Dacomitinib in EGFR-positive non-small cell lung cancer: an attractive but broken option

Antonio Passaro, Filippo de Marinis

Division of Thoracic Oncology, European Institute of Oncology, IEO, Milan, Italy

Correspondence to: Antonio Passaro, MD, PhD. Division of Thoracic Oncology, European Institute of Oncology, IEO, Via G. Ripamonti, 435-20141 Milan, Italy. Email: antonio.passaro@ieo.it.

Provenance: This is an invited Editorial commissioned by Section Editor Hengrui Liang (Nanshan Clinical Medicine School, Guangzhou Medical University, Guangzhou, China).


Submitted Jan 31, 2018. Accepted for publication Feb 05, 2018.
doi: 10.21037/tlcr.2018.02.09

View this article at: http://dx.doi.org/10.21037/tlcr.2018.02.09

The identification of EGFR mutations in non-small cell lung cancer (NSCLC) changed deeply the treatment of this disease harbouring these kind of DNA alterations, that occur respectively in about 10–15% and 45–50% of Caucasian and Asian patients (1,2).

From 2009 to nowadays, many pivotal randomized trials evaluated the efficacy and safety of different first- and second-generation EGFR TKIs in patients carrying EGFR mutations. In these trials, afatinib, erlotinib and gefitinib were compared with standard platinum-based chemotherapy showing a significant improvement of median progression-free survival (10–12 months), response rate (RR), safety profile and quality of life (QoL), in favor of target agents (3-10).

In these different trials, overall survival was globally improved to 25 to 30 months, but without significant difference between both arm (chemotherapy and EGFR TKIs). This lack of OS improvement might be attributed to the high rate of crossover from chemotherapy to EGFR target agents (11).

In the phase IIb LUX-Lung 7, was the first head-to-head randomized clinical trials, comparing two different EGFR TKIs, afatinib and gefitinib, in treatment-naïve patients with stage IIIb/IV NSCLC and a common EGFR mutation (exon 19 deletion/L858R), with three co-primary endpoints as OS, PFS and time-to-failure (TTF). In this trial, there was no significant different in OS with afatinib versus gefitinib (12).

Overall, these results based on many randomized trials, didn’t showed significant differences between first- and second-generation EGFR-TKIs.

Prof. Wu et al. recently reported the results of the ARCHER 1050 trial, the first randomized phase 3 trial comparing directly a first-generation EGFR TKIs with a second-generation TKIs, gefitinib vs. dacomitinib, as a front-line treatment for EGFR-positive NSCLC. Considering that afatinib, the other second-generation EGFR previously tested in this setting, didn’t showed a significant improvement compared with a first-generation TKI, the results of this trials acquired high interesting towards dacomitinib (13).

In the ARCHER 1050, 452 patients with common EGFR mutations (Exon 19 deletion and Exon 21 L858R) were randomized to receive dacomitinib (n=227) or gefitinib (n=225). Progression-free survival, a primary endpoint, was significantly improved for patients treated with dacomitinib; 14.7 vs. 9.2 months (HR 0.50, 95% CI, 0.47–0.74; P<0.001). Progression-free survival was evaluated also considering Asian and non-Asian patients population, showing no comforting data. Indeed, in Asian patients (131 vs. 128), PFS was 18.2 vs. 10.9 (HR 0.43, 95% CI, 0.32–0.59; P<0.0001) in favor of dacomitinib; instead in non-Asian group (39 vs. 33), PFS was 10.9 vs. 9.1 (HR 0.55, 95% CI, 0.32–0.93; P=0.0245), for dacomitinib and gefitinib respectively. Responses were significantly increased for patients receiving dacomitinib, although the
The proportion of patients who achieved an objective response did not differ between the two groups (13).

Over efficacy, safety analysis reported grade 3 of any adverse event in 51% of patients treated with dacomitinib, compared with 30% of gefitinib. This raise of toxicity was confirmed though considering dose reduction rate in dacomitinib group, occurred overall 150 patients (66%). Of these, 38% moved to a lowest dose of 30 mg/day, and the 28% moved through dose reduction, until 15 mg/day (13).

Shortly, these data confirmed a high activity of dacomitinib in EGFR-positive population, though burdened by a considerable toxicity profile, that although apparently does not affect the QoL, is a real Achille’s heel for a long term treatment.

The ARCHER 1050 it must be taken as reference of pivotal head-to-head trial, but showed different limits that do not allow to consider dacomitinib the new first-line treatment for EGFR-positive NSCLC patients.

As first, toxicity profile as discussed above confirming that pan-HER TKIs as afatinib and dacomitinib are clearly more toxic than gefitinib.

Second, the trial did not enroll patients with brain metastases (BM) due as suggested by the authors for the unknown capacity of dacomitinib to penetrate the blood-brain-barrier (BBB).

Considering that in EGFR-positive NSCLC, 30% of patients present BM at baseline, and 50% as lifetime risk, this exclusion criteria became a real limitation to investigate the activity of the drug and to compare indirectly the results with the other randomized trials conducted in the past years (14).

Third, the different patterns of activity between Asian and non-Asian patients enrolled. Considering the confirmed activity of gefitinib and erlotinib, evaluated in two all Caucasian trials, the results reported by the ARCHER 1050 authors, did not explain this issue that remains open and not clearly explained.

Forth, the subsequent results of FLAURA trial that completely shift the view to a new light in the room of EGFR-positive NSCLC. Indeed, a few months later the presentation of ARCHER 1050 final data, the results of the phase 3 FLAURA study were also available, rising significantly the bar in this setting (15). Indeed in the FLAURA trial, osimertinib, a third generation EGFR TKIs, achieved a median PFS of 18.9 vs. 10.2 of first-generation EGFR (erlotinib/gefitinib), in the same setting of EGFR positive TKI naïve (HR 0.46, 95% CI, 0.37–0.57; P<0.001). This significant improvement of PFS, was associated to a longer duration of response and no safety concerns. Over this, the activity of osimertinib was significant superior in both those with BM and no at baseline (14).

The FLAURA trial for EGFR-positive NSCLC and the ALEX trial for the ALK-rearranged NSCLC must be taken as a reference in the era of precision medicine, showing a statistical and clinical significant improvement without any concerns related to the toxicity profile, and with very high activity of BM, reducing the comfortless role of whole-brain palliative radiotherapy.

Dacomitinib, despite confirmed an improvement of median PFS well above all expectations compared with gefitinib, due to different issue related to the study design and activity/safety, didn’t find the power to move in the main street of EGFR-positive naïve NSCLC patients, and remain weakened and unconvincing treatment options.

Acknowledgements

None.

Footnote

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

References

5. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or


Cite this article as: Passaro A, de Marinis F. Dacomitinib in EGFR-positive non-small cell lung cancer: an attractive but broken option. Transl Lung Cancer Res 2018;7(Suppl 2):S100-S102. doi: 10.21037/tlcr.2018.02.09