

## Review Article

# New advances in the treatment of EGFR exon20ins mutant advanced NSCLC

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Received December 29, 2024; Accepted April 16, 2025; Epub April 25, 2025; Published April 30, 2025

**Abstract:** The epidermal growth factor receptor (EGFR) exon 20 insertion (ex20ins) mutations, albeit less frequent, are a clinically significant subset within the EGFR mutation landscape of non-small cell lung cancer (NSCLC), accounting for roughly 4%-12% of all EGFR-altered cases. Ranking as the third most prevalent EGFR mutation type, these ex20ins mutations trail the widely recognized EGFR exon 19 deletion (19-Del) and exon 21 L858R substitution. In advanced-stage NSCLC patients with EGFR exon 20 insertion mutations, conventional treatments such as EGFR tyrosine kinase inhibitors (TKIs), chemotherapy, and immunotherapies often yield suboptimal responses, resulting in unfavorable clinical outcomes. This unmet clinical need underscores the urgency to explore innovative targeted therapies. In the realm of precision medicine, targeted agents specifically tailored for EGFR ex20ins mutations have emerged as promising candidates. This review examines the latest research on targeted therapies for EGFR ex20ins mutations, dissecting the mechanisms of action of these agents, evaluating the results of relevant clinical trials, and integrating the evidence in a systematic manner. The aim is to uncover novel therapeutic insights and strategies to optimize the clinical management of patients with EGFR ex20ins mutation-positive NSCLC.

**Keywords:** NSCLC, EGFR ex20ins, EGFR-TKIs, macromolecular antibodies

## Introduction

Lung cancer, which boasts the highest mortality rate among all malignancies, is marked by its alarming incidence and fatality rates globally [1]. The latest 2022 data analysis projects that lung cancer in China will account for approximately 870,000 new cases and 760,000 deaths, cementing its status as the leading cause of cancer-related mortality [2]. Non-small cell lung cancer (NSCLC), the most prevalent histological subtype, comprises about 80% to 85% of all lung cancer diagnoses. Within the NSCLC cohort, the epidermal growth factor receptor (EGFR) is the most frequently mutated oncogenic driver, with a mutation frequency of about 49.8% among Chinese lung cancer patients [3-5]. In recent years, the advent of targeted therapies has led to a nearly 50% reduction in the overall mortality rate of lung cancer [2]. EGFR mutations mainly include exon 19 deletions (19-Del) and exon 21 point

mutations (21-L858R), which together account for about 85% of all EGFR mutations and are the primary targets for EGFR tyrosine kinase inhibitors (TKIs). These mutations show a robust clinical response to EGFR TKIs, with an objective response rate (ORR) ranging from 27.4% to 84% and progression-free survival (PFS) extending up to 8.5-15.2 months [6, 7].

EGFR exon 20 insertion mutations are the third most common EGFR variant, accounting for 0.3%-2.9% of all NSCLC cases and 2%-5% of EGFR-mutant NSCLC cases [8]. This genetic aberration is most commonly identified in female, Asian, and nonsmoking patients with adenocarcinoma [9]. Molecularly, EGFR ex20ins exhibit significant heterogeneity, promoting an active kinase conformation without enhancing TKI binding affinity. Consequently, individuals harboring the EGFR ex20ins mutation commonly display resistance to targeted therapies, with an ORR ranging from 0-20% and a PFS of 1.4-

3.0 months [7]. The prognosis of NSCLC patients harboring EGFR exon 20 insertion mutations is significantly worse. Real-world data analysis by Flatiron Health shows that the median overall survival (mOS) for patients with EGFR ex20ins mutations is 16.2 months (95% CI, 11.04-19.38 months), compared with the mOS of 25.5 months (95% CI, 24.48-27.04 months) for those with typical 19-Del and L858R mutations. The 1-year PFS rate for patients with EGFR exon20ins mutations is only 13%, and the 5-year overall survival (OS) rate is a mere 8% [10]. These statistics highlight an urgent clinical need for innovative therapeutics. This review provides a comprehensive overview of the molecular characterization and detection of EGFR exon20ins mutations, elucidates the mechanisms of action of drugs targeting these mutations, and summarizes recent advancements in clinical research.

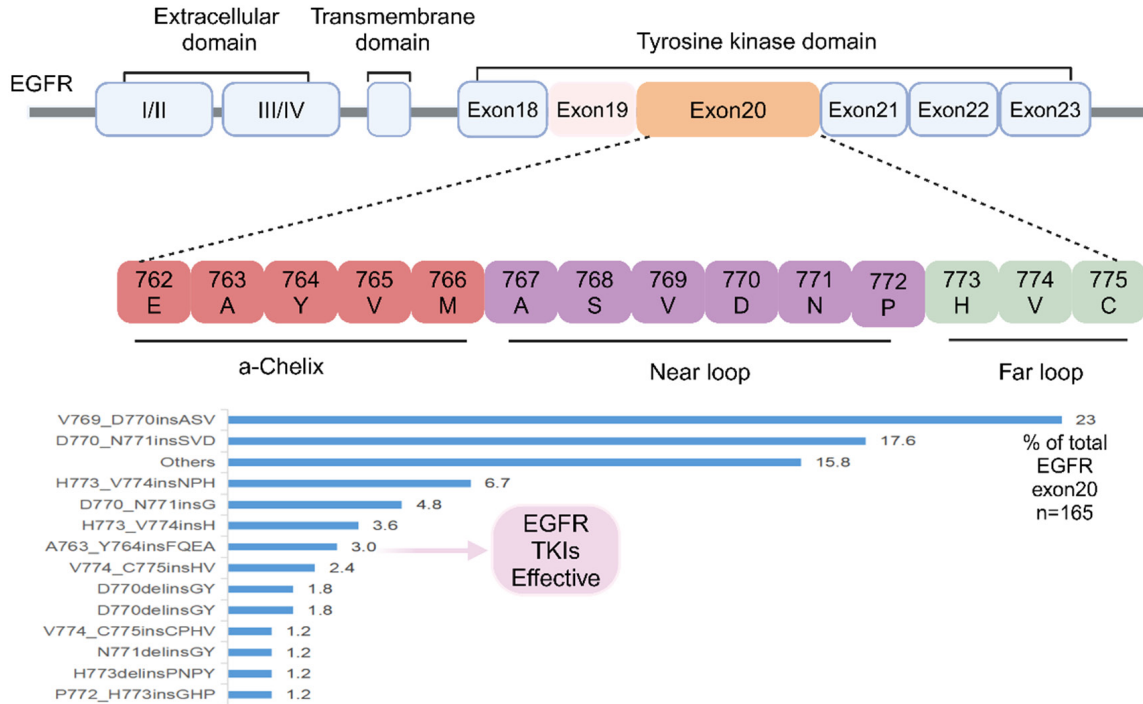
### EGFR ex20ins mutations and resistance mechanisms

The ERBB receptor family, which is also known as the EGFR family, is a key component in the therapeutic arsenal against NSCLC and has established itself as a premier target for intervention [11]. EGFR, a crucial member of the type I tyrosine kinase receptor family, is located on the short arm of chromosome 7 and consists of 28 exons interspersed with 27 introns [12]. This receptor is ubiquitously expressed on the cell membrane of various epithelial cell types and is instrumental in the intricate regulation of cell proliferation through its specific binding to epidermal growth factor or heparin. The EGFR ex20ins mutations encompass a diverse array of variants with significant heterogeneity; since their initial identification in NSCLC in 2004, over 200 distinct mutant subtypes have been cataloged by the global scientific community [13, 14]. Primarily, these mutations are located near the C-helical terminus of the N-lobe within the kinase domain, specifically posterior to the helical loop defined by amino acids E762-M766 and within the loop structural domain of the C-helical loop formed by amino acid sequences A767-C775. Insertional mutations within this domain can be divided into two segments: the proximal loop region (amino acids 767-772) and the distal loop region (amino acids 773-775) [15-17]. Real-world research data indicate that V769\_

D770insASV is the most common insertion variant among EGFR ex20ins mutations, accounting for approximately 23.0% of the mutations, followed by the D770\_N771insSVD variant, which accounts for about 17.6% of all mutation types. It is worth noting that the unique molecular isoform A763\_Y764 exhibits higher sensitivity to first- and second-generation EGFR TKIs. EGFR mutations are one of the major oncogenic mutations in NSCLC and exhibit higher sensitivity to first- and second-generation EGFR TKIs (Figure 1) [18]. EGFR mutations are one of the major oncogenic mutations in NSCLC, and their over-activation or misregulation often drives the development of various cancers. EGFR binds to epidermal growth factor and its ligands, inducing dimerization, phosphorylation, and activation of classical signaling pathways such as RAS-MAPK, PI3K-AKT-mTOR, and JAK-STAT, thereby contributing to the pathogenesis of NSCLC and promoting tumor cell proliferation, invasion, and metastasis [19].

Mutations within the EGFR ex20ins subset confer a distinctive rigid conformation to the C-helix, which sculpts a compact and inaccessible drug-binding site. Notably, one variant of the T790M mutation resides within the ATP-binding pocket, effectively blocking drug access to the binding site through a spatial blockade. This mechanism not only increases the affinity of the mutant EGFR for ATP but also significantly reduces the affinity and binding capacity of reversible TKIs, thereby conferring resistance to first- and second-generation TKIs. In contrast, the C797S mutation induces resistance via a distinct mechanism; it prevents the formation of a covalent bond between TKIs and the cysteine sulfhydryl group (-SH) at position 797 of the EGFR protein. This interference prevents the permanent inactivation of the kinase, resulting in a significant reduction in the therapeutic efficacy of TKIs [20, 21]. Furthermore, the emergence of co-occurring mutations and gene amplification has been identified as a pivotal mechanism underlying drug resistance in cancers that harbor EGFR-activating mutations. These genetic alterations are known to induce structural perturbations within the EGFR proteins, notably the aggregation of EX20 INS/DUP variants within the  $\alpha$ C-helix and the P-loop-key regulatory domains governing the activation state of the EGFR. Such structural modifications hinder the

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**Figure 1.** Structure of EGFR ex20ins. EGFR ex20ins are categorized into the C-helical loop (AA 762-766), near-loop (AA 767-772), and far-loop (AA 773-775). Among these, V769\_D770insASV is the most prevalent insertion variant, whereas A763\_Y764 insertion is sensitive to first- and second-generation EGFR TKIs. EGFR ex20ins, epidermal growth factor receptor exon 20 insertion; TKIs, tyrosine kinase inhibitors.

binding of reversible TKIs to the EGFR proteins, thereby exacerbating drug resistance [22]. Notably, the crystal structures of the NPG isoforms within the EGFR ex20ins mutation show a high degree of structural homology with the wild-type EGFR, particularly at the Osimertinib binding site. This structural congruence not only poses a significant challenge in the development of new drugs but also increases the complexity of developing therapeutics that balance efficacy and safety [23]. In conclusion, the EGFR ex20ins mutations present formidable challenges to therapeutic drug development due to their diverse isoforms, pronounced heterogeneity, constricted ATP-binding pockets, and structural resemblance to the wild-type EGFR. Consequently, there is an imperative demand for the development of targeted therapeutics against EGFR ex20ins mutations to address the clinical management of this recalcitrant disease.

### Inspection methods

In the realm of individualized precision therapy for NSCLC, polymerase chain reaction (PCR)

and next-generation sequencing (NGS) serve as the two primary detection tools in clinical practice [7]. PCR technology, known for its cost-effectiveness and rapid detection cycle, is widely adopted in healthcare institutions and is particularly suitable for rapidly screening single or small numbers of genetic mutations. However, the limitations of PCR in detecting EGFR exon20ins may lead to the omission of relevant mutation information, resulting in incomplete and inaccurate tumor genotyping results for many patients [24]. A retrospective observational cohort study of 22,726 patients revealed that EGFR testing was performed in 75.5% of the cohort during the study period. Among those identified with EGFR ex20ins, NGS technology exhibited a detection rate of 71.1%, markedly surpassing the 9.6% detection rate associated with PCR. This disparity highlights the superior sensitivity of NGS in identifying EGFR ex20ins mutations, thereby reinforcing its position as the leading diagnostic modality for such mutations [25]. Further analysis, drawing on real-world data from the United States, indicated a downward trend in the detection rate of PCR and an upward trajec-

tory for NGS in detecting both overall EGFR-positive and EGFR ex20ins-positive patients. Notably, there was a significant escalation in the utilization of blood samples for EGFR ex20ins detection, with the proportion rising from 0% to 37.2%. This shift is attributed to the substantial increase in the detection rate of EGFR ex20ins in patients with advanced NSCLC, highlighting the burgeoning importance of liquid biopsies in clinical practice [26]. Furthermore, retrospective analysis has highlighted that conventional PCR assays, which are mainly designed to detect common EGFR mutations such as A767\_V769dup (ASV) and S768\_D770dup (SVD), have limited capacity to identify the complex and heterogeneous EGFR ex20ins. Across five different data sources, a total of 104 distinct EGFR ex20ins variants were identified. The detection rate of these variants by NGS was significantly higher than that by PCR. This observation further confirms the superior diagnostic efficacy of NGS and highlights its potential for broad application in detecting EGFR ex20ins mutations [27].

PCR technology exhibits notable constraints in detecting EGFR ex20ins mutant subtypes, with a significant leakage rate of up to 50%. This underscores the limitations of PCR when confronted with the complexity and variability of EGFR ex20ins mutations [28]. In stark contrast, NGS technology provides comprehensive coverage, accurately identifying all subtypes of EGFR ex20ins mutations, including rare and emerging ones, with high sensitivity and specificity. Given the substantial advantages of NGS, it is widely endorsed by experts as the optimal approach for EGFR genetic testing, ensuring the acquisition of more precise and comprehensive mutational profiles [29, 30]. While PCR retains a degree of practicality and convenience as a routine screening tool for EGFR ex20ins, patients with negative PCR results for driver genes are advised to employ NGS for further retesting when feasible. This recommendation aims to reduce the risk of overlooked mutations and facilitate the delivery of more accurate and personalized treatment plans, thereby improving therapeutic outcomes and patients' quality of life.

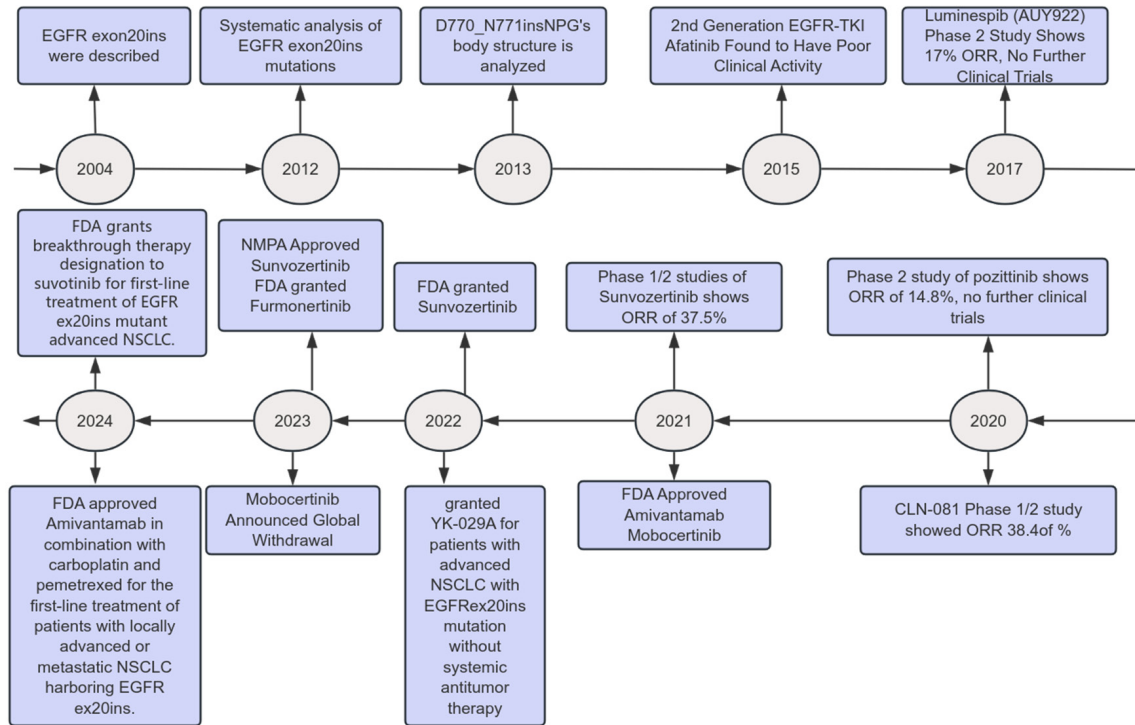
### EGFR ex20ins NSCLC targeted therapies

Hitherto, the utility of conventional chemotherapy-centric first-line treatment protocols for

patients with EGFR ex20ins has been suboptimal. Analysis of real-world data indicates that the response rate (rwORR) for patients administered platinum-based chemotherapy was a modest 19.5% (95% CI: 8.8-34.9), with overall survival (rwOS) averaging 17.0 months (95% CI: 10.5-33.2), and a mPFS of merely 5.7 months (95% CI: 3.0-10.9). Within the sphere of immunotherapy, the efficacy of treatments, whether as standalone interventions or in concert with chemotherapy, has similarly fallen short of anticipated outcomes, with rwORRs recorded at 9.1% and 18.8%, respectively, and median progression-free survival (rwPFS) figures of 3.1 months and 4.5 months, respectively [31]. In contrast to the classical EGFR mutation subtypes, individuals harboring EGFR ex20ins mutations typically exhibit resistance to currently approved TKIs. A real-world meta-analysis has elucidated that patients with EGFR ex20ins mutations who received first-line TKIs had an ORR of a mere 6.8%, with a PFS of 3.0 months and an OS of 16.4 months. Furthermore, for those treated with second-line or subsequent TKIs, the ORR plummeted to 5%, PFS was reduced to 2.1 months, and OS was a mere 14.1 months [32]. These findings unequivocally demonstrate the low responsiveness of patients with EGFR ex20ins driver mutations to TKIs and the suboptimal clinical efficacy of these agents. Hence, there is an exigent need to investigate more potent therapeutic strategies for this patient cohort in clinical practice.

Recent advancements in the therapeutic landscape for EGFR ex20ins mutations have yielded a new generation of targeted drugs (**Figure 2**), broadly categorized into small molecule TKIs and monoclonal antibody therapies. Small-molecule TKIs, such as Sunvozertinib, Mobocertinib, and Furmonertinib, are designed to circumvent the steric hindrance posed by EGFR ex20ins mutations. They achieve this by precisely engaging the structural domain of the EGFR protein's intracellular kinase, employing novel scaffolds or innovative substitutions to significantly enhance target binding affinity and effectively inhibit the EGFR signaling cascade. Conversely, the second class of therapeutics, including large molecule antibodies like Amivantamab, JMT101, and GB263T, targets the extracellular domain of the EGFR protein. These agents not only impede signaling pathways but also modulate immune respons-

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**Figure 2.** Timeline for the discovery of targeted therapies for NSCLC patients with EGFR ex20ins mutations. EGFR, epidermal growth factor; FDA, Food and Drug Administration; NMPA, National Medical Products Administration.

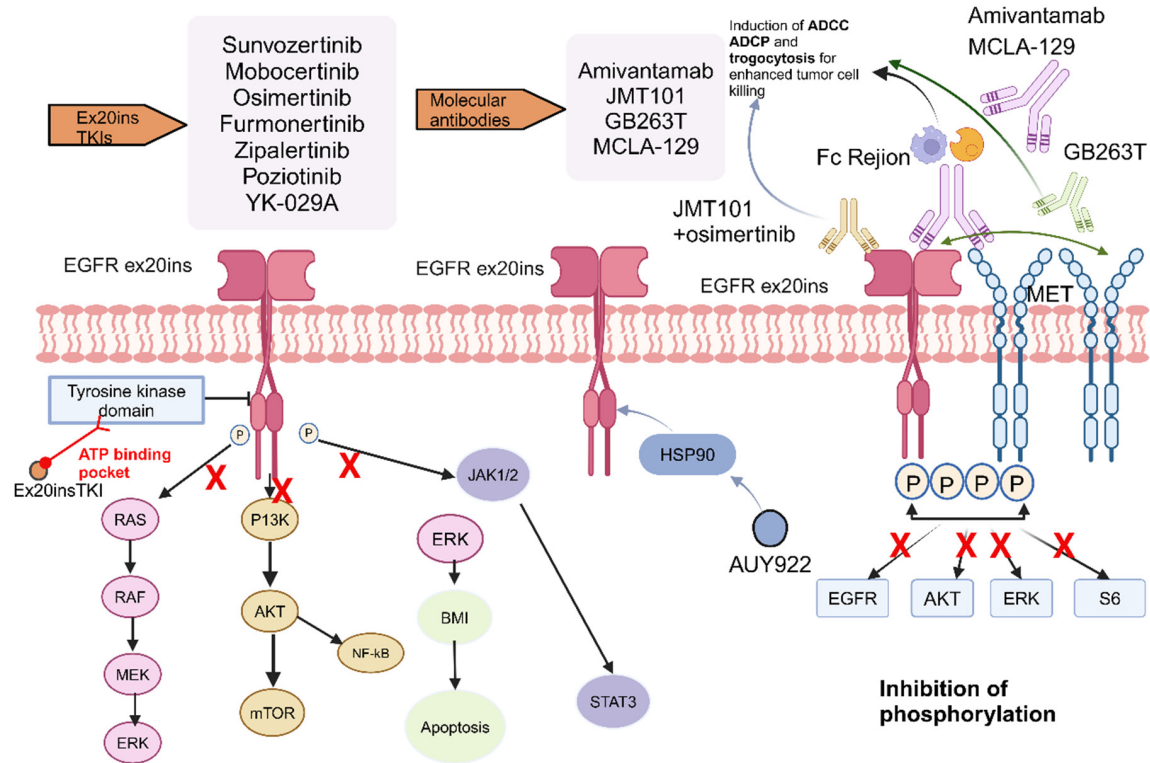
es, inhibiting tumor cell proliferation and dissemination through simultaneous engagement of EGFR and MET receptor tyrosine kinases. These novel agents hold the promise of redefining treatment paradigms for patients with EGFR ex20ins mutations (**Figure 3**). In the subsequent sections, we will systematically delineate the efficacy and safety profiles of approved EGFR-TKIs and emerging therapeutics in the context of EGFR ex20ins-mutated patient populations, aiming to offer valuable insights and guidance for clinical decision-making.

### Small molecule tyrosine kinase inhibitors

**Sunvozertinib:** Sunvozertinib is a pioneering, orally administered, irreversible, and highly selective EGFR TKI designed to target the unique structural features of EGFR variants with specific mutations. The drug's innovative, flexible aniline-based scaffold enhances its ability to engage the ATP-binding pocket, thereby increasing inhibitory potency against mutant EGFR subtypes while maintaining selectivity against the wild-type receptor. The aminomidine component of Sunvozertinib exerts robust inhibition against both EGFR-sensitive and

T790M mutations. Concurrently, the acrylamide group reinforces the inhibitory effect by forming irreversible covalent bonds with cysteine residues. The halogen-substituted aniline-based architecture of the drug optimizes its kinetic profile. Notably, the dimethylaminopyrrolidine segment of Sunvozertinib occupies the solvent channel, a design feature that significantly amplifies the compound's physicochemical attributes and ameliorates its pharmacokinetic and metabolic profiles. This leads to an extended half-life and reduced dosing frequency for patients [33]. In the 2024 edition of the Chinese Society of Clinical Oncology (CSCO) guidelines, Sunvozertinib is prominently endorsed as a pioneering option for subsequent-line therapy for EGFR ex20ins mutations in NSCLC. The efficacy of Sunvozertinib is substantiated by the phase II, multicenter WU-KONG6 clinical trial (NCT05712902), which reported an objective response rate (ORR) of 60.8%, a mDOR of 8.3 months, a mPFS of 6.5 months, and a 12-month OS rate of 87.6% among patients administered Sunvozertinib. The trial further reported that Sunvozertinib treatment achieved an ORR of 60.8%, a DCR of 87.6%, and a 12-month OS rate of 64.9%. Notably, in patient-

## EGFR exon20ins NSCLC treatment advances



**Figure 3.** Mechanism of action of targeted drugs, Ex20ins TKIs bind to the ATP sites of the EGFR kinase domain, inhibiting autophosphorylation and downstream pathway activation, thereby exerting anti-tumour effects. Molecular antibodies targeting EGFR and MET block ligand-induced activation, promote receptor degradation, and induce ADCC, ADCP, and CDC via immune cells, leading to tumour cell death. TKIs, tyrosine kinase inhibitors; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, Complement-dependent cytotoxicity.

ts with brain metastases at baseline, Sunvozertinib achieved an ORR of 48%. In terms of safety, Sunvozertinib's treatment was associated with manageable AEs, including elevated blood creatine phosphokinase (17%), diarrhea (8%), and anemia (6%), none of which severely compromised the therapeutic regimen. These findings provide a strong basis and significant support for advancing to phase III clinical trials [34]. The international, multifaceted phase I/II WU-KONG1/2 trial (NCT03974022) comprehensively evaluated the safety, tolerability, pharmacokinetics, and antitumor efficacy of Sunvozertinib in patients with advanced NSCLC harboring EGFR mutations. The study revealed that 56 patients administered Sunvozertinib exhibited a confirmed ORR of 37.5%, with particular efficacy observed in the 200 mg and 300 mg dose cohorts, exhibiting confirmed ORRs of 45.5% and 41.9%, respectively. The most prevalent TEAEs were diarrhea and rash, all of which were manageable. These prelimi-

nary findings not only substantiate Sunvozertinib's antitumor activity but also attest to its favorable safety and tolerability profile, thereby establishing a robust basis for further clinical investigation [35, 36]. Additionally, the WU-KONG1B component of the study (NCT03974022) specifically evaluated Sunvozertinib's antitumor activity in the 200 mg and 300 mg dosage groups, focusing on patients with EGFR ex20ins NSCLC who had previously received platinum-based chemotherapy. An independent review committee (IRC) confirmed an ORR of 54.3% and a DCR of 90.8%. While data on the mDOR and mPFS remain fully mature, the study's outcomes further substantiate sunvozertinib's substantial antitumor efficacy, presenting a novel therapeutic alternative for patients who have developed resistance to first-line chemotherapy [37]. The WU-KONG1 (NCT03974022) and WU-KONG15 (NCT05559645) clinical trials enrolled patients with previously untreated EGFR ex20ins NSCLC

and administered single-agent oral Sunvozertinib therapy. These trials reported a striking confirmed ORR of up to 78.6%, with a reduction in target lesion size observed in all participants. At the recommended phase II dose (RP2D) of 300 mg, the mPFS extended to 12.4 months, and half of the patients in remission continued on treatment. The mDOR has not been reached, suggesting a durable response [38]. Sunvozertinib also exhibited significant antitumor activity in patients with acquired resistance to EGFR TKIs. A pooled analysis of WU-KONG1, WU-KONG2 (CTR20192097), and WU-KONG15, which included patients with EGFR ex20ins NSCLC post-EGFR-TKI failure, demonstrated an optimal ORR of 21.9%, a mDOR of 4 months, a mPFS of 5.9 months, and the longest treatment duration exceeding 35 months. These results indicate that Sunvozertinib not only alleviates clinical symptoms but also substantially prolongs patient survival [39, 40].

With the publication of several phase II clinical trials confirming the efficacy of Sunvozertinib, the results of the ongoing phase III trial WU-KONG28 (NCT05668988) are highly anticipated [41]. Sunvozertinib in combination with chemotherapy (WU-KONG36, NCT06195189) [42], Anlotinib (WU-KONG32, NCT06348927) [43] and other clinical trials are actively recruiting patients. It is expected that these combinations will achieve even more impressive efficacy in patients with EGFR ex20ins driver gene mutations.

**Mobocertinib:** Mobocertinib, an orally administered TKI designed to target EGFR ex20ins, forms an irreversible covalent bond with cysteine 797 (Cys797) within the EGFR, selectively inhibiting EGFR ex20ins mutations. The drug is designed to occupy a unique binding pocket specific to EGFR ex20ins mutations, distinct from other TKIs like Osimertinib, achieving preferential inhibition of these mutations. In vitro studies have shown that Mobocertinib's half-maximal inhibitory concentration (IC50) values against five distinct EGFR ex20ins variants (FQEA, NPG, ASV, NPH, and SVD) range from 4.3 to 22.5 mol/L, with a notably higher IC50 value of 34.5 mol/L for the wild-type EGFR, indicating a more potent inhibitory effect on mutant EGFR [44]. In September 2021, Mobocertinib received formal approval in the United States as a novel therapeutic agent for the

treatment of patients with EGFR ex20ins-mutated NSCLC who have experienced failure with platinum-based chemotherapy [45]. This therapeutic advancement is underpinned by a seminal Phase I/II clinical trial (NCT02716116), which enrolled NSCLC patients with the EGFR ex20ins mutation who had previously undergone platinum-based chemotherapy. The trial's outcomes demonstrated a confirmed ORR of 28%, a mDoR of 17.5 months, a mPFS of 7.3 months, a DCR of 78%, and a mOS of 20.2 months. Despite the primary treatment-emergent adverse events (TEAEs) including diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%), these findings nonetheless provided a robust scientific and clinical basis for the FDA's approval of Mobocertinib [46-48]. Subsequently, in January 2023, Mobocertinib obtained marketing approval from the National Medical Products Administration (NMPA) in China, thereby expanding its global reach [49]. However, it is noteworthy that the subsequent phase III clinical trial, EXCLAIM-2 (NCT04129502), did not demonstrate a statistically significant superiority of Mobocertinib over chemotherapy in terms of mPFS with 9.59 months compared to 9.63 months, ORR with 32% compared to 30%, and DCR with 87% compared to 80%, with mDoR of 12 months and 8 months, respectively [50]. Moreover, 62% of Mobocertinib-treated patients experienced grade 3 or higher AEs, which poses a concerning safety profile and necessitates a reevaluation of its safety-to-benefit ratio. Consequently, on 2 October 2023, Takeda Pharmaceuticals announced the withdrawal of Mobocertinib from the market, citing safety concerns [51]. The MOON real-world analysis (PMID: 38612799), which included 86 patients with EGFR Ex20ins-mutated NSCLC, reported an ORR of 33.7% (95% CI: 24-45), a mPFS of 5 months (95% CI: 3.5-6.5), and a mOS of 12 months (95% CI: 6.8-17.2). The mDoR was 8 months (95% CI: 3.7-12.3), and the intracranial response rate was 13%. Furthermore, 95% of patients experienced TRAEs, with 38% reporting grade 3 or higher TRAEs, including diarrhea (22%) and rash (8%). These findings indicate that while Mobocertinib monotherapy has demonstrated some efficacy, its overall therapeutic impact is modest, and the associated toxicities are significant [52]. Considering the constraints of Mobocertinib monotherapy, there is a pronounced need to investigate combinatori-

al strategies with other therapeutics. Although current clinical studies on Mobocertinib in combination with other agents are limited, forthcoming research is anticipated to yield novel insights and potentially transformative advances in the treatment paradigm for EGFR Ex20ins-mutated NSCLC.

**Osimertinib:** Osimertinib, a monoanilino-pyrimidine derivative, features a Michael receptor group that forms an irreversible covalent bond with cysteine-797 in the EGFR kinase's catalytic center, inhibiting EGFR kinase phosphorylation and downstream signaling pathways, including AKT and ERK. This interaction, mediated by an unsaturated acryloyl chain, results in the blockade of proliferation and survival signals in tumor cells [53, 54]. The ECOG-ACRIN 5162 study (NCT03191149) evaluated the efficacy of Osimertinib in 20 patients with EGFR ex20ins mutations, administering 160 mg daily, and reported an ORR of 25%, a DCR of 85%, a mDOR of 5.7 months, and a mPFS of 9.7 months, providing preliminary evidence of Osimertinib's activity in EGFR ex20ins-positive patients [55]. The POSITION20 study (NCT03-257124) further investigated Osimertinib's antitumor effects in 25 patients with EGFR ex20ins-positive NSCLC, also treated with 160 mg daily, and observed an ORR of 28%, a mDOR of 5.3 months, a mPFS of 6.8 months, and a mOS of 15.2 months. Despite the most common TRAEs were diarrhea (72%), dry skin (44%), and fatigue (44%), these studies suggest that Osimertinib exhibits some efficacy against EGFR ex20ins mutations [56]. However, due to the relatively small sample sizes, the findings may be influenced by sampling variability, and thus, larger, more comprehensive clinical trials are warranted to confirm Osimertinib's clinical activity and to refine its therapeutic strategy in patients with EGFR ex20ins-mutated NSCLC.

**Furmonertinib:** Furmonertinib, an irreversible third-generation EGFR TKI, features a trifluoroethoxy pyridine hydrophobic moiety that enhances the drug's activity and kinase selectivity, thereby reducing the generation of off-target metabolites. This structural element also increases Furmonertinib's lipophilicity, facilitating its penetration of the blood-brain barrier to combat brain metastases. Additionally, the metabolite AST5902 of Furmonertinib exhibits anticancer activity comparable to that of the

parent compound, exerting dual antitumor effects. Furmonertinib induces cell apoptosis by inhibiting the anti-apoptotic protein Bcl-2 and modulating the Bax/Bcl-2 ratio, and also suppresses endoplasmic reticulum stress and AKT signaling pathways to induce cell death [57-60]. The FAVOUR study (NCT04858958) represents a seminal clinical trial assessing the efficacy of Furmonertinib in patients with EGFR ex20ins-positive advanced NSCLC. In the first-line treatment cohort, 30 patients receiving 240 mg of oral Furmonertinib daily achieved notable outcomes, with an ORR of 69.0%, a DCR of 96.6%, and an extended mPFS of 10.7 months. Among the 49 patients who had received prior treatments, those receiving 240 mg and 160 mg of Furmonertinib exhibited ORRs of 50% and 40.9%, DCRs of 95.5% and 90.9%, and mPFS of 7.0 months and 5.8 months, respectively. These findings confirm the significant efficacy of Furmonertinib in treating EGFR ex20ins-positive NSCLC and indicate that the drug's antitumor responses are robust, irrespective of the mutation's location relative to the ring structure, and demonstrate potent central antitumor activity [61].

In October 2023, Furmonertinib received Breakthrough Therapy designation from the FDA for the first-line treatment of patients with advanced NSCLC harboring EGFR ex20ins [62]. Furthermore, a real-world study confirmed the efficacy and safety of Furmonertinib in a cohort of 53 patients with EGFR Ex20ins-positive advanced NSCLC. This study reported an ORR of 37.7%, a DCR of 92.5%, and a 6-month PFS rate of 69.4%. Regarding safety, the most prevalent AEs were diarrhea (26.4%) and rash (26.4%), with no grade 3 or higher TRAEs recorded. These findings not only reaffirm Furmonertinib's antitumor activity but also highlight its favorable safety profile, indicating that the drug offers effective therapy without inducing severe side effects and is devoid of dose-dependent toxicity, thus providing patients with a safer and more dependable therapeutic alternative [63, 64]. The FURVENT (FURMO-004) study (NCT05607550) marks a pivotal clinical trial comparing Furmonertinib with platinum-based chemotherapy in the first-line treatment of patients with EGFR ex20ins-mutated NSCLC. Preliminary results from this trial have demonstrated compelling efficacy in the Furmonertinib arm, with a confirmed ORR



of 78.6% and a preliminary DOR of 15.2 months. These findings significantly enhance the promising therapeutic landscape of Fumoneertinib for EGFR ex20ins-positive NSCLC patients and raise expectations for forthcoming results that will further elucidate its potential and long-term efficacy in this patient cohort [65].

**Zipalertinib (CLN-081):** Zipalertinib, an orally administered EGFR TKI, contains a novel pyrrolopyrimidine scaffold that enhances selectivity for EGFR ex20ins mutants over wild-type EGFR. This structural innovation enables Zipalertinib to more potently inhibit proliferation in EGFR ex20ins-positive cell lines while minimizing off-target effects on normal EGFR, thereby reducing toxicities associated with wild-type EGFR inhibition [66, 67]. The phase 1/2a REZILIENT study (NCT04036682) evaluated the efficacy and safety of zipalertinib in 73 patients with EGFR ex20ins-mutated NSCLC. The study reported a demonstrated ORR of 38.4%, a DCR of 57.5%, and a prolonged mPFS of up to 10 months. Common adverse events included rash (80%), onychomycosis (32%), diarrhea (30%), and fatigue (21%) [68, 69]. These preliminary data suggest that Zipalertinib exhibits encouraging antitumor activity with a tolerable safety profile in patients with EGFR ex20ins-mutated NSCLC, including those who have undergone extensive prior treatment. The sustained efficacy observed in this challenging patient population offers a promising new therapeutic avenue.

In patients resistant to amivantamab, Zipalertinib has demonstrated notable antitumor efficacy. Data from Phase 2b Cohort C of the REZILIENT1 study (NCT04036682), which evaluated 18 patients, indicated an ORR of 39% and a DCR of 94%. Although the DOR and mPFS data are not yet mature, these preliminary findings offer innovative and compelling therapeutic avenues for the treatment of patients with EGFR ex20ins mutations in later lines of therapy [70]. Furthermore, the therapeutic potential of Zipalertinib is being actively investigated in the REZILIENT3 study (NCT05973773), which aims to assess the efficacy and safety of Zipalertinib in combination with platinum-based chemotherapy for patients with locally advanced or metastatic non-squamous NSCLC harboring EGFR ex20ins mutations. This trial

is ongoing, and the detailed results have not yet been publicly disclosed [71]. An upcoming multicenter Phase 2B study (NCT05967689) is underway to evaluate the efficacy of zipalertinib in patients with locally advanced or metastatic NSCLC harboring EGFR ex20ins. Specifically, this trial includes patients with brain metastases who will receive zipalertinib orally in twice-daily doses. The primary endpoints of interest are IDCR and intracranial duration of response (IDor). This trial design provides an opportunity to further the understanding of zipalertinib's efficacy in the NSCLC patient population and, importantly, offers new therapeutic insights and optimism for the subset of patients with brain metastases [72].

**Poziotinib (HM781-36B):** Poziotinib (HM781-36B) exerts its therapeutic effect by irreversibly inhibiting the activity of EGFR and HER2, thereby blocking the phosphorylation of EGFR and the subsequent activation of downstream signaling pathways, including STAT3, AKT, and ERK [73]. The ZENITH20 (NCT03318939) phase II clinical trial, a multicenter, multicohort study, evaluated the efficacy of Poziotinib 16 mg QD in 79 patients with EGFR ex20ins-mutated NSCLC. The trial reported an ORR of 27.8% and a DCR of 86.1%. With a median follow-up of 9.2 months, the mDOR was 6.5 months, and the mPFS was 7.2 months [74]. These findings robustly confirm the significant efficacy of Poziotinib in treating patients with EGFR ex20ins-mutated NSCLC. The therapeutic efficacy of Poziotinib was further substantiated in a separate phase II clinical trial (NCT03066206), which reported a confirmed ORR of 32%, a DCR of 84%, a mDOR of 8.6 months, and a mPFS of 5.5 months among 50 NSCLC patients receiving treatment. It is noteworthy that the efficacy of Poziotinib was contingent upon the specific location of the ex20ins mutation within the EGFR, with patients exhibiting proximal-loop insertions showing heightened sensitivity to Poziotinib, as evidenced by an ORR of up to 46%. In contrast, patients with distal-loop insertions exhibited no effective remission (ORR of 0%). The most frequently observed TEAEs included diarrhea (92%), skin rash (90%), oral mucositis (68%), onychomycosis (68%), and dry skin (60%), with the majority being grade 1 or 2 in severity, and no grade 4 or 5 treatment-related adverse events were identified [75]. The

ZENITH20 trial, a multi-cohort, multicenter, global phase II study (NCT04044170), enrolled 57 patients with the EGFR ex20ins mutation, achieving an ORR of 27%, a DCR of 73%, a mDOR of 5.0 months, a mPFS of 5.5 months, and a mOS of up to 15 months. All patients experienced TRAEs, with 39% encountering grade 3/4 AEs [76]. Poziotinib, while efficacious, has been associated with a heightened incidence of adverse effects during therapy. Correlative studies have established a link between these toxicities and the maximum plasma concentration (C<sub>max</sub>) of the drug. An intermittent dosing regimen is proposed to mitigate the drug-related toxicity, with the expectation that this approach will not compromise therapeutic efficacy [77]. This strategy potentially positions Poziotinib as a novel therapeutic alternative for NSCLC patients with EGFR ex20ins mutations, particularly for those who have shown insensitivity to existing EGFR TKIs.

**YK-029A:** YK-029A is a promising third-generation EGFR TKI that exerts its inhibitory effect on the target protein by forming covalent bonds with specific amino acid residues. The compound enhances reversible binding affinity for the target through increased hydrophobic interactions with Phe723, thereby augmenting its inhibitory activity against EGFR ex20ins. It is worth noting that YK-029A displays weak inhibition of wild-type EGFR, which has the potential to mitigate impacts on normal cellular function and reduce the risk of adverse events [78]. A phase I dose extension trial (NCT05767866) demonstrated promising results in 28 previously untreated patients with EGFR ex20ins mutations, with an ORR of up to 73.1% and a DCR of 92.3%. Common adverse events included anemia (50.9%), diarrhea (49.1%), and rash (34.3%) [79]. These findings suggest that YK-029A has excellent efficacy and a favorable safety profile in the context of EGFR ex20ins mutations. A phase III trial (NCT05767892) is currently underway to compare the efficacy of first-line YK-029A with that of platinum-containing chemotherapy. While the results are yet to be disclosed, the positive outcomes from the phase I trial provide a rationale to anticipate that YK-029A may offer significant therapeutic benefits and improved quality of life for this patient population [80]. Clinical studies assessing small Molecule EGFR-TKIs in patients with ex20ins-mutant NSCLC are summarized in **Table 1**.

#### *Molecular antibody-based therapeutics*

**Amivantamab:** Amivantamab, a humanized EGFR/MET bispecific antibody, dually inhibits ligand binding to both EGFR and MET receptors, thereby downregulating and suppressing the EGFR/c-Met downstream signaling pathways, including ERK and AKT phosphorylation [81]. The Fc region of Amivantamab mediates antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Upon binding to EGFR and c-MET on tumor cells, Amivantamab can activate natural killer (NK) cells and macrophages through Fc-mediated effector mechanisms, such as ADCC, leading to the destruction of tumor cells. Moreover, Amivantamab not only engages immune effector cells to eliminate tumor cells but also promotes receptor internalization and subsequent degradation in lysosomes, thereby downregulating EGFR and c-MET receptors and their downstream signaling, ultimately achieving antitumor effects [82]. The CHRYSALIS (NCT02609776) phase I dose-escalation extension study examined the efficacy and safety of amivantamab in 81 patients with locally advanced or metastatic NSCLC harboring EGFR ex20ins. Patients received a fixed dose of 1,050 mg amivantamab and achieved an ORR of 40%, mPFS of 8.3 months, mDOR of 11.1 months, and OS of 22.8 months. The most common TEAEs were rash (86%) and infusion-related reactions (66%), with 42% of patients experiencing grade 3 or higher adverse events [83]. Based on these promising results, the FDA granted accelerated approval for amivantamab on May 21, 2021, for treating patients with EGFR ex20ins-mutated NSCLC [84]. Subsequently, the PAPILLON study (NCT04538664), a phase III trial, further validated the efficacy of amivantamab. This trial enrolled 308 patients with EGFR ex20ins mutations, randomizing them in a 1:1 ratio to receive either amivantamab in combination with chemotherapy or chemotherapy alone. The combination therapy demonstrated superior efficacy over chemotherapy alone, with a mPFS of 11.4 months versus 6.7 months, an ORR of 73% versus 47%, and a DOR of 9.7 months versus 4.4 months, respectively. In terms of safety, the most common adverse reactions (incidence  $\geq$ 20%) included rash, nail toxicity, stomatitis, infusion-related reactions, fatigue, constipation, nausea, diarrhea, and

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**Table 1.** Clinical outcomes in patients with NSCLC harboring ex20ins treated with small molecule TKIs analogues

Clinical trial ID	Intervention	Patient number	ORR, %	Median PFS (months)	DCR, %	DOR (months)
NCT05712902	Sunvozertinib	97	60.8	6.5	87.6	8.3
NCT03974022	Sunvozertinib	56	37.5	NA	NA	NA
NCT03974022	Sunvozertinib	28	78.6	12.4	50.0	NA
NCT05559645						
NCT03974022	Sunvozertinib	32	21.9	5.9	NA	4.0
NCT05559645						
CTR20192097						
NCT02716116	Mobocertinib	114	28.0	7.3	78.0	17.5
NCT04129502	Mobocertinib	354	32.0	9.59	87.0	12.0
PMID: 38612799	Mobocertinib	86	33.7	5.0	NA	8.0
NCT03191149	Osimertinib	20	25.0	9.7	85.0	5.7
NCT03257124	Osimertinib	25	28.0	6.8	NA	5.3
NCT04858958	Furmonertinib	30	69.0	10.7	96.6	NA
PMID: 37004599	Furmonertinib	53	37.7	NA	92.5	
NCT05607550	Furmonertinib	375	78.6	NA	NA	15.2
NCT04036682	Zipalertinib	73	38.4	10.0	57.5	10.0
NCT04036682	Zipalertinib	18	39.0	NA	94.0	NA
NCT03318939	Poziotinib	79	27.8	7.2	86.1	6.5
NCT03066206	Poziotinib	50	32.0	5.5	84.0	8.6
NCT04044170	Poziotinib	57	27.0	5.5	73.0	5.0
NCT05767866	YK-029A	28	73.1	NA	96.3	NA

NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; DCR, disease control rate; DOR, duration of response.

vomiting. The majority of these adverse reactions were mild to moderate and manageable with appropriate interventions [85].

On March 1, 2024, the FDA approved the therapeutic combination of amivantamab with carboplatin and pemetrexed for the first-line treatment of patients with locally advanced or metastatic NSCLC harboring EGFR ex20ins mutations [86]. This regulatory decision was based on a landmark multicenter, real-world study (PMID: 38012986) that reported clinical responses in five of 14 evaluable patients (35.7%) with EGFR ex20ins mutations. The study demonstrated a DCR of 64.3% and an ORR of 36%. In terms of safety, the most frequently observed TEAEs were infusion reactions (18%), rash (13.1%), respiratory tract infections (1.6%), and thrombocytopenia (1.6%) [87]. While the amalgamation of amivantamab with chemotherapy has outperformed chemotherapy alone, thereby establishing a new therapeutic standard for EGFR ex20ins-mutated NSCLC, no tyrosine kinase inhibitor (TKI) has yet surpassed the efficacy of conventional

chemotherapy in a pivotal phase 3 clinical trial (NCT04538664). This observation indicates that, despite notable advancements, there is an imperative for continued research to refine the optimal treatment strategies for these patients, with the ultimate goal of achieving more substantial and enduring clinical benefits.

*JMT101:* The combination of JMT101 with osimertinib has been shown to provide a comprehensive blockade of EGFR ex20ins mutations, including inhibition of signaling, receptor internalization, down-regulation, and potential ADCC. This strategy surmounts the limitations of conventional TKIs in this patient group and exhibits efficacy across a wide range of EGFR exon 20 insertion variants [88]. In a multicenter phase 1b clinical trial (NCT04448379) involving 121 patients receiving JMT101 plus 160 mg osimertinib, an ORR of 36.4% and an mPFS of 8.2 months were observed, with rash (76.9%) and diarrhea (63.6%) being the most common AEs. Among patients who had previously received platinum-based therapy, the

ORR was 34.0%, mPFS was 9.2 months, mDOR was 13.3 months, and the intracranial disease control rate reached 87.5% [88]. The efficacy of JMT101 in combination with osimertinib in platinum-refractory patients with EGFR ex20ins mutations was further evaluated in the BE-COME Phase II trial (NCT05132777). The study recruited 112 patients and reported an IRC-confirmed ORR of 50.0%, DCR of 79.5%, mDOR of 6.4 months, mPFS of 6.9 months and mOS of 17.2 months. The most frequent TRAEs included rash (64%), diarrhea (65%), decreased appetite (59%), oral mucositis (3%), and weight loss (32%) [89]. These findings indicate that the JMT101 and osimertinib combination exhibits substantial anti-tumor activity and a tolerable safety profile in patients with EGFR exon 20 insertion-mutated NSCLC. An ongoing Phase III trial (NCT06380348) is comparing JMT101 plus osimertinib with cisplatin plus pemetrexed in the treatment of advanced NSCLC with EGFR exon 20 insertion mutations and is anticipated to demonstrate superior efficacy [90].

**GB263T:** GB263T, a tri-specific antibody targeting EGFR and cMET, has been engineered to neutralize both primary and secondary EGFR mutations as well as the cMET signaling pathway. This therapeutic strategy achieves comprehensive inhibition of EGFR and cMET signaling, enhances receptor-mediated endocytosis, and promotes tumor cell elimination via ADCC. This multi-pronged approach suggests potential efficacy in treating NSCLC with EGFR ex20ins [91]. In the inaugural phase I/II clinical trial (NCT05332574), 15 patients with assessable disease who had been pre-treated with third-generation EGFR TKIs and platinum-based chemotherapy were evaluated. The study reported a confirmed objective response rate (ORR) of 28.6%, with TRAEs including rash (60.0%), fatigue (40.0%), onychomycosis (40.0%), and infusion-related reactions (33.3%). While the efficacy and safety profile of GB263T in EGFR ex20ins-positive patients is promising, the small sample size of this trial necessitates further validation in larger, subsequent clinical trials to substantiate these findings [92].

**MCLA-129:** MCLA-129 is a fully human IgG1 monoclonal antibody engineered to enhance ADCC via Biclomics® technology. This agent uniquely binds both EGFR and c-Met, thereby

preventing receptor dimerization and inhibiting ligand-dependent phosphorylation of EGFR and c-Met. This inhibition of downstream signal transduction suppresses tumor cell proliferation and survival, and enhances ADCC via GlymaxX® technology, thereby augmenting cytotoxic potential against tumor cells. Moreover, MCLA-129 has demonstrated antibody-dependent cytophagocytosis, further amplifying cytotoxic effects by enhancing macrophage-mediated phagocytosis of tumor cells [93]. In the context of a first-in-human phase 1/2 clinical study (NCT04930432), a total of 63 patients with exon 20 insertions in the EGFR gene were administered 1500 mg of MCLA-129 on a daily basis as a monotherapy for the treatment of advanced solid tumors. The study reported an ORR of 28.6%, a DCR of 84.1%, and a mDOR of 7.2 months. The occurrence of TEAEs was observed, with infusion-related reactions (71.9%), hypoalbuminemia (54.8%), decreased neutrophil count (46.1%), and decreased leukocyte count (40.1%), representing the most prevalent events. The majority of TEAEs were found to be grade 1-2 [94]. Clinical studies evaluating molecular antibody-based therapeutics in patients with ex20ins-mutant NSCLC are compiled in **Table 2**.

#### *Emerging therapies*

**AUY922:** AUY922, an inhibitor of the molecular chaperone heat shock protein 90 (Hsp90), plays a crucial role in the correct folding and stabilization of a spectrum of proteins, including those integral to tumorigenesis and oncogenic survival. By targeting Hsp90, AUY922 disrupts the function of this protein, precipitating the degradation of client proteins and consequently impeding the proliferation and viability of EGFR ex20ins mutant NSCLC cells [95]. A phase II clinical trial was performed (NCT01854034) to ascertain the efficacy of AUY922 in patients with EGFR ex20ins mutant NSCLC. The ORR was 17.2%, the mOS was 13 months, and the mPFS was 2.9 months. While AUY922 exhibited modest efficacy in this patient cohort, the relatively brief mPFS and mOS suggest that further exploration and optimization of the drug's therapeutic potential is warranted. With regard to safety, the most prevalent adverse effects associated with AUY922 were diarrhoea (83%), visual distur-

**Table 2.** Clinical outcomes in patients with NSCLC harboring ex20ins treated with macromolecular antibodies

Clinical trial ID	Intervention	Patient number	ORR, %	Median PFS (months)	DCR, %	Median DOR (months)
NCT02609776	Amivantamab	81	40.0	8.3	NA	11.1
NCT04538664	Amivantamab	308	73.0	11.4	NA	9.7
PMID: 38012986	Amivantamab	14	36.0	NA	64.3	NA
NCT04448379	JMT101	121	36.4	8.2	NA	NA
NCT05132777	JMT101	112	50.0	6.9	79.5	6.4
NCT05332574	GB263T	15	28.6	NA	NA	NA
NCT04930432	MCLA-129	63	28.6	NA	84.1	7.2

NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; DCR, disease control rate; DOR, duration of response.

bances (76%), and fatigue (45%), with ocular toxicity being a particularly salient concern that necessitates vigilant monitoring in future investigations and clinical use to safeguard patient well-being [96].

**Tarloxotinib:** Tarloxotinib, a hypoxia-activated pan-HER kinase inhibitor, releases Tarloxotinib-E under pathophysiological hypoxic conditions. It irreversibly binds to HER family members (EGFR, HER2, and HER4), inhibiting their kinase activity. This leads to the blockade of downstream signaling pathways (e.g., ERK and AKT) and, consequently, the suppression of tumor cell proliferation and survival [97, 98]. In a Phase II clinical trial (NCT03805841) of patients with EGFR ex20ins NSCLC, Tarloxotinib was administered to those who had previously undergone platinum-based chemotherapy. The trial results demonstrated an ORR of 0%, with the mPFS not reached. Nevertheless, some patients achieved stable disease. The common adverse events were QTc prolongation (34.8%), rash (4.3%), and diarrhea (4.3%) [99]. Tarloxotinib provides a potential therapeutic option for patients with EGFR ex20ins-mutated NSCLC due to its unique hypoxia-activated mechanism and irreversible inhibition of the HER family. However, the current clinical trial results suggest that its monotherapy efficacy is limited. Future research should focus on optimizing treatment strategies or exploring combination therapy regimens to enhance its clinical value in this patient population.

**Teliso-V:** Teliso-V, an antibody-drug conjugate (ADC) designed to target c-Met protein overexpression, selectively binds to tumor cells that overexpress c-Met. MMAE, a cytotoxic agent, is

conjugated to the antibody through a valine-citrulline linker. Upon release, MMAE is transported to the tumor cell cytoplasm, where it binds to tubulin and disrupts microtubule function, thereby inhibiting tumor cell mitosis and proliferation, and ultimately inducing cell death [100, 101]. In a multicenter, open-label Phase I/II clinical trial (NCT02099058), the combination of Teliso-V and osimertinib was assessed in patients with osimertinib-resistant, EGFR-mutated, c-Met overexpressing NSCLC. The ORR was 50.0%, as determined by ICR. The DOR was not reached. The mPFS was 7.4 months. The most common TEAEs included peripheral sensory neuropathy (50%), peripheral edema (32%), and nausea (24%) [102]. To date, no clinical studies have specifically targeted EGFR ex20ins mutations with Teliso-V. However, the results from studies in patients with EGFR-mutated NSCLC provide a foundation for future research. Further large-scale clinical trials are warranted to verify the efficacy and safety of Teliso-V in patients with EGFR exon20 insertion mutations.

**U3-1402 (HER3-DXd):** U3-1402 (HER3-DXd), an antibody-drug conjugate (ADC), selectively targets the HER3 receptor and delivers cytotoxic agents to cancer cells, ultimately inducing cell death [103]. In the pivotal Phase II HERTHENA-Lung01 trial (NCT04619004), U3-1402 was evaluated in patients with EGFR-mutated NSCLC who had experienced disease progression following treatment with EGFR TKIs and platinum-based chemotherapy. The trial demonstrated an ORR of 29.8% and a mDOR of 6.4 months. mPFS was 5.5 months, and mOS reached 11.9 months. The DCR was 73.8%. The most common TEAEs included thrombocy-

topenia (20.9%), neutropenia (19.1%), and anemia (14%) [104]. Additionally, U3-1402 exhibited significant antitumor activity in patients with EGFR ex20ins mutated NSCLC. Given that the primary data were derived from a broad population of patients with EGFR mutations, these findings suggest that U3-1402 may also be effective in treating patients with EGFR exon 20 mutations.

### Reflections and prospects

Over the past decade, the landscape of advanced NSCLC treatment has been significantly reshaped by the advancement of multimodal therapeutic strategies and the increasing application of precision medicine. Targeted therapies, which offer a more precise and less toxic alternative to traditional chemotherapy, have shown marked superiority in treating patients with lung cancer driven by specific genetic mutations. Notably, these therapies have achieved substantial improvements in ORR among patients with EGFR ex20ins, as well as extended PFS and OS. These advancements have, in turn, led to a notable enhancement in the quality of life for affected individuals. Despite the introduction of multiple targeted therapies, including several innovative agents that have received clinical approval, the treatment of EGFR ex20ins-mutated NSCLC remains a significant challenge.

The EGFR ex20ins has emerged as a significant challenge in the development of targeted therapies for NSCLC. This mutation is characterized by unique structural features, diverse subtypes, and complex resistance mechanisms. Resistance to targeted therapies for EGFR ex20ins mutations is multifactorial, primarily driven by co-occurring mutations and gene amplifications, as well as compensatory signaling pathways and tumor heterogeneity. Co-occurring mutations are highly prevalent among patients with EGFR-mutated lung cancer, with over 92.9% of these patients harboring at least one additional mutation. These co-occurring mutations significantly impact the efficacy of targeted therapies. For example, the presence of TP53, RB1, PTEN, PIK3CA, or KRAS mutations alongside EGFR mutations can alter cellular signaling pathways and metabolic states, thereby diminishing the effectiveness of EGFR-TKIs. TP53 mutations are the most com-

mon co-occurring mutations in EGFR-mutated NSCLC, occurring in 72.5% of cases. The presence of TP53 mutations in patients with EGFR mutations is associated with a significant reduction in mPFS and mOS (6.5 months vs. 14.0 months, and 28.0 months vs. 52.0 months, respectively) [105, 106]. When RB1 and TP53 mutations coexist, there is an increased risk of transformation to small cell lung cancer (18%), and patients with triple mutations (EGFR/TP53/RB1) have a median survival of only 9.5 months [107, 108]. Additionally, PIK3CA coexisting mutations are present in approximately 7.2% of patients with EGFR mutations, and KRAS co-occurring mutations are found in 8.4% of these patients. These co-occurring mutations lead to reduced efficacy of EGFR-TKIs and shorter overall survival [109-111]. MET gene amplification is another significant mechanism of resistance to EGFR-TKIs. The incidence of MET amplification in patients who develop resistance to first- and second-generation EGFR-TKIs ranges from 5% to 22%. In patients who develop resistance to osimertinib, a third-generation EGFR-TKI, the incidence of MET amplification is 7% to 15% after first-line treatment and 5% to 50% after second-line treatment. MET amplification leads to the aberrant activation of the MET signaling pathway, bypassing the inhibitory effects of EGFR-TKIs on the EGFR pathway, thereby allowing tumor cells to continue proliferating and surviving [112, 113]. Other gene amplifications, such as HER2 (1.5%) [106, 112] and FGFR (5.8%) [114, 115], can also contribute to resistance. Tumor cells can further evade the inhibitory effects of EGFR-TKIs by activating alternative signaling pathways, such as PI3K/AKT/mTOR and MAPK, leading to resistance [116].

Amivantamab, in combination with chemotherapy, is currently the primary therapeutic strategy for treating EGFR ex20ins. This combination was approved in China in February 2025 for the first-line treatment of locally advanced or metastatic NSCLC with EGFR ex20ins mutations. As our understanding of resistance mechanisms to EGFR inhibitors continues to advance, novel combination strategies targeting EGFR ex20ins mutations have been developed. EGFR TKIs and molecular antibody-based therapeutics operate via distinct mechanisms. When used in combination, they can achieve dual EGFR blockade, both intracellularly and

extracellularly. Furthermore, molecular antibody-based therapeutics may mitigate the narrow therapeutic window associated with EGFR-TKIs [117]. MET overexpression has been recognized as a pivotal bypass mechanism contributing to resistance against EGFR-TKIs. Combining EGFR-TKIs, exemplified by osimertinib, with MET inhibitors, such as Capmatinib, effectively curtails tumor growth and is particularly advantageous for patients with EGFR ex20ins mutations and concurrent MET amplification or overexpression [118]. Furthermore, targeting downstream signaling pathways presents a promising strategy. The continuous activation of the PI3K/AKT/mTOR and MAPK pathways by EGFR ex20ins mutations can be attenuated by integrating EGFR-TKIs with mTOR inhibitors, such as Everolimus, or SHP2 inhibitors, thereby augmenting antitumor efficacy [118, 119].

A clinical case study has illustrated that patients with EGFR ex20ins mutations treated with a combination of PD-1 therapy (Camrelizumab), antiangiogenic drugs (Apatinib), and stereotactic ablative radiotherapy achieved PFS exceeding 12 months. This multimodal approach enhances immune responses by optimizing the tumor microenvironment, thereby exerting antitumor effects [120]. Additionally, ADCs, such as U3-1402, which target the EGFR ex20ins mutant protein and deliver cytotoxic agents, may help surmount resistance. The advent of novel targeted drugs and combination therapies heralds new hope for patients with EGFR exon 20-mutant NSCLC.

Sunvozertinib and other targeted therapies have shown clinical efficacy but are largely reserved for second-line or later treatments. To date, no targeted therapy has been definitively established as a first-line option. Although the NMPA has approved the combination of amivantamab and chemotherapy for first-line use, the optimal strategies for subsequent treatments and the need to tailor these strategies based on initial therapy outcomes remain to be elucidated. Moreover, the scarcity of real-world data hampers a comprehensive assessment of these drugs' efficacy, highlighting the need for further refinement of combination treatment protocols. Detecting EGFR ex20ins presents significant challenges. The diversity, complexity, high cost, and time consumption of current detection methods, coupled with the

absence of standardized protocols, significantly hinder accurate and efficient testing. To enhance detection capabilities, it is imperative to explore and optimize detection methods and to develop new technologies that can rapidly and accurately identify this mutation. In-depth research into this mutation subtype is essential to provide personalized and precise treatment strategies for patients with EGFR ex20ins mutations, with the goal of identifying new therapeutic targets and developing more efficient, less toxic targeted drugs.

### Acknowledgements

This study was supported by the National Science and Technology Innovation 2030 -- Major program of 'Research on the prevention and treatment of cancer, cardiovascular, respiratory and metabolic diseases' (2024ZD05-21103); the Efficacy and Mechanism of the Core Formula of "Chu Zhu Pei Ben" Combined with Immune Checkpoint Inhibitors in Treating Advanced Non-Small Cell Lung Cancer with Negative Driver Genes (20240204020).

### Disclosure of conflict of interest

None.

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