Review Article

Emerging therapies for non-small cell lung cancer harboring EGFR exon 20 insertion mutations: narrative review

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Background and Objective: Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations (ex20ins) are uncommon in non-small cell lung cancer (NSCLC). These mutations are generally resistant to first-generation EGFR tyrosine kinase inhibitors, unlike common *EGFR* mutations, including exon 19 deletions or exon 21 L858R point mutation. The development of effective targeted therapies for NSCLC harboring EGFR ex20ins has been eagerly anticipated over the years. Recently, the therapeutic landscape of this subgroup of EGFR-mutant NSCLC patients has rapidly evolved due to the emergence of new drugs. In 2021, several novel agents, such as amivantamab and mobocertinib, have been approved by the US Food and Drug Administration for patients with advanced platinum-resistant NSCLC harboring EGFR ex20ins. In this review, we mainly focus on emerging therapies targeting NSCLC with EGFR ex20ins, as well as important ongoing clinical trials.

Methods: Searches were conducted in PubMed and supplemented with recent conference proceedings in November 30th, 2021.

Key Content and Findings: Several novel emerging therapies showed favorable safety profile and promising anti-tumor activity in NSCLC patients with EGFR ex20ins in recent several clinical trials.

Conclusions: There is still room for improvement in the treatment results of NSCLC harboring EGFR ex20ins. Future research should focus on the molecular heterogeneity in the size and location of distinct EGFR ex20ins, the mechanisms of acquired resistance to novel EGFR inhibitors, effective treatment that have good central nervous system penetrance, and the potential role of combination strategy.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); exon 20 insertion; amivantamab; mobocertinib

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1). The identification of epidermal growth factor receptor (EGFR) mutations as oncogenic drivers in non-small cell lung cancer (NSCLC) patients, particularly lung adenocarcinomas, and their association with a remarkable response to EGFR tyrosine kinase inhibitors (TKIs) has led to a paradigm shift in the therapeutic management of advanced NSCLC (2-6). EGFR mutations represent the most prevalent genetic alterations and have been detected

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Table 1 The search strategy summary

Items	Specification
Date of search	November 30th, 2021
Databases and other sources searched	PubMed
Search terms used	Advanced non-small cell lung cancer, epidermal growth factor receptor, exon 20 insertion mutations, targeted therapies
Timeframe	From 2008 to April 2022
Inclusion and exclusion criteria	English literature only
Selection process	Systematic literature search was conducted by NW. Final approval of literature search was conducted by all authors

in approximately 40% of NSCLC cases in East Asians and 10–15% of Caucasians (7-10). The most common EGFR mutations are exon 19 deletion and L858R point mutation in exon 21, which accounts for about 85–90% of all EGFR mutations (11-13). Exon 20 insertion mutations (ex20ins) are the third most common subtype of activating EGFR mutations, comprising approximately 2–12% of all EGFR mutations and approximately 1–3% of all NSCLC cases (11-21). Unlike common exon 19 deletions or exon 21 L858R point mutation, the majority of ex20ins, except for *EGFR A763_Y764FQEA*, exhibit intrinsic resistance to the currently available EGFR-TKIs, including gefitinib, erlotinib, afatinib, and osimertinib (22-31). With the expanded use of next generation sequencing and multiple polymerase chain reaction assays that go beyond genotyping of specific mutations in clinical practice, the detection rate of the aforementioned relatively rare mutations has increased. Thus, there has been a growing interest in this subgroup of EGFR-mutant NSCLC patients, and the development of EGFR inhibitors that can more effectively target NSCLC harboring EGFR ex20ins is of paramount importance.

Recently, early phase clinical trials have reported encouraging clinical activity of two investigational targeted therapies (i.e., amivantamab and mobocertinib) for the treatment of NSCLC patients harboring EGFR ex20ins who have progressed on or after platinum-based chemotherapy (32-34). Based on the results of these clinical trials, the US Food and Drug Administration (FDA) has granted breakthrough therapy designations and subsequently accelerated the approval of these agents.

In this review article, we summarize the current evidence on novel therapeutic drugs for advanced NSCLC patients harboring EGFR ex20ins and discuss future perspectives. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-56/rc).

Methods

In November 30th, 2021, a systematic literature search was conducted by NW. Final approval of literature search was conducted by all authors. An online search of literature utilizing PubMed was employed. Selection criteria included advanced NSCLC, EGFR, ex20ins, and targeted therapies from 2008 to April 2022. Only studies in English were included (*Table 1*).

Clinical, epidemiologic, and molecular characteristics of EGFR ex20ins

In contrast to common exon 19 deletions or exon 21 L858R point mutation, the frequency of EGFR ex20ins do not vary across different ethnicities (14,15). Meanwhile, the clinical and pathological characteristics associated with common EGFR mutations also apply to EGFR ex20ins. In most reports, never-smoker status, female sex, and adenocarcinoma histology are common characteristics of patients with NSCLC harboring EGFR ex20ins (11,14,15,24).

The *EGFR* gene contains 28 exons and is localized on the short arm of chromosome 7. Most EGFR mutations are detected within exons 18–21, and different mutations exert varying effects on the clinical efficacy of EGFR-TKIs. EGFR ex20ins are heterogeneous at the molecular level but can be grouped as inframe insertions or duplications of 1–7 amino acids clustered between the C-helix and the following loop (762–775 amino acid sequence) of EGFR (11,15)

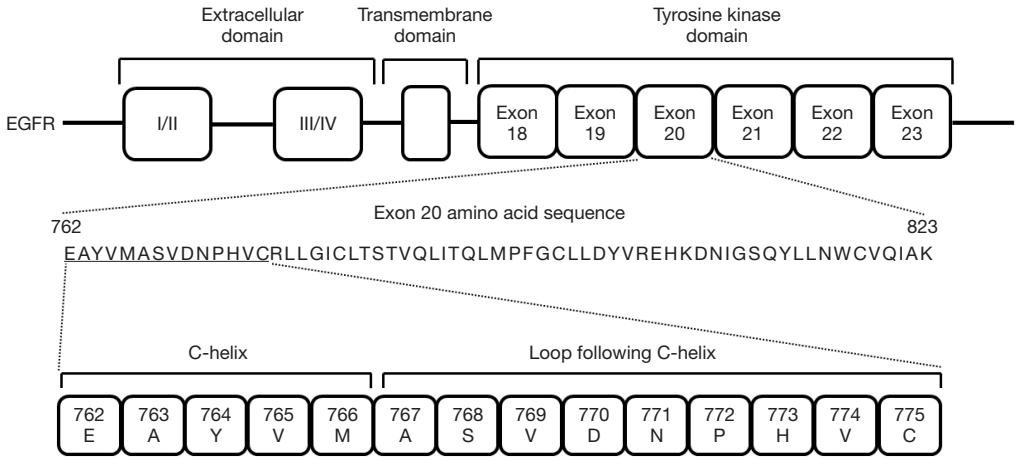

Figure 1 Location and structure of EGFR exon 20. EGFR, epidermal growth factor receptor.

(*Figure 1*). There are several different ex20ins reported, and more than 90% of all reported exon 20 insertions occur at the loop following the C-helix, the region encoding amino acid positions S768 and V774 (11). The most frequently identified EGFR ex20ins variants are *V769_D770ins* and *D770_N771ins*, which together account for almost half of all NSCLC cases harboring EGFR ex20ins (11,12). Different insertion positions affect the kinetics of drugs and ATP binding differently, resulting in various clinical characteristics and ultimately determining their sensitivity to EGFR inhibitors (35). Indeed, the clinical efficacy of EGFR-TKIs in patients harboring *EGFR ex20ins A763-Y764insFQEA* (~5–6% of ex20ins) has been reported in multiple studies, whereas most EGFR ex20ins are resistant to the available EGFR-TKIs (22,26,29,31). Sporadic case studies have also reported the likely response of *H773dup* and *H773_V774insNPH* to afatinib (36,37). However, differential sensitivity of each variant to various EGFR-TKIs has not been fully investigated.

Treatment outcomes with EGFR-TKIs or cytotoxic chemotherapy

Generally, the vast majority of EGFR ex20ins are associated with *de novo* resistance to EGFR-TKIs. Previous reports indicated unfavorable outcomes of EGFR-TKIs in patients harboring EGFR ex20ins, with overall response rate (ORR) of 0–13% and median progression-free survival (PFS) of less than 4 months (15,16,23-25,27,28,31,38-46) (*Table 2*). These results suggest that the clinical efficacy of EGFR-TKIs against EGFR ex20ins is extremely poor. Furthermore, patients harboring EGFR ex20ins have reduced overall survival (OS) compared to those harboring common EGFR mutations (2-6,15,27,40-46). However, the effect of cytotoxic chemotherapy, mainly platinum-based chemotherapy, in patients with EGFR ex20ins is almost comparable to that observed in patients with common EGFR mutations (2-4,15,27,40-47) (*Table 3*). The inferior median OS, despite an approximately equivalent median PFS of platinum-based chemotherapy, is likely due to the limited availability of EGFR-TKIs. Thus, platinum-based chemotherapy is considered a standard treatment for patients harboring EGFR ex20ins, and the development of more effective and specific targeting agents has long been awaited.

Approved novel drugs and ongoing clinical trials

Amivantamab

Amivantamab (JNJ-61186372) is a novel, fully humanized bispecific IgG1 that targets EGFR and the mesenchymal epithelial transition factor (MET) receptor (48,49). Upon binding to the extracellular domain of each receptor, amivantamab blocks the ligand-mediated receptor activation and promotes EGFR and MET internalization and downregulation, which leads to the recruitment of macrophages and natural killer cells (48,49). This increases immune-mediated antitumor activities such as antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and trogocytosis (48,49). Its efficacy and safety in advanced NSCLC patients harboring EGFR ex20ins were assessed in CHRYSALIS (NCT 02609776),

Table 2 Overview of treatment outcomes of EGFR-TKI for NSCLC harboring EGFR ex20ins

Author, year	Treatment	N	ORR (%)	mPFS (months)	mOS (months)	Ref
Oxnard, 2013	Erlotinib	8	0	2.4	16.5	(15)
Leduc, 2017	EGFR-TKIs, unspecified	6	0	2.7	8.3	(16)
Yang, 2021	Osimertinib	62	6.5	2.3	NA	(31)
Wu, 2019	Total	16	6.3	1.8	16.8	(27)
	Gefitinib	10				
	Erlotinib	4				
	Afatinib	2				
van Veggel, 2020	Osimertinib	21	5	3.6	8.7	(28)
Naidoo, 2015	Erlotinib	11	27	2.5	26	(24)
Yang, 2015	Afatinib	23	8.7	2.7	9.2	(25)
Beau-Faller, 2014	EGFR-TKIs, 1st generation	25	8	2	9.5	(23)
Yang, 2020	Total	23	8.7	2.9	NA	(42)
	Gefitinib	10				
	Osimertinib	6				
	Afatinib	3				
	Icotinib	3				
	Erlotinib	1				
Chelabi, 2021	EGFR-TKIs, 1st/2nd generation	6	0	2	17	(46)
Tu, 2017	EGFR-TKIs, 1st generation	12	0	3.0	12.5	(39)
Kuiper 2016	EGFR-TKIs, 1st generation	16	0	2.9	9.7	(38)
Leal, 2021	EGFR-TKIs, 1st/2nd/3rd generation	23	13	3.4	31.0	(45)

NSCLC, non-small cell lung cancer; ex20ins, exon20 insertion mutations; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; NA, not available.

a first-in-human phase I dose-escalation and dose-expansion study that aimed to evaluate the efficacy, safety, and pharmacokinetics of amivantamab monotherapy (32). In the dose-escalation part, patients received intravenous amivantamab at 140–1,750 mg weekly for the first four weeks and biweekly thereafter. No dose-limiting toxicities were observed during dose escalation up to the maximum assessed dose of 1,750 mg; therefore, the recommended phase II dose (RP2D) was 1,050 mg (1,400 mg for patients ≥80 kg) based on safety, pharmacokinetic, and pharmacodynamics data. In the dose expansion study, amivantamab at an RP2D of 1,050 mg was administered to 81 patients with NSCLC harboring EGFR ex20ins who had progressed on platinum-based chemotherapy. Among the 81 response-evaluable patients, the ORR and median PFS were 40% and 8.3 months, respectively. With regard to the toxicity profile, the most common adverse events reported were rash (86%), infusion-related reaction (66%), paronychia (45%), hypoalbuminemia (27%), constipation (24%), and stomatitis (21%). Grade ≥3 adverse events were reported in 35% of patients, and 16% of these were deemed treatment-related. The most common grade ≥3 adverse events were as follows: hypokalemia (5%), rash (4%), diarrhea (4%), infusion-related reaction (3%), and hypoalbuminemia (3%). Treatment-related dose reductions and discontinuation occurred in 13% and 4% of the cases, respectively. Based on these results, the US FDA granted accelerated approval for platinum-pretreated patients with NSCLC harboring EGFR ex20ins in May 2021.

Recently, several treatment approaches combined with

Table 3 Overview of treatment outcomes of cytotoxic chemotherapy for NSCLC harboring EGFR ex20ins

Author, year	Treatment	N	ORR (%)	mPFS (months)	mOS (months)	Ref
Oxnard, 2013	Platinum-doublet	17	41	5.9	16.5	(15)
Wu, 2019	Total	43	21	4.2	16.1	(27)
	Platinum-doublet	36				
	Monotherapy	7				
Morita, 2021	Platinum-based chemotherapy	17	11.8	8.9	29.3	(44)
Xu, 2020	PEM-based chemotherapy	77	41.6	5.5	25.0	(41)
	Platinum + PEM	66				
	PEM monotherapy	11				
	Platinum + PTX or GEM	42	31.0	3.0	19.6	
Byeon, 2019	Platinum-based chemotherapy	22	50.0	4.2	29.4	(40)
Yang, 2020	Platinum-based chemotherapy	105	19.2	6.4	NA	(42)
Chelabi, 2021	Platinum-based chemotherapy	27	41	6.5	17	(46)
Shah, 2022	Platinum-based chemotherapy	18	44	7.1	38.4	(47)
Leal, 2021	Platinum-based chemotherapy	33	43	6.9	31.0	(45)
Wang, 2020	Platinum-doublet	49	23.5	7.6	19.9	(43)

NSCLC, non-small cell lung cancer; ex20ins, exon20 insertion mutations; EGFR, epidermal growth factor receptor; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; PEM, pemetrexed; PTX, paclitaxel; GEM, gemcitabine; NA, not available.

amivantamab have been investigated in other clinical trials. Lazertinib (third-generation EGFR-TKI), one of the candidates for combined use with amivantamab, has been tested in the CHRYSALIS-2 study (NCT04077463). Preclinical data suggest that synergic inhibition of the EGFR pathway using a TKI combined with antibodies directed against EGFR has the potential to exert a more potent inhibition of the EGFR pathway and potentially delay resistance (50). In the dose expansion arm of the CHRYSALIS study, it has been observed that in patients with NSCLC harboring EGFR common mutations that are sensitive to TKIs, the combination of amivantamab and lazertinib is effective after relapse following osimertinib treatment (32). Although first-line afatinib plus cetuximab did not improve clinical outcomes compared with afatinib alone for advanced EGFR-mutant NSCLC in the randomized phase II SWOG S1403 trial, the potential for concomitant use of these kind of drugs still remains an area of interest (51). Furthermore, in the first-line setting, the phase III PAPILLON study (NCT04538664) assessing amivantamab in combination with carboplatin-pemetrexed versus chemotherapy alone in advanced NSCLC patients harboring ex20ins is currently ongoing.

Mobocertinib

Mobocertinib (TAK-788) is an orally administered irreversible TKI designed to selectively target EGFR and human epidermal growth factor receptor-2 (HER2) ex20ins (52). The safety, tolerability, and efficacy of mobocertinib were assessed in a dose-escalation phase I/II clinical trial with expansion cohorts (33,34). After evaluating mobocertinib at once-daily doses of 5, 10, 20, 40, 80, 120, 160, and 180 mg in the phase I dose-escalation part, the RP2D of mobocertinib was determined to be 160 mg daily. During phase I dose escalation and phase II expansion studies, 28 patients with advanced, previously treated NSCLC harboring ex20ins received mobocertinib at the RP2D. Among the 28 patients, the ORR and median PFS were 43% and 7.3 months, respectively. According to the baseline brain metastases status, the ORR and median PFS were 56% and 10.2 months for patients without brain metastases, whereas among patients with brain metastases, the ORR and median PFS were 25% and 3.7 months,

Table 4 Summary of data from selected clinical trials involving NSCLC patients with EGFR ex20ins

Agent	Targets	Property	Trial phase	N	ORR, % (95% CI)	mPFS, months (95% CI)	Ref
Amivantamab	EGFR, cMET	Antibody	I	81	40 (29–51)	8.3 (6.5–10.9)	(32)
Mobocertinib	EGFR, HER2	Small molecule	I/II	114	28 (20–37)	7.3 (5.5–9.2)	(34)
Poziotinib	EGFR, HER2	Small molecule	II	115	15 (8.9–22.6)	4.2 (3.7–6.6)	(53)
CLN-081 (TAS6417)	EGFR	Small molecule	I/II	42	50 (34.9–65.1)	NA	(54)
DZD9008	EGFR, HER2	Small molecule	I/II	56	38 (24.8–50.2)	NA	(55)
BDTX-189	EGFR, HER2	Small molecule	I/II	3	33 (0–86.3)	NA	(56)

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ex20ins, exon20 insertion mutations; MET, mesenchymal epithelial transition factor; HER2, human epidermal growth factor receptor-2; ORR, overall response rate; mPFS, median progression-free survival; CI, confidence interval; NA, not available.

respectively. The most common adverse events of any grade were diarrhea (83%), nausea (43%), rash (33%), vomiting (26%), dry skin (22%), decreased appetite (21%), stomatitis (21%), and fatigue (21%). Grade ≥3 adverse events occurred in 40% of patients, and the only grade ≥3 treatment-related adverse event reported in more than 5% of patients was diarrhea (21%). Dose reduction and treatment discontinuation occurred in 18% and 25% of the cases, respectively.

A more recent analysis reported the data (EXCLAIM) that evaluated mobocertinib (160 mg once daily) in previously treated patients with NSCLC harboring EGFR ex20ins (34). Among the 114 platinum-pretreated patients, the confirmed ORR was 28%, with a median PFS of 7.3 months. Based on these preliminary results, mobocertinib has been recently approved for advanced NSCLC patients harboring EGFR ex20ins whose disease progressed on or following platinum-based chemotherapy (September 2021) as well as amivantamab. Consequently, mobocertinib has become the first approved oral therapy specifically designed to target EGFR ex20ins.

The global phase III study (EXCLAIM-2) (NCT04129502) evaluating the efficacy of mobocertinib as first-line treatment and comparing it with that of platinum-based chemotherapy is currently ongoing among treatment-naïve patients. This is the first study to prospectively evaluate the role of targeted therapy against EGFR ex20ins and compare it with the current standard first-line therapy.

Other EGFR ex20ins targeting agents under investigation

Currently, a number of other agents targeting EGFR ex20ins are being developed (32,34,53-56) (*Table 4*). Poziotinib (formerly HM781-36B) is a covalent and irreversible inhibitor of EGFR and HER2 (57). An initial phase II single-center trial of poziotinib (NCT03066206) in pretreated NSCLC patients with EGFR ex20ins yielded a promising unconfirmed ORR of 58% at 8 weeks (58). However, the follow-up multicenter ZENITH20 study of poziotinib (NCT03318939) involving 115 NSCLC patients with ex20ins demonstrated a lower ORR of 14.8% with a median PFS of 4.2 months, and the study failed to meet its primary endpoint (53). Furthermore, poziotinib has considerable off-target effects on wild-type EGFR activity, contributing to the high rate of treatment-related adverse events (grade ≥3: 60%), which lead to frequent dose reductions (65%) from the starting dose of 16 mg daily. The treatment-related grade ≥3 adverse events reported in more than 5% of patients were rash (28%), diarrhea (26%), stomatitis (9%), dermatitis acneiform (8%), mucosal inflammation (7%), paronychia (6%), and fatigue (5%). Thus, to overcome the toxicity, alternative dosing regimens (e.g., 8 mg BID) are being studied.

CLN-081 (TAS6417) is an orally administered EGFR inhibitor against a variety of EGFR mutations, including ex20ins, while sparing the wild-type EGFR (59,60). A phase 1/2a trial evaluating CLN-081 monotherapy in patients with advanced NSCLC harboring EGFR ex20ins is currently ongoing (NCT04036682). Recently, interim results on safety and efficacy of the ongoing phase 1/2a trial were reported in 45 heavily pre-treated patients (54). Among the 42 response-evaluable patients, 21 (50%) had a partial response and 20 (48%) had stable disease. The common all-grade treatment-related adverse events were rash (76%), diarrhea (22%), paronychia (22%), stomatitis (18%), nausea (18%), anemia (18%), increased aspartate aminotransferase (AST) (16%),

and dry skin (16%). The most common grade ≥3 adverse events were as follows: anemia (9%), increased AST (4%), and increased alanine aminotransferase (ALT) (4%). The FDA has granted a breakthrough therapy designation for CLN-081 in January 2022.

DZD9008 is an oral, selective, and irreversible EGFR-TKI for NSCLC patients with EGFR or HER2 ex20ins. The efficacy and safety of this compound is currently being evaluated in two ongoing phase I/II clinical trials (NCT03974022 and CTR20192097). Preliminary efficacy and safety results have been reported in 102 patients with NSCLC harboring EGFR or HER2 mutations (55). Among them, 59 patients had EGFR ex20ins. Among the 56 response-evaluable patients, 21 (38%) had a partial response and 27 (48%) had stable disease. The common all-grade treatment-related adverse events were diarrhea (54%), rash (40%), nausea (34%), anemia (28%), paronychia (28%), decreased appetite (27%), vomiting (26%), and increased blood creatinine phosphokinase (23%). The most common grade ≥3 adverse events were increased blood creatinine phosphokinase (7%), diarrhea (5%), and anemia (4%). The FDA has granted a breakthrough therapy designation for DZD9008 in January 2022.

BDTX-189 is an oral, selective, and irreversible inhibitor directed against the family of allosteric EGFR and HER2 mutations. BDTX-189 is currently being assessed in the first-in-human phase I/II open-label multicenter Masterkey-01 clinical trial (NCT04209465) to address the issue of allosteric ErbB mutations found in 1%-2% of solid tumors (56). Recently, safety and preliminary efficacy data of BDTX-189 were reported in 46 patients. The common all-grade treatment-related adverse events at RP2D (800 mg QD) were diarrhea (50%), nausea (50%), vomiting (30%), increased ALT (20%), and fatigue (20%). The most common grade ≥3 adverse events were increased ALT (10%), diarrhea (7%), and nausea (7%). Grade ≥3 adverse events were observed in 23% of patients. Three patients with NSCLC harboring EGFR ex20ins dosed at RP2D were evaluable at the time of data cut-off. Among them, one confirmed partial response was observed in a patient who had previously responded and then progressed on poziotinib.

Summary and conclusions

EGFR ex20ins represent a distinctive molecular subset of all EGFR mutations and patients with NSCLC harboring EGFR ex20ins have high unmet medical needs. Therefore, the development of novel effective treatments targeting EGFR ex20ins is the need of the hour.

Recent developments in the subgroup of NSCLC with oncogenic driver alterations have brought significant clinical benefits and have established an individualized treatment approach. On the other hand, no effective EGFR ex20ins targeted therapies had been developed over the past decade, thus, clinical outcomes in NSCLC patients harboring this mutation are significantly worse compared to those harboring common EGFR mutations. Recently, novel targeted therapies against EGFR ex20ins, such as amivantamab and mobocertinib, have been developed, and preclinical and early clinical trials have demonstrated clinically meaningful efficacy of these drugs. Based on the results, FDA has accelerated the approval of amivantamab and mobocertinib. These emerging therapies hold great promise for improved survival in this subset of patients. However, the efficacy data observed with these novel EGFR inhibitors do not come up to those of highly effective molecular targeted therapies (e.g., osimertinib in common EGFR mutations). Therefore, to further improve the prognosis of patients with NSCLC harboring EGFR ex20ins, several issues have to be addressed. First, it is important to determine whether all NSCLC patients with EGFR ex20ins will universally respond to targeted therapies given the significant molecular heterogeneity in the size and location of distinct EGFR ex20ins. EGFR ex20ins are highly diversified in terms of insertion patterns or co-occurring mutations, and these variants exhibit different clinical responses to various EGFR TKIs. Therefore, the selective use of targeted therapies to treat different EGFR ex20ins might be useful for improving tumor responses. Second, our understanding of the mechanisms of acquired resistance to novel EGFR inhibitors is limited. The emergence of secondary resistance to targeted therapy is inevitable, and almost all patients with an initial response to treatment experience disease progression. It is essential to develop innovative approaches to overcome the resistance mechanisms anticipated with novel compounds for NSCLC harboring EGFR ex20ins. Third, although the aforementioned novel drugs demonstrated clinically meaningful benefits, their efficacy might be limited by central nervous system (CNS) disease progression. Brain metastases occur in 20–40% of NSCLC patients with EGFR ex20ins at the time of baseline diagnosis (42,61). As with any other large monoclonal antibody, amivantamab is not expected to cross the blood-brain barrier. In addition, mobocertinib demonstrated a low overall response

in patients with baseline brain metastases, suggesting limited intracranial activity (33,34). Effective therapies targeting EGFR ex20ins that have good CNS penetrance are urgently needed. Lastly, it remains largely unknown whether immune checkpoint inhibitors (ICIs) are suitable for patients with NSCLC harboring EGFR ex20ins. Although ICIs such as programmed cell death protein 1 and programmed cell death 1 ligand 1 antibodies have revolutionized the treatment of NSCLC and improved the survival outcomes of numerous lung cancer patients, their efficacy as monotherapy in EGFR-mutant NSCLC has been disappointing (62-67). On the other hand, conflicting data exist on the efficacy of ICI monotherapy in EGFR ex20ins NSCLC, with an ORR of 4–50% and median PFS of 2–5 months (45,68-70). With regard to the combination treatment of ICI plus chemotherapy, recent subgroup analyses of clinical phase III trials suggested that EGFR-mutant NSCLC may benefit from atezolizumab and platinum-based chemotherapy co-treatment in the first-line setting (71,72). However, whether similar results can be obtained from NSCLC patients having EGFR ex20ins remain unknown, given the limited number of cases treated with combination chemotherapy employing ICI in previous reports (42,73-75). At present, it is difficult to draw firm conclusions as to whether ICI, alone or in combination with chemotherapy, is effective against EGFR ex20ins in NSCLC. To decide the best place of ICI or sequence therapies appropriately, future studies evaluating whether NSCLC patients harboring EGFR ex20ins derive greater clinical benefit from combination chemotherapy with ICI compared with novel targeted therapies will be important. Furthermore, it might be necessary to consider the order in which ICI and these novel targeted therapies are used in terms of safety concern. In an aforementioned phase I/II clinical trial of mobocertinib, grade 3 or higher treatment-related adverse events occurred in 58% of the previously platinum-treated patients subset who received prior ICI and 39% of patients who did not receive prior ICI, respectively (34,76). As these issues are resolved along with the development of several promising agents, clinicians would be able to select the most appropriate treatment strategies for each individual patient. Further investigations on novel targeted therapies are warranted in future clinical trials.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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