Afatinib for patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer: clinical implications of the LUX-Lung 7 study

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We thank Professor Lee for his interest in our recent LUX-Lung 7 publication that assessed afatinib versus gefitinib in patients with epidermal growth factor receptor (*EGFR*) mutation-positive non-small cell lung cancer (NSCLC) (1). We agree that, in an ideal world, afatinib and gefitinib would have been compared in a Phase III trial with a formal hypothesis. However, given the lack of data available at the conception of LUX-Lung 7 (2010–2011), we made the pragmatic decision to undertake an exploratory Phase IIb trial. We felt that it was simply not possible to construct a formal hypothesis based on *a priori* evidence available at the time. Rather, we felt that a flexible trial design that assessed multiple clinically relevant endpoints would be the best way to broadly explore any differences between the agents. Notwithstanding its design, we do not think that the relevance of LUX-Lung 7 should be understated. Firstly, the LUX-Lung 7 population (N=319) was as large as many Phase III trials in this setting. Secondly, it was a global trial that encompassed a multicenter, multiethnic population; recruitment of Asian and non-Asian patients was balanced. Thirdly, signals of improved efficacy with afatinib over gefitinib were observed across multiple, independently assessed, endpoints including progression-free survival (PFS), time to treatment failure (TTF) and objective response rate (ORR). Improvements were generally consistent across key patient subgroups (e.g., Asian *vs.* non-Asian, *EGFR* Del19 *vs.* L858R mutation). We do not believe that the Phase IIb design subverts the clinical relevance of these data, especially when one considers the paucity of head-to-head data in this setting.

Regarding the selection of, and amendments to, the primary endpoints of LUX-Lung 7, we chose endpoints that are most clinically relevant for patients and physicians [overall survival (OS) and TTF], while also acknowledging the relevance of PFS as a critical endpoint in the first-line treatment setting. Thus, OS and TTF were included as co-primary endpoints alongside PFS, and the original co-primary endpoint of disease control was re-defined as a secondary endpoint. These protocol amendments occurred before completion of recruitment or any unblinded efficacy analyses. With regards to PFS, we agree with Professor Lee that the absolute difference in the medians between arms was negligible; however, overall, there was a clear and relevant improvement in PFS (HR: 0.73; P=0.017) that was underpinned by the divergence of curves at later time points (≥10% improvements in 18- and 24-month PFS with afatinib *vs.* gefitinib). We hypothesize that these differences reflect the broader and more durable inhibitory profile of afatinib compared with first-generation tyrosine kinase inhibitors (TKIs), which may delay mechanisms of acquired

resistance commonly observed in *EGFR* mutation-positive NSCLC (2). Clearly, it is impossible to infer whether afatinib has PFS benefit over the other first-generation EGFR TKIs, erlotinib and icotinib, based on LUX-Lung 7. However, we do not believe that Professor Lee is correct to cite the Phase III OPTIMAL trial as evidence that erlotinib confers better PFS than afatinib, as cross-trial comparisons are not possible. Indeed, the recent head-to-head CTONG 0901 Phase III trial did not demonstrate any difference in efficacy and safety between gefitinib and erlotinib (3). Furthermore, the ENSURE trial did not reproduce entirely the outcome of OPTIMAL (4).

TTF was chosen as a co-primary endpoint to reflect 'real-world' clinical practice and guidelines, wherein many NSCLC patients continue treatment with EGFR TKIs beyond radiological progression, in the absence of clinical deterioration. TTF reflects both disease progression and tolerability. Accordingly, the significant improvement of TTF observed with afatinib over gefitinib testifies to the manageability of adverse events (AEs) with afatinib and the willingness of patients and physicians to continue afatinib therapy beyond radiological disease progression despite expected AEs. In our view, it is an oversimplification to cite higher rates of treatment-related grade 3 diarrhea and rash/acne as evidence that afatinib is less tolerable than gefitinib. Although these AEs are clearly more frequent with afatinib, other AE rates, notably elevated liver enzymes and interstitial lung disease, are higher with gefitinib. We would argue that, overall, afatinib and gefitinib do not demonstrate overwhelmingly different tolerability based on the identical rate of treatment-related discontinuations in both arms (6% each). Furthermore, although limited in scope, patient-reported outcomes data indicate no difference in health-related quality-of-life between the two arms. These findings indicate that tolerability-guided dose reductions of afatinib effectively manage AEs and facilitate a favorable tolerability profile close to that of gefitinib.

Updated LUX-Lung 7 data, including primary analysis of OS, were recently presented at the European Society for Medical Oncology (ESMO) 2016 congress (5). In this updated report, afatinib maintained significant improvements versus gefitinib in PFS, TTF and ORR. In addition, a 14% reduction in risk of death was observed with afatinib, corresponding to a numerical difference of 3.4 months in median OS, which did not achieve statistical significance (27.9 *vs.* 24.5 months; HR: 0.86; 95% CI: 0.66–1.12; P=0.2580). It should be noted that, despite being recognized as the preferred first-line treatment for *EGFR* mutation-positive NSCLC, it has proved difficult to demonstrate clear OS advantage versus platinum-based chemotherapy in this setting; only afatinib has shown OS benefit (in patients with Del19). The challenge of demonstrating OS advantage is largely attributable to high rates of post-progression therapy. In this regard, it is interesting to note that ~75% of patients in both arms of LUX-Lung 7 received at least one systemic anticancer therapy, and multiple lines of therapy were common; subsequent use of post-study EGFR TKIs was higher with gefitinib than afatinib (55.6% *vs.* 45.9%). This rate of post-progression therapy is somewhat higher than reported in most previous trials. It is unsurprising, therefore, that significant OS benefit was not achieved, especially given that the trial was not powered for this endpoint.

We acknowledge that these data, obtained from a Phase IIb exploratory trial, are not sufficient to claim superiority of afatinib over gefitinib. However, we believe that the overall findings from LUX-Lung 7 could provide relevant guidance to physicians with respect to clinical decision making in their day-to-day management of patients with *EGFR* mutation-positive NSCLC.

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Footnote

Conflicts of Interest: KP reports personal fees for advisory roles from AstraZeneca, Boehringer Ingelheim, Clovis, Eli Lilly, Hanmi, Kyowa Hakko Kirin, Ono, Novartis, and Roche; and grants from AstraZeneca.

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