make a proper choice among first line treatment options for EGFR positive NSCLC patients, the major points to take into consideration are:

- The rate of patients receiving a second line treatment in both clinical trial and real-life settings;
- The T790M detection rate and the testing availability;
- The T790M-related positive selection bias (when comparing first line osimertinib OS with EGFR-TKI sequencing cumulative OS);
- Resources availability and local reimbursement policies.

Despite the interesting results reported by Eide *et al.* (1) for the second line osimertinib regardless of the T790M mutational status, in our opinion each metastatic *EGFR* positive NSCLC patients with common mutation (L858R and exon 19 deletions) should receive upfront osimertinib when local regulatory policies allows it.

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