# Challenges of EGFR Exon 20 Insertion Targeted Therapy in Non-Small Cell Lung Cancer

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**Abstract.** Epidermal growth factor receptor (EGFR) exon 20 insertion mutations are a distinct molecular subtype of non-small cell lung cancer that inherently resists conventional therapies and has poor clinical outcomes. However, with recent advancements in molecular profiling and drug development, several emerging targeted therapies possess the potential to overcome these obstacles partially. This paper summarizes the biological and structural features of EGFR ex20ins mutations and evaluates the currently available targeted therapies, most notably Amivantamab, Mobocertinib and Poziotinib, with respect to clinical efficacy and safety. While Amivantamab has shown encouraging clinical trial data compared with the other two, several challenges remain, including drug heterogeneity, treatment-related toxicity, acquired resistance and diagnostic limitations. The results of this paper imply that future directions should prioritize the development of more selective inhibitors, combination therapies and improved mutation-detection strategies. This paper also indicates that continued translational and clinical research will be essential to optimize therapeutic outcomes and establish more durable, personalized treatment for patients with EGFR ex20ins mutant NSCLC.

**Keywords:** Non-small-cell lung cancer; EGFR exon 20 insertion; Amivantamab; Mobocertinib; Poziotinib.

## 1. Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide. Among them, non-small cell lung cancer (NSCLC) occurs most frequently. Nearly 85% of all lung cancer cases are diagnosed as NSCLC [1]. It encompasses several major histological categories, most commonly adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Although tobacco smoking partially causes the vast majority of cases, the course of NSCLC treatment has become common among non-smokers, which is why it is important to study its molecular mechanisms and create effective targeted treatment. In non-smokers, a significant proportion of NSCLC cases can be attributed to specific oncogenic driver mutations, especially the notably prevalent epidermal growth factor receptor (EGFR) mutations, including the exon 19 deletion, the exon 21 L858R point mutation, and the exon 20 insertion mutation [2]. These EGFR mutations promote uncontrolled cell proliferation and have become key targets for personalized therapies of advanced NSCLC.

The exon 20 insertion was a relatively uncommon but clinically significant mutation of NSCLC, representing approximately 4–10% of EGFR-mutant tumors and approximately 1–2% of all NSCLC cases overall [3]. Epidemiologically, female populations, non-smokers, and individuals diagnosed with adenocarcinoma appeared to possess these alterations more frequently. While the exon 19 and 21 mutations show remarkable sensitivity to traditional palliative chemotherapy as well as EGFR tyrosine kinase inhibitors (TKIs), and thus can be regulated, exon 20 insertions perform poorly in clinical outcomes to conventional EGFR TKIs. The mutation alters the EGFR kinase domain's structure, which is used to interfere with inhibitor binding. As a result, drug responsiveness is reduced. It is the alternation that makes EGFR ex20ins a distinct and clinically challenging subtype [2]. Therefore, this paper reviews current targeted treatment strategies for ex20ins mutations, examines key clinical challenges associated with these therapies, and discusses future directions and emerging treatments that may improve patient outcomes.

## 2. Current Treatments

Due to ex20ins EGFR mutations' limited sensitivity to old EGFR-TKIs as first-line therapy, several alternative therapeutic strategies have emerged to overcome structural resistance at the kinase active site. The core characteristics, clinical efficacy, and safety profiles of three representative agents are summarized below.

### 2.1. Amivantamab

#### 2.1.1 Mechanism of action

Amivantamab is a bispecific monoclonal antibody that inhibits tumor proliferation by blocking ligand binding, interfering with downstream EGFR and MET signaling, and lowering EGFR and c-MET ligand-dependent phosphorylation. It specifically attaches to the extracellular regions of both EGFR and the mesenchymal–epithelial transition factor (MET) [4]. Unlike small-molecule TKIs, which target the intracellular kinase domain, Amivantamab acts extracellularly and is therefore less affected by the conformational changes caused by exon 20 insertions. Amivantamab not only blocks receptors but also promotes tumor cell destruction via immune mechanisms, including phagocytosis and antibody-dependent cellular cytotoxicity, enhancing its anti-cancer effects [4].

#### 2.1.2 Clinical efficacy

The phase I CHRYSALIS trial, which evaluated the medication in patients who carried advanced EGFR ex20ins mutant NSCLC after platinum-based chemotherapy, showed that Amivantamab was clinically efficacious. In this heavily pretreated population, the objective response rate (ORR) for Amivantamab reached about 40%. Several ex20ins variations showed persistent responses, and an 8.3-month median progression-free survival (PFS) [4,5]. CHRYSALIS trial's results established Amivantamab's role as a second-line treatment.

More recently, the phase III PAPILLON trial supported the drug's position in the first-line setting. Three hundred eight individuals were randomly divided into two groups to take pemetrexed and carboplatin until the disease progressed. One group added Amivantamab to the medication while the other group remained the original. As a result, Amivantamab is recommended for treating advanced ex20ins mutant NSCLC in the first line because it produced a significantly higher ORR of 73% compared to 43% [6]. The PFS was 11.4 months, exceeding the 6.7 months performed in the CHRYSALIS trial by nearly half [6].

#### 2.1.3 Limitations and safety concerns

Rash (86%), infusion-related reactions (IRRs) (65%), and paronychia (42%) were the most frequent minor adverse effects, mostly grades 1 or 2 and easily controlled [5]. Grade 3 or higher adverse events happened in 16% of patients, and only 4% discontinued the drug [5]. These findings demonstrate that Amivantamab's clinical safety and efficacy provide long-lasting clinical benefits for patients. In 2021, the U.S. Food and Drug Administration (FDA) thus approved Amivantamab for previously treated patients [2]. Collectively, these results position Amivantamab as a key targeted therapy for a patient population with historically limited treatment options.

### 2.2. Mobocertinib

#### 2.2.1 Mechanism of action

Mobocertinib is a highly selective, irreversible TKI targeting ex20ins mutant NSCLC. It was designed to exploit a unique binding pocket created by exon 20 insertions, which enabled the drug to attach to the EGFR kinase domain's Cys797 residue. This irreversible interaction increases the inhibitory effect on mutant EGFR while preserving selectivity for wild-type EGFR [7].

#### 2.2.2 Clinical efficacy

Mobocertinib successfully controlled many EGFR ex20ins mutations, according to preclinical research [2]. Promising results from a phase I/II clinical trial of target patients whose disease

progressed after conventional chemotherapy: the ORR was approximately 28%, and the mPFS was 7.3 months. In addition, the treatment provided long-lasting clinical benefit, with a DOR of 15.8 months. These results supported the FDA's approval of Mobocertinib in September 2021 as the first oral targeted therapy for EGFR ex20ins mutations [6].

#### 2.2.3 Safety and tolerability

Despite its initial promise, Mobocertinib demonstrated several limitations. Treatment was frequently associated with particularly grade 1-2 adverse events such as diarrhea and skin reactions. Additionally, reducing dose due to grade 3 or 4 treatment-related events and discontinuing therapy were needed by 25% and 14% of patients, respectively [6]. These rates were higher than those observed with Amivantamab. Moreover, Mobocertinib showed limited central nervous system (CNS) activity. Brain progression was frequently observed in patients with baseline brain metastases. It is also notable that Mobocertinib's performance did not surpass that of traditional palliative chemotherapy in the phase III EXCLAIM-2 trial [8]. Eventually, the drug was voluntarily withdrawn to be a first-line treatment from the U.S. market.

### 2.3. Poziotinib

#### 2.3.1 Mechanism of action

Another orally administered, irreversible EGFR TKI developed to address the structural resistance of exon 20 insertion mutations is Poziotinib. Because 3D modeling has revealed a smaller drug-binding pocket, limiting the effectiveness of many existing TKIs, Poziotinib's relatively smaller size and compact structure, characterized by smaller terminal and substituent linkers, give it the advantages of being more flexible, overcoming steric hindrance, and binding more effectively to the drug-binding pocket [3].

#### 2.3.2 Clinical efficacy

EGFR TKIs were previously used in patient-derived xenograft models with ex20ins mutations, but preclinical investigations demonstrated Poziotinib's advantages. The ZENITH20 trial also showed that its activity is more active in mutations detected in the proximal loop area of the exon 20 compared to the far-loop group, which supported the significance of the site of insertion in determining drug sensitivity [9]. These findings led to multiple clinical evaluations of Poziotinib in treating the mutation. The ZENITH20 study is a phase II clinical trial conducted across multiple centers and cohorts to evaluate the effect of Poziotinib in ex20ins mutant NSCLC. In previously treated patients, ORR ranged from approximately 15% to 28%, with disease control rates (DCRs) of around 70%. The median PFS was around 4–7 months [3]. Nevertheless, the oncologic performance was not effective based on high grade 3 (28%) or high grade (26%) or rasher and diarrhea, and dose interventions or insurgency [10]. Hence, the U.S. FDA denied approval for Poziotinib to enter the market, affecting subsequent research efforts.

## 3. Clinical Challenges

Although Amivantamab, Mobocertinib, and Poziotinib have shown excellent efficacy in the treatment of the EGFR ex20ins-mutated NSCLC, some important clinical issues remain incompletely addressed and do not allow long-term efficacy in treatment. These are challenges that are discussed below.

### 3.1. Acquired Resistance Mechanisms

Clinical resistance emerges rapidly and has already been observed with multiple drugs. Poziotinib has been reported to have the most potential resistance mechanisms, as laboratory studies and patient sample analyses have detected on-target secondary EGFR mutations, such as T790M, C797S, V774A, and D770A, after treatment [11]. For example, T790M mutations alter the pocket of EGFR that ATP binds to, reducing the affinity of Poziotinib for the mutant kinase; C797S mutations abrogate the

covalent bond formation between Poziotinib and EGFR's Cys797 residue, directly reversing drug inhibition. These changes are likely mediators of acquired resistance. Similar resistance patterns have been observed in mutagenesis screens and cell line models, reinforcing the idea that secondary EGFR mutations are a common escape route when covalent TKIs are used. Mobocertinib has also shown emerging resistance signals in molecular analyses of circulating tumor DNA and tumor biopsies. Investigators identified a variety of new EGFR missense mutations after treatment, and retrospective profiling of patients before therapy revealed many co-occurring alterations (e.g., TP53, PIK3CA, and other pathway genes) associated with poor responses [11].

A mechanistic vulnerability shared by several oral EGFR exon-20 inhibitors is their reliance on covalent modification of Cys797; therefore, acquisition of a C797S substitution can confer cross-resistance to multiple agents that use the same binding strategy (Mobocertinib, CLN-081, and others) [7]. This biochemical commonality means that, even when a drug is initially effective, later stages of therapy may be limited unless alternative binding modes or non-covalent approaches are developed.

### 3.2. Heterogeneity of EGFR Ex20ins Mutations

Another major challenge is the heterogeneity of the exon 20 insertions themselves. These insertions vary in size, occur at different positions, and alter the local kinase conformation in distinct ways, so sensitivity to a given drug can depend strongly on the exact insertion site. Multiple trials and preclinical studies have shown a reproducible pattern: mutations in the proximal loop (close to the αC-helix) are generally more drug-sensitive than insertions in the distal loop [10]. For example, some cohorts treated with Poziotinib reported markedly higher ORR in proximal loop variants than in distal loop variants, as mentioned in the previous sections. Consequently, treating exon 20 insertions as a single type masks significant subtype differences and complicates both patient selection and trial design.

### 3.3. Treatment-Related Toxicity and Narrow Therapeutic Window

Toxicity and the narrow therapeutic window further raise questions about the clinical safety of many exon-20-directed TKIs. Agents that inhibit wild-type EGFR as well as mutant receptors commonly cause dose-limiting dermatologic and gastrointestinal toxicities (rash, diarrhea, stomatitis), forcing dose reductions or treatment discontinuation in a high proportion of patients [3]. By contrast, antibody-based approaches have different adverse-event profiles. For example, infusion-related reactions with Amivantamab produce relatively milder adverse events but still require careful management. The main issue that has been trademarked is the potential reduction between potency and tolerability when attempting to enhance drug exposure and activity.

### 3.4. Limited CNS Penetration

Approximately three-thirds of patients are diagnosed with brain metastases, but not all agents (some of which are oral TKI) have an intracranial active metastatic progression, leading to brain progression even when extra-cranial disease is controlled [10]. This will require the enhancement of CNS penetration or systemic drugs used in combination with CNS-targeted methods in order to give a sustainable benefit to most patients.

Finally, clinical outcomes are limited by significant diagnostic and trial design challenges. Next-generation sequencing (NGS) and larger-scale genomic profiling are needed to identify the complete range of insertions, as well as to determine their true prevalence, because routine PCR panels can easily overlook numerous ex20ins variants [12]. Another issue that makes the interpretation of single-arm studies more complicated is variations of mutation types, as well as frequent co-alterations, and analyzing this variation type is better handled in prospective, biomarker-based trials and adaptive designs [12]. Real-time monitoring with liquid biopsy (ctDNA) can help detect emerging resistance and guide therapy changes, but standardized algorithms for how to act on these results are still evolving.

Clinical issues associated with EGFR ex20ins NSCLC in combination with each other are a heterogeneous biology of mutations that results in an irregular drug response, on and off-target resistance, insulated CNS activity of certain agents, severe toxicity that limits dosage, and diagnostic coverage that inhibits patient selection. All of these argue for more selective drugs, smarter combination strategies and biomarker-led clinical trials.

## 4. Future Directions

Given the obstacles, several priorities are needed to address these problems in the future. The marked heterogeneity of EGFR ex20ins variants means that conventional PCR-based assays often fail to detect these mutations accurately [13]. Despite an improved sensitivity and more comprehensive coverage of next-generation sequencing (NGS), its low availability and complexity in terms of interpretation limit its application in clinical practice. It will be necessary to expand the availability of standardized NGS platforms and enhance the annotation of variants to make certain that the correct treatment is selected in time.

From a therapeutic perspective, continued refinement of exon 20–specific targeted agents are needed. While recently approved drugs such as Mobocertinib and Amivantamab represent essential advances, their effectiveness and tolerability in treating classical sensitizing mutations in EGFR TKIs is worse than that of EGFR TKIs [13]. The next-generation inhibitors, such as CLN-081 and Sunvozertinib, demonstrate encouraging preclinical performance and enhancement of selectivity, which illustrates the prospects of rational drug design, taking into account the specifics of exon 20 inserts [2]. Future drug development should prioritize enhancing mutant EGFR selectivity to target mutant EGFR rather than wild-type EGFR, thereby reducing dose-limiting toxicities and enabling sustained treatment exposure.

Another important priority is exploring combination strategies. Rational combinations of exon 20–targeted therapies with chemotherapy, anti-angiogenic agents, or other targeted drugs may enhance response depth and delay the onset of resistance [13]. Nevertheless, taking into consideration the current high toxicity burden linked to EGFR inhibition, these approaches should be considered with caution in further clinical trials with proper health safety considerations and fine-tuning of dose schedules.

As the clinical use of exon 20–targeted therapies expand, a deeper understanding of resistance mechanisms will become increasingly important. Primary and acquired resistance, which occur due to secondary EGFR mutations, pathway evasion signalling, or tumor heterogeneity, are serious impediments to the lasting reaction, and incorporation of long-term tissue and liquid biopsy measurements into clinical studies will assist in promptly identifying resistance and designing subsequent-generation suppressors and adaptive treatment control [14].

Finally, future studies should investigate the role of exon 20–targeted therapies in earlier disease settings. As observed in common EGFR-mutant NSCLC, evaluation in the first-line setting may clarify whether cutting-edge targeted therapy can outperform platinum-based chemotherapy. Moreover, the application of adjuvant and neoadjuvant therapies should also be considered, and the latter can give promising results in terms of understanding the biology of treatment response and resistance. Together, advances in diagnostics, drug design, combination approaches, and resistance profiling will be essential to translating recent scientific progress into meaningful clinical benefit for patients with EGFR ex20ins–mutant NSCLC.

## 5. Conclusion

EGFR ex20ins mutant NSCLCs are considered a particularly challenging subgroup because these alterations make the tumors unresponsive primarily to traditional EGFR TKIs. Structural changes within the EGFR kinase domain limit drug binding and contribute to poorer clinical outcomes than in patients carrying classical EGFR mutations. As a result, patients with EGFR exon 20 insertions

have long faced limited targeted treatment options. Targeted therapies such as Amivantamab, Mobocertinib, and Poziotinib are beginning to develop and demonstrate meaningful clinical activity in this population. Nevertheless, their advantages are limited, and their application is frequently limited by drug vectors related to therapy, minimal CNS activity, and emergence of acquired resistance. In addition, the wide molecular heterogeneity of exon 20 insertion variants leads to variable drug sensitivity, making treatment selection more complex. Because of diagnostic complications, such as under-detection of exon 20 insertions and inequitable access to next-generation sequencing, it becomes even more complicated to achieve effective clinical management. Going forward, the future advancement will be based on how to better detect mutations, create harder-to-target and less-toxic inhibitors, and have a clearer insight into the mechanisms of resistance. Strategies based on variant-specific treatment, rational combination therapies, and previous administration of exon 20-specific agents can assist in improving the long-term outcomes. Further studies that combine the impact of molecular biology, structure, and clinical evidence will be a necessity in enhancing individualized methods of treatment and patient prognosis.

## References

[1] Hendriks, Lizza. E. L., Remon, J., Faivre-Finn, C., Garassino, Marina. C., Heymach, John. V., Kerr, Keith. M., Tan, Daniel. S. W., Veronesi, G., & Reck, M. (2024). Non-small-cell lung cancer. Nature Reviews Disease Primers, 10(1). https://doi.org/10.1038/s41572-024-00551-9

[2] Seo, D., & Lim, J. H. (2024). Targeted therapies for EGFR exon 20 insertion mutation in non-small-cell lung cancer. International Journal of Molecular Sciences, 25(11), 5917–5917. https://doi.org/10.3390/ijms25115917

[3] Hou, J., Li, H., Ma, S., He, Z., Yang, S., Hao, L., Zhou, H., Zhang, Z., Han, J., Wang, L., & Wang, Q. (2022). EGFR exon 20 insertion mutations in advanced non-small-cell lung cancer: Current status and perspectives. Biomarker Research, 10(1). https://doi.org/10.1186/s40364-022-00372-6

[4] Pereira, R. A., Tumelero, M., Schwengber, W. K., & Lenz, G. (2025). Evolving treatment strategies for egfrex20ins-mutated NSCLC: a comprehensive review of amivantamab's role and future directions. Ecancermedicalscience, 19. https://doi.org/10.3332/ecancer.2025.2037

[5] Brazel, D., & Nagasaka, M. (2021). Spotlight on amivantamab (JNJ-61186372) for EGFR exon 20 insertions-positive non-small cell lung cancer. Lung Cancer: Targets and Therapy, 12, 133–138. https://doi.org/10.2147/lctt.s337861

[6] Dorta-Suárez, M., Miguel, M. de, Amor-Carro, O., Calderón, J. M., González-Ortega, Mc., & Rodríguez-Abreu, D. (2023). The state of the art of EGFR exon 20 insertions in non-small cell lung cancer: Diagnosis and future perspectives. Cancer Treatment Reviews, 124, 102671–102671. https://doi.org/10.1016/j.ctrv.2023.102671

[7] Man, X., Sun, X., Chen, C., Xiang, Y., Zhang, J., & Yang, L. (2024). The current landscape, advancements, and prospects in the treatment of patients with EGFR exon 20 insertion mutations warrant scientific elucidation. Frontiers in Oncology, 14. https://doi.org/10.3389/fonc.2024.1367204

[8] Gonzalvez, F., Vincent, S., Baker, T. E., Gould, A. E., Li, S., Wardwell, S. D., Nadworny, S., Ning, Y., Zhang, S., Huang, W.-S., Hu, Y., Li, F., Greenfield, M. T., Zech, S. G., Das, B., Narasimhan, N. I., Clackson, T., Dalgarno, D., Shakespeare, W. C., & Fitzgerald, M. (2021). Mobocertinib (TAK-788): A targeted inhibitor of EGFR exon 20 insertion mutants in non–small cell lung cancer. Cancer Discovery, 11(7), 1672–1687. https://doi.org/10.1158/2159-8290.CD-20-1683

[9] Le, X., Robichaux, Jacqulyne. P., Nilsson, M., Vijayan, K., Ravichandran, A., Wu, J., Elamin, Yasir. Y., Hong, L., Pei, J., He, J., Patel, S., Hibiki Udagawa, Mani, S., Jang, C. W., Clarke, Jeffrey. M., Nishan Tchekmedyian, Goldman, Jonathan. W., Socinski, M., Bhat, G., & Leu, S. (2025). Poziotinib for EGFR exon 20-insertion NSCLC: Clinical efficacy of the phase 2 ZENITH trial and differential impact of EGFR exon 20 insertion location on sensitivity. Nature Communications, 16(1), 8358–8358. https://doi.org/10.1038/s41467-025-61817-8

[10] Bai, R., Chen, X., Song, W., Tian, H., & Cui, J. (2021). Therapeutic exploration of uncommon EGFR exon 20 insertion mutations in advanced non-small cell lung cancer: Breaking through brambles and thorns. Journal of Cancer Research and Clinical Oncology, 148(1), 163–176. https://doi.org/10.1007/s00432-021-03840-y

[11] Bai, Q., Wang, J., & Zhou, X. (2023). EGFR exon20 insertion mutations in non-small cell lung cancer: Clinical implications and recent advances in targeted therapies. Cancer Treatment Reviews, 120, 102605. https://doi.org/10.1016/j.ctrv.2023.102605

[12] Su, P.-L., Furuya, N., Asrar, A., Rolfo, C., Li, Z., Carbone, D. P., & He, K. (2025). Recent advances in therapeutic strategies for non-small cell lung cancer. Journal of Hematology & Oncology, 18(1). https://doi.org/10.1186/s13045-025-01679-1

[13] Passiglia, F., Bironzo, P., Bertaglia, V., Listì, A., Garbo, E., & Scagliotti, G. V. (2022). Optimizing the clinical management of egfr-mutant advanced non-small cell lung cancer: A literature review. Translational Lung Cancer Research, 11(5), 935–949. https://doi.org/10.21037/tlcr-22-1

[14] Pacini, L., Jenks, A. D., Vyse, S., Wilding, C. P., Arthur, A., & Huang, P. H. (2021). Tackling drug resistance in EGFR exon 20 insertion mutant lung cancer. Pharmacogenomics and Personalized Medicine, Volume 14, 301–317. https://doi.org/10.2147/pgpm.s242045