Editorial

Afatinib and gefitinib: a direct comparison

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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.

Submitted Aug 04, 2016. Accepted for publication Aug 09, 2016.
doi: 10.21037/tcr.2016.08.37
View this article at: http://dx.doi.org/10.21037/tcr.2016.08.37

During the last decade, scientific literature had already reported data on frequency and characteristics of EGFR mutations among patients with non-small-cell lung cancer (NSCLC) and their response to tyrosine kinase inhibitors (TKIs) (1). Actually EGFR mutation-positive NSCLC is a well-defined molecular type of lung cancer with specific first-line treatment options.

Gefitinib had been largely studied and developed for treatment in first line settings of patients with advanced EGFR mutation-positive NSCLC compared with chemotherapy (2,3) both in Caucasian and non-Caucasian patients (4-6). Erlotinib had also demonstrated benefits in overall survival (OS), progression free survival (PFS), response rate and quality of life, with a favourable tolerability. These benefits were established in first-line setting versus chemotherapy both in Chinese and European patients with EGFR mutation-positive advanced NSCLC (7,8).

More recently a wide-spectrum preclinical activity against EGFR mutations was demonstrated with afatinib, a second-generation, selective, orally bioavailable TKI that irreversibly blocks signaling from EGFR (EGFR/ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2) and ErbB4 (9,10). Two phase III trials assessed the efficacy of afatinib in first-line setting in patients with advanced or metastatic EGFR mutation-positive NSCLC compared with a standard chemotherapy regimen. In LUX-Lung 3 trial, afatinib was evaluated against cisplatin plus pemetrexed (11) demonstrating a prolongation of PFS compared with chemotherapy (11.1 *vs*. 6.9 months, respectively; HR =0.58; P=0.001), with a greater benefit in patients with exon 19 deletions and L858R mutations. Similarly, in LUX-Lung 6 afatinib was evaluated compared with cisplatin plus gemcitabine. Afatinib led to an increased PFS of 11 versus 5.6 months compared with cisplatin plus gemcitabine (HR =0.28; P<0.0001) (12).

Thus gefitinib, erlotinib and afatinib are actually a standard therapeutic option in advanced-stage NSCLC with activating mutation of EGFR. However there was no trial comparing two TKIs for the treatment of patients with EGFR mutation-positive NSCLC till now.

LUX-Lung 7 is the first trial comparing an irreversible ErbB family blocker (afatinib) and a reversible EGFR TKI (gefitinib) as first-line treatment for this patients population.

Park and colleagues (13) conducted this multicentre, international, open-label, exploratory trial where patients were randomised to receive as first-line treatment afatinib (40 mg per day) or gefitinib (250 mg per day). Patients had a histologically confirmed diagnosis of NSCLC in advanced-stage with a common EGFR mutation (exon 19 deletion or Leu858Arg). They received treatment until disease progression or beyond radiological progression if deemed beneficial. Originally PFS and disease control at 12 months were primary endpoints. Then trial was update to include PFS, time-to-treatment failure (TTF) and OS as co-primary endpoints, while disease control became one of the secondary endpoint. All patients were included in the primary assessment of efficacy and all patients receiving at least one administration of each drug were considered for safety analysis. Number of patients was well balanced between the two treatment arms: 160 patients in afatinib arm and 159 in gefitinib arm respectively. More than 50% of patients were of Asian origin in both arms. In each treatment arm patients with Leu858Arg and those with exon 19 deletion were 42% and 58% respectively. Only one patient in gefitinib arm presented both EGFR common mutations.

Median PFS in afatinib arm was significantly higher

compared with that in gefitinib arm (11 *vs.* 10.9 months; HR =0.73; P=0.017). Also TTF was longer with afatinib than gefitinib: 13.7 versus 11.5 months, respectively (HR =0.73; P=0.0073). Afatinib benefit was observed for PFS and TTF in most patients subgroups except light ex-smokers and, only for TTF, in patients without brain metastases too.

Data about OS were immature at time of analysis, when median OS was 27.9 months in afatinib arm versus 25.0 months in gefitinib arm.

Responses were obtained during the first 16 weeks and objective response rate (ORR) was significantly higher among patients receiving afatinib (70% of patients in afatinib arm and 56% in gefitinib arm; P=0.0083) who presented a longer median duration of response too (12.7 versus 11.1 months, respectively). However patients reached a similar disease control between the two arms (91% for afatinib group versus 87% for gefitinib group, respectively; P=0.24).

PFS and ORR data for afatinib in LUX-Lung 7 are in line with those reported against chemotherapy in LUX-Lung 3 (11.14 months and 56%, respectively) and LUX-Lung 6 (11.0 months and 66.9% respectively).

The significant better PFS in afatinib group increases with time as demonstrated by the progressive separation of curves with time. This could be due to the broader and more durable inhibitory effect of afatinib, blocking irreversibly all ErbB family members (14) and not only EGFR. Although in preclinical studies afatinib had demonstrated activity also in NSCLC with the acquired mutation Thr790Met (9) and the acquired resistance to anti-EGFR TKIs is due in about 50% of cases to this mutation (15).

Similar efficacy patterns were reported for afatinib compared with gefitinib regardless of EGFR mutation. Patients with Leu858Arg presented a median PFS of 10.9 in afatinib arm versus 10.8 months in gefitinib arm (P=0.086), and an ORR of 66% and 42%, respectively. Patients harbouring exon 19 deletion showed a median PFS of 12.7 months in afatinib arm versus 11.0 months in gefitinib arm (P=0.107), and a ORR of 73% and 66%, respectively.

This finding confirmed the evidence of previous literature supporting a better outcome with first generation TKIs for patients with NSCLC harbouring an exon 19 deletion as EGFR mutation (16,17). It suggests that exon 19 deletion and Leu858Arg define two distinct forms of NSCLC.

Among the adverse events in afatinib group any grade of diarrhoea, acne or skin rash were reported, while in gefitinib group were reported liver enzyme elevation and interstitial lung disease as expected. Grade >3 adverse events were increased with afatinib (31%) compared with gefitinib (18%).

The longer TTF could indicate an acceptable and manageable toxicity profile of afatinib besides a clinical benefit beyond radiological progression. Nevertheless, the open-label design of the trial may have biased TTF in favour of newer afatinib treatment.

The trial presented some other limitations. The authors themselves noted that the trial was designed as an exploratory phase 2B trial without a predefined hypothesis, with three co-primary endpoints and a statistical significance not corrected for multiple comparison. Moreover the immature data on OS precluded robust analysis.

However considering the third generation inhibitors in development, as AZD9291 (18) and rociletinib (19), data from LUX-Lung 7 are very interesting to design future trial about combination approaches and/or sequence strategy to overcome the acquired resistance mutations after a first-line treatment with an EGFR TKI.

Although no benefit in OS was reported in this trial in first-line setting, afatinib might be more effective than gefitinib, with a better PFS and response rate and a good toxicity profile, with a low impact on quality of life. These findings and clinical relevant endpoints such as disease control, survival prolongation, tolerability and quality of life are to be taken into account to choose the most appropriate treatment for every patient. In particular the superiority of afatinib versus gefitinib in terms of response rate could be considered for treatment choice in patients with symptomatic disease or with a large tumour burden.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Shao-Hua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: C Gridelli has received honoraria as advisory board and speaker bureau member for Roche, Boehringer and Astra Zeneca.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Gridelli C, Losanno T. Afatinib and gefitinib: a direct comparison. Transl Cancer Res 2016;5(S3):S425-S427. doi: 10.21037/tcr.2016.08.37