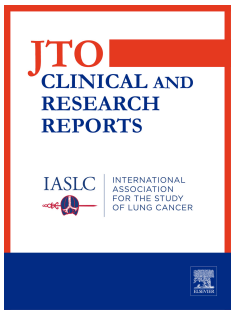

Uncommon *EGFR* mutant Non-Small Cell Lung Cancer - one drug does not fit all

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Conflicts of interest

Surein Arulananda has received speaker fees from Merck-Sharpe & Dohme, Astra Zeneca, Roche, Bristol-Myers Squibb, Merck Serono, travel support from Astra Zeneca, Roche, Merck-Sharpe & Dohme and has been on an advisory board for Boehringer Ingelheim, Roche. Yang Wang has no conflicts of interest.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have revolutionised the treatment landscape for patients with metastatic non-small-cell lung cancer (NSCLC) found to have oncogene driven activating *EGFR* mutations. The 2 most common *EGFR* mutations are the exon 19 in-frame deletion and L858R point mutations which account for the majority (85-90%) of *EGFR* kinase domain mutations seen in NSCLC (1). Numerous studies have demonstrated the presence of these common sensitizing *EGFR* mutations to be predictive of response to EGFR TKIs. Over the past two decades, early generation small-molecule inhibitors such as gefitinib, erlotinib and afatinib have demonstrated improved response rates and progression-free survival (PFS) when compared with chemotherapy (2, 3, 4), hence establishing the role of TKIs in this disease subtype. More recently, the third generation EGFR TKI osimertinib has been demonstrated in the FLAURA trial to result in improved overall survival (OS) (hazard ratio (HR) 0.80; 95% confidence interval (CI), 0.64 to 1.00; p=0.046) compared to first generation EGFR TKIs, underpinning its role as the current standard of care in the treatment of patients with metastatic *EGFR* mutant NSCLC (5).

To date, most clinical trials evaluating the efficacy of EGFR TKIs (including FLAURA) have excluded NSCLC patients harbouring uncommon sensitizing *EGFR* mutations. Therefore, the efficacy of EGFR TKIs in this subset has not been widely studied. Uncommon *EGFR* mutations are varied, however the more prominent ones consist of substitution mutations G719X, S768I, L861Q and exon 20 insertions. The first convincing sign of efficacy in patients with uncommon *EGFR* mutations was from a retrospective analysis of 3 large phase III studies with afatinib, whereby objective responses were seen in 31 of 75 (41.3%) patients (6). Across the 3 trials, the median PFS ranged from 2.7 months to 10.7 months and median OS

9.2 months to 19.4 months. The first prospective study attempting to explore this niche area was from an open label phase II trial by Cho *et al.* that evaluated 37 patients with uncommon *EGFR* mutations treated with osimertinib and found an objective response rate (ORR) of 50% (95% CI, 33% to 67%) with a median PFS of 8.2 months (95% CI, 5.9 to 10.5 months) and a median OS that was not reached (7).

Similarly, Zhang and colleagues provided a literature review of outcomes of patients harbouring these uncommon mutations and found that substitution mutations showed variable response times to EGFR TKIs while *EGFR* exon 20 insertions had a substantially shorter PFS compared with patients with *EGFR* exon 19 deletions and L858R mutations (8). What this surmounts to is that patients with uncommon *EGFR* mutations appear to derive inferior benefit to osimertinib from both a response and survival perspective compared to their common sensitizing *EGFR* mutant counterparts, thus raising the question if there are specific uncommon *EGFR* mutations which predict better outcomes, which warrants a more nuanced analysis.

In this version of the journal, Ji and colleagues report the results of the first large multi-centre retrospective study looking at the outcomes of fifty patients with uncommon *EGFR* mutations treated with osimertinib either in the first- or subsequent-line setting (9). Uncommon *EGFR* mutations in the study included L861X (40.0%), G719X (28.0%), S768I (4.0%), exon 20 insertions (14.0%) and other mutations (20.0%). The primary outcome of measure was time to treatment discontinuation (TTD), defined as time from commencement of osimertinib to discontinuation of therapy for any reason.

TTD has been evaluated to be a potential pragmatic real-world endpoint associated with PFS. In a pooled analysis from 18 randomised controlled trials of patients with advanced NSCLC including two trials of EGFR TKI, Blumenthal *et al.* reported an overall patient-level correlation between TTD and PFS of 0.87 (95% CI 0.78 to 0.98) (10). However, the authors recognised that in the *EGFR* mutation subgroup analysis, the median TTD exceeded the median PFS by 2 months; 13.4 months (95% CI 12.4 to 14.0) *versus* 11.4 months (95% CI 11.1 to 12.8). As surmised by Blumenthal *et al*. and Ji *et al.* (9, 10), patients in these targeted therapy treated groups often continued treatment beyond RECIST progression. This may make it difficult to approximate results in the context of clinical trials that use PFS. In addition, it is unknown whether in this study there were cases of early treatment cessation due to toxicity which in these small sample sizes, may considerably affect the calculation of the median TTD.

In Ji *et* al's study, when all the uncommon *EGFR* mutations were grouped together, the ORR was 31.7% and the median TTD was 10.7 months in the first-line and 7.8 months when treated with osimertinib in the later-line setting. A key finding in the analysis is that there was significant heterogeneity in response to osimertinib with different *EGFR* mutations showing varying sensitivities. Poor responders such as *EGFR* exon 20 insertions exhibited a median TTD of 1.5 months compared with a patient harbouring an L833V/H835L heterozygote *EGFR* mutation with a TTD of more than 4 years. Amongst the study population, the two most common mutations; G719X and L861Q had significantly different median TTD on osimertinib of 7.8 months and 17.2 months respectively, results similar to PFS results reported by Cho *et* al. of 8.2 months and 15.2 months respectively (7). This

highlights that the distinct structural subgroups exhibit a wide range of responses to treatment regardless of the associated exon.

EGFR exon 20 insertions typically account for up to 4% of all *EGFR* mutations and are characterized by in-frame insertions between 3 and 21bp within amino acid positions 767 and 774 of the EGFR protein located after the C-helix (11). The mechanisms of TKI insensitivity in *EGFR* exon 20 insertions are complex and as Robichaux *et al.* highlighted, the location of the insertion influences the pharmacokinetics of TKIs and ATP binding which ultimately determines the sensitivity or resistance to EGFR TKIs (12, 13). This may help to explain why the Yasuda *et al.* found a patient with an A763_Y764insFQEA isoform *EGFR* mutation, which is located at the front of exon 20, who achieved a partial response with erlotinib and Yang *et al*. reported a patient with H773L/V774M mutation achieving 12-month PFS with the use of osimertinib and bevacizumab (11, 14). Furthermore, it remains to be seen whether downstream signalling pathways differ to those activated by common exon 19 deletion or L858R *EGFR* mutations (12, 15).

In this study, Ji *et al*. reported 7 patients with *EGFR* exon 20 insertions treated with osimertinib who had significantly shorter median TTD of 1.5 months in keeping with a well described pattern in the literature of poor response from *EGFR* exon 20 insertions to EGFR TKIs (16, 17). In a retrospective analysis, Naidoo *et* al. reported an ORR of 27% with a median time to progression of 2.5 months (18). However, it is becoming increasingly evident that *EGFR* exon 20 insertions should be categorised separately from all other *EGFR* mutations. Early phase data from selective drugs which inhibit *EGFR* exon 20 insertions, mobocertinib and amivantamab have demonstrated excellent survival outcomes reflective

of their novel mechanisms of action (19, 20, 21). In the platinum pre-treated patients, mobocertinib was associated with an ORR of 28% (95% CI, 20% to 37%), a median PFS of 7.3 months (95% CI, 5.5 to 9.2) and median OS of 24 months (95% CI, 14.6 to 28.8) (20). Similarly, Park *et* al. reported similar findings with amivantamab in a similar cohort of patients progressing on platinum chemotherapy with an ORR of 40% (95% CI, 29 to 51), median PFS of 8.3 months (95% CI, 6.5 to 10.9) and median OS of 22.8 months (95% CI, 14.6 to not reached) (21).

Indeed, the next challenge in the uncommon *EGFR* mutation space is the management of drug resistance. Acquired resistance to first-line osimertinib includes the *EGFR* C797S mutation, *MET* gene amplification and *AXL* activation, amidst others and inhibition of these are the subject of current clinical trials. What remains to be established is whether uncommon *EGFR* mutations treated with osimertinib displays the same upregulation of acquired resistance pathways and whether targeting the same downstream signalling pathways will have a similar effect.

Uncommon *EGFR* mutations account for a proportionally small but nevertheless important group of patients diagnosed with NSCLC. Whilst osimertinib has been shown to significantly improve survival and quality of life for most patients with common sensitising *EGFR* exon 19 deletion and L858R mutations, clinical decision making in the treatment of patients with uncommon *EGFR* mutations remains challenging due to the paucity of available data. Therefore, retrospective series, which includes analysis of specific mutations are critical to help us understand the role of EGFR TKIs in these patients. To this end, we commend Ji *et al*. for reporting on one of the largest multi-centre retrospective series to date and describing

the efficacy across a variety of uncommon *EGFR* mutations. Nevertheless, what is clear is that exon 20 insertion *EGFR* mutations are a separate entity and should not be placed into the same bracket as the other uncommon *EGFR* mutations, especially as there are now potent drugs with high efficacy that have been tested for this molecular subtype. For all other uncommon *EGFR* mutations, osimertinib is efficacious and in some cases, provides durable responses. This further highlights the need for molecular tumour boards so that clinicians can seek advice on these uncommon *EGFR* mutations and offer patients appropriate access to targeted therapies.

Ultimately, the inclusion of uncommon *EGFR* mutations into larger prospective trials will undoubtably assist in our understanding into the effectiveness of EGFR TKIs in this subset. Until then, the best data we have comes from retrospective series such as that from Ji *et al.* and we encourage clinicians to continue reporting on outcomes with targeted therapies on all NSCLC patients with rare molecular gene alterations which will guide decision making.

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CREDIT statement

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