Editorial Commentary

Osimertinib for uncommon EGFR mutations: herding UNICORNs in a field of horses

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Mutations occurring in the epidermal growth factor receptor (*EGFR*) gene, which encodes a transmembrane receptor tyrosine kinase (RTK), have been identified as oncogenic driver mutations in non-small cell lung cancer (NSCLC). Worldwide, approximately one-third of cases of newly diagnosed NSCLC harbor an *EGFR* mutation, with the highest prevalence observed amongst patients who are Asian, female, non-smokers, and those with adenocarcinoma histology (1,2). The prevalence is significantly lower in Caucasian patients from western countries. The majority of *EGFR* mutations occur within exons 18 to 21, with approximately 80% occurring as in-frame deletions in exon 19 or the point mutation L858R in exon 21, termed "common" or "classical" mutations (3). The remainder of *EGFR* mutations, termed "uncommon" or "atypical" mutations, are comprised of a heterogeneous group of alterations with differing rates of response to existing therapies. Among the uncommon *EGFR* mutations, exon 20 insertions account for approximately 10% of *EGFR*-mutant cases and are the third most frequent *EGFR* mutation behind exon 19 deletions and exon 21 L858R mutations (3). The other most prevalent uncommon mutations include exon 18 G719X (variants G719 A/C/D/S), exon 21 L861Q, and exon 20 S768I, which comprise 4.8%, 3.5%, and 2.5% of all *EGFR* mutations, respectively (4). Next generation sequencing should be utilized for mutation screening and identification whenever possible, as uncommon and compound *EGFR* mutations may be missed with conventional polymerase chain reaction testing.

Patients with NSCLC and common *EGFR* mutations have been shown to be sensitive to EGFR tyrosine kinase inhibitors (TKIs), which are small molecules that inhibit the binding of ATP at its catalytic site within the receptor, thereby inhibiting autophosphorylation and downstream intracellular signaling (5). Multiple generations of EGFR-TKIs have been approved for first-line use, however due to acquired resistance mechanisms, such as the Thr790Met (*T790M*) point mutation and others, most patients eventually experience disease progression (6). Osimertinib, a third-generation EGFR-TKI that selectively inhibits *EGFR* mutations and *T790M* resistance variants, has been shown to improve outcomes in multiple stages of disease for patients with NSCLC harboring a common *EGFR* mutation (7,8). Indeed, osimertinib has been associated with improved overall survival (OS) both as adjuvant therapy following surgical resection for early-stage disease and as first-line treatment for advanced or metastatic disease (9,10). Patients with advanced NSCLC containing a common *EGFR* mutation have a median OS (mOS) of up to 38.6 months when treated with osimertinib (10).

EGFR exon 20 insertion mutations are one of the

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uncommon mutations with the most prospective treatment data to date. Unlike the common *EGFR* mutations, exon 20 insertions result in an altered conformation at the typical binding site of TKIs, making them less responsive to these treatments (11). Historically, platinum-based chemotherapy had been the standard first-line therapy for locally advanced or metastatic NSCLC with *EGFR* exon 20 insertions (12,13). However, based on the results of the recently published, phase III PAPILLON trial, amivantamab, an *EGFR* and mesenchymal-epithelial transition (MET) factor bispecific antibody, in combination with platinum-based chemotherapy is now standard of care (14). Amivantamab was also granted Food and Drug Administration (FDA) approval for use in the second line setting and beyond in patients that previously progressed on platinum-based chemotherapy based upon the results from cohort D of the phase I CHRYSALIS trial (15). In September 2021, mobocertinib, an irreversible TKI that selectively targets in-frame *EGFR* exon 20 insertions, was granted accelerated approval by the FDA for use in the second line setting based on improved progression-free survival (PFS) observed in the phase I/II NCT02716116 trial (16). However, the drug was later voluntarily withdrawn from market after not meeting its primary end point in the phase III setting.

For uncommon *EGFR* mutations other than exon 20 insertions, given a historical lack of prospective clinical trials, optimal management of patients with these mutations is not well-defined. Afatinib, a second-generation EGFR-TKI, is currently the only FDA approved treatment in the United States. FDA approval was granted in 2018 based on the results of a combined *post-hoc* analysis of the LUX-Lung 2, LUX-lung 3, and LUX-lung 6 clinical trials. In this analysis, Yang *et al.* showed that among the 75 patients with uncommon *EGFR* mutations enrolled in these trials, afatinib resulted in an objective response rate (ORR) of 71.5% with a median PFS (mPFS) of 11.0 months (17). Despite its observed efficacy, afatinib is associated with significant dermatologic and gastrointestinal toxicities. In *post-hoc* analyses of the LUX-lung 3 and LUX-lung 6 clinical trials, dose-reductions were required in 53.3% and 28.0% of patients, respectively, and thus better tolerated treatments are needed (17).

Here, we discuss the prospective data for the use of afatinib and osimertinib for uncommon *EGFR* mutations and will review retrospective analyses performed in this patient sub-population. Furthermore, we will highlight the treatment implications of specific mutation subsets within the cluster of "uncommon" *EGFR* mutations, impact of compound or co-mutations, and discuss the use of the EGFR structure-function-based system proposed by Robichaux and colleagues (18).

Recently published in *JAMA Oncology*, the open-label, prospective, single-arm phase II UNICORN trial examined the efficacy of osimertinib in 42 patients with advanced NSCLC harboring an uncommon *EGFR* mutation (19). Patients were treatment-naïve and enrolled over a 2-year period across 32 hospitals in Japan participating in the Tokyo Cooperative Oncology Group. The most frequent uncommon *EGFR* mutations observed were G719X (50%), S768I (25%), and E709X (15%); patients with exon 20 insertions or symptomatic brain metastases were excluded. Heterogenous compound *EGFR* mutations with at least 1 uncommon mutation were present in 45% of patients in the cohort. The ORR for all participants was 55% with a mPFS of 9.4 months. The median duration of response (mDoR) was 22.7 months, and mOS was not reached. Sub-group analysis performed based on mutation sub-types revealed ORRs of 45%, 50%, and 75% with mPFS of 5.1, 9.4, and 22.7 months for the G719X, S768I, and L861Q mutations, respectively. The ORRs for patients with solitary or compound mutations were 45.5% and 66.7%, respectively, with mPFS of 5.4 and 9.8 months. Commonly reported toxicities in the study included thrombocytopenia (65%), diarrhea (47.5%), rash (42.5%), and mucositis (32.5%); 3 patients (7.5%) required dose reductions due to toxicity. Limitations of the study include its small sample size, small number of patients harboring each mutation sub-type, inclusion of only patients of Asian ethnicity, and exclusion of patients with symptomatic brain metastases.

The UNICORN trial by Okuma *et al.* joins one other prospective clinical trial to date that has examined the efficacy of osimertinib for treatment of advanced NSCLC with uncommon *EGFR* mutations. In the open-label, phase II KCSG-LU15-09 trial, Cho *et al.* enrolled 36 patients in Korea with recurrent or metastatic NSCLC harboring uncommon *EGFR* mutations (20). Osimertinib was administered as first-line therapy in 61% of patients; the ORR was 50%, mPFS was 8.2 months, mDoR was 11.2 months, and mOS was not reached. Sub-group analysis performed according to the most prevalent *EGFR* mutations observed in the study revealed that objective responses were observed in 78% of patients with the L861Q mutation, followed by 53% and 38% in those with the G719X and S768I mutations, respectively.

The efficacy of osimertinib for uncommon *EGFR* mutations has also been studied retrospectively. A

multicenter, international study recently reported by Bar *et al.* examined the efficacy of osimertinib in 60 patients from 22 centers across nine countries (83% western) (21). The most frequent *EGFR* mutations observed were G719X, L861Q, and *de novo* T790M. Compound mutations including at least one common mutation or a *de novo* T790M mutation were seen in 45% of patients. For the entire cohort, the ORR was 61%, mPFS was 9.5 months, mDoR was 17.4 months, and mOS 24.5 months. Sub-group analysis revealed favorable responses for patients harboring L861Q mutations, with ORR of 78%, mPFS of 15.7 months, and mDoR of 16.0 months in 11 patients examined. Compared to patients with uncommon mutations only, patients with compound *EGFR* mutations, consisting of a combination of common and uncommon mutations, had mOS of 31.4 *vs.* 22.1 months [hazard ratio (HR) =0.55; P=0.19] and mPFS of 30.0 *vs.* 8.6 months (HR =0.24; P=0.0017). Another real-world study examining *EGFR*-mutated NSCLC recently published by Barsouk *et al.* included 36 patients with uncommon mutations treated with either osimertinib, afatinib, or erlotinib (22). The most frequent uncommon *EGFR* mutations observed were G719X (6%), exon 20 (2%), and L861Q (1%) with 6 patients harboring compound mutations. Patients who received osimertinib had improved mPFS and mOS at 22 and 32 months, respectively, compared to afatinib (12 and 21 months, respectively) and erlotinib (9 and 17 months, respectively). Sub-group analysis examining outcomes by mutation type was unable to be performed due to small sample sizes.

The prospective UNICORN trial solidifies osimertinib as a first-line treatment option for the management of patients with advanced NSCLC harboring an uncommon *EGFR* mutation. In the absence of direct, head-to-head comparisons in clinical trials, afatinib and osimertinib are currently both considered reasonable first-line treatment options in this setting. Pooled retrospective analysis published by Wang *et al.* showed similar ORR with afatinib and osimertinib (60.6% *vs.* 50.3%, P=0.610) as well as a significant improvement in PFS with afatinib (11.0 *vs.* 7.0 months, P=0.044) (23). Of note, this analysis was conducted prior to publication of the UNICORN trial, and thus this data was not included.

The UNICORN trial further substantiates the notion that not all uncommon *EGFR* mutations are created equal, and thus EGFR-TKI selection should be individualized. In the UNICORN and KCSG-LU15-09 trials, compared to patients with G719X and S768I mutations, patients with L861Q mutations had improved responses to osimertinib, with ORR of 45–53%, 38–50%, and 75–78%, respectively (19). Similar superior outcomes were observed in a retrospective analysis by Bar *et al.*, which suggested superior efficacy of osimertinib in patients with the L861Q mutation, the majority of which were Caucasian (21). Conversely, in *post-hoc*, sub-group analysis of the LUX-lung series, administration of afatinib resulted in improved outcomes for patients with the G719X and S768I mutations. In this analysis, ORRs for these mutations were 78% and 100% with PFS of 13.8 and 14.7 months, respectively. On the contrary, patients with L861Q mutations had a PFS of 8.2 months with an ORR 56% when treated with afatinib (17). Compound *EGFR* mutations, defined by the presence of multiple genomic alterations, which can include both common and uncommon mutations, have also demonstrated differing rates of response to EGFR-TKI. In the UNICORN trial, for patients with compound *EGFR* mutations treated with osimertinib, the ORR was 67%, mPFS was 9.8 months, and mDoR was not reached (19). Afatinib has also demonstrated efficacy in patients with compound *EGFR* mutations; among the 40 patients with compound mutations included in a retrospective analysis by Yang *et al.*, afatinib resulted in an ORR of 77% with a duration of response of 16.6 months (24). As shown by the differing rates of response and heterogenous clinical outcomes in the studies above, the efficacy of EGFR-TKI is variable depending on the specific mutation, and a universal approach to the treatment of uncommon *EGFR* mutations is antiquated. Use of afatinib or osimertinib should be determined based upon the observed mutation with consideration of side effect profile and toxicity.

The most commonly observed side effects occurring with the use of osimertinib and afatinib include diarrhea (40–50% and 50–60% of patients), rash (30–40% and 60–80% of patients), and fatigue (20–30% and 30–40% of patients, respectively). As noted above, dose-reductions were required in 53.3% and 28.0% of patients treated with afatinib in the LUX-lung 3 and LUX-lung 6 clinical trials, respectively, compared to just 7.5% of patients treated with osimertinib in the UNICORN trial (17,19). Of these two agents, osimertinib is better tolerated, which should be considered when determining treatment options. For mutations where there is little established difference in efficacy between the two agents, such as the G719X mutation and others, toxicity and side effect profile should be weighed based on patient preferences.

Given the variable sensitivities to first, second, and

third-generation EGFR-TKIs, classification systems other than traditional exon-based groupings have been proposed. The most widely accepted is the structure-function-based system proposed by Robichaux and colleagues, which categorizes *EGFR* mutations based on their effects on the structure of the EGFR molecule in order to predict response to treatment (18). The four subgroups identified include: classical-like mutations, which result in structural changes away from the ATP-binding pocket and exert little effect on the EGFR, *T790M*-like mutations, which occur in the hydrophobic core of the receptor and are similar to the T790M TKI-resistance mutation, P-loop alpha C-helix compression (*PACC*) mutations, such as G719X, S768I and others, and *exon 20* loop insertions, which are treated differently than other uncommon *EGFR* mutations as discussed above. Characterizing *EGFR* mutations based on these structure-function-based groups showed that these groupings are more predictive of drug and mutation sensitivity compared to exon-based groups. For example, classical-like mutations, which include the point mutation L858R in exon 21, exon 19 deletion, and L861Q mutations, were shown to be sensitive to all generations of EGFR-TKIs, particularly third-generation TKIs such as osimertinib. Alternatively, patients harboring *PACC* mutations were noted to be more sensitive to treatment with afatinib with significantly longer durations of treatment when compared to stratifications used exon-based groups (18).

Despite the observed efficacies of osimertinib and afatinib in the first-line setting, like patients with common *EGFR* mutations, nearly all patients harboring uncommon *EGFR* mutations eventually have evidence of disease progression. Data are limited, however reported resistance mechanisms are similar to those observed in patients with common *EGFR* mutations. These include acquisition of additional *EGFR* mutations, *TP53* mutations, *c-Met* amplification, *PIK3CA* mutations, and neuroendocrine transformation (8,21,25). The UNICORN trial did not report resistance mechanisms when patients progressed on osimertinib due to a lack of tumor samples (19).

There are multiple ongoing clinical trials examining the safety and efficacy of other EGFR-TKIs, including firmonertinib (NCT05364073), zipalertinib (NCT05967689, REZILIENT2), and NX-019 (NCT05514496), among others. The optimal sequencing of therapies in uncommon EGFR mutations has also not been defined, though is being further evaluated in the CAPLAND trial (NCT04811001), which is specifically examining whether dacomitinib, an EGFR-TKI, before or after osimertinib is most efficacious. The role of amivantamab in combination of the EGFR-TKI lazertinib in either treatment naïve patients or those who have progressed after prior first or second generation TKI is being evaluated in an expansion cohort of the CHRYSALIS-2 trial (NCT04077463).

In summary, the UNICORN trial joins a growing body of data examining the optimal treatment of patients with advanced NSCLC harboring uncommon *EGFR* mutations. Osimertinib was shown to be an effective treatment option for this patient population, particularly those patients with exon 21 L861Q mutations. Given differences in EGFR-TKI sensitivity based on uncommon mutation sub-type, next generation sequencing should be used to accurately identify these mutations, and TKI selection should be individualized based on the specific-mutation and patient preferences regarding balance of efficacy and toxicity.

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Footnote

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