Commentary

# Afatinib in lung cancer harboring *EGFR* mutation in the LUX-Lung trials: six plus three is greater than seven?

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Non-small cell lung cancer (NSCLC) harboring activating mutations of the epidermal growth factor receptor (*EGFR*) gene, about 90% of which is either small deletion in exon 19 (Del19) or a leucine to an arginine substitution at codon 858 (L858R), is very sensitive to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib (1). Phase III trials comparing these agents with platinum doublet chemotherapy showed significant prolongation of progression free survival (PFS) in favor of EGFR-TKIs (*Figure 1A*) (2-5). Nonetheless, those tumors inevitably acquire resistance about half of which are due to secondary *EGFR* mutations resulting in threonine to methionine substitution at codon 790 (T790M) (13). In these clinical trials, patients with acquired resistance to the first-line EGFR-TKI are likely to be treated by platinum doublet as a second-line treatment, while those patients treated initially by platinum doublet therapy are to be treated by EGFR-TKI that works well in this second-line setting. Owing to this "crossover" of treatment, there has been no statistically significant difference in overall survival (OS) of the patients in these trials (2-5) (*Figure 1A*).

Afatinib is one of the so-called 2nd generation (2G) EGFR-TKIs, because it can covalently bind to a cysteine at codon 797 in the presence of T790M whose affinity to 1G EGFR-TKI, i.e., gefitinib or erlotinib, in comparison with ATP is markedly diminished. Hence, IC50 value of afatinib is remarkably lower compared with 1G TKIs (14). However, wild-type *EGFR* is more sensitive to afatinib than *EGFR T790M*, resulting in lack of inhibitory effect of T790M in clinically achievable concentration of afatinib. Indeed, LUX-Lung 1 (afatinib clinical trials are designated as LUX-Lung X, and will be abbreviated as LL hereafter) study did not demonstrate prolongation of OS for patients who acquired resistance to gefitnib or erlotinib, although patients were not tested for T790M mutation but were enriched only by progressive disease after good response to the first-line EGFR-TKIs (15).

LL 3 (9) and LL 6 (10) studies are both phase III trials comparing afatinib with platinum doublet chemotherapy (cisplatin/pemetrexed in LL 3 and cisplatin/gemcitabine in LL 6). Although these studies showed that afatinib prolonged PFS significantly over platinum doublet chemotherapy, apparent difference in OS favoring afatinib did not reach statistical significance. However, when these two studies were combined (LL 3 + LL 6) and *EGFR* mutations were confined to common mutations, i.e., Del19 and L858R, OS of patients in afatinib group was significantly longer than those in chemotherapy group (11). This was the first time that there was a significant OS advantage in the trials comparing EGFR-TKI with platinum doublet chemotherapy although hazard ratio (HR) was 0.81 which was not so impressive (11). This survival advantage is not attributable to low crossover rate to EGFR-TKI in chemotherapy arm. In fact, the higher crossover rate is, the lower the HR is or the more the benefit of afatinib is. For patients in countries where EGFR-TKI is not reimbursed, crossover rate and HR were 52% and 0.84. In contrast, in countries where EGFR-TKI is reimbursed, they were 91% and 0.70 (16).

What is most intriguing in this analysis is the fact that survival advantage from afatinib looks different between Del19 and L858R (11). For patients with Del19, the OS difference is greater than overall population with a HR of 0.59 (11). In contrast, for those with L858R, HR is 1.25, although this difference does not reach statistical significance (*Figure 1B*) (11). In both trials, PFS of afatinib group is significantly prolonged compared with chemotherapy in both Del19 and L858R (*Figure 1B*). It is a

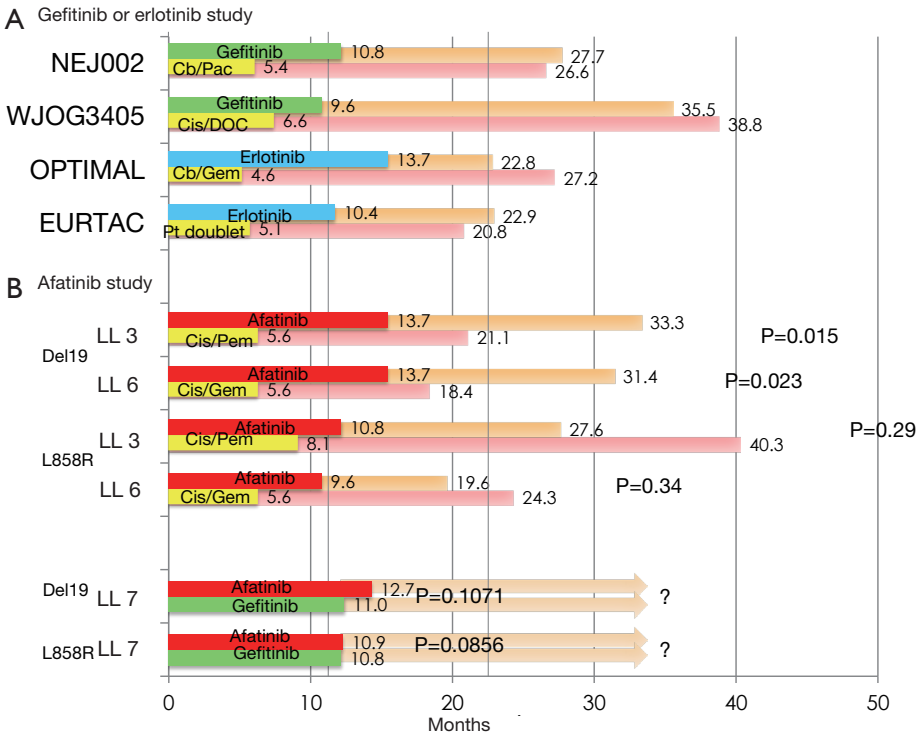


**Figure 1** Progression free survival and overall survival in trials comparing chemotherapy with the first-generation EGFR-TKIs (A) (2-8) and LUX-Lung trials (B) (9-12). EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

little curious to note that the superiority of PFS for patients with L858R in afatinib group is reversed in OS, i.e., post-progression survival (PPS) in afatinib group is far shorter compared with that in chemotherapy group resulting in shorter OS. On the contrary, in Del19 patients, PPS in afatinib group is very long compared with chemotherapy group (*Figure 1B*). Although each LL 3 + LL 6 pooled two trials to increase statistical power with elimination of rare mutations, these trends are consistent in each LL 3 and LL 6 (*Figure 1B*).

There is no plausible explanation for this difference. One may be able to speculate that second-line TKI (mostly gefitinib and erlotinib, because afatinib was not commercially available at that time) in chemotherapy group worked very well and responsible for long PPS for L858R patients. There is a possibility that precedent chemotherapy might have affected the sensitivity to the second line TKI or vice versa (17), depending on *EGFR* mutational status.

Patients in the chemotherapy group in LL 3 or LL 6 trial are thought to have received very similar treatments to those in the chemotherapy group of earlier phase III trials of gefitnib or erlotinib such as WJTOG3405 or NEJ002, in which there was no significant OS difference with gefitinib or erlotinib group as mentioned earlier. Taken these together, it appears that afatinib may not be a drug of choice for patients with L858R and that either IG TKI or chemotherapy may be recommended as the first-line treatment for patients with L858R.

LL 7 trial is a randomized phase IIB study that directly compares afatinib with gefitinib for 319 patients with NSCLC harboring common mutations of the *EGFR* gene (12). PFS, the primary endpoint, is significantly longer in afatinib (HR =0.73, P=0.0165). This trend is true for both Del19 (HR =0.76, P=0.1071) and L858R (HR =0.71, P=0.0856) (*Figure 1B*). Median PFS is numerically better in patients with Del19 than those with L858R in both afatinib and gefitinib group (12.7 *vs.* 10.9 for afatinib and 11.0 *vs.* 10.8 in gefitinib) (12). As expected, toxicity is in general greater in afatinib arm (12).

The authors say "*…our data support the use of afatinib as a treatment option in both patients with L858R and Del19 mutations*" (12). For patients Del19, LL 7 is a confirmation of superiority of afatinib over gefitinib and therefore if the patients are fit enough, afatinib is highly recommend as an

 

initial therapy. Then, how do the LL 7 results compromise with above-mentioned seemingly detrimental OS effect in L858R patients in LL 3 + LL6 trials? Considering that LL 7 is a phase IIB trial without OS results and that LL 3 and LL 6 is phase III studies each of which enrolled more than 300 patients with OS results, until we see very dramatic difference in OS in LL 7 later this year, 1G TKI or chemotherapy still may be recommended even after LL 7 results as discussed earlier.

Last November, osimertinib, 3G EGFR-TKI that is active for T790M secondary mutation, was approved in US and its approval was followed in EU and Japan. Response rates and PFS of patients with acquired resistance due to T790M is ~60% and 10 months, respectively. We do not know exact incidence of T790M after afatinib, although a small study reported the similar incidence of ~50% (18). It is also not very clear whether incidence of T790M is different between Del19 and L858R. Out of 411 patients enrolled in AURA extension cohort and AURA 2 study which are phase II study of osimertinib for patients with T790M, 68% had Del19 while only 29% were L858R (19). Considering that baseline incidence of Del19 is only slightly higher than that of L858R, it appears that Del19 may be more likely to develop T790M. Furthermore, although number of the patients are small, osimertinib as the first-line treatment for patients with EGFR mutations looks promising with a median PFS of ~20 months (20). Therefore, we have to carefully stay tuned for what is evolving in the EGFR world and also we have to keep the enormous value of molecular analysis of patients' specimens in mind.

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## Footnote

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