AURA 3: the last word on chemotherapy as a control arm in EGFR mutant NSCLC?

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AURA 3: a confirmatory trial showing that osimertinib is superior to platinum-pemetrexed in EGFR mutant non-squamous NSCLC manifesting T790M as acquired resistance to 1st–2nd generation EGFR inhibitors

Although first and second generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have led to significant improvements in both objective response rate (ORR) and progression free survival (PFS) in advanced non-small cell lung cancer (NSCLC) patients with EGFR exon 19 deletion (exon 19 del) or p.Leu858Arg (L858R) point mutations, acquired resistance against EGFR TKIs develops after 9 to 13 months in most patients (1-4). At the time of progression, about 60% of patients are found to have an acquired p.Thr790Met (T790M) point mutation in exon 20 of the gene encoding the original EGFR mutation as their dominant mechanism of acquired TKI resistance (5-7).

Osimertinib (AZD9291) is a third generation EGFR inhibitor with prominent activity against both the standard activating EGFR mutations and T790M with relative sparing of the wildtype form of the enzyme (8). In the phase 1, dose-expansion arms of AURA 1, the initial osimertinib trial, where 127 of 138 patients who had T790M confirmed by central testing were evaluable for response, osimertinib produced an ORR of 61% (95% CI, 52 to 70), and a median PFS of 9.6 months (9). In the AURA 2, phase II trial in T790M-positive NSCLC, osimertinib at 80mg once daily (the recommended dose) demonstrated an ORR of 69% among 199 patients with a median PFS of 9.9 months (10). In November 2015, the US Food and Drug Administration granted accelerated approval for osimertinib in T790M positive EGFR mutant NSCLC progressing after prior EGFR TKI therapy. Because many countries will not approve a drug on the basis of single arm data and to solidify the initial accelerated FDA approval, AURA 3 represents a confirmatory, randomized, open-label, international, phase 3 trial. In this trial osimertinib was compared to platinum-pemetrexed therapy (followed by optional pemetrexed continuation maintenance) in previously chemotherapy naive patients with advanced EGFR mutant non-squamous NSCLC and centrally-confirmed T790M-positivity progressing after first or second generation EGFR TKI therapy (11).

The study randomized 279 patients to the osimertinib group and 140 patients to the platinum-pemetrexed group. The most common prior EGFR TKIs were gefitinib > erlotinib >> afatinib. Patients were permitted to enter the trial with known brain metastases provided these were stable and asymptomatic (but not necessarily treated). CNS imaging on study was mandated only for those with known or suspected brain metastases. Patients who did not progress after 4 cycles of platinum-pemetrexed could continue on

Table 1 Comparison of objective response rate and progression free survival of EGFR mutant T790M-positive patients receiving osimertinib post 1st/2nd generation TKIs across AURA trials (9-11)

Endpoint	AURA 1 (n=127)	AURA 2 (n=199)	AURA 3 (n=279)
Objective response rate	61%	69%	71%
Median PFS	9.6 months	9.9 months	10.1 months

PFS, progression free survival; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; PFS, progression free survival.

maintenance pemetrexed per the approved label (which happened in 54% of the cases starting on the chemotherapy arm). Following an amendment 4 months after the study initiated, patients assigned to receive platinum-pemetrexed could cross over to the osimertinib group after objective disease progression (which happened in 60% of cases).

Progression-free survival, the primary study endpoint, had a median of 10.1 months in the osimertinib arm and 4.4 months in the platinum-pemetrexed arm [hazard ratio (HR) 0.30; 95% CI, 0.23 to 0.41; P<0.001]. The ORR was significantly better with osimertinib (71%; 95% CI, 65 to 76) than with platinum-pemetrexed (31%; 95% CI, 24 to 40) (odds ratio, 5.39; 95% CI, 3.47 to 8.48; P<0.001). The median duration of response was 9.7 months (95% CI, 8.3 to 11.6) with osimertinib and 4.1 months (95% CI, 3.0 to 5.6) with platinum-pemetrexed. Overall survival data were incomplete and not reported at the time of publication.

In terms of safety and adverse events, fewer patients reported adverse events of grade 3 or more in the osimertinib arm than in the platinum-pemetrexed arm (23% *vs.* 47%). With osimertinib, the most commonly reported adverse events were diarrhea (41%), rash (34%), dry skin (23%), and paronychia (22%). With platinum-pemetrexed, the most commonly reported adverse events were nausea (49%), decreased appetite (36%), constipation (35%), and anemia (30%). Interstitial lung disease-like adverse events were reported in 4% of the *osimertinib* arm (9 patients with grade 1 or 2 and one death) and 1% in the platinum-pemetrexed arm. Prolongation of QT interval was reported in 4% of the osimertinib arm (all grade 1 or 2 except for one grade 3 event) and 1% in the platinum-pemetrexed arm (all grade ≤2). Osimertinib was less likely to be associated with adverse events leading to permanent discontinuation than platinum-pemetrexed (7% *vs.* 10%, respectively).

Why did we need a randomized phase 3 clinical trial for osimertinib versus chemotherapy?

While there is no doubt that AURA 3 was a positive trial and should comfortably support the full licensing of osimertinib in advanced T790M positive EGFR mutant NSCLC, the results probably did not come as a surprise to anyone. Indeed, the biggest question about AURA 3 may be why regulatory authorities would require this trial to be conducted in the first place.

In EGFR TKI naïve patients with EGFR mutant NSCLC, every previous phase III study that has compared a 1st or 2nd generation EGFR TKI to 1st line platinum doublet therapy has demonstrated a superior ORR and PFS for the TKI approach (1-4,12-15). Two separate single arm studies of osimertinib in T790M-positive EGFR mutant NSCLC demonstrated clinical efficacy highly comparable to that of 1st or 2nd generation EGFR TKIs in TKI naïve EGFR mutant disease (9,10). Therefore, we must ask ourselves what we were trying to convince ourselves of in AURA 3—what were the unknowns? Pre-existing data from AURA 1 and 2 certainly seem to have accurately predicted the activity of osimertinib in AURA 3 within a few percentage points or fractions of a month (*Table 1*). However, given recent insights into how some molecular drivers in NSCLC may alter sensitivity to specific chemotherapies, perhaps the biggest unknown justifying AURA 3 may have been how the chemotherapy arm would perform in the T790M positive setting (16,17).

All biases associated with using a historical control aside, randomizing patients to platinum-pemetrexed would be justified in AURA 3 if there was reason to suspect clinical efficacy of this chemotherapy in EGFR mutant NSCLC could be altered through the acquisition of T790M-positivity. Scientifically, this could be argued both ways. On the one hand, in the presence of initial EGFR tyrosine kinase inhibition, acquisition of T790M could be interpreted as simply a means to re-establish the same EGFR signaling and downstream cellular consequences, and, therefore, potentially the same susceptibility to any specific chemotherapy. On the other hand, the level of EGFR kinase signaling in the presence of T790M may be different from that of the original activating mutations, and,

Table 2 Comparison of objective response rate and progression free survival of EGFR mutant treatment naïve (LUX-LUNG 3), post-gefitinib (NOS) (IMPRESS), post-gefitinib plasma T790M-positive or negative (IMPRESS) and the AURA 3 population receiving platinum-pemetrexed (3,11,20,21)

Endpoint	LUX-LUNG 3 (EGFR TKI naïve) (n=115)	IMPRESS (post-gefitinib, NOS) (n=132)	IMPRESS (post-gefitinib, plasma T790M+) (n=61)	IMPRESS (post-gefitinib, plasma T790M- negative) (n=31)	AURA 3 (n=140)
Objective response rate	23%	34%	39%	32%	31%
Median PFS	6.9 months	5.4 months	5.3 months	4.6 months	4.4 months

as multiple mechanisms of resistance can occur in the same individual, even when T790M is the dominant initial driver, the impact of second- or co-driver mechanisms being elevated above treatment naive levels could potentially have influenced the disease's susceptibility to chemotherapy relative to the TKI naïve setting (18,19).

With regard to clinical data, in LUX-LUNG 3, 345 treatment-naïve non-squamous NSCLC patients with an activating EGFR mutation were randomized to afatinib or cisplatin plus pemetrexed for up to 6 cycles, without continuation maintenance pemetrexed (3). In the chemotherapy control arm the ORR was 23% (by independent review) and the median PFS was 6.9 months. In the IMPRESS trial, 265 patients with EGFR mutant non-squamous NSCLC who progressed on first-line *gefitinib* were randomized to up to 6 cycles of cisplatin-pemetrexed chemotherapy together with continuation of the gefitinib or placebo (20). Continuation maintenance pemetrexed was again not included. In the chemotherapy alone arm the ORR was 34% and the median PFS 5.4 months. While the platinum-pemetrexed efficacy signal does not appear to be significantly different between LUX-LUNG 3 and IMPRESS, we have to recall that the IMPRESS trial enrolled patients who developed resistance to gefitinib without preselecting for T790M and therefore this mechanism of resistance will not have accounted for all cases of progression. Later, a retrospective sub-group analysis utilizing plasma based T790M detection suggested that among T790M positive cases in IMPRESS, patients receiving chemotherapy had an ORR and median PFS of 39% and 5.3 months, respectively, whereas among plasma T790M negative cases it was 32% and 4.6 months, respectively (21). Again, this suggests no significant change in platinum-pemetrexed sensitivity associated with the presence or absence of T790M (*Table 2*). The impact of using 4 versus 6 cycles of a platinum-doublet, or of using pemetrexed continuation maintenance or not could also have factored into some pre-trial uncertainty regarding the relevance of these historical data to AURA 3. However, based on the PARAMOUNT trial which explored the impact of pemetrexed continuation maintenance in detail in a general non-squamous NSCLC population, such differences would be unlikely to alter the ORR by more than a few percentage points or alter the median PFS by much more than a month (22).

A lot of hard work on the part of the investigators, and altruism and hope on the part of the patients and their families went into AURA 3. New data were generated. Yet, while admittedly not all of the data in *Tables 1,2* were available at the time the trial was designed, some were. In retrospect, it is hard to look at these tables and not deduce that the positive results of AURA 3 were inevitable.

Why does this matter?

It matters, because as we move into a world of increasingly complex molecular subgrouping, perhaps we can advance the thinking of regulatory bodies to obviate the need for randomized studies of highly active targeted therapy versus chemotherapy in preselected subgroups of patients. Without this change in mindset, as the results of such studies become less and less surprising and more and more like preaching to the choir, trials conducted in rare subgroups with their attendant accrual challenges may only serve to slow down patients' access to clearly active therapies (23). Of course, for some novel therapies and predictive markers with efficacy signals far closer to those of chemotherapy in a particular line of therapy, this appeal for skipping randomized testing versus chemo shouldn't apply (24,25). But if, as with AURA 3, a robust, dramatic pre-trial clinical efficacy signal exists and, knowing these results, the man-in-the-street wouldn't bet against the drug versus chemotherapy, for some of the best-established oncogene-addicted subtypes of NSCLC, maybe it is time to think about when we could really write the last word on targeted trials that still require chemotherapy as a control arm.

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Footnote

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

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