Review Article

EGFR exon 20 insertion mutations and *ERBB2* mutations in lung cancer: a narrative review on approved targeted therapies from oral kinase inhibitors to antibody-drug conjugates

Daniel Sentana-Lledo[1#^], Emmeline Academia[1#^], Hollis Viray[1#^], Deepa Rangachari[1^], Susumu S. Kobayashi[1^], Paul A. VanderLaan[2^], Daniel B. Costa[1^]

[1]Division of Medical Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [2]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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[#]These authors contributed equally to this work.

Correspondence to: Daniel B. Costa, MD, PhD. Division of Medical Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Av., Boston, MA 02215, USA. Email: dbcosta@bidmc.harvard.edu.

Background and Objective: This review will provide an overview of *EGFR* and *ERBB2* mutations in non-small-cell lung cancer (NSCLC) with a focus on recent clinical approvals.

Methods: We obtained data from the literature in accordance with narrative review reporting guidelines.

Key Content and Findings: *EGFR* mutations are present in up to 15–20% of all NSCLCs; amongst these, 10% correspond to kinase domain insertions in exon 20. Structurally similar, *ERBB2* (*HER2*) mutations occurs in 1–4% of NSCLCs, mostly consisting of insertions or point mutations. The majority of *EGFR* exon 20 insertions occur within the loop following the regulatory C-helix and activate the kinase domain of EGFR without generating a therapeutic window to gefitinib, erlotinib, afatinib, dacomitinib or osimertinib. Mobocertinib represents a novel class of covalent EGFR inhibitors with a modest therapeutic window to these mutants and induces anti-tumor responses in a portion of patients [at 160 mg/day: response rate of <30% with duration of response (DoR) >17 months and progression-free survival (PFS) of >7 months] albeit with mucocutaneous and gastrointestinal toxicities. The bi-specific EGFR-MET antibody amivantamab-vmjw has modest but broad preclinical activity in EGFR-driven cancers and specifically for *EGFR* exon 20 insertion-mutated NSCLC has response rates <40% and PFS of <8.5 months at the cost of both infusion-related plus on-target toxicities. Both drugs were approved in 2021. The clinical development of kinase inhibitors for *ERBB2*-mutated NSCLC has been thwarted by mucocutaneous/gastrointestinal toxicities that preclude a pathway for drug approval, as the case of poziotinib. However, the activation of ERBB2 has allowed for repurposing of antibody-drug conjugates (ADCs) that target ERBB2 with cytotoxic payloads. The FDA approved fam-trastuzumab deruxtecan-nxki in 2022 for NSCLC based on response rate of >55%, DoR >9 months, PFS >8 months and manageable adverse events (including cytopenias, nausea and less commonly pneumonitis). Other therapies in clinical development include sunvozertinib and zipalertinib, among others. In addition, traditional cytotoxic chemotherapy has some activity in these tumors.

Conclusions: The approvals of mobocertinib, amivantamab, and trastuzumab deruxtecan represent the first examples of precision oncology for *EGFR* exon 20 insertion-mutated and *ERBB2*-mutated NSCLCs.

Keywords: *EGFR*; *ERBB2*; mobocertinib; amivantamab; trastuzumab deruxtecan

^ ORCID: Daniel Sentana-Lledo, 0000-0002-7318-0888; Emmeline Academia, 0000-0001-7514-1754; Hollis Viray, 0000-0002-5668-0346; Deepa Rangachari, 0000-0001-9710-6757; Susumu S. Kobayashi, 0000-0003-2262-4001; Paul A. VanderLaan, 0000-0002-7234-5652; Daniel B. Costa, 0000-0002-0689-395X.

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Introduction

The last 20 years have seen the explosion of technological advances that have allowed for translation of biomedical knowledge into routine clinical practice within the field of medical oncology. The culmination of these factors within the field of thoracic oncology has heralded the era of precision oncology for lung cancer care (1-6). Thoracic tumors are a heterogeneous group of malignancies—and even among lung cancers specifically, there are multiple histological variants that represent the epithelial, mesenchymal, and other cells of origin of the neoplastic process (*Figure 1*). Non-small-cell lung cancers (NSCLCs) are the most prevalent of these, comprising of mostly lung adenocarcinoma and squamous cell carcinoma (*Figure 1A*). Both larger entities can then be further subdivided into clinically relevant subgroups based on tumor biomarkers (7-12). Of these, identification of actionable oncogenic driver alterations (mutations or gene rearrangements) and tumor programmed death ligand 1 (PD-L1) cell surface expression are critical for optimal treatment selection and outcomes in these cancers (13-16). Lung adenocarcinomas are far more robustly enriched with these mostly non-overlapping actionable driver oncogene aberrations that have common intracellular properties leading to constitutive activation of proliferative signaling cascades and induce the anti-apoptotic cellular machinery (32-35). The majority of clinically-relevant *de novo* driver oncogenes are truncal evolutionary events that are retained by NSCLCs (36,37). Presently, the list of driver oncogenic alterations tied to precision therapies approved by international regulatory bodies include: *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *KRAS*, *ERBB2*, and *NTRK* (*Figure 1A*)—with many others rapidly emerging (13,38-40).

Activating events of ErbB family members are common across all cancer types and represent some of the most frequent driver oncogenes in NSCLC (24-26,41-43). ErbB-1 (also known as epidermal growth factor receptor, *EGFR*) and ErbB-2 (also known as *Her2*) are two of the most successful examples of actionable driver oncogenes. Mutations of the *EGFR* gene are present in more than 15–20% of all NSCLC, particularly in lung adenocarcinomas occurring in younger patients, those of Asian descent, and in the presence of limited/no tobacco exposure as compared to NSCLCs occurring in other patient cohorts (10,17,44-47). Mutations of the *ERBB2* gene are present in less than 5% of all NSCLCs and with similar enrichment amongst the populations previously noted (26-31). In both *EGFR*- and *ERBB2*-affected NSCLCs, the hotbed of oncogenic driver alterations is within the exon 20 kinase domain. Moreover, these are almost exclusively somatic events—very few cases of *EGFR*- or *ERBB2*-mutated NSCLC are associated with germline genetic susceptibility (48).

This review will provide an overview of *EGFR* and *ERBB2* mutations in NSCLC, with a focus on recent clinical approvals of kinase inhibitors and antibodies that have added to the armamentarium of precision oncology within this cohort of cancers with previously unmet need. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-98/rc).

Methods

Information used to write this review article was collected from a PubMed.gov search from years 2000 to 2023 using key words EGFR, ERBB2, and exon 20 insertion; hand searches of the references of retrieved literature; personal searches for texts on literature reviews of lung cancers with different ErbB mutations; discussions with co-authors and experts in the field; and personal experience of the senior authors participating in and writing expert reviews of the literature on similar topics. Both preclinical and clinical studies were evaluated. *Table 1* summarizes the search strategy for this narrative review.

Preclinical models of EGFR and ERBB2-directed therapies in NSCLC

The biomedical community has performed extensive characterization of ErbB mutant proteins, with the majority of focus on EGFR and ERBB2 wild-type (WT) proteins and kinase domain mutations (*Figure 2*). Many of these preclinical models of isolated proteins or rudimentary cell lines have been quite informative of patterns of response and resistance to EGFR/ERBB2 tyrosine kinase inhibitors (TKIs) with close relationship to clinically-observed activity

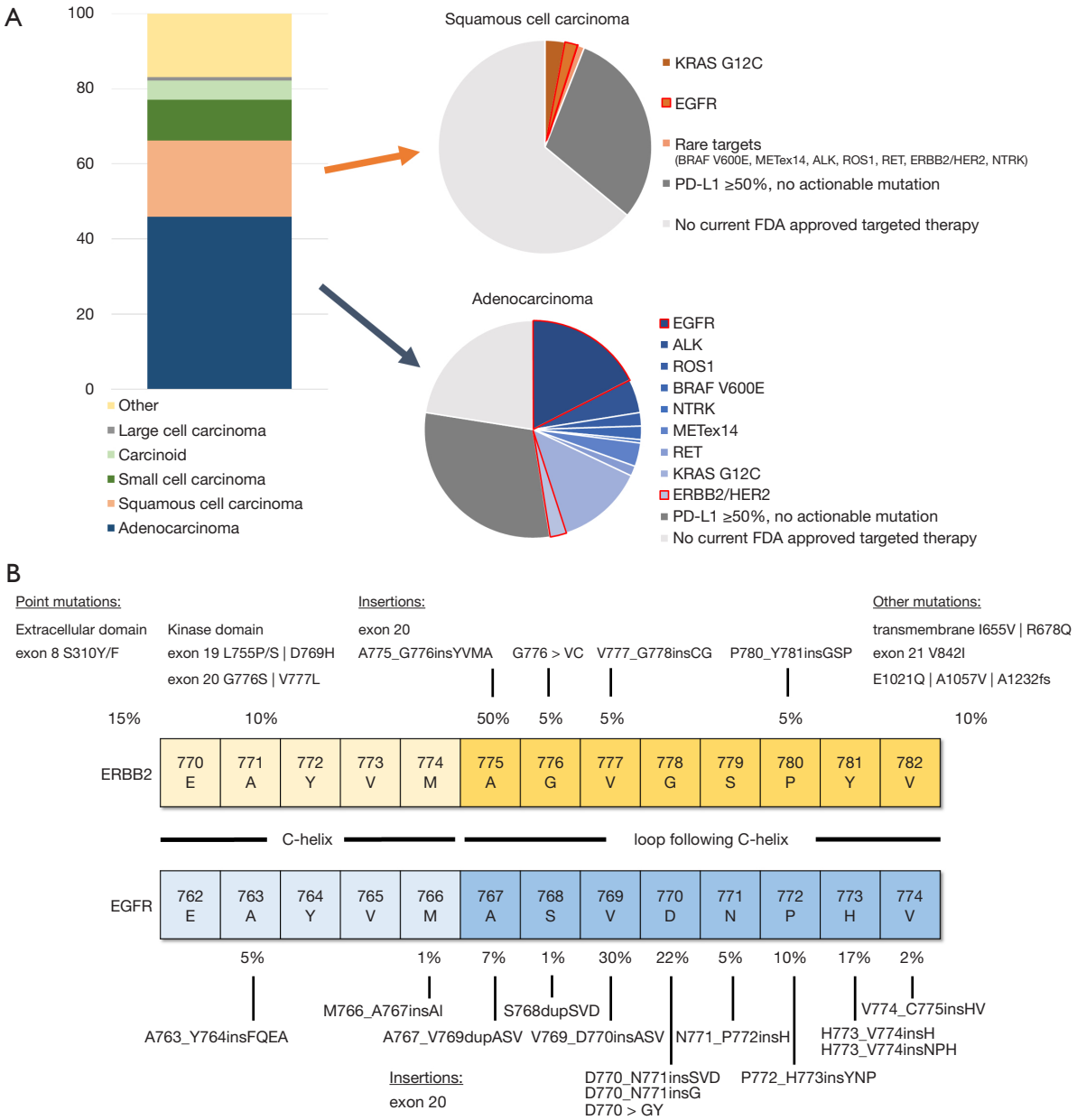


Figure 1 Frequency of driver oncogenes in lung cancer with a focus on *EGFR* and *ERBB2* mutations. (A) Bar of frequency percentages of the major subtypes of lung cancer with pie charts of the prevalence of the most common driver oncogene mutations and PD-L1 immunohistochemistry tumor proportion score expression ≥50% in both squamous cell carcinoma and adenocarcinoma histologies [data adapted from (7-16): for adenocarcinoma the prevalence of *EGFR* mutations is approximately 15–40%, *ALK* rearrangements 3–5%, *MET* exon 14 skipping mutations 2–4%, *BRAF*-V600E mutation 1–2%, *ERBB2/HER2* mutations 1–2%, *ROS1* rearrangements 1%, *RET* rearrangements 1%, *NTRK* rearrangements 0.1%, and *KRAS*-G12C mutation 15–35%; for squamous cell carcinoma the prevalence of *KRAS-G12C* is approximately 2–10%, *EGFR* mutations 1–5%, and the rare targets of *BRAF*-V600E mutations, *MET* exon 14 skipping mutations, *ALK* rearrangements, *ROS1* rearrangements, *RET* rearrangements, *ERBB2/HER2* mutations, and *NTRK* rearrangements: all less than 0.5%]. (B) Highlights of the amino-acid sequence of EGFR and ERBB2 within the exon 20 kinase domain sequence. The frequency of *EGFR* exon 20 insertion mutations by amino-acid position with representative examples are displayed. For *ERBB2* mutations, the frequency of mutations within the kinase, transmembrane and extracellular domains indicated with representative examples displayed. The frequency of *EGFR* mutations was obtained from (17-23). The frequency of *ERBB2* mutations was obtained from (18,24-31).

Table 1 The search strategy summary

Items	Specification
Date of search	11/01/2022 to 02/01/2023
Databases and other sources searched	PubMed.gov, ASCO annual meeting abstracts, AACR annual meeting abstracts, ESMO annual meeting abstracts, IASLC annual meeting abstracts
Search terms used	EGFR, ERBB2, and exon 20 insertion
Timeframe	06/04/2004 to 01/31/2023
Inclusion and exclusion criteria	No exclusion was made to maximize source identification. Manual searches of the references of retrieved literature, personal searches for texts on literature reviews, discussions with co-authors and experts in the field, personal experience of the senior authors (DC, PV, SK) participating in and writing expert reviews of the literature on similar topics were used to maximize inclusion
Selection process	Four authors (DS, EA, HV, DBC) conducted the initial selection and then consensus was obtained from all authors on literature, meeting abstracts and online references to be used

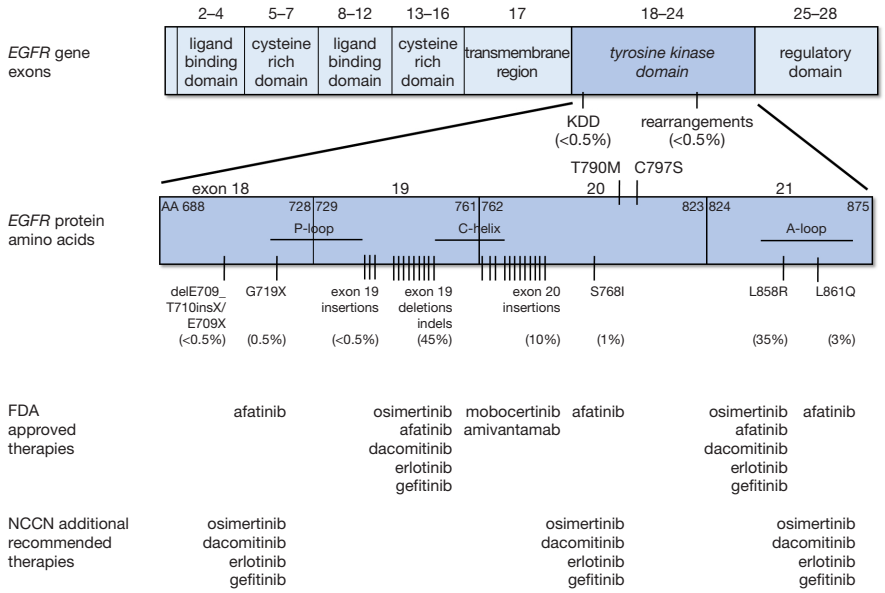
of the same compounds.

There is significant heterogeneity in the prevalence of EGFR kinase domain aberrations noted, with most mutations occurring within exons 18 to 21 of the kinase domain of the *EGFR* gene (10,17,44-47) (*Figure 2A*). The most common mutations center on in-frame deletions or indels of exon 19 (*EGFR*-delE746_A750 the typical example of LREA-type amino-acid deletions) and the exon 21 L858R mutation (*Figure 2A*). These common canonical mutants lead to structural changes that change ATP kinetics, enhance EGFR activation (promoting an "on" instead of "off" switch), and generate a favorable therapeutic window to almost all EGFR TKIs that have completed clinical development, including: 1st generation reversible inhibitors (gefitinib, erlotinib), 2nd generation irreversible inhibitors (afatinib, dacomitinib), 3rd generation mutation-selective covalent inhibitors (osimertinib), and *EGFR* exon 20 insertion active inhibitors (poziotinib, dacomitinib) (33,63-69). This mutation-to-drug response phenotype translates well to the clinical realm, where tumors driven by common *EGFR* mutations are highly responsive to EGFR TKIs and experience clinical outcomes that far exceed what is typically seen with cytotoxic chemotherapy or immunotherapy (70-77). Hence, these EGFR TKIs have gained regulatory approval for use as frontline treatment options for those with advanced stage disease and are now entering the adjuvant arena (osimertinib) for those with earlier stage disease (78).

However, not all driver alterations in *EGFR* have proven to be equally actionable, and those with canonical exon 19 deletions or L858R point mutations have experienced the greatest progress with application of available targeted therapies to date. Head-to-head clinical trials have been able to show that for patients with tumors harboring *EGFR*-exon 19 deletions/indels or L858R, the 3rd generation EGFR TKI osimertinib outperforms others with higher and more durable response rates both systemically and in the central nervous system (CNS) along with lower rates of mucocutaneous/gastrointestinal toxicities and better overall tolerability (79). Osimertinib is therefore the preferred option for palliative first line therapy in cases with advanced disease and following surgery and chemotherapy in the adjuvant setting (78,79).

Other less common *EGFR* mutations (*Figure 2A*) display similar structural, drug inhibition, and clinical translational characteristics—but with far greater heterogeneity in their overall efficacy (*Figure 2B*). Some investigators have proposed using a structure-function subgrouping to better classify *in vitro* sensitivity of these different structurally-defined categories of *EGFR* mutants: (I) classical-like (exon 19 deletions/indels, L858R, L861Q) with broad sensitivity to multiple generations of EGFR-directed TKIs; (II) P-loop αC-helix compressing (*PACC*) (G719X, S768I) with highest sensitivity to 2nd generation irreversible EGFR TKIs (*Figure 2B*); (III) T790M-like hydrophobic core mutants (such as compound *EGFR*-T790M), and (IV) exon 20 loop insertions (80). Case series and non-randomized trials (49,81,82) have confirmed activity of afatinib and led to the approval of this drug for tumors with *EGFR*-G719X, -S768I or -L861Q mutations (*Figure 2*). Single arm studies have also confirmed the activity of osimertinib (83,84); use of this agent for these

A



B

	preclinical sensitivity + selectivity pattern against *EGFR*-WT of EGFR inhibitors			
EGFR mutant subtype	1st gen EGFR TKI (gefitinib, erlotinib)	2nd gen EGFR TKI (dacomitinib, afatinib)	3rd gen EGFR TKI (osimertinib)	exon 20 insertion active EGFR TKI (mobocertinib)
Most common mutations				
exon 19 deletions/exon 19 indels	+++	+++	+++	++
exon 21 L858R	+++	+++	+++	++
Less common mutations				
exon 18 G719X	+	++	+	+
exon 21 L861Q	++	++	++	+
exon 20 S768I	+	+	+	+
exon 19 insertions/ K745_E746insIPVAIK	++	++	++	+
Exon 20 insertion mutations				
exon 20 insertions most prevalent (A767_V769dupASV, D770_N771insSVD, H773_V774insH)	– – –	– – –	–	+
exon 20 D770 > GY	– – –	++	–	+
exon 20 A763_Y764insFQEA	++	++	++	+
Resistance mutations				
exon 19 indel or L858R + T790M	– – –	– – –	+++	– –
exon 19 indel or L858R + C797S	+++	– –	– – –	– – –
exon 19 indel or L858R + T790M + C797S	– – –	– – –	– – –	– – –

Figure 2 Subtypes of *EGFR* mutations with a focus on preclinical patterns of response/resistance to EGFR TKIs. (A) Representation of the EGFR protein by key gene numbers, overlaid with clinically-relevant types of mutations mostly centered within the kinase domain. The prevalence of these mutation subtypes are indicated by exon location. The frequency of *EGFR* mutations was obtained from (17-22,49-56). (B) Summary of preclinical models driven by selected *EGFR* mutations paired with the *in vitro* sensitivity and also *in vitro* selectivity pattern against *EGFR* WT of the diversity of approved EGFR TKIs. Data was extrapolated from (23,50,57-62) and unpublished data from the authors' translational thoracic oncology laboratory. The degree of sensitivity and resistance is indicated by number of + (sensitive/selective) or – (resistant/non-selective) signs as extrapolated from preclinical studies. Please, refer to aforementioned references for each individual half maximal inhibitory concentration (IC_{50}) for preclinical proliferation assays. EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2 (also known as HER2, human epidermal growth factor receptor-2); WT, wild-type; TKIs, tyrosine kinase inhibitors.

less common mutations is thus also endorsed by expert consensus groups due to its more favorable toxicity profile the National Comprehensive Cancer Network (NCCN) (39) (*Figure 2*). Other less common but also variably EGFR TKI-responsive mutations in preclinical models and patients with NSCLC include: *EGFR* exon 19 insertions (17,50), *EGFR* exon 18 indel delE709_T710insX or E709X (51-53), *EGFR* kinase domain duplications (54) and *EGFR* fusion genes (55) (*Figure 2*).

EGFR exon 20 insertion mutations as a group account for close to 10% of all *EGFR* mutations (*Figure 2A*) and the most heterogeneous cohort with multiple types on insertions/indels occurring along the span of the exon (*Figure 1B*) along with highly variable patterns of response to EGFR-directed therapies (18-22,56) (*Figure 2B*). The most prevalent mutants cluster around insertions spanning amino-acids EGFR-A767, -V769, -D770, -P772 and -N773 (*Figure 1B*), which localize to the loop following the C-helix of the kinase domain. The crystal structure of one of these *EGFR* exon 20 insertion mutations reveals an unaltered ATP binding pocket in relation to *EGFR* WT; the inserted amino acid residues form a wedge at the end of the C-helix that promotes the active kinase conformation and related kinetic changes (19). Quite unlike the mechanism of activation seen with other types of *EGFR*-affecting alterations, this conformal change renders an unfavorable therapeutic window for 1st, 2nd, and most 3rd generation EGFR TKIs (19,20,56,85). Preclinical models have confirmed primary insensitivity of these exon 20 mutants to these prior EGFR TKIs (*Figure 2B*).

Multiple academic and pharmaceutical groups have used the growing structural and biochemical knowledge of these mutants to screen for or design EGFR TKIs that could exploit the non-ATP binding pocket structural changes and yield modest therapeutic windows in relation to *EGFR* WT (23,57-59,86). Most of the small molecules that fit this profile are covalent EGFR inhibitors and include poziotinib, mobocertinib, sunvozertinib, and zipalertinib among others. Preclinical models of the most frequent *EGFR* exon 20 insertion mutants consistently show only modest sensitivity and selectivity of mobocertinib and similar drugs (*Figure 2B*). The clinical development of such agents is outlined further below.

However, not all *EGFR* exon 20 insertion mutations are insensitive to previously existing EGFR TKIs. Notably, the EGFR-A763_Y764insFQEA mutation (and the identical EGFR-D761_E762insEAFQ)—accounting for 5% of exon 20 insertion mutations—stands at the transition between exons 19 and 20 and alters the register of the C-helix toward its N-terminus resulting in structural and kinetic alterations that resemble those seen with other EGFR TKI-sensitizing mutations (such as exon 21 L858R and exon 21 L861Q). This leads to favorable preclinical therapeutic windows for all approved classes of EGFR TKIs (19,60) (*Figure 2B*). When translated into the clinic, patients whose tumors harbor this mutation have had prolonged responses to aforementioned EGFR TKIs. It is thus reasonable to offer off-label gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib in these cases.

Other rare *EGFR* exon 20 mutations with unique patterns of responsiveness to available therapies include the *EGFR*-D770 to -G770 alteration that permits response to the irreversible 2nd generation EGFR-TKIs afatinib and dacomitinib (61,62) (*Figure 2B*). These variants also have modest sensitivity to mobocertinib (*Figure 2B*) and other similar EGFR TKIs and have been included in completed and ongoing clinical studies investigating novel agents for exon 20 insertion mutations.

In contrast, previously existing EGFR-directed monoclonal antibodies like cetuximab have almost no preclinical or clinical activity as monotherapy for *EGFR*-mutated NSCLCs (87,88). Novel classes of bivalent EGFR antibodies have had better success in both preclinical and clinical realms. Amivantamab (formerly called JNJ-61186372) is a bispecific antibody targeting extracellular domain of EGFR-MET that shows preclinical activity in TKI-sensitive and TKI-resistant *EGFR*-mutated NSCLC models. Its activity may be dictated by direct signal inhibition of EGFR plus MET and/or induction of immune-directed antitumor activity (89-92). Antibody-drug conjugates (ADCs) that target other ErB family members that heterodimerize with EGFR also have activity against TKI-sensitive and TKI-resistant *EGFR*-mutated NSCLC models, and the ErbB3-directed ADC patritumab deruxtecan (HER3-Dxd) is one of the lead drugs undergoing clinical development (93).

ERBB2 (*Her2*) mutations are also heterogeneous (*Figure 1B*) and span aberrations including point mutations and exon 20 insertions closely resembling those previously discussed for *EGFR*. Unlike in other malignancies, *ERBB2* mutation—rather than gene amplification or overexpression—appears most predictive of clinical benefit with leverage of *ERBB2*-directed therapies in NSCLC. The most prevalent *ERBB2* exon 20 insertion mutation in lung cancers is *ERBB2*-A775_G776insYVMA (28,94-100). Preclinical characterization has disclosed that this mutant

does not lead to favorable therapeutic windows in relation to EGFR or ERBB2 WT proteins, and clinically-available pan-EGFR/ERBB2 TKIs (such as afatinib, dacomitinib, neratinib) have been tested and have not proven to be effective (101-104). Some pan-EGFR/ERBB2 TKIs narrow therapeutic windows in preclinical models include pyrotinib, poziotinib, and mobocertinib (105,106). However, other *ERBB2* exon 20 insertion mutations are less recalcitrant in preclinical models. The ERBB2-P780_Y781insGSP (*Figure 1B*) and other rare *ERBB2* insertions that lead to glycine insertions at positions similar to EGFR-D770>GY are most sensitive to irreversible EGFR/ERBB2 TKIs such as afatinib, dacomitinib and poziotinib (62,107,108). Some patients with these less common *ERBB2* exon 20 insertion mutations have had more robust clinical responses to afatinib or dacomitinib (62) and have been amongst those with greatest benefit from poziotinib in clinical studies (109,110). ERBB2 TKIs are minimally active in models with *ERBB2* point mutations (27). Novel pan-ERBB TKIs with improved efficacy against *ERBB2* exon 20 insertion mutations and CNS penetration, such as TAS2940, continue to undergo preclinical development (111).

Irrespective of location/type of mutation within *ERBB2* (*Figure 1B*), activating mutants lead to enhanced expression of ERBB2 protein that can be exploited to target the extracellular domain of this receptor tyrosine kinase with antibodies and ADCs. Preclinical analyses of both *ERBB2*-mutated and *ERBB2*-amplified cancers demonstrate that ERBB2 ubiquitination and internalization are the main events underlying receptor endocytosis and the efficacy of the anti-ERBB2 ADCs ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) in lung cancer models (112,113).

Mechanisms of resistance to EGFR/ERBB2 TKIs and other oncogene-directed therapies fall into four main categories: (I) on-target resistance mutations [e.g., *EGFR*-T790M and *EGFR*-C797S (*Figure 2B*)]; (II) off-target activation of co-occurring bypass pathways usually through genomic events (alternative oncogene mutation, amplification or rearrangement); (III) epigenetically-mediated histological transformation (usually from adenocarcinoma to high grade neuroendocrine tumors that no longer express/depend on the truncal oncogene); (IV) or as yet unidentified mechanisms that may include changes other than in the genomic landscape alone and that alter the tumor microenvironment and/or pharmacokinetic/pharmacodynamic effects of the drug (47,114-122). In the case of *EGFR*-mutated NSCLC, these events are present in different frequencies depending on the line of therapy and class of EGFR TKI used. On-target resistance seems to be more frequent when 1st or 2nd generation EGFR TKIs are used in preclinical models and clinical care. *EGFR*-T790M is the single most common mechanism of resistance with early generation EGFR TKIs, while far more heterogeneous mechanisms of acquired resistance (including *EGFR*-C797S and others) are more commonly seen with mutation-selective advanced generation covalent TKIs like osimertinib. With the latter, the *EGFR*-C797S mutation and other definable mechanisms of on-target resistance are identified in less than 15% of rebiopsy series (123). Osimertinib resistance is instead defined by a spectrum of off-target aberrations in parallel signaling pathways involving *MET*, *BRAF*, *ALK*, and *RET* (123,124).

The mechanisms of acquired resistance to novel exon 20-directed therapies are still being elucidated in evolving post-approval analyses and routine clinical practice. It is likely that both on-target and off-target aberrations similar to those seen with other *EGFR*-mutated NSCLCs will be identified with time. Our group and others have described in preclinical models that *EGFR*-C797S is a pan-resistance mutation when occurring in compound with typical *EGFR* exon 20 insertions in cell lines treated with mobocertinib, poziotinib, and zipalertinib (58,125). *EGFR*-T790M in compound with exon 20 insertions appears to render resistance to mobocertinib and poziotinib (58,109,126). Less is known about mechanisms of resistance to antibodies and ADCs where resistance may not be solely from biological effects on the target, but may reflect more complex pharmacokinetic and immune changes in the tumor or host.

From bench to bedside: use of *EGFR* and *ERBB2* exon 20-directed therapies in the clinic

Building upon evolving preclinical knowledge amassed by our group and others over the past decade, clinical approvals of several *EGFR* and *ERBB2* exon 20-directed therapies in NSLC have been forthcoming in recent years: mobocertinib [2021], amivantamab [2021], and trastuzumab deruxtecan [2022]. Each will be discussed below.

Mobocertinib

Mobocertinib (formerly named TAK-788 or AP-32788) is a novel EGFR TKI that forms a covalent bond to EGFR (at *EGFR*-C797) and ERBB2 (at *ERBB2*-C805). As most exon 20 insertion mutations result in preservation of the

typical ATP binding pocket relied upon for activity of 1st, 2nd, and 3rd generation EGFR TKIs, its development hinged on identifying structural changes that would create conformational selectivity for the mutated receptor so as to afford efficacy with manageable toxicity (57). To block oncogenic kinase activation, mobocertinib forms a covalent bond with *EGFR*-C797 and interacts with the gatekeeper residue through its isopropyl ester moiety which further selects for activity against *EGFR* exon 20 mutants (57). The drug is a derivate of osimertinib that was modified to achieve its properties in structural modeling and systems (127,128). As previously discussed, mobocertinib has demonstrated *in vitro* activity against models with *EGFR* or *ERBB2* exon 20 insertion-mutated NSCLC (57,58,105).

Mobocertinib was first clinically studied in a phase I/II multicenter clinical trial NCT02716116 (129). Eligible patients had previously treated metastatic disease with exon 20 insertion mutations in either *EGFR* or *ERBB2*. The suitable (and maximum tolerated) dose was found to be 160 mg daily in the dose escalation phase (130). Across all patients, there were 96% treatment-related adverse events (TRAEs), 40% of which were grade ≥3. The most common TRAEs were: diarrhea (83%, 21% ≥ grade 3), nausea (43%), and rash (33%); 54% of patients required dose interruption, 17% dose reduction, and 16% discontinued the medication (130). In terms of pharmacokinetics, maximum plasma concentration was achieved at 4 hours, with half-life in the range of 11–17 hours. At the target dose of 160 mg (n=28) in patients with *EGFR*-mutated NSCLC, the investigator assessed objective response rate (ORR) was 43% (95% CI: 24–63%), median duration of response (DoR) 13.9 months [5.0–not reached (NR)], and median progression-free survival (PFS) 7.3 months (4.4–15.6 months). Response was independent of the specific *EGFR* exon 20 mutant variant in this small cohort (130). However, a lower response rate in patients with baseline brain metastasis (intracranial ORR 25%, with a range of 5–57%), suggests limited CNS activity in this small (n=12) subset of patients (130).

Building upon these findings, the trial was expanded (131): newly recruited patients joined the EXCLAIM extension cohort (n=96); of those, patients who had previously received platinum-based chemotherapy (n=86) joined the initial group of patients involved in the dose escalation phase (n=28) to form the platinum-pretreated patients (PPPs) cohort (n=114). Importantly, recruitment for the expansion portion of the trial was international, and over half of the patients were recruited from Asian centers. In the PPP cohort, the independently reviewed ORR was 28% (95% CI: 20–37%), median DoR 17.5 months (7.4–20.3 months), median PFS remained 7.3 months (5.5–9.2 months), and median overall survival (OS) was 24.0 months (14.6–28.8 months). In turn, the EXCLAIM cohort had similar ORR at 25% (17–35%), median DoR was NR (5.6–NR), median PFS was also 7.3 months (5.5–9.1 months), and median OS was NR (13.1–NR). No subgroups were noted to derive specific benefit in either cohort, including when stratified by type of *EGFR* exon 20 insertion mutation, prior therapy, or baseline brain metastases (131). Most sites of progression were in the brain (22/58), again hinting at reduced CNS efficacy. There were no new safety signals observed, with a predominance of diarrhea (91%, 21% ≥ grade 3) and similar rates of dose reduction (25%) and discontinuation (17%) as seen in the initial phase of the trial (131).

Patient-reported outcomes (PROs) were also captured using the EORTC QLQ-C30 [general quality of life (QoL)] and QLQ-LC13 (lung cancer module). Improvements in dyspnea, cough, and chest pain were noted. Nevertheless, there were no positive or negative changes on overall QoL, although there was a transient reduction in diarrhea scores that improved by study completion (131). A more detailed analysis of PROs with mobocertinib 160 mg daily detailed the frequent detriments in QoL scores related to diarrhea and appetite loss, while improvements were observed for dyspnea, insomnia, and constipation (132). Investigators have since published proposals for proactive management of both dermatologic and gastrointestinal toxicities to minimize the need for mobocertinib dose reductions/interruptions (133). Real-world experience with mobocertinib has mirrored that seen in these initial clinical studies (134).

The findings from NCT02716116 and its expansion cohorts (such as EXCLAIM) are limited by the lack of a control arm (phase I/II design). However, as the outcomes with use of this agent meet an important unmet clinical need, mobocertinib was granted accelerated approval September 2021 by the United States Food and Drug Administration (FDA) for *EGFR* exon 20 insertion-mutated advanced NSCLC for treatment following disease progression on platinum-based chemotherapy. The use of mobocertinib in the first line setting for metastatic disease is being evaluated in the ongoing phase III trial EXCLAIM-2 (NCT04129502) (135), which is nearing accrual completion and will hopefully determine if mobocertinib should overtake platinum-based chemotherapy as the *de facto* evidence-based frontline

therapy for patients with advanced NSCLC harboring an *EGFR* exon 20 insertion mutation (135).

To date, there are no published clinical studies specifically studying the effects of mobocertinib in *ERBB2* exon 20 insertion-mutated NSCLC. While there were some patients (n=21) in the NCT02716116 trial, the published outcomes reference the *EGFR*-mutated cohort exclusively (130). Only one preclinical study thus far has studied mobocertinib in two models of *ERBB2*-mutated NSCLC, driven by ERBB2-A775_G776insYVMA and ERBB2-G776>VC, and with an eye towards identifying activity, dosing, and resistance mechanisms (105). Although mobocertinib has preclinical activity against other *EGFR* mutations (*Figure 2B*), there are no ongoing clinical studies targeting common and uncommon mutations that have already been paired with other FDA-approved targeted agents (*Figure 2A*).

Amivantamab-vmjw

Amivantamab is a humanized, bispecific antibody that binds EGFR and MET extracellularly to target activating mutations, including *EGFR* exon 20 insertion mutations, as well as *MET* mutations and amplification (89). Three distinct mechanisms inhibit tumor growth in the setting of aberrant EGFR and MET signaling: (I) immune effector cells (such as NK cells and macrophages) target mutated tumor cells for destruction through antibody-dependent cellular cytotoxicity, trogocytosis and phagocytosis (89); (II) inhibition of ligand binding prevents ligand-induced activation, phosphorylation, and downstream signaling that promote cellular proliferation; and (III) downmodulation or degradation of EGFR and MET receptors, thereby decreasing tumor volume (89).

The antibody amivantamab was first studied in a phase I/II dose-escalation and dose-expansion study (NCT02609776/CHRYSALIS) (136). Eligible patients were previously treated with, ineligible for, or declined standard chemotherapy for metastatic NSCLC harboring *EGFR* exon 20 insertion mutations. The maximum tolerated dose identified was 1,050 mg (1,400 mg for patients ≥80 kg) once weekly administered intravenously for four weeks, followed by once every 2 weeks starting on week 5. Safety and efficacy were evaluated in the recommended phase two dose cohort (n=258), which included all patients given the maximum tolerated dose (137). Within this cohort, patients who had previously received platinum-based chemotherapy were included in the safety population (n=114), while those who had at least 3 disease assessments at the clinical cutoff were included in the efficacy population (n=81). In the efficacy population, the investigator-assessed ORR was 36% (95% CI: 25–47%), median PFS 8.3 months (5.5–10.6 months), and median OS 22.8 months (14.6–NR), although this endpoint was immature (137). Responses were seen irrespective of *EGFR* exon 20 insertion mutation type (137). In the safety population, 99% of patients experienced a TRAE (35% ≥ grade 3), most commonly rash (86%, 4% ≥ grade 3), infusion-related reaction (66%), paronychia (45%), and constipation (24%). Infusion-related reactions were observed primarily during the first dose, split over two days, with most occurring on day 1 (93%) as compared to day 2 (4%) of the infusion (137). TRAEs led to dose reductions (13%) and discontinuations (10%), most commonly for rash at 10% and 1.8%, respectively (137).

Though data are limited by the early phase nature of the trial, the FDA granted accelerated approval May 2021 to amivantamab for the treatment of advanced *EGFR* exon 20 insertion-mutated advanced NSCLC following prior platinum-based chemotherapy. The CHRYSALIS trial is ongoing and analyses of activity in other cohorts of *EGFR*-mutated advanced NSCLC are expected shortly (136). Use of amivantamab in the second-line setting with/without the third-generation EGFR inhibitor, lazertinib, is being evaluated in the ongoing phase I trial, CHRYSALIS-2 (NCT04077463) (138). In the first-line setting, amivantamab in combination with carboplatin and pemetrexed is ongoing in the phase III PAPILLON trial (NCT04538664) in patients with advanced *EGFR* exon 20 insertion-mutated NSCLC (139). A subcutaneous formulation is also currently being evaluated in the phase I PALOMA trial (NCT04606381) (140). There is no data studying the use of amivantamab in *ERBB2*-mutated NSCLC, and the absence of direct targeting of ERBB2 likely limits applications of this agent to tumors with *EGFR* or *MET* activation.

Fam-trastuzumab deruxtecan-nxki (T-DXd)

T-DXd is an ADC that consists of a humanized monoclonal antibody directed at ERBB2 with a cleavable tetrapeptide-based linker attached to a potent topoisomerase I inhibitor (a derivative of the camptothecin analog exatecan: DXd; DX-8951 derivative) as its cytotoxic drug payload (141). Preclinical models have shown T-DXd has a higher drug-to-antibody ratio and shorter payload half-life than other ERBB2-directed ADCs (mainly T-DM1) (142).

T-DXd initially received FDA approval as a breakthrough therapy in December 2019 for use in *ERBB2*-overexpressing,

unresectable/metastatic breast cancer based on the results of the DESTINY-Breast01 trial (141). A phase I dose-expansion trial in multiple advanced solid tumors (n=60) with ERBB2 overexpression (immunohistochemistry of at least 1+) or *ERBB2* mutations included 18 patients with advanced NSCLC (143), 11 of which had tumors with *ERBB2* mutations (almost all of which were exon 20 insertions). ORR and median PFS in the overall cohort *vs.* *ERBB2*-mutated NSCLCs were 28.3% *vs.* 72.7% and 7.2 months (95% CI: 4.8–11.1 months) *vs.* 11.3 months (95% CI: 8.1–14.3 months), respectively (143).

DESTINY-Lung01 next specifically explored use of T-DXd exclusively in *ERBB2*-mutated NSCLC (144). The trial was conducted as a phase II, single arm trial of patients with previously treated, refractory metastatic *ERBB2*-mutant NSCLC (n=91). The trial reported an ORR of 55% (95% CI: 44–65%) with median DoR 9.3 months (95% CI: 5.7–14.7 months), median PFS 8.2 months (95% CI: 6.0–11.9 months), and median OS 17.8 months (95% CI: 13.8–22.1 months). Responses were seen across all *ERBB2* mutation types and regardless of type/extent of prior cancer therapy, including prior pan-EGFR/ERBB2-directed therapies in 14% with some responses to T-DXd (144). Our group has similarly published our clinical experience with poziotinib following T-DXd (145). Though limited by small numbers, these outcomes suggest possible non-overlapping mechanisms of drug resistance between TKIs and ADCs directed against *ERBB2*. DESTINY-Lung02 study next endeavored to assess the safest and most effective dose of T-DXd in previously treated, *ERBB2*-mutated advanced NSCLC. T-DXd was evaluated at a dose of 6.4 *vs.* 5.4 mg/kg in a randomized dose-finding trial (146,147). The ORRs were similar across the two doses. Of note, the efficacy cohort of 5.4 mg/kg (n=52) disclosed ORR of 58% (95% CI: 43–71%) and the median DOR of 8.7 months (95% CI: 7.1–not estimable) (146,147).

Cytopenias are amongst the most prevalent TRAEs with use of T-DXd in the published studies to date. The most common TRAEs in DESTINY-Lung01 trial were neutropenia (15% grade 3) and anemia (10% grade 3) (144). Of particular importance is the identification of drug-induced interstitial lung disease (ILD) in both initial and sequent trials of T-DXd across cancer types, including treatment-related respiratory failure and death in 1 patient in the initial phase I trial. Drug-related ILD was reported in 26% of participants in DESTINY-Lung01 and resulted in death in 2% of all patients included in the trial (144). In DESTINY-Lung02, higher rates of drug-induced ILD at the 6.4 *vs.* 5.4 mg/kg dose (14.0% *vs.* 5.9%, respectively) led to selection of the 5.4 mg/kg dose administered intravenously every 3 weeks for further study and approval (146,147). In this study, any grade drug-related ILD event occurred in 5.9% and 14.0% of cases receiving T-DXd 5.4 or 6.4 mg/kg, respectively (147). This has resulted in a black box warning for ILD. As use of these agents evolves in real-world settings, it will be necessary to assess whether the risk of ILD is exacerbated by prior chest radiotherapy and/or immune checkpoint inhibitor (ICI) use as are commonly the case in the care of patients with NSCLC. Given poor tolerability of respiratory toxicities in patients with significant baseline pulmonary comorbidities, a high index of clinical suspicion and low threshold to identify, evaluate, and manage patients experiencing such toxicities will be necessary in this patient population (144). Clinical guidance on best practice for diagnosis and management of T-DXd-induced pneumonitis has been published (148).

On the basis of these results, T-DXd was granted accelerated approval in August 2022 by the FDA for use in metastatic or unresectable *ERBB2*-mutated NSCLC with disease progression following prior therapy. While the current approval is for patients with previously treated, *ERBB2*-mutated advanced NSCLC, important questions still remain regarding optimal combinations and sequencing of T-DXd with other biologically active systemic therapies in NSCLC (145). The ongoing DESTINY-Lung03 trial (NCT04686305) is investigating the safety of T-DXd in combination with platinum doublet chemotherapy and durvalumab (149). Also ongoing, DESTINY-Lung04 (NCT05048797) will investigate the safety and efficacy of T-DXd versus standard-of-care first-line treatments (platinum-doublet +/– pembrolizumab) in advanced NSCLC with *ERBB2* exon 19 or 20 kinase domain mutations (150).

Therapies in development: *poziotinib*, *sunvozertinib*, *zipalertinib*

Poziotinib is an irreversible pan-ErbB inhibitor with activity against EGFR, ERBB2, and ERBB4. *In vitro*, poziotinib has demonstrated its abilities as a potent inhibitor of cells with *EGFR* or *ERBB2* exon 20 insertions (23). However, concerns regarding toxicity have limited its use in the clinical setting. A phase II trial of poziotinib in *EGFR*-mutated advanced lung adenocarcinoma with acquired resistance to erlotinib/gefitinib (n=37) showed limited clinical efficacy with ORR of 8% and median PFS 2.7 months (151). Of note, this trial included predominantly patients with acquired *EGFR*-

T790M; no patients with *EGFR* exon 20 insertions were included.

Subsequent preclinical studies further characterized the potential utility and clinical activity of poziotinib in *EGFR* exon 20 insertion mutations and *ERBB2* mutations specifically, ultimately leading to clinical studies yielding more favorable results (23). A phase II trial was published in which patients with *ERBB2* exon 20 insertion-mutated advanced NSCLC (n=30) received poziotinib 16mg daily; both previously treated and treatment-naïve patients were included (109). Investigators reported an ORR of 43% (95% CI: 25–63%), disease control rate (DCR) of 73%, and median PFS of 5.5 months (95% CI: 4.9–7.0 months). Another trial by the same group included patients with advanced NSCLC harboring *EGFR* exon 20 mutations (n=50) and yielded similar findings: ORR of 32% (95% CI: 20.7–45.8%), DCR of 84%, and median PFS again 5.5 months (95% CI: 5.0–9.4 months) (152). Patients in this latter trial were heavily pretreated (94%), 34% of whom had received prior EGFR TKI therapy. Acquired mechanisms of resistance to poziotinib were also explored in this study, with identification of *EGFR*-T790M, *MET* amplification, and epithelial to mesenchymal transition as has been seen with other EGFR-directed agents (152).

ZENITH20-2 is a phase II, single arm trial of poziotinib in previously treated advanced NSCLC with *ERBB2* exon 20 insertion mutations (110,153). The trial enrolled 90 patients, all of whom were treated with poziotinib 16 mg daily. Similar to prior studies, the ORR was 27.8% (95% CI: 18.9–38.2%), DCR 70% (95% CI: 59.4–79.2%), and median PFS 5.5 months (95% CI: 3.9–5.8 months). Response rates were noted to be similar regardless of prior therapy, including 27.8% of patients who had received prior anti-EGFR/ERBB2 targeted therapy. Additionally, there was no difference in response based on the type of *ERBB2* mutation present; ERBB2-A775_G776insYVMA was present in 65 out of 90 patients. ZENITH20-4 subsequently investigated poziotinib in treatment-naïve *ERBB2*-mutated advanced NSCLC (153,154). The results of this trial were presented in abstract form at the 2022 ESMO Targeted Anticancer Therapies Congress (154). The trial included 70 patients and reported a combined ORR of 41% (95% CI: 30–54%) with a median PFS of 5.6 months (range, 0–20 months) (154).

These phase II trial results have been further corroborated in a real-world study (n=30) describing clinical outcomes in an expanded access program that provided poziotinib for compassionate use to patients with advanced NSCLC with *EGFR* and *ERBB2* exon 20 insertion mutations (155). In keeping with prior studies, an ORR of 30% with median PFS of 5.6 months (95% CI: 3.6–6.7 months) was reported (155).

High-grade gastrointestinal and mucocutaneous toxicities have been of significant concern with poziotinib and have limited the prospect for its use in routine clinical practice. In the ZENITH20-2 trial, the most common grade 3 TRAEs included rash and diarrhea in 78.9% of all patients, with 13% ultimately discontinuing poziotinib as a result (152). Other studies have shown similarly high rates of drug-induced rash, diarrhea, mucositis, paronychia, and xerosis in up to one-third of all patients and resulting in dose reduction in the majority (72%) of patients (109). Due to concerns regarding low overall response rates with minimal DoR and poor tolerability, the FDA elected not to approve poziotinib for use in *EGFR*- or *ERBB2*-mutated NSCLC (156), and enrollment in a phase 2 study of poziotinib in advanced NSCLC harboring *EGFR* or *ERBB2* exon 20 insertion mutations was halted in early 2023 as a result (153).

Sunvozertinib (formerly DZD9008) is a newly developed *EGFR* exon 20 insertion mutation-active TKI which also irreversibly binds EGFR-C797 like mobocertinib, instead using an anilino-phenyl moiety to interact with the C-helix of EGFR (86). Sunvozertinib is currently being studied in an international phase I study in advanced NSCLC (157). With median follow-up thus far under 6 months, early clinical data suggests an ORR around 40% in heavily pretreated patients (86). Similar to other TKIs in this class, the primary toxicities appear to again be mostly gastrointestinal and dermatologic (86). There is additionally evidence that sunvozertinib may have anti-tumor activity against other *EGFR*-sensitizing mutations as well as *ERBB2* exon 20 insertion mutants (86).

Zipalertinib (formerly TAS6417/CLN-081) is a pan-mutation-selective EGFR TKI with potent activity against exon 20 insertion mutations in preclinical studies, however with limited efficacy in *ERBB2*-mutated lung cancer (59). Zipalertinib fits into the ATP binding site of the EGFR hinge region, conferring its antitumor activity (158). Currently, the drug is being evaluated in an international phase I/II trial (159), with interim results suggestive of an ORR around 40% (159). Rash was present in more than half of the study participants; conversely, diarrhea appears less common than with other EGFR TKIs (159). Additionally, a phase II trial for *EGFR* exon 20 insertion-mutated NSCLC and phase III trial against standard-of-care chemotherapy in the first line setting are planned.

Other *EGFR* exon 20 insertion mutant active TKIs undergoing initial clinical trial development include BLU-451 and BAY2927088.

Platinum doublet chemotherapy and ICIs

Even despite the ongoing advances in targeted therapies outlined above, the evidence-based standard of care for first line therapy in advanced NSCLC harboring *EGFR* or *ERBB2* exon 20 insertion mutations remains platinum-based chemotherapy, with or without an ICI even as outcomes have remained stagnant and generally modest (39). In a large retrospective review of 105 patients receiving first line platinum doublet chemotherapy, an ORR 19.2% and median PFS of 6.5 months were noted (160-165). Another retrospective study of 77 patients receiving first line pemetrexed (alone or in combination with a platinum agent) reported a better ORR of 41.5%, however again with limited median PFS of 7.6 months and median OS of 25 months (161). In the second line setting, responses to single agent chemotherapy have been reported with similarly limited efficacy and median PFS of 4.0 months (95% CI: 3.2–4.8 months) (160).

In a recent retrospective cohort of advanced NSCLC with *EGFR* exon 20 insertion mutations receiving chemotherapy as either first or second line treatment was reported (162). Amongst 41 patients receiving first line platinum-based treatment, median PFS was 5.7 months (95% CI: 3.0–10.9 months); for those receiving ICI in addition to chemotherapy, a median PFS of 4.5 months (1.2–10.3 months) was reported, though the subset was small (n=16). Of the 50 patients who received chemotherapy in the second line, median PFS was 3.3 months (95% CI: 2.3–5.9 months) (162). Notably, reported outcomes with chemotherapy-based regimens have superseded those seen with 1st and 2nd generation EGFR TKIs in this molecularly-defined subgroup, where median PFS for this earlier generation targeted agents have not exceeded 3 months (160).

The largest study was a multi-center retrospective evaluation of 93 patients who received platinum-based chemotherapy. The ORR was 43.5% and median PFS was 6.0 months (95% CI: 5.0–7.1 months). Outcomes of second line chemotherapy were not specifically shown in this cohort (163). A second smaller study included 25 patients that received platinum/pemetrexed in the first line, with an ORR of 36% and median PFS of 5.1 months (95% CI: 4.9–5.3 months) (164). A retrospective study of NSCLC patients with either *EGFR* or *ERBB2* exon 20 insertion mutations reported a median PFS of 6 months (95% CI: 5.7–7.0 months) with first-line platinum-containing chemotherapies (162).

Outcomes with contemporary regimens including the addition of ICI to platinum doublet chemotherapy are still being vetted, and there have been very few case series evaluating the efficacy of ICIs advanced NSCLC with either *EGFR* or *ERBB2* exon 20 insertion mutations (162-165). The largest study is a retrospective evaluation of 15 patients with *EGFR* exon 20-mutated advanced NSCLC who received ICI (either as first or second line treatment). Limited efficacy was noted with ORR 6.7%, median PFS of 2.0 months (95% CI: 0.6–2.7 months), and median OS of 5.3 months (95% CI: 1.8–12.5 months). There was a trend towards decreased OS (12.9 *vs.* 25.2 months, P=0.08) in those receiving *vs.* not receiving ICI therapy compared to *EGFR* exon 20 insertion-mutated NSCLCs that never received immunotherapy. In this limited sample as has been true elsewhere in the literature surrounding ICI use in *EGFR*-mutated NSCLC, tumor PD-L1 expression does not appear predictive of treatment response (165). In a retrospective, single-center cohort study of 122 *ERBB2*-mutated advanced outcomes of 26 patients receiving ICI therapy were evaluated. In the ICI-treated cohort, the ORR with was 12% (95% CI: 3–30%), median PFS 1.9 months (95% CI: 1.5–4.0 months) and median OS 10.4 months (95% CI: 5.9–NR) (166).

Additional data can be extrapolated from larger retrospective studies evaluating ICIs in a pooled analysis of oncogene-driven NSCLCs. A multi-center study included two groups of *ERBB2*-mutated NSCLC reported dismal responses to single agent ICI, with median PFS ranging from 1.9 months (95% CI: 1.6–2.1 months; n=15 patients from one center) to 3.0 months (95% CI: 1.8–NR; n=21 patients from a different center) (167). In another study, 29 patients who had received ICI therapy at any point in their treatment course were evaluated; ICI-associated ORR of 7% and median PFS of 2.5 months (95% CI: 1.8–3.5 months) were reported (168). In yet another retrospective study of 23 patients that receiving ICI therapy in the second line and beyond, showed reported improved ORR of 27.3%, though with still poor median PFS of 2.2 months (1.7–15.2 months) (169).

Similar to what has been previously described in other *EGFR*-mutated NSCLC subgroups (170,171), these findings raise important questions regarding the relevance of ICI-based approaches in patients whose tumors harbor exon 20 alterations in *EGFR* and *ERBB2*. It is postulated that

Table 2 Summary of published results on the EGFR/ERBB2 directed therapies mobocertinib, amivantamab and trastuzumab deruxtecan

Treatment (type)	Mutation	Ref.	Type of study	No. of patients	ORR (%) [95% CI]	mPFS (months) [95% CI]	mOS (months) [95% CI]	Common adverse events (CTCAE)	CTCAE grade ≥3 adverse events
Mobocertinib (covalent *EGFR* ex20ins active TKI)	*EGFR* ex20ins, *ERBB2* ex20ins	(130)	Phase I/II	28	43 [24–63]	7.3 [4.4–15.6]	–	Diarrhea, nausea/vomiting, rash	Diarrhea, nausea, stomatitis
	EGFR ex20ins	(131)	Phase I/II	Platinum-pretreated patients: 114	28 [20–37]	7.3 [5.5–9.2]	24 [14.6–28.8]	Diarrhea, rash, paronychia, anorexia, nausea/vomiting	Diarrhea, stomatitis
Amivantamab (bi-specific EGFR-MET antibody)	*EGFR* ex20ins	(137)	Phase I	Efficacy: 81; safety: 114	36 [25–47]	8.3 [5.5–10.6]	22.8 [14.6–NR]	Rash, infusion-related reaction, paronychia, constipation	Hypokalemia, diarrhea, rash
Trastuzumab deruxtecan (ERBB2 antibody-drug conjugate)	*ERBB2* mutations	(143)	Phase I	Ex20ins: 8; other: 3	73 [39–94]	11.3 [8.1–14.3]	17.3 [17.3–NR]	Cytopenias, nausea/vomiting, diarrhea, anorexia, fatigue, alopecia	Anemia, neutropenia, thrombocytopenia, nausea, pneumonitis
	ERBB2 mutations	(112)	Phase II	Total: 91; Ex20ins: 78	55 [44–65]	8.2 [6–11.9]	17.8 [13.8–22.1]	Cytopenias, nausea/vomiting, fatigue, alopecia, diarrhea	Anemia, neutropenia, nausea, pneumonitis

EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2 (also known as HER2, human epidermal growth factor receptor-2); ORR, objective response rate; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival; CTCAE, Common Terminology Criteria for Adverse Events; ex20ins, exon 20 insertion mutations; TKI, tyrosine kinase inhibitor; MET, MET proto-oncogene, receptor tyrosine kinase; ref., reference; NR, not reached.

limited/absent tobacco exposure in these molecularly defined subgroups may render an immune microenvironment that is not favorable for engagement of the immune system. ICI use (particularly as a sole agent) in these patients should be used with caution, possibly deferring until other targeted and/or chemotherapeutic strategies have been exhausted first.

Conclusions

Evolving insights into the biologic importance of oncogenic driver pathways and opportunities for novel drug development have led to brisk advances in the identification and management of oncogene-driven NSCLCs, thus linking scientific discovery in the lab to innovations in the clinic that have transformed the care of many patients. However, due to unique challenges stemming from protein structure and biology, leveraging the power of targeted therapeutics for an important molecularly-defined subset—those with *EGFR* and *ERBB2* exon 20 insertion mutations—has lagged beyond others of its kind and represents an ongoing albeit evolving area of unmet need. Identifying agents that possess the hallmark characteristics of other targeted therapies already available for use in advanced NSCLC—deep, durable, and tolerable efficacy—has proven challenging in this molecularly-defined subset and has necessitated diversification of the targeted therapeutics armamentarium, including development of novel EGFR-directed TKIs, bivalent antibodies, and ADCs.

This review provides an overview of *EGFR* and *ERBB2* mutations in NSCLC with a focus on the recent clinical approvals of mobocertinib, amivantamab, and T-DXd that have added to the armamentarium of precision oncology. *Table 2* summarizes the major clinical studies of the EGFR TKI mobocertinib, EGFR-MET antibody amivantamab, and anti-ERBB2 ADC T-DXd, with a focus on efficacy and toxicity. Though promising efficacy (even in treatment-refractory disease) and manageable toxicities have been demonstrated in studies to date, currently ongoing and future studies will hopefully shed light on ways to optimize treatment selection, dosing, and sequencing so as to maximize outcomes for these important subsets of patients with advanced NSCLCs harboring *EGFR* exon 20 insertion mutations and *ERBB2* mutations.

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Footnote

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