Review Article

Advances in the Diagnosis and Treatment of Advanced Non–Small-Cell Lung Cancer With EGFR Exon 20 Insertion Mutation

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Abstract

The discovery of epidermal growth factor receptor (EGFR) mutations has greatly changed the clinical outlook for patients with advanced non–small-cell lung cancer (NSCLC). Unlike the most common EGFR mutations, such as exon 19 deletion (del19) and exon 21 L858R point mutation, EGFR exon 20 insertion mutation (EGFR ex20ins) is a rare mutation of EGFR. Due to its structural specificity, it exhibits primary resistance to traditional epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), leading to poor overall survival prognosis for patients. In recent years, there has been continuous progress in the development of new drugs targeting EGFR ex20ins, bringing new hope for the treatment of this patient population. In this regard, we conducted a systematic review of the molecular characteristics, diagnostic advances, and treatment status of EGFR ex20ins. We summarized the latest data on relevant drug development and clinical research, aiming to provide reference for clinical diagnosis, treatment, and drug development.

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Introduction

Lung cancer stands as the leading cause of cancer-related fatalities worldwide, bearing the highest incidence and mortality rates within our nation.[1] Non–small-cell lung cancer (NSCLC) accounts for roughly 85% of cases.[2] The epidermal growth factor receptor (EGFR) emerges as the most prevalent driver mutation gene in NSCLC, particularly among non-smoking Asian patients, boasting a mutation rate as high as 40% to 55%.[3] EGFR gene mutations predominantly encompass exon 19 deletions (19del) and exon 21 L858R point mutations, both categorized as sensitive mutations. At present, numerous targeted drugs tailored for EGFR-sensitive mutations have garnered approval, significantly enhancing long-term survival prospects for patients harboring these sensitive mutations.[4]

In recent years, due to the continuous advancement of genetic testing technology, an increasing number of EGFR mutation subtypes have come to light. Among these, EGFR exon 20 insertion (ex20ins) has emerged as the most prevalent EGFR mutation type following EGFR exon 19 deletions and L858R point mutations, constituting approximately 4% to 12% of EGFR-mutated cases in NSCLC.[5-9] Given the annual incidence of approximately 2 million newly diagnosed NSCLC patients around the world,[10] nearly 50,000 cases of EGFR ex20ins NSCLC are diagnosed each year, a substantial figure that should not be underestimated. However, real-world studies have unequivocally demonstrated that patients with EGFR ex20ins mutations experience a notably worse prognosis and reduced survival benefits when compared to those with classical EGFR mutations.[11,12] The persistent absence of a standardized first-line treatment regimen has remained a prominent and challenging issue within clinical practice. With the marketing approval of the novel EGFR ex20ins-targeted drugs, amivantamab, and mobocertinib, by the Food and Drug Administration (FDA), there is newfound hope for patients with EGFR ex20ins NSCLC. However, mobocertinib underwent global delisting for previously approved second-line indications due to unsatisfactory first-line treatment outcomes. In summary, significant challenges persist in the clinical management of EGFR ex20ins NSCLC. As such, this article endeavors to comprehensively review the molecular structure, diagnostic advancements, current clinical treatment strategies, and ongoing clinical research pertaining to EGFR ex20ins. Our objective is to provide fresh and valuable insights to inform clinical therapy and drive the development of new pharmaceutical agents.

Molecular Characterization of EGFR ex20ins

EGFR, a member of the receptor tyrosine kinase family located on the cell surface, plays a critical role in regulating cell proliferation and apoptosis by controlling signal transduction. The kinase domain of EGFR primarily comprises exons 18 to 21. Exon 20 of EGFR encodes amino acids 762 to 823 of the EGFR protein,

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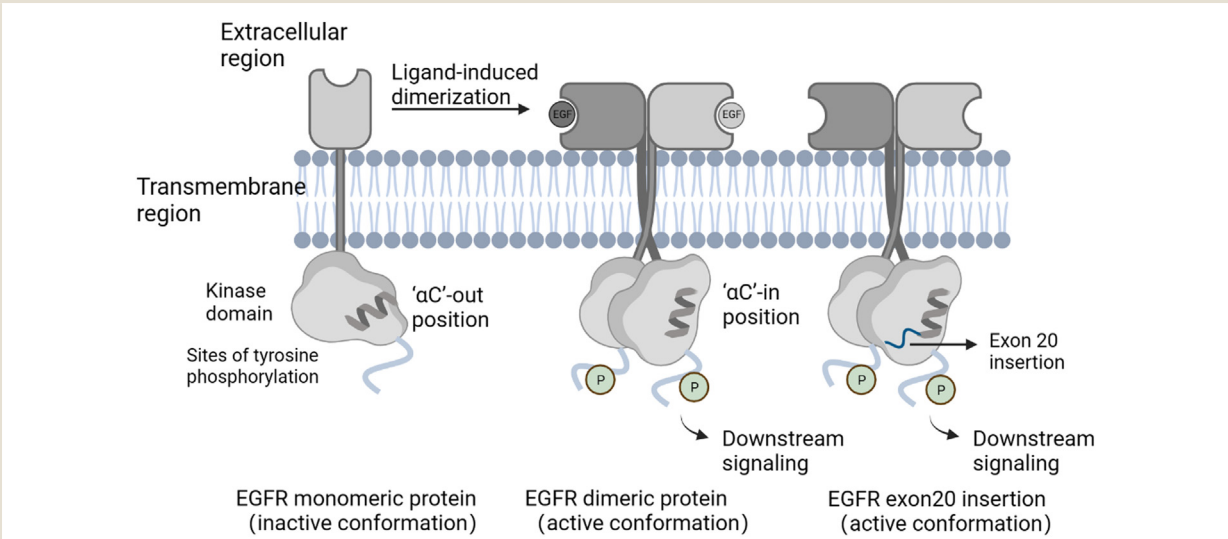
Figure 1 **Activation of wild-type and mutant EGFR proteins. In wild-type EGFR, the regulatory C-helix rotates from an initially inactive outward-facing conformation to an active inward-facing conformation upon binding of EGFR to a ligand, leading to the activation of EGFR. In EGFR ex20ins, even in the absence of a ligand, the C-helix can be pushed into a permanently active conformation, resulting in the non–ligand-dependent activation of the EGFR pathway.**



including the C-helix (composed of amino acids D761-M766) and the phosphate-binding loop (p-loop, composed of amino acids A767-C775).[13] Notably, the C-helix is pivotal in kinase activation. More than 90% of EGFR exon 20 insertions (ex20ins) mutations occur within the "loop" after the C-helix. These mutations induce a conformational change in receptor activity by shifting the C-helix from the exterior to the interior, resulting in the activation of ligand-independent EGFR pathways (Figure 1).[14]

EGFR ex20ins generally demonstrates a less favorable response to conventional EGFR-TKI treatments, a characteristic closely linked to its unique structure. Unlike EGFR-sensitive mutations, EGFR ex20ins induces an active conformation within the drug-binding pocket, forming a "wedge-shaped structure." This configuration increases spatial hindrance effects, making it challenging for traditional targeted medications to bind effectively and exert their typical inhibitory functions. In 2021, Heymach et al. proposed a structural-functional reclassification of EGFR mutations to enhance the prediction of drug efficacy.[15] Conversely, the crystal structure of EGFR ex20ins closely mirrors that of wild-type EGFR, with a high degree of overlap. It closely resembles the ATP binding mode and apparent affinity, resulting in a narrow therapeutic window for drugs. Additionally, EGFR ex20ins displays diversity in insertion sites and sequences, with over 100 subtypes identified globally.[4,6] While reports indicate that the A767_769dup and S768_D770dup subtypes, commonly located near the loop region, are the most prevalent, only the A763_Y764insFQEA subtype demonstrates sensitivity to traditional EGFR-TKIs such as gefitinib and erlotinib.[13,16] Consequently, the development of new drugs effective against all subtypes remains a formidable challenge.

Diagnostic Progress

The foundation of targeted therapy lies in establishing a precise diagnosis, and the timely identification of driver genes directly impacts patients' prognoses. Currently, both domestic and international guidelines emphasize the significance of detecting EGFR ex20ins and recommend its inclusion in routine EGFR testing. Commonly employed genetic testing methods encompass Polymerase Chain Reaction (PCR) and Next-Generation Sequencing (NGS). However, due to the pronounced heterogeneity of EGFR ex20ins, traditional PCR testing exhibits a substantial false-negative rate of up to 50%.[17,18] Hence, NGS plays a pivotal role in EGFR ex20ins detection. According to national and international guidelines, NGS-based tissue typing is presently regarded as the gold standard for analyzing NSCLC patients. Nevertheless, given the multitude of NGS testing providers, it is equally imperative to establish a standardized operating procedure (SOP) for NGS testing and enhance future quality control management. Additionally, in clinical scenarios where NGS may not be feasible, Droplet Digital Polymerase Chain Reaction (ddPCR) offers a straightforward, efficient, and cost-effective alternative. When tissue biopsy is unattainable, liquid biopsy based on Circulating Free DNA (cfDNA) also emerges as a viable option.[19,20]

Treatment Progression: Conventional Approaches

Chemotherapy

EGFR ex20ins has not yet received approval as a first-line treatment with targeted therapies, and platinum-based chemotherapy currently stands as the most commonly employed initial treatment regimen. Several retrospective studies have demonstrated that

the progression-free survival (PFS) for EGFR ex20ins NSCLC patients undergoing first-line chemotherapy spans from 3.0 to 7.6 months, with an overall survival (OS) ranging between 18.3 and 32.03 months.[21-27] Combining chemotherapy with antiangiogenic therapy has shown promise in extending PFS for patients. Nevertheless, the efficacy of first-line chemotherapy notably diminishes in individuals with central nervous system (CNS) metastases compared to those without brain involvement. Furthermore, earlier investigations have suggested that chemotherapy regimens centered on pemetrexed yield superior results when contrasted with nonpemetrexed-based chemotherapy.[22,23] However, the efficacy of chemotherapy has seemingly reached a plateau, underscoring the urgent need for novel targeted therapies to further enhance the survival prospects of patients harboring such mutations.

In a European real-world study, 175 patients with advanced NSCLC carrying EGFR ex20ins mutations were enrolled in the EXOTIC European Registry. The study aimed to compare the therapeutic efficacy of chemotherapy, chemotherapy combined with immunotherapy, and targeted agents such as amivantamab in EGFR ex20ins NSCLC patients. The results demonstrated that newer targeted agents could offer longer survival benefits for individuals with EGFR ex20ins mutations compared to conventional chemotherapy or chemotherapy combined with immunotherapy.[28] The Papillon study further indicated that the combination of Amivantamab with chemotherapy extended median PFS from 6.7 months to 11.4 months, reducing the risk of disease progression or death by over 60% when compared with chemotherapy alone.

Immunotherapy

The advent of immune checkpoint inhibitors (ICIs) has ushered in unprecedented clinical benefits for NSCLC. However, the efficacy of ICIs in NSCLC with driver gene alterations remains relatively poor. While there have been reports of rare EGFR mutations benefiting from immune therapy, the effectiveness of ICIs in advanced EGFR ex20ins NSCLC is suboptimal.[29] The Metro study demonstrated that EGFR ex20ins advanced NSCLC patients receiving immunotherapy experienced a median progression-free survival (mPFS) of 2.0 months and a median overall survival (mOS) of 5.3 months.[30] Another real-world study indicated that,[31] regardless of the treatment line, patients receiving single-agent immunotherapy showed inferior treatment outcomes compared to patients undergoing platinum-based chemotherapy or immunotherapy combined with platinum-based chemotherapy. The speculated reasons may be attributed to a significantly lower tumor mutation burden (TMB) and programmed death-ligand 1 (PD-L1) expression in EGFR ex20ins NSCLC patients compared to patients without driver gene alterations in NSCLC.[24] Reports have indicated that a high ratio of infiltrating CD8+ T cells to CD4+ T cells in tumor tissue is a favorable prognostic feature for NSCLC patients.[32] Some EGFR ex20ins patients, in contrast to other NSCLC types, exhibit a higher CD8+/CD4+ T cell ratio, suggesting potential immune reactivity in EGFR ex20ins. It is speculated that immunotherapy for EGFR ex20ins may rely on the development of immune pathways beyond the PD-(L)1 axis.

Conventional Tyrosine Kinase Inhibitors

Numerous targeted drugs have been developed for EGFR mutations, and they have now progressed to the third generation of EGFR-TKIs. Except for the A763_Y764ins FQEA subtype, patients with advanced EGFR ex20ins NSCLC have exhibited a poor response to first-generation EGFR-TKIs, such as erlotinib and gefitinib.[33,34]

The second-generation EGFR-TKI, afatinib, is considered a potential therapeutic option for the A767_V769dup mutation site in EGFR ex20ins.[35] However, prospective studies have indicated that afatinib is not an effective treatment for EGFR ex20ins NSCLC. The objective response rate (ORR) in the treatment group is below 10%, and the mPFS is only 2.7 months.[36]

As a third-generation EGFR-targeted drug, osimertinib is the preferred first-line treatment for EGFR-sensitive mutation NSCLC patients.[37] However, at the standard dosage, osimertinib exhibits limited efficacy in EGFR ex20ins NSCLC, with an ORR of less than 10%.[38,39] The results of the Phase II clinical study ECOG-ACRIN 5162, presented at the 2020 American Society of Clinical Oncology (ASCO) conference, revealed that a high dose of osimertinib (160 mg) increased the ORR to 25% and achieved a median PFS of 9.7 months in patients with EGFR ex20ins mutations.[40] It is important to note limitations in the study, as it only included patients beyond the second line and did not cover the entire EGFR ex20ins subtype. In another Phase II clinical study, POSITION20, a more extensive exploration was conducted,[41] involving 25 patients with advanced EGFR ex20ins NSCLC. After the administration of 160 mg osimertinib, the ORR was 28%, with a median PFS of 6.8 months. However, there was a significant increase in the incidence of adverse events, notably with diarrhea occurring in up to 72% of patients.

Emerging Therapies

Overall, the conventional treatment outcomes for EGFR ex20ins advanced NSCLC have been disappointing. However, this challenge has spurred scientists to delve further into the development of novel drugs targeting this specific mutation in NSCLC. Currently, 2 primary categories of drugs are aimed at EGFR ex20ins: large molecular antibodies and small molecule TKIs. Large molecular antibodies focus on the extracellular region of the EGFR protein, blocking the entry of EGFR signals into the cell. An example of such a drug is amivantamab. On the other hand, small molecule TKIs, such as mobocertinib, sunvozertinib, furmonertinib,zipalertinib, and poziotinib, target the intracellular kinase domain of the EGFR protein, disrupting the downstream transmission of EGFR signals. This mechanism aims to inhibit cell proliferation and promote apoptosis.

Large Molecular Antibodies

Amivantamab. Amivantamab is the first bispecific antibody targeting both EGFR and mesenchymal-epithelial transition factor (MET) signaling pathways to combat EGFR ex20ins mutations. It exerts antitumor effects by simultaneously inhibiting both pathways. In vitro experiments have revealed that amivantamab's inhibition of tumor growth surpasses the efficacy of combining monoclonal antibodies targeting EGFR and MET individually.[42] Additionally, amivantamab disrupts target cells through antibody-dependent

cellular cytotoxicity and antibody-dependent cellular phagocytosis mechanisms.[43] As of 2021, based on the CHRYSALIS trial results, amivantamab received approval from both the FDA and the European Medicines Agency (EMA) for application in patients with EGFR ex20ins NSCLC who have encountered failure with platinum-containing chemotherapy. This signifies a groundbreaking achievement, positioning amivantamab as the world's first globally accessible targeted therapy for EGFR ex20ins lung cancer.[44] In the CHRYSALIS trial, 81 advanced NSCLC patients with EGFR exon 20 insertion mutation, previously treated with platinum-based chemotherapy, underwent treatment with amivantamab, revealing a notable ORR of 40%, a median duration of response (mDOR) of 11.3 months, and a mPFS of 8.3 months.[45,46]

Building upon the promising preliminary efficacy observed in Phase I clinical studies, the Papillon trial investigated the application of amivantamab in conjunction with chemotherapy for the initial treatment of advanced EGFR ex20ins NSCLC. This comprehensive study enrolled 308 previously untreated patients diagnosed with advanced EGFR ex20ins NSCLC. The primary endpoint of the trial was PFS, independently assessed by a blinded independent central review (BICR). Outcomes unveiled at the 2023 European Society for Medical Oncology (ESMO) Congress demonstrated a mPFS of 11.4 months for the amivantamab combination therapy group, in stark contrast to 6.7 months for the chemotherapy-alone control group. The ORR stood at 73% for the combination group and 47% for the chemotherapy-alone group. Regarding safety, the amivantamab combination therapy exhibited consistent and manageable safety profiles. Predominant treatment-emergent adverse events (TEAEs) encompassed neutropenia, paronychia, and rash, with an infusion reaction rate of 42%. The proportion of discontinuations attributable to treatment-related adverse reactions remained at 7%.[27,47]

In addition, at this year's ESMO conference, a phase III study of combination therapy, including amivantamab after osimertinib resistance, was announced.[48] The study results demonstrated that the combination regimen with amivantamab significantly extended PFS and reduced the risk of disease progression or death by more than 50% compared to chemotherapy alone. For patients with pre-existing brain metastases who did not receive brain radiation, the regimen containing amivantamab also exhibited significantly better control of intracranial disease than chemotherapy. The MARIPOSA-2 study has the potential to reshape future clinical practices, offering a new option for follow-up therapy for patients with third-generation EGFR-TKI resistance. However, the use of drug combinations comes with increased toxicity. Therefore, exploring how to selectively administer to appropriate populations and optimize therapeutic strategies to enhance efficacy and reduce toxicity is a crucial direction for future exploration.

Small Molecule TKIs

Mobocertinib. Mobocertinib, an orally selective TKI designed for EGFR ex20ins, demonstrates superior anti-tumor activity and heightened selectivity for wild-type EGFR in various EGFR ex20ins mutation subtypes, as evidenced in cellular and murine models. In the Exkivity Phase I/II single-arm trial,[49] 114 patients with previously platinum-treated EGFR ex20ins-mutated NSCLC were enrolled. Daily treatment with 160 mg of mobocertinib resulted in a confirmed ORR of 28%, as assessed by IRC, and 35%, as evaluated by the investigator. The trial reported mPFS of 7.3 months and a mOS of 24.0 months. Common adverse events linked to mobocertinib encompassed diarrhea (91%), rash (45%), and paronychia (38%), with a ≥3-grade diarrhea incidence of 21%.Overall, the adverse events associated with mobocertinib were comparable and manageable when compared to other EGFR TKIs. Based on outstanding trial results, mobocertinib received accelerated approval from the FDA in September 2021.

However, the Phase III confirmatory Exclaim-2 trial of mobocertinib, which designed to assess the safety and efficacy of mobocertinib alone compared to platinum-containing chemotherapy in patients with advanced or metastatic NSCLC harboring first-line EGFR ex20ins, was terminated prematurely. The trial concluded that mobocertinib did not significantly improve patients' PFS. Takeda recently announced, through a statement on its website, its voluntary application for delisting. This decision is attributed to noncompliance with the data requirements of confirmatory studies necessary for the accelerated approval/conditional approval for the marketing of mobocertinib by the FDA and other national and regional regulatory authorities.

The delisting of mobocertinib is surprising but somewhat expected. Despite mobocertinib receiving accelerated approval from the FDA based on promising results from the Exkivity Phase I/II studies, its status as a single-arm trial rendered it lacking in sufficient evidence, necessitating confirmation through Phase III confirmatory trials. Therefore, EXCLAIM-2 not only delves into first-line treatment but also serves as confirmation of mobocertinib's efficacy as a monotherapy for EGFR ex20ins NSCLC. Takeda opted not to pursue second-line applications and instead took a bold approach by seeking efficacy in first-line treatment for EGFR ex20ins advanced NSCLC with mobocertinib as a monotherapy. Additionally, in the Exkivity trial, EGFR ex20ins NSCLC patients with baseline brain metastases showed an ORR of only 18% and a mPFS of 3.7 months.[49] Real-world studies also suggest limited intracranial activity of mobocertinib, with significant differences in median duration of treatment between patients with and without baseline brain metastases, at 14.8 and 5.4 months, respectively.[50]

Sunvozertinib. Sunvozertinib is an irreversible, highly selective next-generation EGFR-TKI that targets various EGFR mutation subtypes, including EGFR ex20ins, with low affinity for wild-type EGFR. Early data indicates that sunvozertinib has a half-life of up to 50 hours in the human body, and its pharmacokinetic curve remains stable. This allows for sustained therapeutic effects while minimizing adverse events associated with excessively high peak drug concentrations.[51,52]

In August 2023, Sunvozertinib received official approval from the National Medical Products Administration (NMPA) of China for the treatment of advanced EGFR ex20ins NSCLC patients who had previously experienced failure with platinum-based chemotherapy or exhibited intolerance to it. This approval represents a significant milestone as it signifies the emergence of the first innovative drug tailored specifically for patients with advanced EGFR ex20ins NSCLC in China. The approval is based on the results

of the WU-KONG6 study, a China-registered clinical trial. In the population receiving postline treatment with sunvozertinib, the IRC-confirmed ORR reached 60.8%.[53] For patients with baseline brain metastases, the ORR was 48.4%. The study included 30 EGFR ex20ins mutation subtypes, all of which exhibited significant clinical efficacy.[53] Preliminary results for sunvozertinib as a first-line treatment for EGFR ex20ins mutation NSCLC patients were presented at ESMO 2023, indicating a single-agent first-line treatment ORR of 78.6% and mPFS exceeding 1 year. However, given the relatively limited sample size of this study, further validation is required in the Phase III "WUKONG 28″ trial.

Following a comprehensive analysis of multiple research datasets, Sunvozertinib demonstrates an overall favorable safety profile. Common treatment-related adverse events (TRAEs) are akin to traditional EGFR-TKIs, primarily encompassing diarrhea and skin rash, with the majority falling within grades 1 to 2. Importantly, these AEs are largely reversible and recoverable with supportive therapy.

In terms of both efficacy and safety, sunvozertinib emerges as a promising choice within its therapeutic class, holding the potential to evolve into a superior treatment option for patients with advanced EGFR ex20ins NSCLC. Presently, its Phase III multicenter clinical trial is in progress, and we eagerly await further substantiation of sunvozertinib 's effectiveness as a first-line treatment for patients with EGFR ex20ins.

Furmonertinib. Furmonertinib is an orally administered, small-molecule, highly brain-penetrantm, pan-EGFR mutation inhibitor.[54,55] Its chemical structure closely resembles that of the third-generation EGFR-TKI, osimertinib. However, furmonertinib has been modified based on the structure of osimertinib, introducing a strongly hydrophobic trifluoroethoxypyridine structure.[54,56] This modification allows it to bind to the hydrophobic pocket in the ATP-binding region, consisting of residues such as L792 and M793. This alteration not only enhances furmonertinib's binding activity to EGFR and its kinase selectivity but also improves its metabolic properties. In the Phase IB FAVOUR study of furmonertinib,[56,57] advanced NSCLC patients with EGFR ex20ins were treated with different doses. Thirty treatment-naive patients received furmonertinib at 240 mg, while 49 previously treated patients were randomly assigned to 2 cohorts, receiving furmonertinib at either 240 mg or 160 mg. Among treatment-naive patients, the ORR was 69.0%. In previously treated patients, both the 240mg and 160mg doses were effective, with ORRs of 50.0% and 40%, respectively. These rates surpass standard platinum-containing 2-agent chemotherapy regimens and exhibit a predictable and manageable safety profile. Based on the clinical results of the FAVOUR study, on October 30, 2023, furmonertinib received Breakthrough Therapy designation from the FDA for the treatment of previously untreated, locally advanced or metastatic non-squamous NSCLC with EGFR ex20ins mutations. Currently, a pivotal Phase III registration clinical trial, FUVENT, investigating furmonertinib as a first-line treatment for EGFR ex20ins mutation NSCLC is ongoing.

Poziotinib. Poziotinib is a pan-human epidermal growth factor receptor (HER) inhibitor that irreversibly blocks the signaling pathways of EGFR, HER2, and HER4, exerting an anti-tumor effect.[58] In vitro studies have demonstrated that poziotinib exhibits remarkable selectivity and efficacy against EGFR ex20ins mutations compared to traditional EGFR TKIs.[58] However, in the Phase II multicenter ZENITH20 study,[59,60] cohort 1 comprised 115 patients with EGFR ex20ins-positive NSCLC who had previously experienced treatment failure. The results revealed an ORR of merely 14.8% and a mPFS of 4.2 months. Notably, there was a high incidence of diarrhea and rash, with approximately 60% of patients encountering Grade 3 adverse reactions. About 68% of patients necessitated dose reductions, and approximately 10% discontinued treatment due to TRAEs.

The ZENITH20 study investigated the efficacy of poziotinib in patients with untreated HER2 exon 20 insertions in NSCLC in Cohort 4.[61] Participants received either 16 mg once daily or 8 mg twice daily poziotinib. The results showed an overall ORR of 39%, with ORRs of 45% and 30% in the once-daily and twice-daily groups, respectively. The most common Grade 3 treatment-related adverse events were rash, stomatitis, and diarrhea.

While poziotinib demonstrated clinically significant efficacy in the ZENITH20 study, the side effects resulting from the inhibition of wild-type EGFR fail to meet the expectations for a novel EGFR-TKI. In clinical trials, a noticeable dose-response relationship in patients is observed, necessitating dose reductions, which in turn lead to a corresponding decrease in ORR. Considering that the risks for patients outweigh the benefits, the FDA rejected the marketing application for poziotinib at the end of 2022. Currently, phase II studies of poziotinib in advanced NSCLC with exon 20 insertions in EGFR or ERBB2 have also been terminated.

Zipalertinib. Zipalertinib (also known as TAS6417 or CLN-081) is a novel broad-spectrum EGFR-TKI. Beyond its application for EGFR ex20ins, it extends its efficacy to rare mutations such as EGFR ex18ins and ex21ins.[62] In terms of drug design, zipalertinib features a unique pyrrolopyrimidine structure as the core, demonstrating selective affinity for EGFR ex20ins.[62] In vitro kinase assays confirm zipalertinib's selective kinase inhibitory activity against EGFR p.D770_N771inNPG mutations, while exhibiting weaker activity against wild-type EGFR.[63] Utilizing Ba/F3 cell lines expressing human EGFR In cell viability assays, zipalertinib exhibits robust inhibition against various EGFR ex20ins compared to wild-type EGFR.[62,63] Furthermore, in a murine lung orthotopic transplantation model, zipalertinib demonstrates promising antitumor activity.

In a phase I/IIa clinical study aimed at evaluating the antitumor activity, safety, tolerability, and pharmacokinetic characteristics of zipalertinib, previously treated advanced NSCLC patients carrying EGFR ex20ins were enrolled.[64] The median number of prior treatment lines for patients was 2, with 4% having received other targeted EGFR ex20ins TKI therapies. The results revealed an ORR of 38.4% for the entire population, with an ORR of 41% at the 100 mg BID dose of zipalertinib. Additionally, zipalertinib demonstrated activity in patients with CNS target lesions. Common treatment-related adverse events include rash (80%), paronychia (32%), diarrhea (30%), etc. Anemia is the only Grade 3 or higher treatment-related adverse event with an incidence ≥5%.

The ongoing Phase III randomized controlled Rezilient3 study is currently further evaluating the efficacy and safety of zipalertinib in combination with platinum-based chemotherapy in locally advanced or metastatic nonsquamous NSCLC patients carrying EGFR ex20ins.

YK-029A/PH001. YK-029A represents a third-generation EGFR-TKI that introduces structural enhancements, demonstrating notable efficacy in the treatment of various EGFR mutations in NSCLC, including EGFR ex20ins, all while maintaining a high selectivity for wild-type EGFR.[65] Remarkably, it holds the distinction of being the only Class I innovative drug with Breakthrough Therapy Designation (BTD) in the realm of first-line treatment for EGFR ex20ins.The Phase I clinical study results for YK-029A were unveiled at the 2023 ASCO Annual Meeting. This study comprised 26 treatment-naïve patients with EGFR ex20ins NSCLC, with a confirmed objective response rate (cORR) of 73.1% and a mPFS of 9.3 months. Safety analysis, encompassing 108 patients, revealed a 94.4% incidence of treatment-related adverse events (TRAEs), including a 27.8% incidence of grade ≥3 TRAEs. Notably, the most frequent treatment-emergent adverse events (TEAEs) included diarrhea (46.3%), anemia (38.0%), and rash (32.4%). These results collectively underscore the outstanding efficacy and safety profile of YK-029A.Presently, a Phase III clinical study investigating its first-line treatment efficacy in advanced EGFR ex20ins NSCLC is in the process of clinical enrollment.

PLB1004. PLB1004 is a highly selective novel oral EGFR-TKI. According to data from a Phase I clinical study published by the American Association for Cancer Research (AACR) in 2023, out of the 26 EGFR ex20ins NSCLC patients included in the efficacy analysis, the investigator-assessed ORR was 57.7%, and the DCR (Disease Control Rate) was 100%. Among these patients, 8 had baseline brain metastases, and 3 achieved a partial response (PR) in the efficacy assessment, resulting in an ORR of 37.5%.Regarding safety, common adverse events associated with PLB1004 were akin to those of traditional TKI drugs and were generally reversible with clinical treatment. These findings indicate that PLB1004 presents promising clinical prospects. Currently, Phase II evaluation of its efficacy and safety in late-stage NSCLC patients with EGFR ex20ins mutations is underway.

BDTX-189. BDTX-189 is an efficient, orally active, and selective allosteric inhibitor targeting EGFR and HER2 mutations. Preclinical studies demonstrate its inhibitory effects on both EGFR and HER2 ex20ins mutations as well as extracellular domain mutations. Phase I trial results, presented at the 2021 ASCO conference, revealed an ORR of 7% and a DCR of 19% among 27 evaluable patients. The FDA has granted BDTX-189 fast track designation for post-line treatment in adult patients with solid tumors carrying EGFR or HER2 ex20ins mutations.

NIP142. NIP142 primarily achieves inhibition of tumor growth by blocking the activity of EGFR or HER2 ex20 insertion mutations and subsequently disrupting downstream signaling pathways. In preclinical studies, NIP142, as a potent and highly selective EGFR/HER2 ex20 insertion inhibitor, demonstrated excellent antitumor activity in various xenograft models and exhibited good tolerability. Compared to the same-class drug mobocertinib, NIP142 possesses superior pharmacokinetic properties and a larger safety margin, indicating its potential as a novel treatment option for EGFR/HER2 ex20 insertion mutated NSCLC.

Moreover, there is a diverse range of targeted drugs currently advancing in clinical trials for the treatment of EGFR ex20ins-positive NSCLC. These ongoing clinical trials are detailed in the table below Table 1.

Combination Therapy of Antibodies and TKIs

In vitro experiments and animal models have demonstrated the significant antitumor effects of cetuximab when combined with EGFR-TKI in the treatment of advanced EGFR ex20ins NSCLC.[66] However, clinical studies with limited sample sizes have shown that the efficacy of cetuximab in combination with EGFR-TKIs for EGFR exon 20 insertion treatment is constrained, resulting in a mPFS of approximately 5 months.[67,68] In the Phase Ib clinical study of the EGFR monoclonal antibody JMT101 combined with osimertinib for the treatment of EGFR exon 20 insertion-mutated NSCLC, the B2 cohort consisted of 121 patients who completed the tolerability assessment and received JMT101 in combination with oral osimertinib at a daily dose of 160 mg. The results revealed a cORR of 36.4% and a mPFS of 8.2 months, as determined by the IRC. Among platinum-resistant patients, a cORR of 34.0% and an mPFS of 9.2 months were observed. Notably, remissions were observed in different EGFR exon 20 insertion mutation subtypes, with a central nervous system disease control rate of 87.5%. For patients with confirmed brain metastases, the confirmed objective remission rate was 25%. The most frequently reported adverse events were rash (76.9%) and diarrhea (63.6%).[69]

Other Therapies

Other innovative treatment approaches for EGFR ex20ins mutations are currently under investigation, including luminespib (NVP-AUY922) and tarloxotinib. These compounds are inhibitors of heat shock protein 90 (HSP90) and hypoxia-activated pan-HER kinases, respectively. Preclinical studies have demonstrated their potential efficacy against EGFR ex20ins NSCLC. However, clinical research data on their effectiveness is currently limited, necessitating further research and exploration.[70-72]

Conclusion and Prospects

In clinical practice, broad-spectrum exon 20 mutations include alterations in the 20th exon of both the EGFR and HER2 genes. The HER2 gene, also known as ERBB2, is a member of the epidermal growth factor receptor family, similar to EGFR. Exon 20 mutations in both EGFR and HER2 occur at comparable positions, showcasing molecular, biological, and drug response characteristics that are notably similar. This signifies a substantial area of unmet clinical need. In this article, we meticulously review the diagnostic and therapeutic advancements associated with EGFR ex20 insertions.

EGFR ex20ins represents the third major category of EGFR mutations in NSCLC. Historically, due to the lack of effective treat-

Table 1 Summary of Ongoing Clinical Trials for EGFR Ex20Ins Targeted Therapies

Drug Name	Trial Number	Treatment Lines	Phase	Treatment	Primary Outcome	Recruitment Status
Sunvozertinib	NCT05668988	Frontline	III	Sunvozertinib vs. platinum-based chemotherapy	PFS	Recruiting
Furmonertinib	NCT05607550	Frontline	III	Furmonertinib vs. platinum-based chemotherapy	PFS	Recruiting
Zipalertinib	NCT05973773	Frontline	III	Zipalertinib+platinum-based Chemotherapy vs. platinum-based chemotherapy	PFS	Recruiting
YK-029A	CTR20230490	Frontline	III	YK-029A vs. platinum-based chemotherapy	PFS	Recruiting
JMT101	NCT05132777	Backline	II	JMT101+Osimertinib	ORR	Recruiting
PLB1004	CTR20231534	Backline	II	PLB1004	ORR	Recruiting
BEBT-109	CTR20213409	Backline	II	BEBT-109	ORR	Recruiting
AP-1898	NCT04993391	Backline	I/II	AP-L1898	Safety and Tolerability , ORR	Recruiting
BDTX-189	NCT04209465	Backline	I/II	BDTX-189	Phase1:Safety and Tolerability, PR2D;Phase II:ORR	Recruiting
HS-10376	NCT05435274	Backline	I/II	HS-10376	Phase1a:MTD,PR2D;Phase1b/II:ORR	Recruiting
BLU-451	NCT05241873	Backline	I/II	BLU-451	Phase1:MTD,PR2D;Phase II:ORR	Recruiting
BAY 2927088	NCT05099172	Backline	I	BAY 2927088	Safety and Tolerability	Recruiting
NIP142	CTR20220597	Backline	I	NIP142	Phase1a:DLT and MTD,Phase IB:ORR	Recruiting
FWD1509 MsOH	NCT05068024	Backline	I	FWD1509 MsOH	Safety and Tolerability	Recruiting

Abbreviations: DLT = dose limiting toxicity; MTD = maximal tolerated dose; ORR = objective response rate; PFS = progression-free survival; PR2D = recommended phase II dose.

ment options, patients with this form of NSCLC have faced a bleak prognosis. In recent years, significant progress has been made in the development of novel drugs tailored to treat EGFR ex20ins-positive NSCLC. Due to the failure of Phase III clinical trials, mobocertinib, despite obtaining accelerated FDA approval, has currently initiated a voluntary market withdrawal. Meanwhile, both the FDA and EMA have approved amivantamab, and in China, sunvozertinib has been approved for the treatment of refractory EGFR ex20ins-mutated NSCLC. The precision era of targeted therapy for EGFR ex20ins NSCLC has now arrived.

With the introduction of novel targeted therapies, there has been some improvement in patient prognosis. however, EGFR ex20ins NSCLC continues to be associated with a grim prognosis. In clinical practice, several challenges persist. Firstly, due to the highly heterogeneous nature of EGFR ex20ins mutations, NGS testing is recommended as a top priority based on domestic consensus due to its comprehensive capabilities. Nevertheless, NGS remains costly, time-consuming, and lacks clear testing standards and guidelines. Secondly, the currently approved drugs are primarily indicated for second-line treatment and beyond. There is a significant clinical demand for first-line therapies among EGFR ex20ins NSCLC patients, necessitating an urgent need for targeted first-line treatments to address this gap. Thirdly, EGFR ex20ins comprises numerous subtypes, often accompanied by complex mutations involving tumor suppressor genes such as TP53 or activation of alternative bypass pathways. Further exploration is required to determine whether targeted therapies can be tailored to specific mutation subtypes. Investigating combinations of inhibitors targeting different pathways for various complex mutations represents a future research direction. Lastly, the development of resistance to targeted therapies is an inevitable challenge. Strategies to delay resistance, elucidate resistance mechanisms, and select subsequent treatments are vital topics for further discussion.

We anticipate that in the near future, individuals with advanced-stage EGFR ex20ins-positive NSCLC will gain access to a multitude of accessible, safe, and effective targeted therapies. This expansion of treatment options holds the promise of enhancing the survival prospects for EGFR ex20ins-positive patients, similar to those with EGFR-sensitive mutation.

Disclosure

The authors declare no conflict of interest.

CRediT authorship contribution statement

Jingwen Liu: Conceptualization, Writing – review & editing. **Yan Xiang:** Methodology. **Tingwen Fang:** Writing – original draft. **Lulin Zeng:** Writing – original draft. **Ao Sun:** Data curation. **Yixiang Lin:** Data curation. **Kaihua Lu:** Conceptualization, Supervision, Funding acquisition.

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