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Review

Advances in the management of non-small-cell lung cancer harbouring *EGFR* exon 20 insertion mutations

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***Abstract*:** Epidermal growth factor receptor (*EGFR*) mutation is one of the key oncogenic mutations in non-small-cell lung cancer with adenocarcinoma histology. Exon 19 deletions and exon 21 L858R substitutions account for 90%, while *EGFR* exon 20 insertions constitute 4–10% of *EGFR* mutations and are the third most prevalent activating *EGFR* mutations. *EGFR* exon 20 insertions are associated with decreased sensitivity to EGFR tyrosine kinase inhibitors and, until recently, effective targeted therapy against these tumours remained an unmet clinical need and chemotherapy was the only treatment of choice available. The approval of amivantamab and mobocertinib for patients who have progressed after chemotherapy represents an important step forward in the management of these patients. Here in this review, we summarize the epidemiology, structure and the tumour microenvironment of *EGFR* exon 20 insertion and also review the systemic treatments, including targeted therapies and ongoing clinical trials in *EGFR* exon 20 insertion mutations, as well as detection methods for *EGFR* exon 20 insertion. Lastly, resistant mechanisms and future directions are addressed.

Keywords: EGFR exon 20 insertion mutations, EGFR inhibitor, lung cancer, non-small cell lung cancer, tyrosine kinase inhibitor

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Introduction

Epidermal growth factor receptor (*EGFR*) mutations represent a key oncogenic driver alteration in non-small-cell-lung cancer (NSCLC) with a frequency ranging from 10–15% and up to 50% in Caucasians and East Asians, respectively.[1] Of the *EGFR* mutations, exon 19 deletions and exon 21 Leu858Arg point mutation (L858R), also known as common mutations, account for 90% of all *EGFR* mutations.[2] These mutations are sensitive to EGFR tyrosine kinase inhibitors (TKIs), including first-generation EGFR TKIs gefitinib and erlotinib, second-generation afatinib and dacomitinib and third-generation osimertinib.[3–8] Uncommon mutations, including exon 18 G719X, exon 20 S768I, exon 21 L861Q, exon 20 insertions and complex mutations are resistant to first-generation EGFR TKIs.[9] Thus, afatinib remains the preferred regimen for uncommon *EGFR* mutations such as G719X, S768I and L861Q. Patients with NSCLC with *EGFR* exon 20 insertion mutations are usually resistant to EGFR TKIs, and until recently, chemotherapy was the only treatment of choice available.[10] The recent approval of two targeted agents, amivantamab[11] and mobocertinib[12] for patients with advanced NSCLC harbouring *EGFR* exon 20 insertion mutations who have progressed after chemotherapy (Figure 1) confirms this molecular alteration is an actionable target that warrants further exploration.

Herein, the epidemiology, structure, and genomic and tumour microenvironment of *EGFR* exon 20 insertion mutations are covered. The review highlights the systemic treatments, including targeted therapies and ongoing clinical trials in *EGFR* exon 20 insertion mutations, as well as detection methods for *EGFR* exon 20 insertion mutations. Lastly, resistant mechanisms and future directions are addressed.

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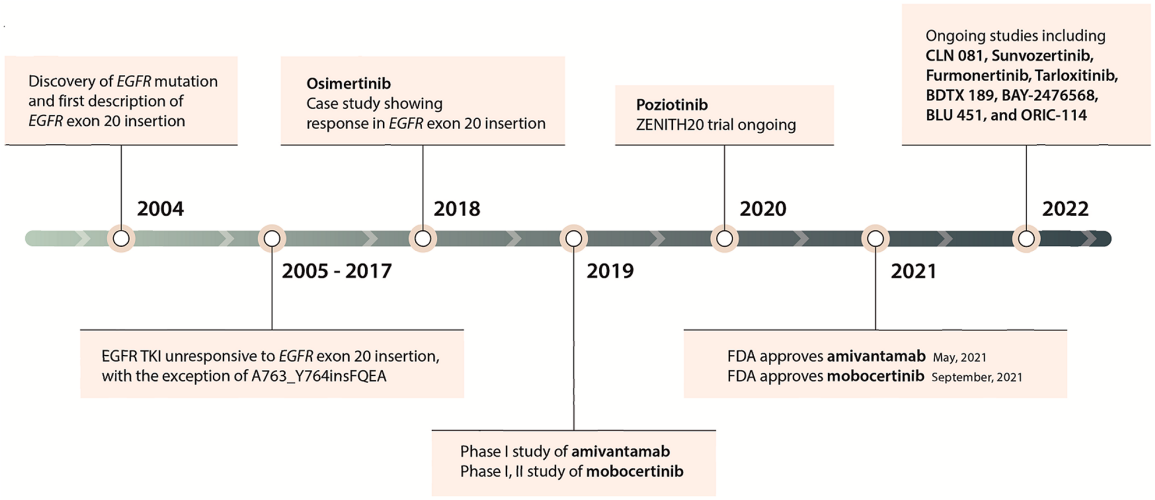

Figure 1. Timeline of development of targeted therapies for EGFR exon 20 mutations.
EGFR, epidermal growth factor receptor.

Epidemiology of EGFR *exon 20 insertion mutations*

When considered as separate molecular subset, *EGFR* exon 20 insertion mutations constitute about 1–2% of all NSCLC cases, but among *EGFR* mutations, 4–10% of all observed *EGFR* mutations in NSCLC.[10,13,14] In addition to lung adenocarcinoma, other solid tumours such as glioblastoma, urothelial carcinoma and endometrial adenocarcinoma harbour *EGFR* exon 20 insertion mutations, and overall, *EGFR* exon 20 insertion mutations comprise of 0.35% of identified mutations in AACR project GENIE.[15] Similar to other oncogenic molecular alterations in NSCLC, *EGFR* exon 20 insertion mutations are usually mutually exclusive with other genetic driver alterations, and have similar clinical characteristics with the classical activating *EGFR* mutations, which are enriched in non-smokers, Asian and adenocarcinoma histology.[16] A recent literature studied the frequency of mutation according to population ethnicity or global region.[17] *EGFR* exon 20 insertion mutations accounted for 1–12% of *EGFR* mutations, and the frequency was 0.1–4% for all NSCLC cases. Comprehensive genomic profiling of NSCLC also revealed that *EGFR* exon 20 insertion mutation was identified in 12% of all *EGFR*-mutant NSCLC, with various spectrum of *EGFR* exon 20 insertion variants.[18] The most common variants were D770_N771>ASVDN and N771_P772>SVDNP, which account for 21% and 20% of all *EGFR* exon 20 insertion mutations, respectively. The frequency of *EGFR* exon 20 insertion mutations was as high as 4% in Asia Pacific, whereas it was reported 1.3% of all NSCLCs in Europe.[17] It is difficult to conclude that there is geographic variation, because the frequency of *EGFR* exon 20 insertion mutations may be underestimated due to insufficient testing methods that may only detect common *EGFR* mutations.[17]

Structure of EGFR *exon 20 insertion mutations*

EGFR exon 20 insertion mutations can be largely classified as inframe insertions or duplications of 3–21 base pairs typically occurring between AA761 and AA775.[13,18] *EGFR* exon 20 insertion mutations contains two essential regions: the regulatory C-helix domain (AA762-766) and the adjacent loop (AA767-774) following C-helix. The most frequent site of mutations identified in *EGFR* exon 20 insertion mutation is in the loop following C-helix, specifically between exons 767 and 774. More than 100 unique activating *EGFR* exon 20 insertion mutations have been identified, unlike the homogeneous mutations in common *EGFR* mutations. The location and frequency of each *EGFR* 20 insertion mutation is described in Figure 2.[13,18,19]

The unique mechanism of *EGFR* exon 20 insertion mutations is associated with the altered structure upon mutations. As reported by Yasuda *et al.*, the crystal structure of D770_N771insNPG revealed a shift of the C-helix, creating an inward position that keeps the active state of EGFR in the absence of ligand binding.[13] Thus, this shift in conformation enables continuous activation of EGFR with markedly hinderance in TKI binding, resulting in resistance to EGFR TKIs used in the treatment of common sensitizing *EGFR* mutations.[19]

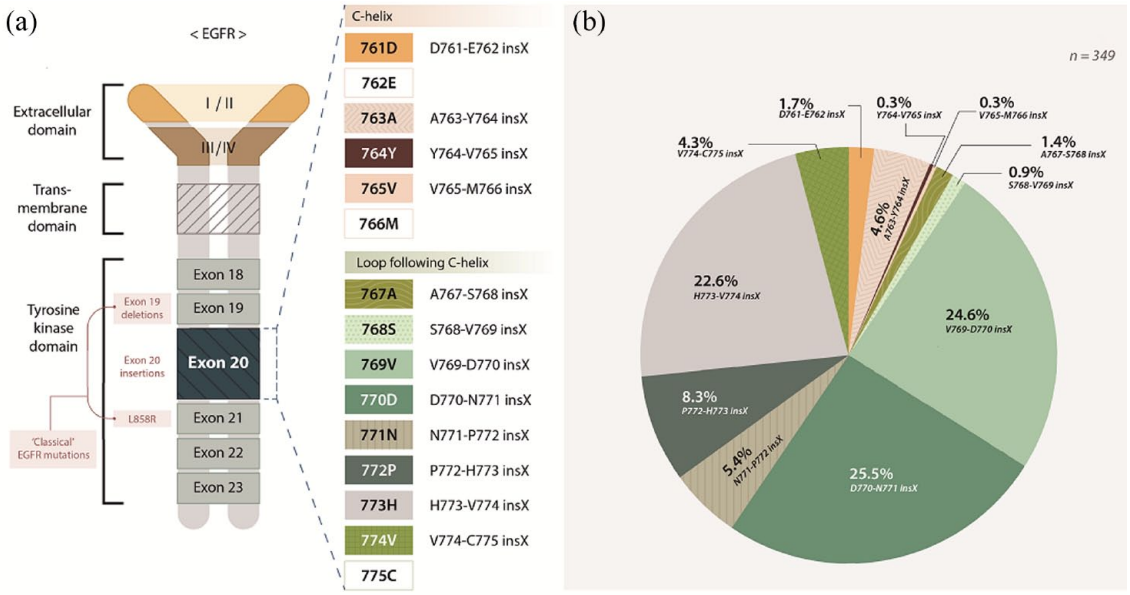

Figure 2. Location of EGFR exon 20 insertion mutations (a) and various spectrum of EGFR exon 20 insertion (b) 13,18,19.
EGFR, epidermal growth factor receptor.

Ins 20 variant (Parental BaF3)	Erlotinib (IC50 values)	Gefitinib	Afatinib	Osimertinib	Mobocertinib	Poziotinib	Amivantamab	BAY2576568	BLU-451	Oric-114	Furmonertinib	Tarloxitinib
WT EGFR	71.0	55.5	3.8	350.5	34.5	6.49	0.9	273	921	2.3	109.9	N/A
A763_Y764insFQEA	21.0	90.0	0.4	51.1	3.1	1.90	N/A	N/A	61	0.9	N/A	15.2
V769_D770insASV	80.0	287.4	10.3	61.1	2.1	2.13	0.6	15.3	78	N/A	14	675.9
D770_N771insNPG	469.0	941.0	9.0	27.2	1.3	0.73	N/A	N/A	7	2.7	11	N/A
D770_N771insSVD	528.0	918.4	41.3	226.7	6.5	1.5	1.4	11.1	53	N/A	N/A	990.1
H773_V774insNPH	191.2	1132.8	18.9	153.6	2.6	31.93	N/A	67.9	75	N/A	20	714.0

IC50 >100 | IC50 < 10 to ≤ 100 | IC50 ≤ 10

Figure 3. Heat map representation of IC50 values for proliferation of therapeutic agents in EGFR exon 20 insertion. The colours mark the sensitivity to different agents: sensitive (green, <10), intermediate (yellow, 10–99) and resistant (red, >100).
EGFR, epidermal growth factor receptor.

Due to their heterogeneous location of the insertions, the *in vitro* sensitivity to EGFR inhibitors may be variable (Figure 3).[13,20–22] A classic example of *EGFR* exon 20 insertion mutation is D770_N771insNPG, which activates but has no affinity for first-generation EGFR TKIs. In contrast, A762_Y764insFQEA insertions may respond to first-generation EGFR TKIs, and have shown 10-fold higher binding affinity than other *EGFR* exon 20 insertion mutations.[13] Isolated case reports have been published on the sensitivity of H773dup, H773_V774insNPH and N771delinsKG mutations to afatinib, but the clear mechanism of response needs to be further investigated in prospective studies.[20–22]

Genomic and tumour microenvironment characteristics

The characterization of genomic and immune microenvironment of *EGFR* exon 20 insertion mutant NSCLC-tumours currently remains scarce. NSCLC harbouring *EGFR* exon 20 insertion mutation is associated with co-occurring genomic alterations associated with tumour suppressor and cell cycle alterations, notably with *TP53* mutations, cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/2B*) genes, as well as *NK2* homebox 1 (*NKX2-1*), and *RB* transcriptional co-repressor 1 (*RB1*) genes.[18] These alterations were also noted in other sensitizing *EGFR*

mutations such as exon 19 del and L858R at comparable frequency. Similarly, *TP53* and *CDKN2A* were identified as co-occurring mutations in addition with *PIK3CA* and *EGFR* amplifications.[23]

With regards to programmed death-ligand 1 (PD-L1) tumour expression, in one study, 76% (107/141) of tumour samples were negative for PD-L1 expression. The tumour mutational burden (TMB) have tended to be low, with reports ranging between 3.4 and 4.6 mutations/Mb.[24] The low TMB observed in tumours with *EGFR* exon 20 insertion mutation is similar to NSCLC with common *EGFR* exon 19 del and L858R mutations.[18] Taken together, the data suggest the activity of immune checkpoint inhibitors (ICIs) is likely to be blunted in NSCLC harbouring *EGFR* exon 20 insertion mutations and the immune phenotype of these tumours should be further evaluated.

Systemic therapies

Currently, the first-line treatment for patients with *EGFR* exon 20 insertion mutations is platinum-based chemotherapy, and amivantamab or mobocertinib in second-line setting. In this section, we discuss on the role of chemotherapy ± immunotherapy, and the development of novel targeted agents

Chemotherapy ± immunotherapy

In patients with advanced NSCLC with *EGFR* exon 20 insertion mutations, treatment with a platinum chemotherapy was associated with a longer time to treatment discontinuation (TTD) of 7 months, and a median overall survival (OS) of 20 months, whereas in patients without molecular alterations the TTD and OS was 4 and 12 months, respectively.[25] Other retrospective studies have reported an overall response rate (ORR) of 11–39% and median progression-free survival (PFS) of 6.4–8.9 months with platinum-based chemotherapy.[26,27] These results are in sharp contrast to treatment with EGFR TKIs, with an ORR of 13%, and median PFS and OS of 3.4 and 9.5 months respectively.[28–30] While chemotherapy is the standard of treatment for patients with *EGFR* exon 20 insertion mutations, clinical trials with targeted therapies for *EGFR* exon 20 insertion mutations are strongly recommended due to the limited activity and toxicity of platinum-based chemotherapy.[31]

As alluded previously, *EGFR* exon 20 insertion mutations have reduced efficacy with ICIs.[32,33] In patients treated with ICIs as monotherapy as first-line treatment, the ORR was 9.1% and a median PFS and OS of 3.1 and 11 months, respectively.[34] A meta-analysis on *EGFR* exon 20 insertion mutations reported similar outcomes.[35] When treated with ICIs, *EGFR* exon 20 insertion mutations demonstrate higher disease control rate of 6 and 12 months of 36% and 11% compared with classic *EGFR* mutations of 16% and 0%, respectively.[32] The addition of platinum-based chemotherapy to ICIs have reported an ORR of 18.8% with a median PFS and OS of 4.5 and 11.3 months.

Targeted therapies

Until recently, effective targeted therapy against NSCLC tumours with *EGFR* exon 20 insertion mutations remained an unmet clinical need. The tyrosine kinase (TK) domain of EGFR induces activation of signalling pathway such as phosphatidylinositol 3-kinase (PI3K)/AKT, Janus kinase 2/signal transducer and activator of transcription 3, and Ras/mitogen-activated protein kinase (MAPK) and stimulates downstream components involved in cell proliferation, cell cycle progression, survival and motility.[36–39] Gefitinib and erlotinib reversibly bind to EGFR while afatinib and dacomitinib irreversibly bind to EGFR covalently.[40] However, these first- and second-generation EGFR TKIs have shown disappointing clinical against most *EGFR* exon 20 insertion mutations[41] due to steric hindrance, except for *EGFR* A763_Y764insFQEA, occurring in 6% of *EGFR* exon 20 insertion mutations NSCLC, which has been reported as being sensitive to a first-generation EGFR TKI.[13] The use of the third-generation TKI osimertinib in *EGFR* exon 20 insertion mutations is described below. None of these EGFR TKIs are approved by United States Food and Drug Administration (FDA) for use in patients with *EGFR* exon 20 insertion mutations.

A key challenge with *EGFR* exon 20 insertion mutations is the diverse mutational landscape. However in the past 5–10 years, several emergent therapies and clinical trials have been specifically developed for this unique molecular subgroup[14] (Figure 1). With a variety of mechanisms of action, these novel treatments represent an important step forward in the management of patients with *EGFR* exon 20 insertion mutations NSCLC. Results of these trials are summarized in Table 1. The frequency of treatment-related toxicites of key agents are summarized in Supplementary Figure 1.

Table 1. Clinical trials in patients with *EGFR* exon 20 insertion mutations.

Study	Agent	Phase	*N*	Patient population	ORR	DOR, months (95% CI)	PFS, months (95% CI)	OS, months (95% CI)	G3+ TRAEs	TRDR/ discontinuation rate
Zenith 20-1[42]	Poziotinib	II	115	At least one prior systemic therapy	14.8%	7.4	4.2	NR	Rash 28%, diarrhoea 26%, stomatitis 9%, paronychia 6%	Not reported
Study 101[43,44]	Mobocertinib	I/II	114	Prior platinum-based therapy	28%	17.5 (7.4–20.3)	7.3 (5.5–9.2)	24 (14.6–28.8)	Diarrhoea 21%, nausea 4%, stomatitis 4%, prolonged QTc 3%	25%/17%
Study 101[43]	Mobocertinib	I/II	96	Prior chemotherapy ± EGFR TKI	25%	Not estimable (5.6 months to not estimable)	7.3 (5.5–9.1)	NR	Diarrhoea 16%, nausea 3%, stomatitis 3%, prolonged QTc 3%	22%/10%
Chrysalis[45]	Amivantamab	I	158	Prior or ineligible for platinum chemotherapy	40%	11.1 months (6.9 to not reached)	8.3 (6.5–10.9)	22.8 (14.6–NR)	Diarrhoea 4%, rash 3%, infusion related 3%, hypoalbuminemia 3%	10%/7%
ECOG-ACRIN 5162[46]	Osimertinib	II	21	Prior chemotherapy	25%	5.7 (CI, 4.73–NA)	(4.07–NA)	NR	Anaemia 9.5%, fatigue 9.5%, prolonged QTc 9.5%	–/5%
POSITION 20[47,48]	Osimertinib	II	25	Prior chemotherapy ± immunotherapy	28%	6.8 (4.6–9.1)	5.3 (2.7–27.6)	15.2 (14.3–16.0)	Pneumonitis 4%, left ventricular systolic dysfunction 4%	0%/8%
ETCTN California cancer consortium[49,50]	Osimertinib plus necitumumab	I	18	Prior chemotherapy	19%	–	6.9 (4.1–11.4)	–	Rash (13%)	–
WU-KONG 1[51,52]	Sunvozertinib	I/II	56	No more than 1–3 lines of prior chemotherapy ± immunotherapy ± 1st- to 3rd-generation EGFR TKI	50%	5.6 months for 300-mg cohort	6 months PFS for 100-mg, 200-mg, 300-mg and 400-mg cohorts: 50%, 53.3%, 44.6% and 44.4%	NR	Diarrhoea 4.9%	15.7%/5.9%
CLN 081[53]	CLN-081	I/IIa	73	Prior or ineligible for platinum chemotherapy ± EGFR TKI (only for dose escalation cohorts)	40%	40%	>15 (estimated)	12 months	Rash 1%, diarrhoea (3%), anaemia (10%)	14%/8%
FAVOUR 1[54]	Furmonertinib	Ib	10	Treatment naive	71%	–	–	–	No grade 3 or above adverse events reported	Not reported
RAIN[55,56]	Tarloxotinib	II	11	Prior platinum-based chemotherapy	SD in 55%	–	–	–	Prolonged QTc 34.8%, rash 4.3%, diarrhoea 4.3%, increased ALT 4.3%	21.7%/4.3%

ALT, alanine aminotransferase; CI, confidence interval; DoR, duration of response; EGFR, epidermal growth factor receptor; G3, grade 3; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TRAEs, treatment-related adverse events; TRDR, treatment-related dose reduction; TTD, time to treatment discontinuation.

Mobocertinib. Mobocertinib (TAK-788) is a first-in-class, potent, oral, irreversible TKI. Mobocertinib and its two active metabolites, AP32960 and AP32914, are approximately equally potent in inhibiting EGFR. Its isopropyl ester domain targets proteins in the vicinity of the alpha C-helix, a binding site not exploited by osimertinib.[57–59] The covalent interaction and irreversible binding with EGFR cysteine 797 also lead to increased potency *via* higher affinity binding, more sustained EGFR kinase activity inhibition and greater overall selectivity. Preclinical *in vitro* studies demonstrated selectivity of mutant EGFR over wildtype (WT) EGFR, with more potent inhibition of Ba/F3 cells expressing *EGFR* exon 20 insertion than WT EGFR (IC_{50} 4.3–22.5 nmol/L and 34.5 nmol/L, respectively). There is also *in vivo* anti-tumour efficacy in patient-derived models and murine orthoptic models.[58] Based on this, mobocertinib was evaluated in a phase I/II dose-escalation/expansion trial which identified 160 mg/day as the recommended phase II dose.[43]

In September 2021, mobocertinib 160 mg/day was granted FDA approval. This is the first approval of an oral targeted therapy for patients with *EGFR* exon 20 insertion mutations. Results were promising with ORR 28% and median PFS 7.3 months in the platinum pre-treated cohort. There was high incidence of EGFR-driven toxicities. Common adverse events (AE) included diarrhoea, rash, paronychia, decreased appetite, nausea, dry skin, vomiting and stomatitis which occurred in >20% of patients. However, most gastrointestinal and skin events were grade 1–2 in severity except for diarrhoea which is the only grade 3–4 treatment-related AE reported in greater than 10% of patients. One patient died from heart failure that was considered treatment related and its product labelling includes a boxed warning for QTc prolongation and Torsades de Points.[44]

Amivantamab. Amivantamab is a bispecific antibody targeting MET and EGFR with three distinct mechanisms of actions: inhibition of ligand binding to its target receptors; degradation of these receptor *via* the lysosome pathway; and Fc-dependent phagocytosis by M1/M2 macrophages and antibody-dependent cellular toxicity by natural killer cells[60,61] (Table 1). The phase I CHRYSALIS study is a dose-escalation, dose-expansion study which included a population with *EGFR* exon 20 insertion mutations ($N=187$). In the efficacy population ($N=81$) of post platinum population treated with amivantamab, a response rate of 40% and PFS of 8.3 months was reported. Safety profile was manageable.[45] AE associated with EGFR inhibition included rash, paronychia, stomatitis, pruritis and diarrhoea while that associated with MET inhibition included hypoalbuminemia and peripheral oedema with most being grade 1–2. Interstitial lung disease was reported in 4% of patients in the CHRYSALIS study. These findings are clinically meaningful considering the population of interest has relapsed metastatic or unresectable NSCLC with a 5-year survival rate of less than 10%.[62] Based on these results, amivantamab received accelerated approval from the FDA in May 2021 for patients with advanced NSCLC harbouring *EGFR* exon 20 insertion mutations with progression on or after platinum-based chemotherapy.

In both Study 101 and CHRYSALIS, a variety of *EGFR* exon 20 insertion mutations were identified and there does not appear to be a clear association of likelihood or depth of response with mutation variants.[55] Although the response rate with amivantamab was numerically greater than mobocertinib (40% *versus* 28%, respectively), this should be interpreted with caution given cross-trial comparisons. It should be highlighted the OS and PFS appeared similar at 22.8 months and 24 months, 8.3 and 7.3 months for amivantamab and mobocertinib, respectively. There are several differences between amivantamab and mobocertinib. Amivantamab is administered intravenously, initially weekly, then biweekly while mobocertinib is administered orally daily. While both have on-target EGFR toxicities, amivantamab more commonly caused skin rash yet has much lower rates of diarrhoea than mobocertinib. Mobocertinib also had higher rates of treatment-related discontinuations. All grade infusion reactions occurred in 65% of patients receiving amivantamab although the incidence of grade 3 or more infusion reactions was only 3%. Amivantamab's unique mechanism of action as an antibody to both EGFR and cMet, as well as low fructose backbone with high affinity for FcYRIIIa/CD16a[63] may account for increased selectivity and efficacy with decreased toxicity when compared to other targeted therapies for *EGFR* exon 20 insertion mutations NSCLC.[62]

Other TKIs targeting *EGFR* exon 20 insertion mutations are under development and are discussed in the following section.

Poziotinib. Poziotinib is an irreversible pan-human epidermal growth factor receptor (HER) inhibitor with activity against mutations or insertions of HER1, HER2 and HER4. Owing to its small size and flexibility and increased halogenation, poziotinib can circumvent steric changes of the *EGFR* exon 20 insertion mutations drug binding pocket. *In vitro* testing demonstrated that poziotinib had an average IC50 value of 1.0 nM in Ba/F3 cell lines with an *EGFR* exon 20 insertions, making it approximately 100 times more potent than osimertinib and 40 times more potent than afatinib.[19]

Given its preclinical activity, ZENITH20 study was initiated to evaluate poziotinib in patients with *EGFR* exon 20 insertion mutations.[64] The 16 mg/day dose was chosen as it was the highest daily dose without dose-limiting toxicity in a phase I study involving *HER2* amplified breast cancer.[65] Furthermore, 16 mg/day dosing was also used in a single centre phase II clinical trial enrolling previously treated patients with NSCLC harbouring exon 20 insertions which demonstrated a promising 8-week unconfirmed ORR of 58%.[66] Unfortunately, while the results of the ZENITH20 study[64] reported clinically meaningful activity with an ORR of 14.8% as well as PFS of 4.2 months for previously treated *EGFR* exon 20 NSCLC, it was tempered by significant side effects due to inhibition of WT EGFR. 28% and 26% of patients had grade 3 or more treatment related rash and diarrhoea, respectively. The incidence of treatment related pneumonitis was 4% although some cases may have been confounded by prior treatment with checkpoint inhibitors.

Pharmacokinetic (PK) simulation demonstrated that twice a day (BID) dosing could reduce toxicity while preserving activity compared to once a day (QD) dosing due to the relatively short half-life (T1/2).[67] The ZENITH20-5 randomized patients to either 10, 12, 16 mg OD or 6, 8 mg BID of poziotinib. Randomized cohorts of QD *versus* BID dosing (16 mg QD *versus* 8 mg BID; 12 mg QD *versus* 6 mg BID) indicate that incidence of ⩾grade 3 AE of rash, diarrhoea and stomatitis was lower with BID dosing (31% *versus* 21% and 27% *versus* 16%, respectively) in cycle 1. BID dosing *versus* QD schedules also resulted in the relative reduction in dose interruptions by 38% and 52%, respectively.[67,68]

While poziotinib is effective against EGFR exon 20 insertion mutations, heterogeneity in responses may be observed depending on the location of *EGFR* exon 20 insertion mutation. This is due to marked conformations of distinct regions of receptor known to effect drug binding. Near loop region mutations proximal to the C-helix (AA767-772) influences the orientation of distinct residues of the P-loop which helps to stabilize poziotinib and increase drug binding affinity, which is distinct to insertions occurring at the distal far loop region (AA773-775) (PMID: 34526717). The response rate of poziotinib for near and far loop region mutations was 46% and 0%, respectively ($p = 0.0015$). *In vitro* testing has also demonstrated a positive correlation between drug sensitivity and mutation location ($R = 0.67$, $p = 0.0003$).[69]

CLN 081 (TAS6417). CLN 081 is another promising novel oral irreversible EGFR TKI with a unique pyrrolopyrimidine scaffold, with potent, broad-spectrum activity against *EGFR* mutations.[70,71] A unique feature of CLN-081 is its potency and selectivity for inhibition of *EGFR* exon 20 insertion mutations *versus* WT *EGFR*. Cell line models harbouring various *EGFR* exon 20 insertion mutations demonstrated that CLN-081 has a WT to mutant half-maximal inhibitory concentration (IC50) ratio of 134-fold for A763_Y764insFQEA, 17.4-fold for D770_N771insSVD, 17.2-fold for D770_N771insG, 6.37-fold for V769_D770insASV, 4.55-fold for H773_V774insPH and 4.51-fold for H773_V774insNPHA[14] This is in contrast to the first- and second-generation EGFR TKIs erlotinib and afatinib which shows minimal selectivity for mutant receptors.[71]

A phase I/II dose-escalation/dose-expansion trial is ongoing with preliminary results reported at ASCO 2022.[53] In all, 73 patients were enrolled across doses ranging from 30 to 150 mg BID. Enrolment at 150 mg BID was stopped after 11 patients based on toxicity. In a heavily pretreated cohort with 66% patients receiving ⩾2 prior lines of treatment and 36% of patients with prior EGFR TKI, the ORR and PFS was 38.4% and 10 months, respectively. There is also a manageable safety profile. Most AEs were grade 1 and 2, dose reductions and dose discontinuations due to AE were uncommon at doses below 150 mg BID at 11% and 6%, respectively, with no ⩾grade 3 rash observed at doses <150 mg. Pneumonitis were observed in four patients, but cases were asymptomatic or confounded by comorbid medical illness.[72]

Osimertinib ± necitumumab. While the third-generation EGFR TKI osimertinib has activity against both canonical activating and T790M mutant forms of *EGFR*, there significant overlap in terms of conformation between *EGFR* exon 20 insertion mutations and WT *EGFR* in the ATP-binding pocket. Pre-clinical studies have reported that osimertinib was active in *EGFR* exon 20 insertion mutant cell lines and tumour xenografts with a wide therapeutic window.[73–75] This translates to variable clinical responses for *EGFR* exon 20 insertion mutations variants. For instance, responses have been reported in patients with A767_V769dup, A763_Y764insFQEA, H773_V774insAH, S768_D770dup and D770_N771insG.[76,77]

While pre-clinical data proposed a potential activity of osimertinib, there has been conflicting reports of efficacy. Retrospective studies have reported an ORR of 16.7–67.7%.[76] However, in a prospective study of 14 patients treated with osimertinib 80 mg OD, none experienced an objective response.[78]

Studies have reported an association between area under the curve (AUC)/IC50 and PFS, indicating the concentration dependent efficacy of osimertinib in *EGFR* exon 20 insertion mutations. Coupled with data from pre-clinical studies showing a IC50 approximately 10–100 higher for *EGFR* exon 20 insertion mutations than for *EGFR* exon 19 deletion, exon 21 L858R and T790M mutations,[74,75] this provides a rationale for increase dose intensity of osimertinib.[77–79] Furthermore, there is also known safety profile of 160 mg daily for patients with central nervous system (CNS) metastasis.[80–83] Based on this rationale, osimertinib at 160 mg OM has been evaluated in two phase II trials ECOG-ACRIN 5162 and POSITION20.[46–48] The reported ORR and PFS was 25% and 27%: 9.7 and 5.5 months, respectively, as well as AEs consistent with other reports of this regimen.

Necitumumab is a fully human lgG1 monoclonal antibody targeting EGFR. As a fully human monoclonal antibody, risks of hypersensitivity are expected to be lower.[84] It works by binding to EGFR with higher affinity and specificity than EGF, blocking ligand induced phosphorylation of EGFR and downstream pathway activation. In addition, the Fc portion can also induce antibody-dependent cell-mediated cytotoxicity (ADCC), an important mechanism of antitumour activity related to complement activation and triggering of immune effector cells.[85] The combination of necitumumab and osimertinib was tested in select settings of EGFR TKI resistance including *EGFR* Exon 20 insertion mutations in the phase I ETCTN California Cancer Consortium study. In this *EGFR* exon 20 insertion population pre-treated with platinum chemotherapy, RR was 22% (4/18) with a PFS of 6.9 months. Rash was the most common grade 3 AE, occurring in 13% of patients.[49,50]

Sunvozertinib (DZD9008)

Sunvozertinib is an oral, potent, irreversible and selective TKI targeting *EGFR* exon 20 insertion mutations as well as *EGFR* sensitizing, T790M and uncommon *EGFR* mutations with weak activity against WT *EGFR*. It has 1.4- to 9.6-fold selectivity on *EGFR* exon 20 insertion mutations compared with *EGFR* WT. Oral administration of sunvozertinib also demonstrated profound anti-tumour efficacy in a dose-dependent manner in patient-derived xenografts model.[51]

Two ongoing phase I trials for sunvozertinib, WU-KONG 1 and WU-KONG 2, are being conducted for metastatic NSCLC harbouring *EGFR* or *HER2* mutations. A pooled analysis was performed to assess safety, PK and antitumour efficacy.[52] In the 56 patients with *EGFR* exon 20 insertion mutations, the confirmed ORR was 50% across all dose levels. PFS rate at 6 months for 100-mg, 200-mg, 300-mg and 400-mg cohorts was 50%, 53.3%, 44.6% and 44.4%, respectively, and has not been reached. The drug appears tolerable. All grade diarrhoea and rash occurred in 53.9% and 40.2% of patients, respectively, but the incidence of ⩾grade 3 diarrhoea was only 4.9% and no patients experienced ⩾grade 3 rash. Based on safety and tolerability data in the dose-escalation cohorts, 400 mg was defined as the maximum tolerated dose (MTD), and 200 mg to 400 mg were selected for dose expansion.[51,86]

Furmonertinib (Alflutinib, AST2818)

Furmonertinib is a novel third-generation EGFR TKI targeting both *EGFR* sensitizing mutations, T790M and sparing WT *EGFR*.[87] It has shown superior efficacy compared with gefitinib as first-line therapy in patients with *EGFR* mutation positive (exon 19 deletion or exon 21 L858R) along with an acceptable safety profile.[88] Furmonertinib has also been approved in China on 3 March

2021, for the treatment of *EGFR* T790M mutant NSCLC based on a phase IIb study showing RR of 74% in patients with de novo or acquired *EGFR* T790M mutations.[89] There is also an encouraging antitumour activity in *EGFR* exon 20 insertion mutations NSCLC based on preclinical studies. Furmonertinib effectively inhibited BaF3 cells expressing *EGFR* exon 20 insertion mutations with mean IC50 of 11–20 nM and was active in patient-derived xenograft models harbouring *EGFR* exon 20 insertion mutations. In a phase Ib study of previously untreated patients with *EGFR* exon 20 insertion mutations NSCLC treated with furmonertinib, the ORR was 71% (5/7 patients).[54]

Tarloxitinib

Tarloxitinib is a prodrug that harnesses tumour hypoxia to generate high levels of a potent, covalent pan-HER TKI, tarloxotinib-effector (tarloxotinib-E), within the tumour environment. This tumour-selective delivery mechanism was designed to minimize the dose-limiting toxicities of EGF*R* WT inhibition.[56] PK analysis also confirmed markedly higher levels of tarloxitinib-E in tumour tissue than plasma or skin. *In vitro*, tarloxitinib-E was demonstrably active, inhibiting cell signalling and proliferation in patient-derived cancer cell lines. *In vivo*, tarloxotinib induced tumour regression and growth inhibition in murine xenograft models. The RAIN-701 trial of tarloxotinib 150 mg/m^2 IV weekly exhibits antitumour activity with stable disease in 6/11 (55%) of patients. Most common AEs included prolonged Qtc (All grade 60.9%, ⩾grade 3 34.8%), rash (All grade 43.5%, ⩾grade 3 4.3%) and diarrhoea (All grade 21.7%, ⩾grade 3 4.3%). Treatment-related dose reductions and discontinuations occurred in 21.7% and 4.3%, respectively.[56] Tarloxitinib is also approved in China for treatment of NSCLC after two lines of chemotherapy based on the ALTER 303 trial.[90]

BDTX 189

BDTX 189 is an orally available, ATP competitive and irreversible small molecule TKI against families of allosteric *HER2* and *EGFR* mutations while sparing WT *EGFR*. In the phase I/II Masterkey-01 trial of BDTX-189 in patients with advanced solid tumours harbouring any one of more than 48 oncogenic alterations in *EGFR* or *HER2* oncogene, responses were seen in 1 out of 3 evaluable NSCLC patients. The most frequent AEs occurring in ⩾20% of patients were diarrhoea (All grade: 36%, ⩾G3: 8%), nausea (all grade: 28%, ⩾G3: 0%) and vomiting (all grade: 25%, ⩾G3: 3% G3).[91] Despite encouraging safety and efficacy of BDTX-189 as an inhibitor of oncogenic mutants of *EGFR* including *EGFR* exon 20 insertion mutations, its development has been discontinued by Black Diamond Therapeutics as part of a restructuring plan to prioritize the development of other drugs.

BAY-2476568

BAY-2476568 is a potent and selective, reversible inhibitor with 20-fold selectivity for *EGFR* insertion mutations compared to WT *EGFR* in EGFR-expressing Ba/F3 cells.[92] Activity has also been demonstrated *in vivo* in xenograft models. It also shows potent activity against the classical activating *EGFR* exon 19 deletions and exon 21 L858R substitutions and retained its potency in the presence of C797S, typically an acquired resistance mutation to osimertinib.[92]

BLU 451

BLU 451 is a brain penetrant, EGFR WT sparing, covalent small molecular inhibitor of *EGFR* exon 20 insertion mutations, atypical *EGFR* mutations (G719C, G719S and L861Q) as well as the more common sensitizing mutations. Preclinical data have demonstrated antitumour activity in an intracranial xenograft model. BLU 451 is currently undergoing evaluation in a phase I/II global open label to determine the MTD, safety, tolerability as well as to evaluate the antitumour activity in patients with or without brain metastasis.[93,94]

ORIC-114

ORIC-114 is a brain penetrant, orally bioavailable, irreversible small molecular inhibitor was designed to target exon 20 insertions in *EGFR* and *HER2*. In preclinical biochemical assays, ORIC-114 sub-nanomolar IC50 potency and greater average fold selectivity for exon 20 mutations over *EGFR* WT compared with poziotinib, CLN-081 and BDTX-189. Promising responses at 3 mg/kg were observed with 9 out of 10 complete responses observed in patient-derived xenograft model. Furthermore, ORIC-114 also demonstrated high brain penetration with good brain to plasma unbound ratio in mice and efflux transporters that limit brain penetration seem to

have minimal impact on ORIC-114.[95] In view of the promising preclinical efficacy, there is an ongoing phase I study to evaluate the safety and MTD of ORIC-114 in patients with advanced solid tumours with *EGFR* or *HER2* exon 20 alternations or *HER2* amplification and will allow enrolment of patients with asymptomatic treated or untreated CNS metastases.

Ongoing trials for *EGFR* exon 20 insertions are summarized in Table 2.

Detection of *EGFR* exon 20 insertion mutations

EGFR exon 20 insertion mutations can be detected through several methods such as polymerase chain reaction (PCR)-based or next-generation sequencing (NGS)-based technologies using tissue or liquid biopsy.[96] However, *EGFR* exon 20 insertion mutations are molecularly heterogeneous, and comprehensive identification of wide range of variants is challenging.[97] Using PCR-based methods may miss approximately 50% of cases with *EGFR* exon 20 insertion mutations and therefore the sole reliance on PCR methods to identify these subset of patients may result in underdiagnoses.[96] In contrast, NGS platforms are able to capture diverse array of *EGFR* exon 20 insertion mutations, including rare variants. As a result, the detection rate of *EGFR* exon 20 insertion mutations increased over the last decade due to the shift from PCR to NGS. The recent approval of targeted therapies for *EGFR* exon 20 insertion mutations, including amivantamab and mobercertinib, further supports the importance for NGS testing.[31] Currently, US FDA-approved companion diagnostics are Guardant360® CDx (Guardant, California, CA) and FoundationOne® Liquid CDx (Foundation Medicine, Cambridge, MA).[98] Other detection methods, such as Sanger sequencing, RNA sequencing, direct sequencing and mass spectroscopy, are alternative options that are less commonly used.[17]

Mechanisms of acquired resistance

Although preliminary, several pre-clinical studies have shown that on-target secondary mutations, bypass pathway activation and epithelial–mesenchymal transition (*EMT*) confer resistance to therapies targeting *EGFR* exon 20 insertion mutations (Figure 4).[99] Identified on-target mechanisms to poziotinib[69] and tarloxotinib[100] include *EGFR* C797S and T790M mutations. Bypass pathway activations have been identified as acquired resistance to poziotinib, including reactivation of MAPK/phosphoinositide 3-kinase (MAPK/PI3K) pathway such as *PIKCA* E545K and *MAP2K2* S94L, and amplifications in *MET*, *EGFR* and *CDK6*.[101] Furthermore, *in vitro* analysis shows that resistance to poziotinib is associated with *EMT* with increase in *AXL* expression and downregulation of E-cadherin.[69] In patients showing progression with osimertinib, *EMT* and histologic transformation to squamous cell carcinoma and small-cell carcinoma have been reported.[102,103] Currently, the mechanisms of acquired resistance to osimertinib remain unknown.

With emerging treatment options for *EGFR* exon 20 insertion mutations, including amivantamab and mobocertinib, and data on new targeted agents awaiting results, the potential resistance mechanisms of these agents remain to be elucidated.[14] More than 100 *EGFR* exon 20 insertion mutations subtypes have been identified with similar therapeutic sensitivity and depth of response to new targeted agents.[104] Whether these specific variants show unique resistance to the new targeted agents remains unknown.[14] Moving forward, identifying and characterizing the potential mechanisms of resistance will inform on future drug development and may pave way to overcome acquired resistance.

Upcoming therapies and future directions

The proportion of patients with *EGFR* exon 20 insertion mutations represents a substantial group.[13] Despite recent progress with multiple agents in clinical development and showing signs of activity for patients with *EGFR* exon 20 insertion mutations, further work is required to improve the care of patients with *EGFR* Exon 20 insertion mutations to determine the optimal sequencing of treatment, safety profile and treatment of patient with brain metastasis.

While both amivantamab and mobocertinib are FDA approved for the treatment of patients with *EGFR* exon 20 insertion mutations, these drugs are approved in the post-platinum setting. Platinum-based doublet remains the standard first-line regimen and trials are underway to move targeted therapy in *EGFR* exon 20 insertion mutations to the front-line setting. The randomized PAPILLON study, for example, is comparing amivantamab plus chemotherapy *versus*

Table 2. Ongoing trials for patients with *EGFR* exon 20 insertion mutations.

Trial number	Trial name	Phase	Recruitment status
NCT04129502	TAK-788 as first-line treatment versus platinum-based chemotherapy for non-small cell lung cancer (NSCLC) with *EGFR* exon 20 insertion mutations	III	Recruiting
NCT05132777	Efficacy and safety of JMT101 combined with osimertinib in patients with non-small cell lung cancer	II	Recruiting
NCT04036682	A phase 1/2a trial of CLN-081 in patients with non-small cell lung cancer	I/IIa	Recruiting
NCT04553887	Almonertinib as upfront treatment for uncommon *EGFR* mutation harboring non-small-cell lung cancer patients: a multicenter, open-label, phase II trial (AUTUMN)	II	Not yet recruiting
NCT03727724	Afatinib and cetuximab in epidermal growth factor receptor (EGFR) exon 20 insertion positive non-small-cell lung cancer (AFACET)	II	Recruiting
NCT05435274	Phase 1/2 study of HS-10376 in patients with non-small cell lung cancer	I/II	Recruiting
NCT05364073	Study of furmonertinib in patients with advanced or metastatic non-small cell lung cancer with activating *EGFR* or *HER2* mutations, including exon 20 insertion mutations	I	Recruiting
NCT05466149	Efficacy and safety of furmonertinib in patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion	II	Not yet recruiting
NCT04858958	Study of FURMONERTINIB in patients with NSCLC having exon 20 insertion mutation	Ib	Recruiting
NCT04974879	Osimertinib combined with bevacizumab in the treatment epidermal growth factor receptor (*EGFR*) exon 20 insertions metastatic non-small cell lung cancer	II	Recruiting
NCT03974022	Assessing an oral EGFR inhibitor, DZD9008 in patients who have advanced non-small cell lung cancer with *EGFR* or *HER2* mutation (WU-KONG1)	I/II	Recruiting
NCT04538664	A study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in participants with advanced or metastatic non-small cell lung cancer characterized by epidermal growth factor receptor (*EGFR*) exon 20 insertions	III	Recruiting
NCT02609776	Study of amivantamab, a human bispecific EGFR and cMet antibody, in participants with advanced non-small cell lung cancer	I	Recruiting
NCT03318939	Phase 2 study of poziotinib in patients with NSCLC having *EGFR* or *HER2* exon 20 insertion mutation	II	Recruiting
NCT04402008	Study of poziotinib in Japanese patients with NSCLC	I	Recruiting
NCT04382300	Pyrotinib plus thalidomide in advanced NSCLC patients harboring *HER2* exon 20 insertions	II	Recruiting
NCT05241873	Study of BLU-451 in advanced cancers with *EGFR* exon 20 insertion mutations	I/II	Recruiting
NCT05315700	Study of ORIC-114 in patients with advanced solid tumors harboring an *EGFR* or *HER2* alteration	1/1b	Recruiting
NCT05099172	First in human study of BAY2927088 in participants who have advanced non-small cell lung cancer (NSCLC) with mutations in the genes of epidermal growth factor receptor (*EGFR*) and/or human epidermal growth factor receptor 2 (*HER2*)	I	Recruiting
2019-001845-42	A randomized phase 3 multicenter open-label study to compare the efficacy of TAK-788 as first-line treatment versus platinum-based chemotherapy in patients with non-small cell lung cancer with *EGFR* exon 20 insertion mutations	III	Recruiting
2021-000203-20	Phase 1/2 dose escalation and expansion study evaluating MCLA-129, a human anti-EGFR and anti-c-MET bispecific antibody, in patients with advanced NSCLC and other solid tumors	I/II	Recruiting

EGFR, epidermal growth factor receptor.

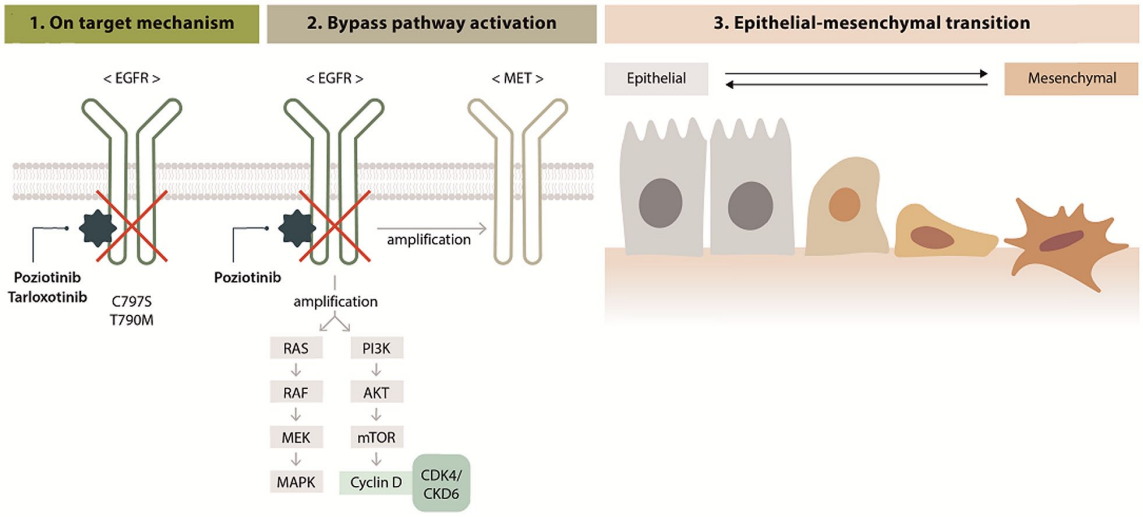

Figure 4. Potential mechanism of resistance to therapeutic agents in EGFR exon 20 insertion. Various resistance mechanisms include (1) on target mechanism such as C797S and T790M after poziotinib and tarloxitinib treatment, (2) bypass pathway activation such as MAPK/PI3K activation and MET amplification and (3) EMT after treatment with poziotinib.
EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition.

chemotherapy alone.[105] The optimal sequencing of currently available approved agents mobocertinib and amivantamab also deserves further investigation.

Given the high propensity for brain metastasis in lung cancer,[106] further research is needed to investigate the effects of drugs against untreated brain lesions. CHRYSALIS[45]and STUDY101[58] only included patients with treated asymptomatic brain metastasis. In the CHRYSALIS study, 38 out of 114 (33%) of patients had baseline brain metastasis. Intracranial only disease progression occurred in 11% of patients, and 12 out of 38 (32%) with baseline brain metastasis *versus* 5 out of 76 (6.6%) without baseline brain metastasis had intracranial progression.[107] In STUDY101, 25% of patients had intracranial disease progression.[108] WUKONG also allowed enrolment of patients with stable and asymptomatic brain metastasis. In all, 23 out of 56 (41%) had baseline brain metastasis and although intracranial lesions were not assessed as target lesions, encouraging antitumour activity was seen with a RR of 30%.[51,52]

To treat metastatic brain disease effectively, blood–brain barrier (BBB) permeability is essential. However, the EGFR-TKIs are also substrates for human BBB efflux transporters to varying degrees, with the P-glycoprotein and breast cancer resistance protein[109] playing a crucial role and this influences the distribution of the compound at equilibrium.[110,111] Osimertinib, for instance, is a weak efflux transporter substrate (efflux ratio 3.2) and has the most BBB penetrance with a brain to free plasma ratio (Kp) value of 0.21 compared with other first-, second-generation TKIs as well as poziotinib which have a Kp value $\leqslant$0.12.[112] BLU 451 and ORIC-114 are brain penetrant small molecular inhibitors with promising preclinical intracranial penetrance with ongoing clinical trials to evaluate its clinical efficacy in patient with brain metastasis.[93–95] ORIC 114 has a low efflux ratio of 0.7, and this predicts for brain penetrance. ORIC 114 also exhibits high exposure in the brain at 1 and 4 h after administration in mice models, compared to poziotinib and BDTX-189, where brain exposure levels are below quantification limits.[95] In preclinical brain metastasis xenograft model carrying the T790M mutation, sunvozertinib-induced tumour regression was also observed at 25 mg/kg BID and 50 mg/kg BID.[51] These drugs have demonstrated promising preclinical activity and are candidates for development in patients with brain metastasis. An *in vitro* transporter assays as an early screen may also identify drugs with better CNS activity.

Conclusion

Patients with NSCLC with *EGFR* exon 20 insertion mutations have *de novo* resistance to EGFR TKIs due to steric hindrance affecting binding of

TKIs used in common sensitizing *EGFR* mutations. The development of several novel small molecule compounds that selectively inhibit *EGFR* exon 20 insertion as well as the approval of amivantamab and mobocertinib for patients who have progressed after prior chemotherapy holds promise for effective therapeutic options for these group of patients. Several challenges lie ahead. The frequency of *EGFR* exon 20 insertion mutations may be underestimated due to insufficient testing methods and the diverse mutational landscape. There is also substantial unmet need for first-line treatment strategies. Finally, resistance mechanisms and strategies to overcome them as well as management of patients with CNS metastasis require further research. Nevertheless, new drugs in development beyond mobocertinib and amivantamab provides exciting prospect that novel treatments will provide a wider range of effective treatment options for patients with *EGFR* exon 20 insertion mutations.

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