Editorial Commentary

How to select between osimertinib or afatinib in P-loop and αC-helix compressing (G719X, S768I) or classical-like (L861Q) EGFR mutations: what preclinical models and clinical data have taught us in the early 2020s

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The discovery of epidermal growth factor receptor (*EGFR*) mutations in 2004 ushered in an explosion of precision oncology into the clinical care of non-small cell lung cancer (NSCLC) over the last two decades. Different EGFR tyrosine kinase inhibitors (TKIs) have been approved for both locally advanced and metastatic cases of *EGFR* mutated NSCLC—becoming the cornerstone of management of the 15–20% of all patients with NSCLC who harbor these genomic aberrations. However, there is both significant heterogeneity in the types of *EGFR* kinase domain mutations (*Figure 1A*) and the susceptibility of EGFR TKIs to different EGFR mutants (1).

The University of Texas MD Anderson Cancer Center (MDACC) has proposed a subgrouping of EGFR mutations into structurally-defined subcategories that better reflect the preclinical (*in vitro*) sensitivity of these mutations (*Figure 1A*): (I) classical-like (exon 19 deletions/indels, L858R, L861Q) with broad sensitivity to multiple generations of EGFR-directed TKIs and where 3rd generation EGFR TKIs have broadest therapeutic windows; (II) P-loop αC-helix compressing (*PACC*) (G719X, S768I) with highest relative sensitivity to 2nd generation irreversible EGFR TKIs; (III) exon 20 loop insertions that are insensitive to the majority of approved 1st, 2nd and 3rd generation EGFR TKIs but are susceptible to novel classes of EGFR exon 20 insertion mutation active TKIs; and (IV) *T790M*-like hydrophobic core mutants (such as compound EGFR-T790M or EGFR-T790M + C797S) that may or may not retain sensitivity to 3rd generation EGFR TKIs (15). How well these structurally-defined subcategories predict real-world clinical efficacy is an active area of investigation based on retrospective clinical data and reports from maturing clinical trials—including the UNICORN trial (Japan Registry of Clinical Trials Identifier: jRCTs071200002) (2).

Osimertinib, a 3rd generation EGFR TKI, has been well-studied in the most common classical EGFR mutations, with most clinical trials and regulatory approvals including tumors with *EGFR*-exon 19 in-frame deletions plus/minus insertions (ex19indel) or *EGFR*-L858R. Osimertinib is now the evidence-based recommendation for adjuvant treatment after surgical resection or chemoradiotherapy for locally advanced stages and for first-line therapy, alone or in combination with chemotherapy, for advanced stage *EGFR* mutated NSCLC (3,4,16). Lazertinib, a similar 3rd generation EGFR TKI, is also approved in combination with the EGFR-MET antibody amivantamab as first-line treatment for locally advanced and metastatic disease

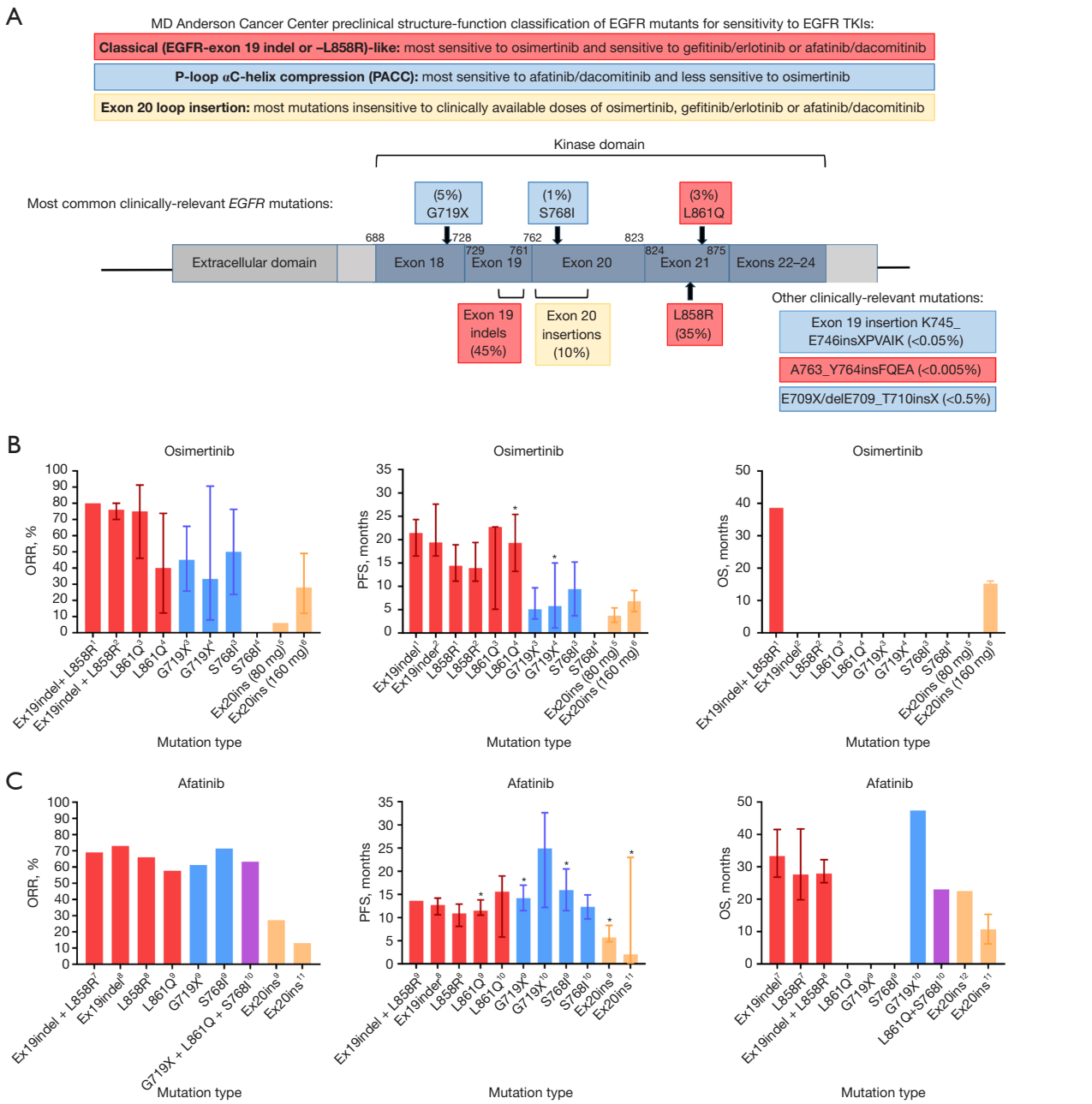

Figure 1 Structure-function classification of EGFR mutants and clinical outcomes of *EGFR* mutated lung cancers. (A) Graphical description of the tyrosine kinase domain of *EGFR* gene and frequency of *EGFR* mutations [as adapted from reference (1)] overlaying the type of mutant with the newly recognized MD Anderson Cancer Center preclinical structure-function classification of EGFR mutants for sensitivity to EGFR TKIs. (B) Summary of outcomes from clinical trials and observation cohorts of patients with *EGFR* mutated lung cancer treated with osimertinib, with a focus on ORR, PFS, TTF and OS. Data obtained from references (2-7). (C) Summary of outcomes from clinical trials and observation cohorts of patients with *EGFR* mutated lung cancer treated with afatinib, with a focus on ORR, PFS, TTF and OS. Data obtained from references (8-13). In the figure, the mutation type outcome reference indicates: 1 = reference (3), 2 = reference (4), 3 = reference (2), 4 = reference (5), 5 = reference (6), 6 = reference (7), 7 = reference (8), 8 = reference (9), 9 = reference (10), 10 = reference (11), 11 = reference (12), 12 = reference (13). One cohort of osimertinib, reference (14), was not used for (B). The MD Anderson Cancer Center structure-function classification was initially described in reference (15). In the figure, * indicates when TTF was used instead of PFS. EGFR, epidermal growth factor receptor; ORR, overall response rate; PFS, progression-free survival; TTF, time to treatment failure; OS, overall survival.

after the MARIPOSA trial (that also included only tumors with *EGFR*-ex19indel or *EGFR*-L858R mutations) demonstrated improved clinical outcomes for the combination of amivantamab + lazertinib over osimertinib monotherapy (17). The clinical data for patients whose tumors harbor even less common *EGFR* mutants, such as *EGFR*-L861Q, *EGFR*-G719X, and *EGFR*-S768I (*Figure 1*, *Table 1*) is not as robust and primarily consists of retrospective and single-armed studies evaluating overall response rate (ORR), disease control rate (DCR), duration of response (DoR), time to treatment failure (TTF), progression-free survival (PFS) and occasionally overall survival (OS) (8-14,19,20). Preclinical models predict that classical-like EGFR mutations (e.g., EGFR-L861Q) will have a similar response to osimertinib to classical mutations while PACC-like mutations (e.g., EGFR-G719X, -S768I) may have a lesser therapeutic window and activity (*Figure 1A*) (15). The evolving clinical data for these mutations seems to corroborate the preclinical data not only for osimertinib but also for other generations of approved EGFR TKIs (*Figure 1B*,*1C*, *Table 1*).

Afatinib, a 2nd generation EGFR TKI, has also been studied primarily in patients with tumors carrying common classical EGFR mutations (EGFR-ex19indel or EGFR-L858R) and was found to be superior to chemotherapy and to gefitinib in the treatment of NSCLC with these mutations in the LUX-Lung 3 and LUX-Lung7 trials (8,9). Afatinib received regulatory approval for any line of treatment in patients with tumors harboring the less common *EGFR* mutations (*EGFR*-L861Q, -G719X, and -S768I) based upon a pooled analysis of only 32 patients in the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials (19). This limited dataset showed an ORR of 66% with a median DoR of nearly 12 months. Patient-level ORR by individual tumor mutation was 56.3% for *EGFR*-L861Q mutated NSCLC, 77.8% for *EGFR*-G719X mutated NSCLC, and 100% for *EGFR*-S768I mutated NSCLC (19).

Other data to support the use of afatinib in tumors with uncommon *EGFR* mutations come from patient series outside the context of clinical trials. Yang *et al.* reported results of treatment with afatinib in a pooled analysis that included 305 patients with uncommon *EGFR* mutated (*EGFR*-L861Q, -G719X, and -S768I) NSCLC from a prospective database and from published case studies and case series. In EGFR TKI-naïve patients, ORR was 59.0% and median TTF was 12.6 months (10). For *EGFR*-L861Q mutated NSCLC, ORR was 57.7% and TTF was lower at 11.5 months [95% confidence interval (CI): 10.5–13.8]. For *EGFR*-G719X mutated NSCLC, ORR was 61.3% and TTF was 14.2 months (95% CI: 11.5–17.0). For *EGFR*-S768I mutated NSCLC, ORR was 71.4% and TTF was 15.9 months (95% CI: 11.5–20.5). Hsu *et al.* performed a retrospective study of 90 patients with tumors with *EGFR*-L861Q, -G719X, and -S768I mutations treated with first-line afatinib at three hospitals in China which showed ORR 63.3%, PFS 17.3 months, and median OS 28.5 months (11). By individual single mutations, this showed a median PFS of 15.6 months for *EGFR*-L861Q mutated NSCLC, 24.9 months for *EGFR*-G719X mutated NSCLC, and 12.3 months for *EGFR*-S768I mutated NSCLC. Moran *et al.* reviewed 67 patients with uncommon *EGFR* mutated tumors treated with afatinib, primarily as a first-line agent, in Spain, with ORR of 54% (12). *Figure 1C* and *Table 1* depict the ORR, PFS/TTF, and OS for individual patients and tumors with less common *EGFR* mutations based on these studies. Individual mutations are grouped into structurally-defined groups according to the scheme from MDACC. Overall, these data support the use of afatinib with similar effectiveness across structural subgroups of PACC (EGFR-G719X, -S768I) mutations when compared to classical-like (EGFR-exon 19 indel, -L858R, -L861Q) mutations (*Figure 1A*,*1C*, *Table 1*). Indeed, the first phase III randomized trial for less common *EGFR* mutated NSCLC was recently completed (ACHILLES/TORG1834 trial, Japan Registry of Clinical Trials: jRCTs031180175) and demonstrated the superiority of afatinib to platinum-based chemotherapy in terms of PFS and other clinical parameters, with the majority of the benefit driven by patients with *EGFR*-PACC mutated NSCLC (20).

Osimertinib has become the preferred EGFR TKI for patients with common *EGFR* mutated (exon 19 indel, L858R) NSCLC after head-to-head comparisons with other EGFR TKIs demonstrated an improved adverse event profile (lower rates of rash, diarrhea and mucosal issues), improved activity in brain metastases, and improved clinical outcomes including ORR, PFS and OS when compared to 1st or 2nd generation EGFR inhibitors gefitinib, erlotinib, afatinib or dacomitinib (*Figure 1B*) (3,18). Osimertinib—at its approved dosing (80 mg daily) or even higher (160 mg daily)—is not active, however, in the less common group of *EGFR* exon 20 insertion mutations, which comprise ~10% of all *EGFR* kinase domain mutations (*Figure 1A*,*1B*, *Table 1*) (6,7,21). Its activity in tumors with other uncommon *EGFR* mutations has been the subject of several recent investigations. Evidence for the use of osimertinib in patients with less common *EGFR* mutated tumors includes

Table 1 Summary of outcomes from clinical trials and observation cohorts of patients with *EGFR* mutated lung cancer

Main *EGFR* mutation	ORR [95% CI], %	PFS (95% CI), months	OS (95% CI), months
Osimertinib (3rd generation EGFR TKI)			
Ex19indel and L858R (3)	80 [75–85]	18.9 (15.2–21.4)	38.6 (34.5–48.1)
Ex19indel and L858R (4)	76 [70–80]	16.7 (14.1–21.3)	–
Ex19indel (3)	–	21.4 (16.5–24.3)	–
Ex19indel (4)	–	19.4 (16.5–27.6)	–
L858R (3)	–	14.4 (11.1–18.9)	–
L858R (4)	–	13.9 (11.1–19.4)	–
L861Q (2)	75 [46–91]	22.7 (5.1–22.7)	NR (19.2–NR)
L861Q (5)	40 [12–73]	19.3* (13.2–25.4)	–
G719X (2)	45 [25–65]	5.1 (3.0–9.7)	NR (6.1–NR)
G719X (5)	33 [8–90]	5.8* (1.1–15.0)	–
S768I (2)	50 [23–76]	9.4 (3.7–15.2)	NR (23.0–NR)
Ex20ins (osimertinib 80 mg) (6)	6	3.7 (2.3–5.4)	–
Ex20ins (osimertinib 160 mg) (7)	28 [12–49]	6.8 (4.6–9.1)	15.2 (14.3–16.0)
Afatinib (2nd generation EGFR TKI)			
Ex19indel and L858R (8)	69	13.6	–
Ex19indel and L858R (9)	–	12.8 (10.9–14.7)	27.9 (25.1–32.2)
Ex19indel (8)	–	–	33.3 (26.8–41.5)
Ex19indel (9)	73	12.7 (10.6–14.2)	–
L858R (8)	–	–	27.6 (19.8–41.7)
L858R (9)	66	10.9 (8.1–12.9)	–
L861Q (10)	57	11.5* (10.5–13.8)	–
L861Q (11)	–	15.6 (5.8–18.9)	–
G719X (10)	61	14.2* (11.5–17.0)	–
G719X (11)	–	24.9 (12.1–32.6)	47.4
S768I (10)	71	15.9* (11.5–20.5)	–
S768I (11)	–	12.3 (9.7–14.9)	–
G719X and L861Q and S768I (11)	63	–	23.0
Ex20ins (10)	27	5.7* (4.8–8.3)	–
Ex20ins (12)	13	2.1* (0.5–23.0)	10.7 (6.2–15.3)
Ex20ins (13)	–	–	22.5

The updated OS data for reference (3), as depicted in the table and *Figure 1*, was obtained from reference (18). *, time to treatment failure reported instead of PFS. EGFR, epidermal growth factor receptor; ORR, overall response rate; CI, confidence interval; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

a small prospective study and several retrospective cohorts. KCSG-LU15-08 was a multicenter, open-label, single-arm phase II study of osimertinib which included 37 patients with uncommon *EGFR* mutations in Korea and showed an ORR 50%, median PFS 8.2 months, and median DoR 11.2 months (22). Individual mutation data showed *EGFR*-L861Q mutated NSCLC ORR was 78% and PFS 15.2 months, *EGFR*-G719X mutated NSCLC ORR was 53% and PFS 8.2 months, and *EGFR*-S768I mutated NSCLC ORR was 38% and PFS 12.3 months. Pizzutilo *et al.* reported a retrospective study of 50 patients with uncommon *EGFR* mutated NSCLCs (ARTICUNO) treated with osimertinib in Italy (23). For *EGFR*-L861X mutated NSCLC, ORR was 55%, DCR 90%, median PFS 8.5 months, median DoR 5 months, and median OS 28 months. For *EGFR*-G719X mutated NSCLC, ORR was 44%, DCR 85%, median PFS 8.5 months, median DoR 13 months, and median OS 20 months. For *EGFR*-S768I mutated NSCLC, ORR was 58%, DCR 92%, median PFS 17 months, median DoR not reported, and OS not reported. An international case series on first-line use of osimertinib in patients with uncommon *EGFR* mutated NSCLC included 60 patients, with ORR 61%, median PFS 9.5 months, median DoR 17.4 months and median OS 24.5 months (14). For *EGFR*-L861Q mutated NSCLC, ORR was 80%, median PFS 16 months, and median DoR 16 months. For *EGFR*-G719X mutated NSCLC, ORR was 47%, median PFS 8.8 months, and median DoR 9.1 months. *EGFR*-S768I mutated NSCLCs were uncommon in this cohort at 5%. Ji *et al.* conducted a retrospective multicenter study of 50 patients treated with osimertinib at United States comprehensive cancer centers with uncommon *EGFR* mutated NSCLCs (5). Overall, the ORR was 31.7% with TTD 9.7 months. For *EGFR*-L861Q mutated NSCLC, ORR was 41.2% and TTD was 17.2 months. For *EGFR*-G719X mutated NSCLC, ORR was only 10% and TTD was 7.8 months. *EGFR*-S768I mutated NSCLC was uncommon in this cohort, with only 2 patients (4%).

UNICORN, a multicenter phase II nonrandomized trial of first-line treatment with osimertinib in advanced NSCLC with less common *EGFR* mutations, attempts to generate data to support or refute the use of this EGFR TKI in this patient population (2). The UNICORN trial, designed and implemented in Japan, further improves upon the existing evidence for the use of osimertinib in uncommon *EGFR* mutated NSCLC by providing additional prospective data, by assessing the response to treatment using a blinded, independent central review committee and by restricting enrollment to patients receiving osimertinib as first-line therapy. The study included 40 eligible patients with tumors harboring less common *EGFR* mutations, including *EGFR*-L861Q (n=8), G719X (n=20), -S768I (n=10), and -E709X (n=6). Notably, 18 patients (45%) had compound mutations. The trial showed an ORR 55%, median PFS of 9.4 months and median DoR of 22.7 months, while data on OS was not available (*Figure 1B*, *Table 1*). The ORR for solitary less common *EGFR* mutated NSCLC was 45.5% with median PFS 5.4 months, while the ORR for compound uncommon *EGFR* mutated NSCLC was 66.7% with median PFS 9.8 months (compound mutations included some patients with a compound common ex19indel or L858R combined with an uncommon mutation). For *EGFR*-L861Q NSCLC, ORR was 75.0%, median PFS 22.7 months, mDoR 22.7 months, and OS not reported. Response rate for solitary *EGFR*-L861Q NSCLC was even higher at ORR 85.7%, with median PFS 22.7 months, median DoR 22.7 months and OS not reported. For *EGFR*-G719X NSCLC, ORR was 45.0%, median PFS 5.1 months, median OS not reported, and median DoR 9.7 months. Response rate was lower for solitary *EGFR*-G719X NSCLC with ORR 30.0%, median PFS 3.6 months, median OS not reported, and median DoR 9.3 months. For *EGFR*-S768I NSCLC, ORR was 50.0%, with median PFS 9.4 months and DoR not reported. Response rate was lower for solitary *EGFR*-S768I NSCLC with ORR 33.3% with median PFS 3.7 months and DoR not reported (*Figure 1B*, *Table 1*). A comparison of the UNICORN data with other representative studies, subdivided by mutation, shows that patients with tumors with classical-like *EGFR* mutations such as *EGFR*-L861Q have a similar response to osimertinib as the classical *EGFR*-ex19indel and -L858R mutations (*Figure 1B*), while patients whose tumors have *EGFR*-G719X and *EGFR*-S768I mutations have less favorable clinical outcomes (including ORR and more notably PFS) to osimertinib (*Figure 1B*, *Table 1*). The difference in response rate between classical-like EGFR mutants (EGFR-L861Q) versus PACC mutants (*EGFR*-G719X and -S768I) was even more pronounced for solitary mutations in the UNICORN data (2).

Summary

It is unlikely that there will be a randomized trial with a direct comparison between osimertinib (or other 3rd generation EGFR TKIs) and afatinib (or other 2nd

generations EGFR TKIs) in patients with tumors harboring less common *EGFR* mutations, and therefore studies such as UNICORN provide the clinical evidence for choosing an EGFR TKI for patients whose tumors have these mutations (2). These data question the universal recommendation to consider osimertinib as one of the preferred EGFR TKIs for patients *EGFR* PACC (*EGFR*-G719X, -S768I) mutated NSCLC and point towards the need to consider alternative EGFR TKIs, such as afatinib (*Figure 1C*, *Table 1*), in these cases. The combined clinical data suggest that patients with tumors driven by the PACC mutations E*GFR*-G719X and -S768I have similar clinical outcomes with afatinib (in terms of ORR, PFS and OS) when compared to patients with classical-like mutations (*Figure 1C*, *Table 1*). These data simultaneously support that osimertinib (in countries where it is the only 3rd generation EGFR TKI available) is a preferred treatment in patients whose tumors harbor less common *EGFR* classical-like mutations, such as for *EGFR*-L861Q mutated NSCLC. *Figure 1* summarizes both the preclinical and clinical data that support these observations, and our comprehensive cancer service (Beth Israel Deaconess Medical Center, a member of the Dana-Farber/Harvard Cancer Center) recommends the use of the aforementioned EGFR TKIs for these distinct types of *EGFR* mutated NSCLC.

As the treatment options for *EGFR* mutated NSCLC continue to expand, there is ongoing investigation into the efficacy of newer regimens in NSCLCs with less common *EGFR* mutations. Amivantamab plus lazertinib was studied in a cohort of patients with less common *EGFR* mutated tumors in the CHRYSALIS-2 study, with ORR that exceed 50% in *EGFR* PACC mutated tumors and activity after prior use of afatinib (24); results that need to be confirmed in larger cohorts. In addition, the current wave of clinical trials of novel EGFR TKIs better dovetails the structural and preclinical knowledge of EGFR mutants into enrollment into clinical trials. This is best exemplified by the development of novel EGFR exon 20 insertion mutation active TKIs [reviewed by our group in a prior report (25)], such as mobocertinib, sunvozertinib and zipalertinib, that have complete clinical trial portfolios restricted to *EGFR* exon 20 insertion mutated NSCLC (25). The same type of trial selection pathway is also at play for *EGFR* PACC mutated NSCLC, where recently the pan-active EGFR TKI firmonertinib (formerly furmonertinib) was specifically studied in a well-designed trial (FURTHER, ClinicalTrials.gov ID: NCT05364073) showing encouraging clinical outcomes. Stratification of future clinical trials of these less common EGFR mutations into structurally-defined groups can help to better define the best treatment options for this heterogeneous group of NSCLCs.

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References

1. Le X, Nadler E, Costa DB, et al. EGFR Tyrosine Kinase Inhibitors for the Treatment of Metastatic Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Podcast. Target Oncol 2023;18:807-17.
2. Okuma Y, Kubota K, Shimokawa M, et al. First-Line Osimertinib for Previously Untreated Patients With NSCLC and Uncommon EGFR Mutations: The UNICORN Phase 2 Nonrandomized Clinical Trial. JAMA Oncol 2024;10:43-51.
3. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
4. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med 2023;389:1935-48.
5. Ji J, Aredo JV, Piper-Vallillo A, et al. Osimertinib in NSCLC With Atypical EGFR-Activating Mutations: A Retrospective Multicenter Study. JTO Clin Res Rep 2023;4:100459.
6. van Veggel B, van der Wekken A, Hashemi S, et al. Osimertinib treatment for patients with EGFR exon 20 insertion positive non-small cell lung cancer. Ann Oncol 2018;29:VIII524-5.
7. Zwierenga F, van Veggel B, Hendriks LEL, et al. High dose osimertinib in patients with advanced stage EGFR exon 20 mutation-positive NSCLC: Results from the phase 2 multicenter POSITION20 trial. Lung Cancer 2022;170:133-40.
8. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
9. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016;17:577-89.
10. Yang JC, Schuler M, Popat S, et al. Afatinib for the Treatment of Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: An Updated Database of 1023 Cases Brief Report. Front Oncol 2022;12:834704.
11. Hsu PC, Lee SH, Chiu LC, et al. Afatinib in Untreated Stage IIIB/IV Lung Adenocarcinoma with Major Uncommon Epidermal Growth Factor Receptor (EGFR) Mutations (G719X/L861Q/S768I): A Multicenter Observational Study in Taiwan. Target Oncol 2023;18:195-207.
12. Moran T, Taus A, Arriola E, et al. Clinical Activity of Afatinib in Patients With Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Spanish Retrospective Multicenter Study. Clin Lung Cancer 2020;21:428-436.e2.
13. Miura S, Hsia T, Hung J, et al. P50.03 A Real-World Cohort Study of EGFR TKIs in Patients with NSCLC with Uncommon EGFR mutations (UpSwinG). J Thorac Oncol 2021;16:S1115-6.
14. Bar J, Peled N, Schokrpur S, et al. UNcommon EGFR Mutations: International Case Series on Efficacy of Osimertinib in Real-Life Practice in First-LiNe Setting (UNICORN). J Thorac Oncol 2023;18:169-80.
15. Robichaux JP, Le X, Vijayan RSK, et al. Structure-based classification predicts drug response in EGFR-mutant NSCLC. Nature 2021;597:732-7.
16. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
17. Cho BC, Lu S, Felip E, et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med 2024;391:1486-98.
18. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med. 2020;382:41-50.
19. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 2015;16:830-8.
20. Miura S, Tanaka H, Misumi T, et al. LBA66 Afatinib versus chemotherapy for treatment-naïve non-small cell lung cancer with a sensitizing uncommon epidermal growth factor receptor mutation: A phase III study (ACHILLES/TORG1834). Ann Oncol 2023;34:S1310-1.
21. Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med 2013;5:216ra177.
22. Cho JH, Lim SH, An HJ, et al. Osimertinib for Patients With Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09). J Clin Oncol

2020;38:488-95.
23. Pizzutilo EG, Agostara AG, Oresti S, et al. EP08.02-046 Activity of OsimeRTInib in NSCLC with Uncommon EGFR Mutations: Retrospective Observational Multicenter Study (ARTICUNO). J Thorac Oncol 2022;17:S418-9.
24. Cho BC, Wang Y, Felip E, et al. Amivantamab plus lazertinib in atypical EGFR-mutated advanced non-small cell lung cancer (NSCLC): Results from CHRYSALIS-2. J Clin Oncol 2024;42:8516.
25. Sentana-Lledo D, Academia E, Viray H, et al. EGFR exon 20 insertion mutations and ERBB2 mutations in lung cancer: a narrative review on approved targeted therapies from oral kinase inhibitors to antibody-drug conjugates. Transl Lung Cancer Res 2023;12:1590-610.

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