Editorial Commentary

The heterogenous landscape of EGFR Del19 mutation subtype: not all are the same for osimertinib

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The discovery of druggable genomic alterations represents a significant advancement in the management of non-small cell lung cancer (NSCLC). The presentation of these alterations, varies from mutation to translocation or gene amplifications, thereby demonstrating a high degree of heterogeneity. Notably, different subtype of oncogene driven alterations may correlate with distinct clinical characteristics and actionability. For instance, in the case of BRAF mutations, only class I mutations are druggable with anti-BRAF and anti-MEK inhibitors, while class II and III of BRAF-mutant tumors are associated with higher risk of brain metastases and less favorable outcome (1). Similarly, KRAS mutant NSCLCs exhibit different subtypes based on smoking pattern, and personalized approvals exists only for KRAS G12C subtype (2). Sensitizing common epidermal growth factor receptor (*EGFR*) mutations (deletion in exon 19, Del19, and point mutations in exon 21, L858R) are among the most common targetable driver mutations in patients with NSCLC (3), occurring in up to 10% of NSCLCs in Western-population (4). These mutations confer sensitivity to EGFR tyrosine kinase inhibitors (TKIs), with osimertinib, a third-generation EGFR TKI, emerging as the preferred treatment option in the metastatic setting. This preference is based on a significant prolongation in progression-free survival (PFS) and overall survival (OS) when compared with first-generation EGFR TKIs. Additionally, osimertinib has become the standard adjuvant treatment among patients with completely resected early-stage NSCLC harboring common *EGFR* mutations (5,6). However, data reported in clinical trials do not consider the subtypes of common EGFR-mutations, which could potentially impact in the clinical efficacy. It is suggested that EGFR-mutant tumors should be classified more based on the structural changes rather than exon position, as it may influence the sensitivity to EGFR TKI (7). There are more than fifty *EGFR* Del19 mutations described, and their prognostic and predictive role are poorly understood. In preclinical models, these *EGFR* Del19 variants other than EA746-A750 have reported a different degree of activity to different EGFR TKI with lower efficacy to the first-generation TKI erlotinib, but also for osimertinib, while afatinib, a second-generation EGFR TKI reported clinical activity (8,9). These observations may provide an explanation for the divergent outcomes observed in daily practice when all common *EGFR*-mutant NSCLCs are uniformly treated with osimertinib. It underscores the importance of considering structural subclassification and others factors to refine prognostic and treatment strategies in this population.

In the article accompanying this editorial, Grant *et al.* reported that that *EGFR* Del19 made up 45% of *EGFR* mutations (10). The E746_A750del was the most common

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EGFR Del19 (27.3% of all *EGFR* mutations), followed by L747_P753>S (2.8%), and the L747_A750delinsP represented 1.8% of all EGFR Del19 mutations. The authors, retrospectively assessed the clinical activity of osimertinib in 200 patients with NSCLC harboring *EGFR* Del19 from six institutions. This cohort included 122 patients with tumors harboring E746_A750del (n=86), 36 tumors harboring the L747_A750delinsP (n=36), and 78 patients with tumors harboring other uncommon Del19. A non-significantly higher proportion of patients with tumors harboring L747_A750delinsP received osimertinib in the first-line setting *vs.* those with E746_A750del (81% *vs.* 64%, P=0.07), and in both cohorts up to one-third of patients were females and current or former smokers. In the first-line setting, there was a 48% increased risk of progression with osimertinib for patients with tumors harboring L747_A750delinsP compared to those with E746_A750del [median PFS: 11.7 *vs.* 21.3 months, adjusted hazard ratio (HR) =0.52; 95% confidence interval (CI): 0.28–0.98; P=0.043], with a 1-year PFS rate of 48% and 79%, respectively. Indeed, there was a similar non-significant trend in OS (26 months *vs.* not reached, HR =0.52; 95% CI: 0.23–1.19; P=0.120).

While most clinical trials evaluating EGFR TKIs in the first-line setting for patients with NSCLC harboring common *EGFR* mutations have consistently reported better outcomes for Del19 compared to L858R mutation (11), the data presented by Grant *et al.*, carry potential implications for the future classification and treatment of these patients. This data provides clinical evidence that the *EGFR* Del19 subtype may exhibit variable sensitivity to specific EGFR TKIs. Preclinical data supports the notion that common structural consequences of *EGFR*-mutations lead to different susceptibility to EGFR TKIs. Notably, the L747P/S mutations, despite being in exon 19, are classified as PACC mutations with lower sensitivity to third-generation EGFR TKI (7).

This preclinical data correlates with clinical data reported by Grant *et al.*, however, it is important to note that this is retrospective data and the sample size for *EGFR* L747_A750>P subtype remains small (n=36) requiring cautious interpretation of the results. Furthermore, according to the *EGFR* Del19 subtype (L747_A750>P *vs.* E746_A750del), the authors did not report imbalances in relevant clinical characteristics, such as the baseline incidence of brain metastases; or tumor characteristics related to the incidence of co-mutations, particularly *TP53* co-mutation. This information is crucial, as it could potentially correlate with an aggressive disease phenotype and inferior outcomes on EGFR TKIs (12).

It is noteworthy that the heterogeneous landscape of *EGFR*-mutant NSCLC may explain the varying sensitivity of EGFR TKI based on different subtypes. This is observed both in tumors harboring common *EGFR*-mutation and among those NSCLC harboring uncommon *EGFR*-mutant tumors. In NSCLC with EGFR exon 20 insertions, there are differing response rate when treated with poziotinib based on the mutation subtype (13). Furthermore, variable TKI sensitivity has also been described for uncommon *EGFR* variants like G719X, L861X, and S768I when treated with osimertinib. Despite all this data, in current clinical practice, EGFR TKI therapy for common *EGFR*-mutant NSCLC is not tailored to specific activating exon 19 deletions. Indeed, the treatment landscape in the first-line in this setting is also rapidly evolving, particularly with the introduction of maximalist combination strategies. Two phase III clinical trials have reported significantly prolonged PFS with the combination of third-generation EGFR TKI, either with platinum-based chemotherapy (in the FLAURA 2 trial—NCT04035486) or amivantamab (a bi-specific monoclonal antibody anti-EGFR and anti-MET evaluated in the MARIPOSA trial—NCT04487080), in comparison to EGFR TKI monotherapy. Nonetheless, it remains unclear which subgroup of patients with *EGFR*-mutant NSCLC benefits the most from these strategies, and the activity of these combinations according to the *EGFR* Del19 subtype has not been reported. However, considering the limited PFS with upfront osimertinib monotherapy in *EGFR* L747_A750>P subtype, a combinational approach would likely be more suitable.

In conclusion, the reported data underscore that a one-size-fits-all is not applicable, and there exists a differential sensitivity to osimertinib based on the Del19 *EGFR*-mutation subtype. This has practical implications for treatment decision in daily practice. Additionally, for future clinical trials assessing new strategies in this context, the Del19 EGFR-mutation subtype should be considered as a stratification criterion. Finally, the correlation between uncommon Del19 mutations and other unfavorable clinical characteristics or a higher incidence of co-mutations that may negatively impact outcomes remains unknown. Therefore, it is crucial to embark on prospective academic initiatives that explore these issues within this population. This research should not only encompass the metastatic setting but also extend to early stages of the disease, where EGFR TKIs are becoming a standard practice.

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