

# Osimertinib as first-line treatment of *EGFR* mutant advanced non-small-cell lung cancer

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*Provenance:* This is an invited Editorial commissioned by Guest Section Editor Dr. Feichao Bao, MD (Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University, Hangzhou, China).

*Comment on:* Ramalingam SS, Yang JC, Lee CK, *et al.* Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2017. [Epub ahead of print].

Submitted Oct 01, 2017. Accepted for publication Oct 16, 2017.

doi: 10.21037/tlcr.2017.10.10

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.10.10>

The epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib and afatinib are currently recommended for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring EGFR-TKI-sensitizing mutations (*EGFRm*) (1,2). However, after a period of 9 to 11 months of treatment, acquired resistance to these first- and second-generation EGFR-TKIs inevitably develops. In 50–60% of the cases, acquired resistance is due to *EGFR T790M* mutation, which is the substitution of threonine with methionine at amino acid position 790, *EGFR<sup>T790M</sup>* (3,4). Osimertinib (AZD9291) is a third-generation irreversible EGFR-TKI designed to overcome the *T790M* substitution mutation while also having inhibitory activity on *EGFRm* but less affinity for wild-type *EGFR*, thereby minimizing the skin and gastrointestinal toxicities associated with first- and second-generation EGFR-TKI therapy (5). *In vitro*, osimertinib considerably delays the emergence of resistance in *EGFR* exon 19 deletion (*Ex19del*) PC9 cells compared with other EGFR-TKIs (6) which suggests osimertinib could be effective as first-line therapy in patients harboring *EGFRm* and has the potential to delay the emergence of resistance.

The osimertinib clinical development and registration program, Osimertinib First Time in Patients Ascending Dose (AURA) which spans phase I to III trials, primarily investigated osimertinib as a second-line therapy following prior EGFR-TKI therapy and consists of three studies—

AURA (ClinicalTrials.gov, NCT01802632) which comprises a phase I dose escalation and expansion component and a phase II AURA extension component, AURA2 (ClinicalTrials.gov, NCT02094261) which is a pivotal phase II study, and AURA3 (ClinicalTrials.gov, NCT02151981) which is a phase III confirmatory comparator study.

The phase I and II AURA trial was conducted to determine the safety and efficacy of osimertinib in patients with *EGFR*-mutated advanced NSCLC who had disease progression after prior EGFR-TKI treatment (7). The study included a total of 253 patients: 31 patients not selected by *T790M* status in the dose-escalation cohorts and 222 patients according to prospective *T790M* status in five dose-expansion cohorts. In the expansion cohorts, all patients underwent tumor biopsy for central assessment of *T790M* mutation status. Eighty percent of the patients had received prior chemotherapy. In the dose-escalation part of the study in which patients received osimertinib at doses of 20–240 mg once daily, no dose-limiting toxicities were observed at any dose level and the maximal tolerated dose was not reached at any dose level. Of the 239 patients evaluable for response, the objective response rate (ORR) was 51% and the disease control rate (DCR) was 84% (7). The median progression-free survival (PFS) was 8.2 months. In the *T790M*-positive subgroup, the ORR was 61%, DCR was 95% and median PFS was 9.6 months. In contrast, in *T790M*-negative patients, the ORR was 21% and median PFS was 2.8 months. To maximize efficacy and minimize

skin and gastrointestinal toxicity the 80 mg once daily dose was chosen for subsequent phases II and III studies, even though a true dose-limiting toxicity was not observed at this dose level (7).

Data from the AURA phase II extension component confirms the high activity of osimertinib at 80 mg once-daily in patients with *EGFR*<sup>m</sup> NSCLC progressing after EGFR-TKI treatment and who harbor *T790M* mutation (8). Among 198 evaluable patients, the ORR was 62%, DCR was 90%, and median duration of response (DoR) was 15.2 months.

The subsequent AURA2 trial, a multicenter, phase II, single arm study which enrolled a total of 201 patients with locally advanced or metastatic NSCLC who had progressed on prior EGFR-TKI therapy and who were *EGFR*<sup>T790M</sup>-positive to receive osimertinib 80 mg once daily demonstrated an ORR of 70% and DCR of 92% among 199 evaluable patients (9). The median DoR was 11.4 months and the median PFS was 9.9 months. A higher number of objective responses and a longer PFS were observed in patients with exon 19 deletions (ORR: 77% and PFS: 10.9 months) than in patients with *L858R* mutations (ORR: 59% and PFS: 8.5 months) although the difference was not statistically significant.

A pre-planned pooled analysis of two phase II studies, the AURA phase II extension cohort and AURA2 trial, confirmed the efficacy findings (10). Among 397 evaluable patients with *EGFR*<sup>m</sup> NSCLC which had progressed following previous EGFR-TKI therapy and whose tumors harbored *EGFR*<sup>T790M</sup> and who were treated with osimertinib at 80 mg once daily, the confirmed ORR was 66% and DCR was 91%. The median PFS for 411 patients was 11.0 months (10).

Based on its impressive clinical activity and good safety profile shown in these early phase I and II trials (AURA and AURA2), osimertinib received accelerated approval by the US FDA on November 13, 2015 and conditional approval by European Medicines Agency on February 2, 2016 for the treatment of *EGFR*<sup>T790M</sup>-positive NSCLC patients whose disease have progressed after therapy with first- or second-generation EGFR-TKIs (1,2).

AURA3 was a phase III randomised controlled trial conducted to confirm the results of single-arm, phase II studies of AURA and AURA2 and to demonstrate the superiority of osimertinib over standard chemotherapy with platinum and pemetrexed in the treatment of *EGFR*<sup>m</sup> advanced NSCLC patients with disease progression after first-line EGFR-TKI therapy and who harbor *T790M*

resistance mutation (11). Patients randomised to the osimertinib arm had a significantly longer median PFS than those in the chemotherapy arm (10.1 *vs.* 4.4 months), had better ORR compared with chemotherapy (71% *vs.* 31%), and had more durable response than chemotherapy (median DoR: 9.7 *vs.* 4.1 months). These more recent results from the confirmatory phase III AURA3 trial established the role of osimertinib as a standard of care (SOC) treatment for patients who progress on first-line EGFR-TKI and who harbor *T790M* resistance mutation.

Since osimertinib is also active against *EGFR*<sup>m</sup> and is associated with less skin toxicities and diarrhea, it was tested as a first-line treatment for metastatic *EGFR* mutation-positive NSCLC. Two of the five expansion cohorts in the phase I component of AURA trial enrolled treatment-naïve patients with locally advanced or metastatic *EGFR* mutation-positive NSCLC and investigated the efficacy and safety of first-line osimertinib monotherapy. Osimertinib was tested at two dose levels of 80 or 160 mg once daily and a total of 60 treatment-naïve patients were enrolled with 30 patients in each cohort. Ramalingam and colleagues report the results of these two cohorts of patients in the *Journal of Clinical Oncology* in August 2017 (12). This is the first full publication reporting the anticancer activity and safety of osimertinib as first-line treatment in patients in these two expansion cohorts of the phase I component of AURA trial (12). With median follow-up of 19.1 months the confirmed ORR was 67% in the 80-mg cohort and 87% in the 160-mg cohort. The DCR was 93% in the 80 mg once daily cohort and 100% in the 160-mg cohort. The median DoR was 19.3 months in the 80-mg cohort and 16.7 months in the 160-mg cohort. The median PFS was 22.1 and 19.3 months in the 80- and 160-mg cohort, respectively. The median PFS values are much longer than that of 8.4 to 13.1 months associated with first-line first- and second-generation EGFR-TKI treatment. Across the 80- and 160-mg once daily doses, median PFS was 23.4 months in patients with an *ex19del* mutation, 22.1 months in patients with an *L858R* mutation, and 8.3 months in those with other *EGFR* mutations which included *G719X*, *S768I*, and *L861Q*.

The toxicity profile was manageable. Similar to the adverse effects of the first- and second-generation EGFR-TKIs, the most commonly reported adverse effects of osimertinib were rash, diarrhea, and dry skin. Side effects and dose reductions due to treatment-related adverse events were more frequent in the 160-mg cohort.

The data from these two expansion cohorts of the

phase I component of AURA trial (12) further support the recommended 80 mg once daily dose in view of the similar PFS observed with the 80- and 160-mg treatment groups and the better tolerability of the 80-mg dose with fewer dose reductions, lower frequency of skin disorders, nail side effects, and diarrhea compared with the 160-mg dose consistent with data from later-line patients treated with osimertinib in the AURA phase I study (7,13). The approval of the 80-mg dose was also based on pharmacokinetic analyses showing the 80 mg dose ensured exposure levels that are greater than those observed for the 20 or 40 mg dose, which had also demonstrated clinical activity in the AURA phase I study.

In the AURA study, circulating cell-free tumor DNA (ctDNA) extracted from baseline plasma samples was genotyped using the beads, emulsions, amplification, and magnetics (BEAMing) digital polymerase chain reaction (PCR) (Sysmex Inostics Inc., Mundelein, IL, USA) for three *EGFR* mutations: exon 19 deletion, *L858R*, and *T790M* (12). With central tissue genotyping (cobas; Roche Molecular Diagnostics, Pleasanton, CA, USA) as a reference, high sensitivity and specificity were observed with plasma genotyping using BEAMing digital PCR (14). In an analysis of 216 patients included in the AURA phase I trial in whom both central tumor and plasma samples for diagnostic comparison were available, plasma genotyping using BEAMing technology had a sensitivity of 82–86% for sensitizing mutations and 70% for *T790M* mutation (14). In the two expansion cohorts of 60 treatment naïve patients, 40% had *EGFR* exon 19 deletion mutation, 42% exon 21 *L858R* mutation, and five patients had *de novo EGFR<sup>T790M</sup>* confirmed by central laboratory tissue genotyping at study entry (12). Plasma genotyping identified two additional *de novo T790M* patients. All seven *de novo T790M* mutations coexisted with *L858R*. Treatment outcomes seemed similar in patients with and without *de novo EGFR<sup>T790M</sup>* and patients with only an *EGFR* activating mutation. Six of the seven patients with concomitant *de novo EGFR<sup>T790M</sup>* had a partial response, with DOR ranging from 6.9 to 27.7 months (12).

The frequency of *de novo EGFR<sup>T790M</sup>* has been reported to be 25–65% depending on the detection methods used (15–17). In the EURTAC trial, pretreatment *EGFR<sup>T790M</sup>* was detected in about 65% of patients using highly sensitive peptide nucleic acid clamping PCR and associated with shorter PFS compared with patients without *de novo EGFR<sup>T790M</sup>* (17). The presence of *de novo EGFR<sup>T790M</sup>* in pretreatment tumors further supports the use of osimertinib upfront. The safety and efficacy of osimertinib as first-

line therapy in patients with metastatic NSCLC harboring concomitant sensitizing and *T790M* mutations at diagnosis is being evaluated in the investigator initiated AZENT trial (ClinicalTrials.gov, NCT02841579).

With the concordance rates between tissue and liquid biopsy results being high (14), the application of liquid biopsies is one of the attractive features of the AURA trials. To investigate resistance mechanisms to osimertinib in the two expansion cohorts of 60 treatment naïve patients, plasma samples were collected at or after patients experienced disease progression and analyzed by next-generation sequencing using a 56-gene panel (AstraZeneca, Cambridge, United Kingdom) and a 73-gene panel (Guardant Health, Redwood City, CA, USA) (12). Of 38 patients with post-progression plasma samples, 19 had no detectable ctDNA while ctDNA was detected in post-progression samples from the other 19 patients. Putative resistance mechanisms identified included amplification of *MET*, *EGFR* and *KRAS*; somatic mutations in *MEK1*, *KRAS*, *PIK3CA* and *JAK2*; *EGFR C797S* mutation; and *HER2* exon 20 insertion. Since tissue rebiopsy was not performed other possible resistance mechanisms such as histological transformation to small cell could have been missed. It is noteworthy that acquired *EGFR<sup>T790M</sup>*, the mutation that osimertinib is approved to treat, was not detected.

The promising preliminary efficacy results of osimertinib treatment in the first-line setting in the AURA phase I trial (12) need to be confirmed and this has led to the FLAURA study (ClinicalTrials.gov, NCT02296125), a phase III randomized, double-blind, multicenter confirmatory trial assessing the efficacy of osimertinib as first-line therapy for treatment-naïve patients with advanced NSCLC with *EGFR* common mutations compared with gefitinib or erlotinib. Based on the efficacy and tolerability data from the AURA first-line cohorts, the 80-mg dose was selected for the FLAURA study in which 556 patients with treatment-naïve locally advanced or metastatic NSCLC with exon 19 deletion or *L858R EGFR* mutation were randomized 1:1 to receive osimertinib 80 mg once daily or current SOC *EGFR*-TKI, gefitinib 250 mg once daily or erlotinib 150 mg once daily, as first-line therapies the results of which were presented at the European Society for Medical Oncology (ESMO) 2017 Congress ESMO in September 2017 (18). The study not only shows a robust improvement in efficacy with osimertinib when compared to other commonly-used *EGFR* inhibitors, the side effects profile was also more favorable with osimertinib. At data cut-off on June 12, 2017, median PFS for patients receiving

osimertinib was 18.9 compared with 10.2 months for patients receiving SOC therapies. The PFS benefit for patients with and without brain metastases was almost identical, suggesting that osimertinib is active in the brain as well as in systemic sites. For patients with central nervous system (CNS) metastases which is 21% of the total study population, median PFS was 15.2 versus 9.6 months for patients receiving osimertinib *vs.* SOC, respectively. For patients without CNS metastases, median PFS was 19.1 versus 10.1 months. Median DoR was almost double for patients receiving osimertinib, at 17.2 compared to 8.5 months for SOC. Overall survival appeared to favor osimertinib with a hazard ratio of 0.63 although this was not statistically significant at the interim overall survival analysis at 25% maturity. PFS in patients with tumors harboring *de novo* T790M which is a key secondary objective of the FLAURA study has not been announced. The adverse event profile of osimertinib was comparable to the SOC group while osimertinib treated patients reported fewer grade  $\geq 3$  adverse events and fewer discontinuations of therapy (18).

Besides determining the role of T790M-selective EGFR-TKIs in the first-line setting, such head-to-head comparison studies between osimertinib and first- or second-generation EGFR-TKIs may help to tackle the issue of tumor heterogeneity where *EGFR*<sup>T790M</sup>-positive clones can coexist in untreated patients with an *EGFR*-sensitizing mutation. At the present moment, the question remains open as to whether sequencing first- or second-generation EGFR-TKIs followed by osimertinib may be superior for overall survival compared with starting with first-line osimertinib. In this regard, it is yet to be determined whether baseline T790M status is a deciding factor as to which patients may derive greater benefit from osimertinib treatment upfront.

## Acknowledgements

None.

## Footnote

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

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**Cite this article as:** Liam CK. Osimertinib as first-line treatment of *EGFR* mutant advanced non-small-cell lung cancer. *Transl Lung Cancer Res* 2017;6(Suppl 1):S62-S66. doi:10.21037/tlcr.2017.10.10