Research Highlight

# Afatinib in first-line setting for NSCLC harbouring common *EGFR* mutations: new light after the preliminary results of LUX-Lung 7?

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**Abstract:** The development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) changed dramatically the history of non-small cell lung cancer (NSCLC) harboring EGFR sensitive mutations. Several randomized prospective trials confirmed the superiority of these target agents about survival and response rate when comparing with platinum-based chemotherapy. Knowledge about EGFR mutations increased gradually during the development of target agents and different clinical trials. EGFR mutations cannot be considered all equal, but different entities should be considered in our clinical practice: exon 19 deletions, exon 21 mutation (L858R) and uncommon mutation (exon 20, exon 18 and double mutation). Nowadays, we dispose of three different EGFR TKIs (afatinib, erlotinib and gefitinib) approved for the treatment for first-line treatment of patients di NSCLC carrying EGFR, that was compared only by indirect analysis, producing data not always clear and convincing. This research highlight is an overview of data about EGFR TKIs in first-line setting, focusing on differences about exon 19 deletions and L585R mutation in patients treated with different TKIs. In addition, we report the preliminary results of the first head-to-head randomized clinical trial between two different EGFR TKIs, the LUX-Lung 7 (LL7) that compared afatinib and gefitinib showing interesting results.

**Keywords:** Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); afatinib; common mutations; LUX-Lung 7 (LL7)

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The history non-small cell lung cancer (NSCLC) is changing deeply in the last years. In patients with advanced or metastatic NSCLC harboring driving mutation, the survival improved significantly using target agents as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) or ALK inhibitors, prolonging survival when compared with standard chemotherapy (1,2).

In patients harboring EGFR mutations, different randomized trials confirmed the significant superiority of EGFR TKIs versus standard platinum-based chemotherapy in first-line setting about progression-free survival (PFS), quality of life (QoL) and safety profile. No randomized clinical trials evaluating erlotinib, gefitinib, or afatinib, showed a statistical improving in overall survival for patients treated with EGFR TKIs, when considered individually and based on overall population (3-11).

Although these trials seems to be very similar, exploring the same indication and end-points with different EGFR TKIs (afatinib, erlotinib, gefitinib), presents many differences about study design, patients population and statistical analysis.

The Iressa Pan-Asia Study (IPASS) trial was performed to confirm that first-line therapy with an oral EGFR TKI would be at least as effective as chemotherapy with carboplatin-paclitaxel, in a selected Asian population, with lung adenocarcinoma. On a total of 1,038 patients enrolled, 261 were positive for EGFR mutations [53.6% Del19/42.5% L858R/4.2% exon 20 (T790M)/3.8% other

mutations/4.2% multiple mutations]. In a mutation positive subgroup of patients, PFS was significantly longer among patients treated with gefitinib than among those that received chemotherapy (HR =0.48; 95% CI, 0.36–0.64; P<0.0001) (4).

After the IPASS trial, different prospective randomized clinical trial, all undertake in Asian population, showed that gefitinib and erlotinib, improved PFS and response rate, in EGFR-mutant NSCLC.

The European Tarceva vs. chemotherapy (EURTAC) trial was the first randomized phase III trial that evaluated the efficacy of erlotinib in non-Asian population of patients with NSCLC harbouring EGFR mutations. In this trial, 173 patients were randomly assigned to receive erlotinib or standard platinum-based chemotherapy. In this trial, a pre-specified evaluation about type of mutation (exon 19 deletion vs. L858R) was performed. These results confirm the just well-known data that EGFR TKIs are most effective than chemotherapy, improving PFS. In addition, the EURTAC trial reported interesting data about the efficacy of erlotinib about of exon 19 deletion and L858R mutation. In patients with EGFR exon 19 deletion, median PFS was 11.0 months (95% CI, 8.8–16.4), and in patients with L858R mutation was 8.4 months (95% CI, 5.2–10.8) (5).

Based on the results of the IPASS trial and EURTAC trial, gefitinib and erlotinib were approved for the treatment of EGFR mutation positive NSCLC.

Thanks to the results achieved by these first generation EGFR TKIs (erlotinib and gefitinib), the history of patients with NSCLC harbouring EGFR mutation changed dramatically in the last years, doubling survival and improving QoL, also thanks to manageable safety profile. Recently, many evidences confirmed the high activity of afatinib, a second-generation irreversible TKI that inhibits signaling from all dimers of ERBB receptor family members (including EGFR, HER2, ERBB3, and ERBB4) (12).

Afatinib was evaluated in the LUX-Lung3 (LL3) conducted on a mixed population (Caucasian and Asian patients) and LUX-Lung 6 (LL6) conducted exclusively on Asian population. In both trials, mutation-positive patients were stratified by mutation type (exon 19 deletion, L858R, or other), and PFS analysis was prespecified for patients with common EGFR mutation, considering together exon 19 deletions and L858R mutations. For both trials, the primary end point was PFS assessed by independent review. Secondary end points included tumor response, overall survival, adverse events, and patient-reported outcomes (PROs) (9,10).

Considering singularly the LL3 and LL6 trials, the results confirmed the efficacy of afatinib in EGFR mutation positive NSCLC, overlapping the previous trials with reversible EGFR TKIs. Indeed, this trials showed a median PFS in ITT with afatinib of about 11.0 months compared with 6.9 months of chemotherapy arm (HR =0.58; 95% CI, 0.43–0.78; P=0.001). The results reported by the authors of LL3, considered only patients with common mutations (exon 19 deletions and L858R) showed an increased PFS of 13.6 months (HR =0.47; 95% CI, 0.34–0.65; P=0.001). PFS resulted more improved in patients with tumours harbouring exon 19 deletion followed by L858R mutation.

Data regarding overall survival of patients treated with afatinib in LL3 and LL6 was evaluated in a pooled analysis including only patient with common EGFR mutations (exon 19 deletions =355 and L8585R =276). Median OS based on overall population was 27.3 *vs.* 24.3 months, HR =0.81 (95% CI, 0.66–0.99; P=0.037). The median OS of patients with deletion 19 mutations, was 33.3 months (95% CI, 26.8–41.5) in the afatinib group *vs.* 21.1 months (95% CI, 16.3–30.7) in the chemotherapy group (HR =0.54; 95% CI, 0.36–0.79; P=0.0015) in LL3; and was 31·4 months (95% CI, 24.2–35.3) *vs.* 18.4 months (95% CI, 14.6–25.6), respectively (HR =0.64; 95% CI, 0.44–0.94; P=0.023) in LL6. By contrast, there were no significant differences by treatment group for patients with EGFR L858R-positive tumours in either trial: in LL3, median overall survival was 27.6 months (95% CI, 19.8–41.7) in the afatinib group *vs.* 40.3 months (24.3–not estimable) in the chemotherapy group (HR =1.30; 95% CI, 0.80–2.11; P=0.29); in LL6, it was 19.6 months (95% CI, 17.0–22.1) *vs.* 24.3 months (95% CI, 19.0–27.0), respectively (HR =1.22; 95% CI, 0.81–1.83; P=0.34) (13).

Considering individually the overall survival data coming out from all randomized clinical trials with erlotinib, gefitinib and afatinib, it is not possible to found a statistically significant superiority of one drug on the other.

However, the results of pooled analysis showed that a significant improvement in overall survival with afatinib was achieved in patients with tumours harboring the EGFR del19 mutation.

These data confirmed the multiple evidences suggesting that exon 19 deletions and L8585R are two different disease entities. Notably, different retrospective analysis considering both reversible and irreversible TKIs using for NSCLC carrying exon 19 deletions, showed that treatment with EGFR TKI improve OS when compared with standard chemotherapy (14).

In addition to these data about the efficacy of different EGFR TKIs compared with chemotherapy, recently during ESMO-Asia congress was presented the preliminary results of LL7, a phase IIb trial of afatinib versus gefitinib for the treatment of first-line EGFR mutation-positive adenocarcinoma of the lung. In the LL7, the first randomized clinical trial evaluating two different EGFR TKIs, 319 patients with adenocarcinoma of the lung carrying common EGFR mutation (Del19 and L858R), were randomized at a 1:1 ratio to receive afatinib 40 mg/daily or gefitinib 250 mg/daily. Patient population was stratified by mutation type (Del19/L858R) and brain metastases (present/absent). Primary endpoint was independent PFS, time to treatment failure (TTF) and OS; secondary endpoints were overall response rate (ORR), time to response, duration of response (DoR), duration of disease control, tumour shrinkage, QoL and safety profile.

Considering overall randomized population, results about PFS showed no difference between two arms: 11.0 *vs.* 10.9 months (HR =0.73%; 95% CI, 0.57–0.95; P=0.0165). But it is very interesting to underline that 2-year survival rate was 18% *vs*. 8% (P=0.0184) in favour of afatinib treatment. In patients with Del 19 mutations, median PFS was 12.7 *vs.* 11.0 months (HR =0.76%; 95% CI, 0.55–1.06; P=0.1071), while in patients with L858R mutation, median PFS was 10.9 *vs*. 10.8 months (HR =0.71%; 95% CI, 0.47–1.06; P=0.0856). Interesting results coming out from the analysis of TTF that showed a statistical significant clear improvement in favor of patients that received afatinib treatment: 13.7 *vs*. 11.5 months (HR =0.73%; 95% CI, 0.58–0.92; P=0.0073). Afatinib treatment was associated with an improvement of objective response rate (70% *vs*. 56%; P=0.0083) and DoR (10.1 *vs*. 8.4), evaluated by independent review. Safety profile overlaps the results of the previous clinical trial; discontinuation rate was low and equal for both treatment arms (6.3%). Discontinuation rate was more frequent due to diarrhea (3.1%) skin toxicities (1.3%) and fatigue (1.3%) in patients treated with afatinib while due to ALT increase (3.1%), AST increase (1.95%) and interstitial lung disease (ILD) (2.5%) for patients that received gefitinib (15).

These preliminary results regarding PFS, TTF, ORR and DoR, confirm a slight trend in favor of afatinib. Indeed considering the median PFS, only the results about Del19 showed a difference in favour of afatinib, although not statistically significant (P=0.1071). Survival curves about PFS in Del19 and L858R showed a durable response in favor of afatinib after 1 year of treatment, maybe for the activity of afatinib in delaying the development of resistance.

In the era of precision medicine, it will be very interesting to understand the T790M rate in patients treated with afatinib as front-line therapy. Indeed, the only preliminary results of a prospective trial that evaluated the presence of T790M in TKI-naïve patients that progressing to afatinib, showed that the presence of T790M mutation was less common (33%) then is expected with first generation EGFR TKIs, thought these data are based on a small group of patients (16).

Waiting the results of the first randomized phase III trial, comparing two different EGFR TKIs (dacomitinib *vs.* gefitinib) ARCHER-1050 trial, the LL7 (phase IIb) open a new era of clinical trial evaluating two different EGFR target agents, reducing statistical issue developed from indirect comparison analysis (17).

As reported by the discussant Pasi Jänne, probably the choice of first-line EGFR-TKI has no effect on subsequent therapy, considering that the development of EGFR T790M mutations is one the major causes of resistance to first-generation TKIs, also in patients treated with afatinib. The combination of first-generation TKI plus bevacizumab or the treatment new EGFR TKI, could be change our approach to our patients, developing the most effective and tolerable strategy to prevent or delay resistance for as long as possible.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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