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The aftermath of LUX-Lung 7 study—what have we learnt from it?

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Park *et al.* are congratulated for their excellent results of the LUX-Lung 7 study. This phase IIb randomized-controlled trial directly compared afatinib with gefitinib as first-line treatment for epidermal growth factor receptor (EGFR)-mutated metastatic non-small-cell lung cancer (NSCLC) (1). It is the first multi-center randomized trial comparing the two approved EGFR tyrosine-kinase inhibitors (TKI) in terms of efficacy and safety in a head-to-head manner. It was commenced in 2011 with 64 participating centers in 13 countries. All recruited and eligible patients must have stage IIIB (ineligible for curative intent surgery or local radiotherapy) or stage IV (recurrent or metastatic) pulmonary adenocarcinoma with documented either exon 19 deletion or exon 21 L858R mutation as confirmed by the central laboratory. They were then randomized (1:1) to either afatinib 40 mg daily or gefitinib 250 mg daily stratified by EGFR mutational status (exon 19 deletion *vs.* L858R mutation) and baseline brain metastases (presence *vs.* absence). Those who were randomized to afatinib arm were allowed to escalate the dose of afatinib to 50 mg daily after 4 weeks of treatment if they did not experience rash, diarrhea, mucositis or any other drug-related adverse events of more than grade 1. The three co-primary study endpoints were progression-free survival (PFS), time-to-treatment failure (TTF) and overall survival (OS) while the secondary endpoints were best objective response (OR), time to and duration of OR, disease control rate (DCR), duration of disease control, tumor shrinkage and change in quality of life scores.

A total of 319 patients were randomized to either afatinib (160 patients) or gefitinib (159 patients). After a median follow-up duration of 27.3 months, the median PFS was 11.0 months [95% confidence interval (CI), 10.6–12.9 months] with afatinib and 10.9 months (95% CI, 9.1–11.5 months) with gefitinib

[hazard ratio (HR) =0.73; 95% CI, 0.57–0.95; P=0.017] and TTF [median 13.7 months (95% CI, 11.9–15.0 months) with afatinib] compared to 11.5 (95% CI, 10.1–13.1 months) with gefitinib [HR =0.73; 95% CI, 0.58–0.92; P=0.0073]. In addition, OR was also significantly higher with afatinib (70%) as compared to gefitinib (56%, P=0.0083) though the DC rates were similar (91% *vs.* 87%). It was also translated to a longer median duration of response with afatinib (10.1 months) compared to gefitinib (8.4 months). With regards to the type of EGFR mutation, there was a trend of improved PFS with afatinib compared to gefitinib in patients who had either exon 19 deletion (12.7 *vs.* 11.0 months; HR =0.76; 95% CI, 0.55–1.06; P=0.107) and L858R mutation (10.9 *vs.* 10.8 months; HR =0.71; 95% CI, 0.47–1.06; P=0.087). Finally, OS data was yet to mature.

For the safety profiles, the frequency and severity of all-cause adverse events and \geq grade 3 events were similar between the 2 arms. While diarrhea (13% *vs.* 1%) and rash (9% *vs.* 3%) were more commonly encountered in those who received afatinib, liver enzyme elevations were more prevalent with gefitinib. Apart from that, similar improvements in quality of life scores from baseline were seen in both arms.

Based on the results of LUX-Lung 7 trial, can we say afatinib, compared to the other two first-generation TKI namely gefitinib and erlotinib, is the better drug of choice as first-line treatment for metastatic EGFR-mutated NSCLC? All three drugs have been approved as first-line treatment based on the multicenter phase III randomized-controlled trials which demonstrated superb PFS, better ORs and more manageable toxicity profiles compared to platinum-based doublet chemotherapy for EGFR-mutated advanced NSCLC (2-11). This together with icotinib, another EGFR TKI developed, manufactured, approved and widely

adopted in China based on its ICOGEN study in the same setting, are acceptable first-line therapies (12). No doubt, LUX-Lung 7 trial is the first showing the superior PFS with afatinib than gefitinib as first-line treatment for EGFR-mutated advanced NSCLC. This, in general, may represent the broader and more durable anti-tumor activity with this second-generation irreversible inhibitor against ErbB family of receptors (EGFR/ErbB1, HER2/ErbB2, ErbB3, and ErbB4) compared to the mere and reversible blockade of EGFR signaling with gefitinib and erlotinib (13,14). In addition, preclinical evidence suggested that afatinib also exhibits anti-tumor activity against T790M gatekeeper mutation (13,15). However, the results of this study should be interpreted with cautions. First and may be one of the most important criticisms against this study is its study design. It is still poorly understood why the study was conducted as a phase IIb rather than a phase III study, even though the authors explained that there might be insufficient data, at the time of trial concept and initiation, to construct a formal testing strategy with respect to the difference of effects between afatinib and gefitinib in this treatment setting. Secondly no hypotheses were generated for this study and the sample size estimation was merely based on controlling the width of confidence interval for the HR of PFS. The sample size required in this study may be underestimated, even though the sample size was later increased to 316 patients after study protocol amendment. The corollary was that the study may not be powered enough to draw any conclusion. Thirdly, the primary and secondary endpoints have been amended during the study periods by including OS as the co-primary endpoint and shifting disease control as secondary endpoint. The study team explained that this change was made to distinguish the primary endpoints from the less important secondary endpoints. In addition, the study protocol was also amended to mandate the balancing of recruitment in Asian versus non-Asian countries, leading to increase in sample size.

Notwithstanding, these modifications still could not change the setting of this study as a phase IIb instead of phase III study and might in fact impede the contemplation of a subsequent phase III trial. In addition, the nuance of difference in PFS between afatinib and gefitinib (only about 3 days) has to be balanced at the expense of more diarrhea and acneiform rash with afatinib. Finally, the study did not clearly elucidate if there was any statistical difference in quality of life scores between afatinib and gefitinib. Of note, though the PFS with afatinib (11.0 months) in LUX-Lung 7 trial fully concurred with those reported in LUX-

Lung 3 (11.1 months) and LUX-Lung 6 (11.0 months) (10,11), this is not probably the best when compared to PFS with erlotinib, another 1st generation inhibitor erlotinib in OPTIMAL study (13.1 months) (5). One interesting finding from LUX-Lung 7 trial was that the two PFS curves started to divide at 12 months after commencement the respective TKI. We are expecting to see if there is OS difference between the two arms after longer follow-up.

In summary, afatinib was found to have significantly longer PFS compared with gefitinib, albeit the modest absolute difference. It is still immature to conclude that afatinib is superior to gefitinib due to the inherent limitations of the study design and the lack of longer follow-up to observe the impact on OS. Up till now, gefitinib, erlotinib and afatinib are equally acceptable first-line treatment for metastatic EGFR-mutated NSCLC.

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Footnote

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Comment on: Park K, Tan EH, O'Byrne K, *et al.* Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol* 2016;17:577-89.

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