Featured Article

# Patient reported outcomes from LUX-Lung 3: first-line afatinib is superior to chemotherapy—would patients agree?

**Sanjay Popat**

Department Medicine, Royal Marsden Hospital, London, SW3 6JJ, UK

*Corresponding to:* Sanjay Popat, FRCP, PhD. Department Medicine, Royal Marsden Hospital, London, SW3 6JJ, UK. Email: sanjay.popat@rmh.nhs.uk.

**Abstract:** The LUX-Lung 3 trial was an important randomized phase 3 trial in patients with *EGFR* mutant advanced non-small cell lung cancer (NSCLC). Here, patients were randomized to either afatinib or cisplatin-pemetrexed and the primary endpoint of progression-free survival (PFS) was easily met (HR=0.58, P=0.001). This was the first large-scale trial of this type using a modern chemotherapy comparator, including Asian and non-Asian patients, central radiology review, and utilizing comprehensive patient-reported outcomes. Whilst efficacy for afatinib was markedly superior to chemotherapy, do the patient-reported outcomes reflect this superiority? The symptom control and quality of life (QoL) data from this trial has now been published. Analysis of these demonstrate clear superiority of afatinib over chemotherapy for delay in cough deterioration, and dyspnoea. Notably, given the toxicity profile of afatinib, these improvements translated into significant improvements in global health status, physical, role, and cognitive functioning. The clinical benefits for afatinib over cisplatin-pemetrexed chemotherapy for *EGFR* mutation-positive advanced non-small cell lung patients seem overwhelming, and are clinically meaningful. These results are also consistent with QoL data from other trials of gefitinib/erlotinib, but much more robust, given the larger patient numbers. Would patients agree that afatinib is superior to chemotherapy? On the basis of data presented, the answer is probably "Yes". However, the key unanswered question remaining is "*Which is the best EGFR-tyrosine kinase inhibitor (TKI) to use up front?*" and we will have to wait until ongoing trial data can help answer this.

**Keywords:** Afatinib; quality of life (QoL); survival

Submitted Dec 01, 2013. Accepted for publication Dec 26, 2013.

doi: 10.3978/j.issn.2224-5820.2013.12.03

**Scan to your mobile device or view this article at:** http://www.amepc.org/apm/article/view/3202/4132

Eight large-scale clinical trials have now demonstrated the superiority of first-generation *EGFR*-tyrosine kinase inhibitor (TKI) (gefitinib/erlotinib) over platinum doublet chemotherapy (1-8). Afatinib is a second-generation *EGFR*-TKI designed to irreversibly inhibit *EGFR* kinase, including the T790M gatekeeper mutation that accounts for acquired resistance to gefitinib/erlotinib therapy in around 50% of cases (9). The LUX-Lung 3 trial was the first randomized trial of a second generation *EGFR*-TKI compared to a modern chemotherapy doublet—cisplatin-pemetrexed—in patients with treatment naïve *EGFR* mutant advanced non-small cell lung cancer (NSCLC) (6). The trial recruited both Asian and non-Asian patients, as was the largest trial in this indication thus far, utilizing independent radiology review. Afatinib demonstrated marked clinical efficacy over cisplatin-pemetrexed [progression-free survival (PFS) median 11.1 *vs.* 6.9 months, HR=0.58, 0.43-0.78, P=0.001; improving to PFS median 13.6 *vs.* 6.9 months, HR=0.47, 0.34-0.65, P=0.001 when restricted to the common mutations L858R and exon 19 deletions]. Toxicities for afatinib were as observed in previous trials, with diarrhoea, rash, and paronychia the most prevalent (≥ grade 3 adverse events 14.4%, 16.2%, 11.4%, respectively). Of course, these were the worst grade of toxicity reported per patient, and duration of afatinib therapy was markedly longer than that of cisplatin-pemetrexed.

The patient reported outcomes (PROs) from this trial, subsequently reported by Dr Yang are therefore welcome, to put the toxicity and efficacy balance into patient-related context (10). PROs were comprehensively assessed every

21 days until progression using the established EORTC QLQ-C30 and QLQ-LC13 tools, and compliance was high. Compared to chemotherapy afatinib significantly delayed time to deterioration of cough, and dyspnoea; more so in patients symptomatic at baseline. Whilst chemotherapy was associated with a greater proportion of patients reporting worsening of fatigue and nausea, afatinib was associated with worsening of diarrhoea, sore mouth, and dysphagia, but significant improvements in individual items related to activity. Afatinib-treated patients had significantly better mean scores over time for global health status/quality of life (QoL), physical role, and cognitive functioning. Whilst improvements in emotional and social functioning were not significantly improved compared to chemotherapy, mean treatment differences favoured afatinib.

So how do we interpret these findings? Overall afatinib therapy results in significantly improved symptoms that matter to lung cancer patients (dyspnoea and cough); symptoms that are difficulty to effectively palliate by symptom-control alone. These differences are important for a therapy type that has demonstrated marked clinical efficacy by nearly doubling PFS but not improving overall survival (likely due to cross-over to alternative *EGFR* TKI use in the chemotherapy arm post progression), thereby validating the clinical benefit of this therapy. Whilst the typical afatinib toxicities of diarrhoea, skin rash, and paronychia featured in the PRO symptom analyses, longitudinal analysis of global health status compares favourably for afatinib over chemotherapy. Moreover, rates of afatinib-related adverse events seem to have reduced in more recent trials, perhaps due to increasing pre-emptive management strategies, and increased clinical experience with afatinib, although under-reporting cannot entirely be excluded. Thus, in the LUX-Lung 6 trial of afatinib versus cisplatin-gemcitabine in *EGFR* mutant NSCLC (a trial identical to LUX-Lung 3 other than the use of gemcitabine in place of pemetrexed, and set entirely in East Asia) rates of grade 3-4 toxicities diarrhoea, rash, and paronychia have reduced to 5.4%, 14.6%, and 0%, respectively (7). Clearly the patient-reported outcome data from this trial will be important to review to understand the clinical relevance of this reduced reported toxicity profile.

So, would patients agree that afatinib is superior to chemotherapy? The answer is probably "Yes". However, the key question that remains unanswered, is "*What is the optimal EGFR TKI to use in this setting*?" Other first generation *EGFR* TKIs gefitinib and erlotinib have both demonstrated marked clinical efficacy over platinum-doublet chemotherapy. These studies have also demonstrated similar improvements in PRO metrics, for an improvement in lung-cancer associated symptoms and prolongation of time to deterioration of symptoms for gefitinib/erlotinib, although the instruments used in these trials were different to LUX-Lung 3, thereby prohibiting direct comparisons.

Overall, the field is now replete with randomized trials that have comprehensively identified that *EGFR*-directed therapy with gefitinib, erlotinib, or afatinib is clinically superior to platinum-doublet chemotherapy in treatment-naïve *EGFR* mutant advanced NSCLC, and further trials in this paradigm should not now be performed. However, the key question now unanswered for both patients and oncologists alike is "*Which is the best EGFR-TKI to use up front?*" The suggestion of a median PFS for common *EGFR* mutants of 13.6 months with afatinib from LUX-Lung 3, compared with 9-10 months typically observed for gefitinib/erlotinib might suggest potential superiority, but such cross-trial comparisons are fraught with danger and are perilous at best. However, the LUX-Lung 7 trial (NCT01466660) may potentially answer this question. This randomized trial of afatinib versus gefitinib for *EGFR* mutant NSCLC has now completed accrual and results are awaited. In the interim, treatment-naïve *EGFR* mutant patients have robust, clinically-meaningful data to support the use of afatinib should they and their oncologists chose.

## Acknowledgements

SP acknowledges NHS funding to the Royal Marsden Hospital/Institute of Cancer Research NIHR Biomedical Research Centre.

*Disclosure:* Consultant/Advisory Role, Astra-Zeneca, Roche, and Boehringer Ingeleim; Research funding, Boehringer Ingeleim.

## References

1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
2. Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 2012;30:1122-8.
3. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.

 

4. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
5. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
6. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
7. Wu YL, Zhou C, Hu CP, et al. LUX-Lung 6: A randomized, open-label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. J Clin Oncol 2013;31:abstr 8016.
8. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
9. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005;2:e73.
10. Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3342-50.

**Cite this article as:** Popat S. Patient reported outcomes from LUX-Lung 3: first-line afatinib is superior to chemotherapy—would patients agree? Ann Palliat Med 2014;3(1):19-21. doi: 10.3978/j.issn.2224-5820.2013.12.03

 