Osimertinib in first-line treatment—is a comparison not proof?

Jacques Cadranel

Chest Department and Expert Center in Thoracic Oncology, Hôpital Tenon/AP-HP and Pierre & Marie Curie University Paris 6, Paris, France

Correspondence to: Prof. Jacques Cadranel. Service de Pneumologie, Hôpital Tenon, 4 rue de la Chine, 75970 Paris, France. Email: jacques.cadranel@tnn.aphp.fr.

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Considerable progress has been made in the treatment of advanced non-small-cell lung carcinoma (NSCLC) harboring an epidermal growth factor receptor (EGFR) gene mutation (EGFR-NSCLC) since the publication of the BR21 trial (1). That trial showed erlotinib to have a modest effect compared with placebo in the second and subsequent lines of treatment in the all-comers NSCLC population. Because the effect was most pronounced in Asians and non-smokers, it was soon revealed that responders harbored an activating mutation of EGFR (2). Further advances have since been made by breaking down the various types of mutations into common, rare, and complex (3), by developing molecular techniques to screen real-world patients for these mutations (4), and by conducting randomized controlled therapeutic trials that compared the efficacy and safety of tyrosine kinase inhibitors of EGFR (EGFR-TKIs) against successive standards of care (summarized in *Tables 1* and *2*). However, as the French proverb has it, *comparaison n'est pas raison* (a comparison is not proof).

Comparison between tyrosine kinase inhibitors and chemotherapy (CT) proves conclusive in the 1st line

At least eight phase III therapeutic clinical trials (*Table 1*) (5-12) have shown that first- (erlotinib, gefitinib) and second-generation (afatinib) EGFR-TKIs were safer and more effective and resulted in better quality of life than a doublet regimen of platinum-based CT. The trials also showed that: (I) only L858R mutations and exon 19 deletions (common mutations) clearly benefited from TKIs; (II) tumor progression occurred between a median of 9 and 12 months after TKI initiation; (III) the brain was the most common site of recurrence; (IV) molecular mechanisms could be identified by performing a rebiopsy of the tumor or analyzing circulating tumor DNA (ctDNA) (2,17). But the trials did not show whether it was worth beginning the treatment sequence with a TKI rather than with CT, nor did it show us which TKI was most effective. The LUX-lung 3 and 6 trials' planned subgroup analysis by mutation (L858R *vs.* del19) (11,12) and pooled analysis (18) finally revealed that to begin treatment by a TKI rather than by a CT resulted in better overall survival (OS), particularly in the del19 subgroup suggesting the importance of the therapeutic sequence.

Comparison between 1st and 2nd generations proves inconclusive in the 1st line

Two trials (*Table 2*) then compared the efficacy of first- (gefitinib) and second-generation (afatinib, dacomitinib) TKIs. The LUX-lung 7 trial (13,14) statistically demonstrated afatinib to have better efficacy than gefitinib based on a reduced risk of progression on afatinib. However, the curves did not separate until after 12 months, OS was the same and the proportion of patients who had grade 3 or more adverse events was twice as high on afatinib. The more recent ARCHER 1050 trial (15) clearly showed the superiority of dacomitinib over gefitinib in first-line treatment as the PFS curves separated after 6 months of treatment, although that trial only included Asian patients

Table 1 Phase 3 trials evaluating EGFR tyrosine kinase inhibitors vs. chemotherapy in first-line treatment of advanced EGFR-mutated NSCLC

Study	Population	Mutation	n	TKI	Chemotherapy	Response rate (%)	PFS (months)	HR (95% CI)	OS (months)	HR (95% CI)
IPASS (5)	Asian	Common and rare	261	Gefitinib	Carboplatin paclitaxel	71/47	9.5/6.3	0.48 (0.36–0.64)	21.6/21.9	1.00 (0.76–1.33)
WJTOG 3405 (6)	Asian	Common and rare	172	Gefitinib	Cisplatin docetaxel	62/32	9.6/6.6	0.52 (0.38–0.72)	35.5/38.8	1.18 (0.77–1.83)
NEJ002 (7)	Asian	Common and rare	228	Gefitinib	Carboplatin paclitaxel	74/31	10.8/5.4	0.32 (0.24–0.44)	27.7/26.6	0.88 (0.63–1.24)
OPTIMAL (8)	Asian	Common and rare	154	Erlotinib	Carboplatin gemcitabine	83/36	13.1/4.6	0.16 (0.11–0.26)	22.8/27.2	1.19 (0.83–1.71)
EURTAC (9)	European	Common	173	Erlotinib	Platinum doublet	58/15	9.7/5.2	0.37 (0.25–0.54)	19.3/19.5	1.04 (0.65–1.68)
ENSURE (10)	Asian	Common	217	Erlotinib	Cisplatin gemcitabine	62/33	11.0/5.5	0.34 (0.22–0.51)	26.3/25.5	0.91 (0.63–1.31)
LUX-lung 3 (11)	Asian/ Caucasian	Common and rare	345	Afatinib	Cisplatin pemetrexed	56/23	11.1/6.9	0.58 (0.43–0.78)	28.2/28.2	0.88 (0.66–1.17)
LUX-lung 6 (12)	Asian	Common and rare	364	Afatinib	Cisplatin gemcitabine	67/23	11.0/5.6	0.28 (0.20–0.39)	23.1/23.5	0.93 (0.72–1.22)

NSCLC, non-small-cell lung carcinoma; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival. EGFR, epidermal growth factor receptor; IPASS, Iressa Pan-Asia Study; WJTOG, West Japan Thoracic Oncology Group 3405 trial; NEJ, North-East Japan 002 trial; EURTAC; European Tarceva versus Chemotherapy trial.

Table 2 Phase 2 and 3 trials evaluating head-to-head comparison between EGFR tyrosine kinase inhibitors in first-line treatment of advanced EGFR-mutated NSCLC

Study	Population	Mutation	n	TKI	Comparator	Response rate (%)	PFS (months)	HR (95% CI)	OS (months)	HR (95% CI)
LUX-lung 7 (13,14)	Asian	Common	319	Afatinib	Gefitinib	70/56	11.0/10.9	0.57 (0.57–0.95)	27.9/24.5	0.86 (0.66–1.12)
ARCHER 1050 (15)	Asian	Common	452	Dacomitinib	Gefitinib	75/72	14.7/9.2	0.59 (0.47–0.74)	NE	NE
FLAURA (16)	Asian/ Caucasian	Common	556	Osimertinib	Gefitinib/erlotinib	80/76	18.9/10.2	0.46 (0.37–0.57)	NE	0.63 (0.45–0.88)

NSCLC, non-small-cell lung carcinoma; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; HR, hazard ratio; 95%CI, 95% confidence interval; OS, overall survival; NE, not evaluable; EGFR, epidermal growth factor receptor.

and did not include any patients with brain metastasis. What is more, 64% of patients suffered adverse events of grade ≥3 on dacomitinib and the median survival data was not mature. The role of second-generation TKIs in the first line is hard to clearly define, and they have no proven utility in the second line after first-generation TKIs fail.

Comparison between osimertinib and CT proves conclusive in the 2nd line for T790M-EGFR-NSCLC

Osimertinib is a third-generation irreversible TKI specifically for EGFR-mutated forms that is active *in vitro* and in phase I and II trials against T790M resistance mutations (19,20). It is also characterized by very good brain exposure, displaying a cerebrospinal fluid to plasma concentration ratio of 0.39 (17). With the results of the AURA 3 trial (21), osimertinib soon proved its value in the second line compared with a doublet regimen of platinum-based CT plus pemetrexed in patients who progressed while on a first or second-generation TKI. Eligible patients were those whose tumor harbored T790M mutation identified by rebiopsy or ctDNA analysis. Median PFS was higher in the osimertinib arm (10.1 *vs.* 4.4 months) with the risk of progression or death reduced by 70% [hazard ratio (HR): 0.30; 95% confidence interval (CI), 0.23 to 0.41; P<0.001]. A similar effect was observed in all patient subgroups, and particularly in patients with cerebral metastases. The proportion of grade ≥3 adverse events was lower in the osimertinib arm, and quality of life also favored the TKI arm. OS data has yet to be reported however. Lastly, new resistance mechanisms (22-24) have been identified and include: (I) new acquired resistance mutations (such as C797S) of the EGFR gene in addition to the T790M mutation; (II) loss of the T790M mutation; (III) acquisition of mutations in the intracellular signaling pathways (such as RAS/RAF, MEK, PI3K, JAK); (IV) amplification of a parallel signaling pathway (MET, HER2, FGFR) that leads to bypass of the EGFR pathway; and (V) histological transdifferentiation, particularly into small-cell lung carcinoma.

Comparison between osimertinib and 1st/2nd TKIs favors osimertinib in the 1st line

Even more recently, osimertinib has been propelled into first-line treatment, initially following the results of a phase I trial (25) but especially during the European Society of Oncology Congress with the communication of results from the FLAURA trial (16) investigating the efficacy of osimertinib in the first line compared with first-generation TKIs (gefitinib, 64%; erlotinib, 36%) in NSCLC patients with common EGFR mutations (del19, 63%; L858R, 37%). Median PFS was higher in the osimertinib arm (18.9 *vs.* 10.2 months) with the risk of progression or death reduced by 54% (HR: 0.46; 95% CI, 0.37 to 0.57; P<0.0001), while the survival curves separated within the first weeks of treatment. A similar effect was observed in all patient subgroups, especially in non-Asians (HR =0.34), male subjects (HR =0.58), smokers (HR =0.48), patients with cerebral metastases (HR =0.47), and patients with L858R mutations (HR =0.51). Even though the response rate did not differ between the two treatment arms, the duration of treatment was practically double in the osimertinib arm (17.2 *vs.* 8.5 months). The proportion of treatment-related grade ≥3 adverse events was lower in the osimertinib arm (18% *vs.* 28%). Notably there were clearly fewer cases of hepatic (25% *vs.* 48%) and cutaneous (9% *vs.* 25%) toxicity of all grades. Data on quality of life was, however, not reported. Finally, interim analysis—although only 25% mature—showed promising survival with a 47% reduction in the risk of death in favor of osimertinib versus the first-generation TKIs [HR: 0.63; 95% CI, 0.45 to 0.88; P=0.0068 (not significant), while P<0.0015 expected]. Nevertheless, we do not currently have the data to define the type of clinical progression (slow *vs.* rapid, cerebral *vs.* systemic) and resistance mechanisms that will be induced by using osimertinib in first-line treatment (25).

Comparison proves inconclusive for choosing the best treatment sequence

The best treatment sequence for any patient being followed for advanced EGFR-mutated NSCLC is the one that provides the longest OS with an acceptable safety profile and maintained quality of life. Hence OS for real-world patients is determined by summing the treatment durations for each line of treatment administered, be it TKI, CT, or local treatment. This sum cannot be simply anticipated by the sum of median PFS figures as observed in the different therapeutic trials. This is because the populations are highly selective, the effectiveness of previous treatments is unknown, post-progression treatment options are not considered, and the biological impact of each line on the next is also unknown. Only strategy trials will be able to elucidate this question.

Nevertheless, *Figure 1* summarizes the main PFS and

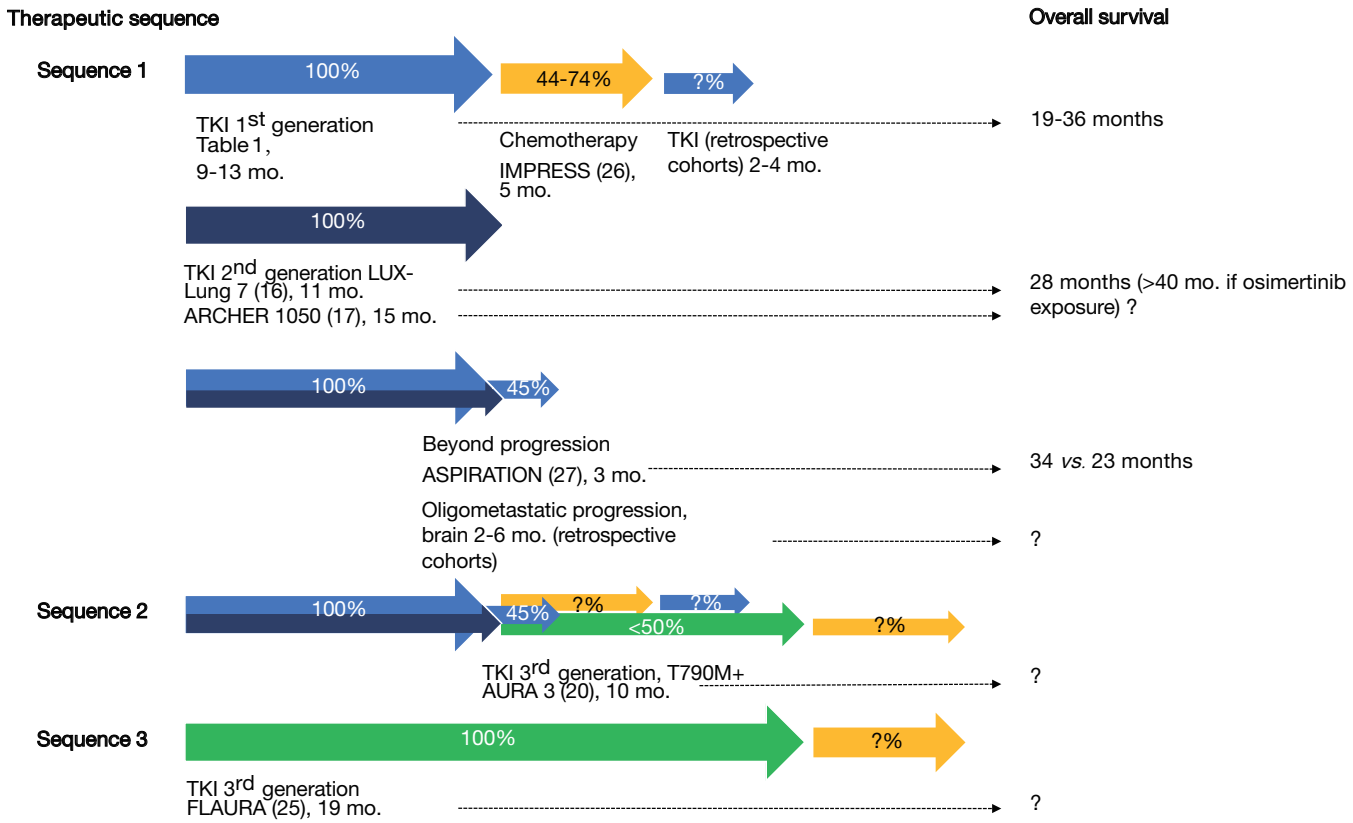

Figure 1 Main therapeutic sequences used for the treatment of advanced EGFR-mutated NSCLC. TKI, tyrosine kinase inhibitor; mo., months; NSCLC, non-small-cell lung carcinoma; EGFR, epidermal growth factor receptor.

OS data from the various phase III trials while factoring in international guidelines on the management of NSCLC. Sequence 1 is obviously taken from the phase III trials of first- and second-generation TKIs evaluated in the first line of treatment. In those trials, between 44% and 65% of patients were able to receive a second line of CT in the end (8-12), while the IMPRESS trial showed that CT (pemetrexed/platinum doublet and pemetrexed maintenance) resulted in a median PFS of 5 months in second-line treatment (26). With this treatment sequence, OS varies considerably between 19 and 36 months. These differences in OS depend not only on access to medication for subsequent treatment lines but also on differing medical practices in real-world patients, including pursuing TKI beyond progression which prolongs median PFS by 3 months in around 45% of patients with or without locoregional therapy in cases of oligo progression (27). Sequence 2 will certainly soon predominate in countries where it is possible to screen for T790M mutation using rebiopsy and/or ctDNA and where osimertinib will be available, but this will apply to less than 50% of patients who progress—in other words, not to patients who die during first-line treatment, not to patients whose T790M mutation cannot be established, and not to patients who are indeed T790M-negative—with the others continuing to receive CT.

The results of the FLAURA trial may bear out the comparison, especially since this sequence ensures that 100% of patients are exposed to osimertinib, but the evidence is still inconclusive for adopting sequence 3, in particular because of the lack of OS data. In the future, it seems vital to consider strategy trials or at least to obtain data from large real-world cohorts to improve our knowledge of the prognostic impact of treatment sequences. The utility of first-line combination strategies based on first- and second-generation TKIs must continue to be assessed (with anti-angiogenesis, immunotherapy, anti-HER, anti-MET) (17,28). Moving osimertinib to

the first line of treatment will cancel out the utility of analyzing ctDNA upon progression, restricted to the emergence of a single resistance mechanism, and it will make it necessary to evaluate next-generation sequencing against rebiopsy results. Finally, this new data will again raise the question of the role of first-line combinations with osimertinib to prevent the emergence of resistance mechanisms independent of the EGFR pathway, which may come to predominate. In any event, CT will continue to play a significant role in treatment sequences for managing EGFR-mutated NSCLC.

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Footnote

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