Editorial

# Complex *EGFR* mutations in non-small cell lung cancer: a distinct entity?

**Michał Bieńkowski[1], Rafał Dziadziuszko[2], Jacek Jassem[2]**

[1]Department of Pathomorphology, Medical University of Gdańsk, Gdańsk, Poland; [2]Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

*Correspondence to:* Prof. Jacek Jassem, MD, PhD. Department of Oncology and Radiotherapy, Medical University of Gdańsk, Smoluchowskiego 17, 80-214 Gdańsk, Poland. Email: jjassem@gumed.edu.pl.

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Small-molecule tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) have revolutionized the treatment of *EGFR* mutation-positive non-small cell lung cancer (NSCLC). Consequently, EGFR TKIs currently constitute standard therapy in this group of patients. There are three generations of EGFR-TKIs approved for this indication: the first generation (erlotinib, gefitinib, and icotinib), the second generation (afatinib, and dacomitinib), and the third generation (osimertinib).

*EGFR*-activating mutations are typical for lung adenocarcinomas and are relatively frequent in non-smokers, females, and East Asian patients. Common (classical) mutations, constituting up to 90% of *EGFR* mutations, include small in-frame deletions within exon 19 (codons 746-750) and a point mutation within exon 21 (L858R) (1). The remaining *EGFR* mutations (uncommon; non-classical) may be intrinsic (primary) or secondary, related to acquired resistance to EGFR TKIs (2-4). A small subset of *EGFR*-mutated tumors (1% to 9%) harbor two or more different primary *EGFR* mutations (5-9). Such complex mutations include double common, double uncommon, or mixed *EGFR* mutations. Complex mutations involving L858R have been consistently found to be more frequent than those involving exon 19 deletions (8-10).

Due to the rarity of complex mutations, their biological significance remains unclear. The combination of both common mutations (L858R and exon 19 deletions) seems to be more sensitive to TKIs than other combinations (9), and the coexistence of two uncommon mutations shows a better response to TKIs than single uncommon mutations (10,11). The latter may be due to a lower activating potential (and thus a lower extent of oncogene addiction) of single uncommon mutations (10,11). Most recently, data on a large cohort of NSCLC patients with uncommon and very rare mutations and their combinations (n=856) have been reported (12). The study indicated a general benefit of EGFR-TKI treatment (versus chemotherapy) for NSCLC with any mutation other than exon 20 insertions, for which new treatment modalities (i.e., mobocertinib and amivantamab) have been recently approved by the Food and Drug Administration. In turn, the clinical data on the combination of common and uncommon *EGFR* mutations are scarce.

The retrospective study by Li *et al.* (13) provides real-world data on the efficacy of a second-generation TKI dacomitinib in NSCLC patients with single common and complex (common plus uncommon) *EGFR* mutations in the Chinese population. The reference group in this study were patients with common *EGFR* mutations. Dacomitinib has been less frequently used than other EGFR TKIs, and there is relatively little post-marketing information on this compound. However, the genuine values of this study are novel data on dacomitinib efficacy in a subset of patients with unique complex *EGFR* mutations. The response rate of 40% argues for the moderate activity of dacomitinib in this population, but this outcome should be interpreted cautiously. The study group was small (15 evaluable patients), heterogeneous in stages (III and IV), location of

metastases, number and type of prior therapies, and drug dosing. Somewhat surprisingly, there was an apparent overrepresentation of patients with L858R mutation in both subgroups (76% of cases with single and 89% with complex mutations). The latter may be explained by a generally lower occurrence of exon 19 deletions within complex mutations (8-10). On the other hand, L858R mutation in general East Asian populations is less frequent than exon 19 deletions (1), indicating a possible selection bias.

A few randomized studies compared first- *vs.* second- and third-generation EGFR TKIs (14-18). Second-generation compared with first-generation EGFR-TKIs have shown higher antitumor activity, but at the expense of increased toxicity, likely due to their irreversible mode of EGFR inhibition. There have been no direct comparisons of second- *vs.* third-generation EGFR TKIs. Several network meta-analyses using indirect comparisons have consistently shown the superiority of osimertinib over any other EGFR-TKI, including dacomitinib (19-21). Additionally, osimertinib can overcome T790M mutation, which is resistant to first- and second-generation EGFR-TKIs, and has an acceptable safety profile. Finally, as opposed to other EGFR TKIs, osimertinib shows impressive efficacy against brain metastases (22). Several other third-generation EGFR-TKIs have demonstrated promising activity in preclinical and clinical trials (23). Hence, whether dacomitinib or other first- or second-generation TKIs should still be considered the first-line option in *EGFR*-mutated NSCLC patients is questionable.

Different mutations seem to have disparate effects on EGFR activity and sensitivity to individual TKIs (3,4). However, the majority of industry-sponsored randomized clinical trials (with the exception of the afatinib development program) allowed exclusively common *EGFR* mutations. The largest report on the afatinib activity in *EGFR* uncommon mutations (24) included 693 patients from prospective Lux-Lung studies, cohort studies, and case series. Of those, 35 subjects with complex mutations were identified, including 23 with major uncommon mutations. About half of these patients were TKI-pretreated. The objective response rate of 77% and median duration of response of 16.6 months appear to be at least equal to the afatinib outcomes in patients with common *EGFR* mutations. Since afatinib and dacomitinib have a similar mechanism of action (both are irreversible second-generation EGFR inhibitors), their clinical activity is likely comparable. With virtually no clinical data on dacomitinib in this patient subset, the study by Li *et al.* (13) provides further insight into this underexplored area.

Despite impressive responses, most patients managed with EGFR TKIs will develop drug resistance via acquired *EGFR* mutations or other non-EGFR mediated molecular mechanisms. Thus, there is a sore need for new therapies targeting such resistance-related *EGFR* mutations. Novel third and fourth-generation EGFR TKIs, or other targeted agents against non-EGFR pathways may contribute to achieving this goal (25).

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