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Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications

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Abstract

Substantial therapeutic advancements have been made in identifying and treating activating mutations in advanced non–small cell lung cancer (NSCLC); however, resistance to epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) inhibitors remains common with current targeted therapies. Amivantamab, a fully human bispecific antibody targeting EGFR and MET, is approved in the United States and other countries for the treatment of patients with advanced NSCLC with *EGFR* exon 20 insertion mutations, for whom disease has progressed on or after platinum-based chemotherapy. Preliminary efficacy and safety have also been demonstrated in patients with common EGFR- or MET-mutated NSCLC. Amivantamab employs three distinct potential mechanisms of action (MOAs) including ligand blocking, receptor degradation, and immune cell–directing activity, such as antibody-dependent cellular cytotoxicity and trogocytosis. Notably, efficacy with amivantamab does not require all three MOAs to occur simultaneously, broadening applicability by using diverse antitumor mechanisms. This review focuses on the molecular characteristics of amivantamab and its unique MOAs leading to *in vitro* and *in vivo* efficacy and safety in preclinical and clinical studies.

Keywords

immune cell–directing activity, ligand blocking, targeted therapy, exon 20 insertions, resistance pathways

Introduction

Non–small cell lung cancer (NSCLC)[*] is the leading cause of cancer-related mortality worldwide.[1, 2] The disease is typically diagnosed in advanced or late stages for which treatment options are limited, and outcomes are generally poor. NSCLC has a 5-year survival rate of 14% for stage 3A, which drops to <5% for stages 3B and 4.[3] Advancement in treatment options for this disease has accelerated in the last 10 to 20 years due to the identification of activating mutations, improved diagnostic techniques, and the development of targeted therapies. Although these advancements have improved outcomes in some subtypes of NSCLC, resistance to these treatments is common.

This review describes the molecular characteristics, mechanisms of action (MOAs), and clinical efficacy of amivantamab, a fully human bispecific antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) with enhanced crystallizable fragment (Fc):Fc receptor (FcR) binding, leading to activation of innate immune response. Amivantamab was approved by the US Food and Drug Administration (FDA) in May 2021 for the treatment of patients with advanced or metastatic NSCLC (mNSCLC) with *EGFR* exon 20 insertion (ex20ins) mutations, whose disease has progressed on or after platinum-based chemotherapy. The goal of this article is to summarize published data augmented with clinician hands-on experience to promote understanding of amivantamab's molecular design, MOAs, and clinical impact to address unmet needs.

Overview and Discussion

NSCLC is the second most commonly diagnosed malignancy and the leading cause of cancer-related mortality worldwide.[1, 2] Among the most frequently mutated genes in NSCLC is *EGFR*, which globally accounts for 23% to 30% of activating mutations in NSCLC.[4, 5] Oncogenic *EGFR* mutations increase the activity of the receptor (EGFR), resulting in elevated ligand-independent downstream signaling. Although baseline levels of EGFR signaling are essential for normal

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Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADCR, antibody-dependent cytokine release; ADCT, antibody-dependent cellular trogocytosis; CNS, central nervous system; CI, confidence interval; DOR, duration of response; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; Fab, antigen-binding fragment; Fc, crystallizable fragment; FcγRs, Fcγ receptors; FDA, US Food and Drug Administration; HER, human epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; IRR, infusion-related reaction; MET, mesenchymal-epithelial transition factor; MOA, mechanism of action; mNSCLC, metastatic non–small cell lung cancer; mAbs, monoclonal antibodies; NSCLC, non–small cell lung cancer; ORR, overall response rate; SC, subcutaneous; TGI, tumor growth inhibition; TKI, tyrosine kinase inhibitors.

cellular activities, including DNA synthesis and cell proliferation, excess activity can result in uncontrolled growth and tumorigenesis.[6]

The current standard of care for patients diagnosed with EGFR-mutated NSCLC varies based on the nature of the mutation. Common mutations account for up to 85% of *EGFR* mutations and typically include exon 19 deletions or L858R substitution in exon 21.[7] Common mutations can be effectively targeted with EGFR tyrosine kinase inhibitors (TKIs), including the third-generation EGFR TKI osimertinib, which results in an objective response rate of up to 80% in first-line treatment.[8] The next most common type of *EGFR* mutations consists of *EGFR* ex20ins, which account for 4% to 10% of all *EGFR* mutations and are typically resistant to first-, second-, and third-generation EGFR TKIs. Until FDA approval of the bispecific antibody amivantamab, no targeted therapies were available for the treatment of *EGFR* ex20ins. Mobocertinib, an oral, irreversible TKI targeting *EGFR* ex20ins, was subsequently approved by the FDA for the treatment of adult patients with locally advanced or mNSCLC with *EGFR* ex20ins whose disease had progressed on or after platinum-based chemotherapy.[9] Other therapies being evaluated for the treatment of ex20ins NSCLC include osimertinib in combination with bevacizumab (ClinicalTrials.gov Identifier: NCT04974879), and poziotinib, a TKI in development for *EGFR* and *HER2* exon 20 mutations, in combination with ramucirumab (ClinicalTrials.gov Identifier: NCT05045404). In addition, the small molecules CLN-081 (ClinicalTrials.gov Identifier NCT04036682), DZD9009 (ClinicalTrials.gov Identifier NCT03974022), and LNG-451[10] are being evaluated for the treatment of *EGFR* ex20ins.

For all EGFR-mutated NSCLC, resistance to EGFR TKIs and chemotherapy is inevitable, leaving this large patient population with limited treatment options when progression occurs. Most resistance mechanisms to EGFR TKIs involve alterations of EGFR itself, such as upregulated expression or the acquisition of additional mutations. For example, the T790M mutation accounts for approximately half of acquired resistances to first- and second-generation EGFR TKIs.[11] In addition to EGFR-dependent resistance mechanisms, alterations to the MET receptor are common resistance pathways. Like EGFR, baseline MET signaling promotes survival in healthy cells but can be oncogenic at abnormally high expression levels. MET-dependent resistance can manifest through point mutations or gene amplification. *MET* amplification is a particularly common resistance mechanism, occurring in 10% to 20% of patients treated with osimertinib.[12] Increased levels of hepatocyte growth factor (HGF), a MET ligand, can also induce EGFR TKI resistance through the activation of MET.[13]

Of note, *MET* amplifications and *MET* exon 14 skipping mutations account for 2% to 4% and 3% to 4% of primary activating mutations in mNSCLC, respectively. Tumors with *MET* mutations can be treated with MET TKIs or other MET-specific inhibitors but are associated with poor prognosis.[14] Moreover, upregulation of the EGFR pathway has been demonstrated as a mechanism of resistance to MET TKIs.[15, 16] Capmatinib and tepotinib are FDA-approved MET TKIs for the treatment of patients with mNSCLC whose tumors have *MET* exon 14 skipping mutations; however, no targeted agents are currently approved for *MET* amplified cancers.

In addition to their reciprocal resistance upon TKI treatment (MET-dependent resistance in EGFR-mutated cancers and EGFR-dependent resistance in MET-mutated cancers), EGFR and MET have been shown to dimerize to promote oncogenic signaling and remodeling of the tumor microenvironment.[17-19] Cross-talk between EGFR and MET signaling is well documented, and these pathways can compensate for one another when signaling from either individual protein is inhibited.[20] The interdependence between these two pathways suggests that simultaneously targeting EGFR and MET could improve clinical outcomes by concomitantly inhibiting both pathways and reducing occurrence of MET- and/or EGFR-mediated resistance. Therefore, the bispecific antibody, amivantamab, was designed to simultaneously inhibit EGFR and MET pathways.

Amivantamab is a fully human Fc-active immunoglobulin G1 (IgG1) bispecific antibody with high affinity (K_D) binding to both EGFR (1.4 nanomolar/liter) and MET (K_D of 40 picomolar/liter).[21, 22] Amivantamab targets the extracellular domains of EGFR and MET, leading to inhibition of both pathways independent of their intracellular cancer-driving or treatment-acquired mutation(s). The potential broad applicability of amivantamab can be attributed to its novel design leading to dual targeting of EGFR and MET, activation of innate immune cells through enhanced FcR binding, and improved safety profile. We review the design, MOAs, and activity of amivantamab by highlighting key published preclinical data, as well as clinical efficacy and safety.

Design of amivantamab enables multiple MOAs

Amivantamab architecture and engineering are depicted in **Figure 1**. Briefly, amivantamab was derived from two parental monoclonal antibodies (mAbs), one targeting EGFR and one targeting MET.[23] The parental mAbs were combined using the Genmab DuoBody controlled antigen-binding fragment (Fab) arm exchange process,[24, 25] resulting in a bispecific antibody with single arm binding sites (i.e., monovalent) to each antigen. In addition, the parental mAbs were produced in an engineered cell line incorporating low levels of fucose into the Fc region,[21, 22, 26] to enhance antibody binding to FcRs on immune effector cells, thus promoting antitumor immune cell–directing activity.[21, 26]

Preclinical studies demonstrated that amivantamab elicits its anti-tumor activity through three potential MOAs: 1) ligand blocking, 2) receptor degradation, and 3) immune cell–directing activity (**Figure 2**). Each of these mechanisms is described next and shown in this **Video**.

Ligand blocking

The binding of amivantamab's Fab arms to each receptor prevents EGFR and MET ligands from binding to their respective receptors. *In vitro* studies have demonstrated that amivantamab, with single Fab binding to each receptor, inhibits ligand binding to EGFR and MET with similar potency as the parental, bivalent mAbs.[21] In a cellular context, ligand blocking by amivantamab reduces ligand-induced receptor activation, measured by inhibition of receptor phosphorylation and downstream signaling. Ligand-induced EGFR and MET phosphorylation were reduced by the binding of amivantamab in cell lines with EGFR activating (L858R) and/or acquired

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resistance (T790M) mutations and *MET* amplification.[21] This provided early evidence for potential anti-tumor activity of amivantamab in patients with *EGFR* mutations.

The ligand-blocking activity of amivantamab was compared with that of the combination of monovalent EGFR and MET antibodies of equimolar concentration. These monovalent anti-EGFR and anti-MET antibodies are engineered with one arm binding to EGFR or MET and the second arm binding to an inert antigen absent on the test cell line. These studies demonstrated that amivantamab more potently blocked ligand-induced receptor phosphorylation than the combination of the monovalent anti-EGFR and anti-MET antibodies.[27] The enhanced blocking of downstream signaling observed with amivantamab may result from the increased intrinsic propensity of amivantamab to bind both EGFR and MET targets when expressed on the same tumor cell through cross-arm binding.[27, 28]

Receptor degradation
When bound to EGFR and/or MET on the tumor cell surface, amivantamab triggers receptor internalization and degradation, a process by which antibody-bound receptors are engulfed by the cell membrane, internalized, and trafficked to lysosomes, where the antibody-receptor complex is degraded.[26] In pre-clinical models, EGFR and MET protein levels were significantly reduced in tumors treated with amivantamab.[21] The interaction of amivantamab with immune cells was determined to further enhance the loss of receptors from the cell surface, both *in vitro* and *in vivo,*[26] as discussed in detail in the next section.

Immune cell–directing activity
The binding of the Fc region of amivantamab to immune cells induces several effector functions. This important MOA hinges on the activation of these immune cells through amivantamab-Fc binding to their Fcg receptors (FcgRs) on immune cells (**Figure 2**).[29] Immune cell–directed activities triggered by amivantamab include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cytokine release (ADCR), and antibody-dependent cellular trogocytosis (ADCT); these mechanisms are summarized briefly in **Table 1**.[21, 26]

The impact of effector functions on the overall efficacy of amivantamab has been studied extensively in *in vitro* and *in vivo* models and compared with that of an EGFR- and MET-targeting bispecific Fc-silent antibody (referred to as amivantamab-Fc-silent). For example, in an EGFR- and MET-driven xenograft model, treatment with amivantamab resulted in nearly 80% tumor growth inhibition (TGI), while treatment with amivantamab-Fc-silent resulted in <10% TGI. Moreover, amivantamab-Fc-silent had reduced ability to inhibit receptor phosphorylation, demonstrating that in addition to driving efficacy, binding of amivantamab's Fc region to FcgRs on immune cells also plays an important role in receptor and signal downmodulation.[30]

In addition, cell culture experiments comparing amivantamab and amivantamab-Fc-silent have shown that the Fc interaction of amivantamab with immune cells is essential to drive innate cell effector functions and that the low fucosylation of amivantamab enhances natural killer-mediated

ADCC.[30] Furthermore, amivantamab induced ADCC, ADCT, and ADCR more potently than cetuximab, a bivalent (normal fucose) anti-EGFR mAb indicated for colorectal and head and neck cancers.[26]

Notably, trogocytosis was recently identified as a novel Fc-mediated effector function for amivantamab. Trogocytosis, or "cellular gnawing," is a process in which cell surface proteins from the tumor cell membrane are removed by immune effector cells, such as monocytes, macrophages, and neutrophils. Amivantamab led to monocyte- and macrophage-dependent downmodulation of EGFR and MET through trogocytosis in cell culture and xenograft mouse models.[26] It has been hypothesized that this mechanism may extend to other nearby receptors, such as other human epidermal growth factor receptor family members, which could contribute to suppression of signaling pathways that lead to resistance.[26]

Table 1. Immune Cell–Directing Activity Triggered by Binding of the Fc Region of Amivantamab

Effector function	Amivantamab-activated immune cell type	Brief MOA description	References
ADCC	NK cells	Release of cytotoxic granules causes death of target cell	21, 26, 30
ADCP*	Macrophage	Target cell is engulfed and destroyed	30
ADCR	Various, including macrophage and monocyte	Secretion of cytokines and chemokines that can cause death of target cell or activate other immune cells	26
ADCT*	Macrophage, monocyte	Mediates transfer of cell surface proteins from target to effector cells	26

*Most prominent immune cell-directing activities.
ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADCR, antibody-dependent cytokine release; ADCT, antibody-dependent cellular trogocytosis; Fc, crystallizable fragment; MOA, mechanism of action; NK, natural killer.

Broad spectrum of amivantamab activity
Although the overall activity of amivantamab encompasses multiple MOAs, not all mechanisms occur concomitantly or are required for clinical activity. Amivantamab's MOAs are tumor and context dependent. For example, amivantamab can bind to either EGFR or MET alone to successfully induce Fc-independent and -dependent effector functions.[30] Accordingly, amivantamab treatment has demonstrated efficacy in EGFR-mutated xenograft tumor models

independent of MET alteration status,[21] and in *MET* amplified and MET-driven cell lines independent of the EGFR alteration status.[26] Thus, while amivantamab binding simultaneously to EGFR and MET demonstrated synergistic antitumor efficacy, its activity extends beyond EGFR- and MET-co-mutated tumors because of the independent activity of either arm alone. The broad spectrum of amivantamab activity is particularly beneficial in light of tumor heterogeneity, including the high variability of the solid tumor microenvironment.[31] Due to its multiple MOAs, amivantamab treatment achieves broad spectrum tumor killing despite the molecular alterations of the tumor and its microenvironment context.

Amivantamab precision engineering

Amivantamab was designed to target tumors expressing and driven by EGFR and/or MET signaling. EGFR and MET were chosen as targets for the following reasons:

1) EGFR and MET are both highly expressed on NSCLC tumors, including co-expression in 70% of tumors with *EGFR* mutations.[32, 33]
2) Both EGFR and MET receptors signal through the same pro-proliferation and pro-survival pathways (extracellular signal–regulated kinase and protein kinase B), thus potentially compensating for each other upon inhibition of only one of these two receptors.[20] This interactive relationship suggests that stronger pathway inhibition is achieved by blocking both receptors simultaneously. Supportively, in an NSCLC xenograft model with *EGFR* mutations and *MET* amplification, dual inhibition of both receptors by amivantamab was more efficacious than anti-EGFR treatment alone (erlotinib).[21]
3) Resistance to EGFR TKIs most commonly occurs through alterations of EGFR and/or MET, retaining treatment-resistant cancer growth dependence on this pathway.[11, 12]

Amivantamab was selected from a panel of bispecific molecules targeting EGFR and MET.[23] Parental mAbs were screened for target-specific binding, ligand-blocking activity, and lack of agonistic signaling activity. Multiple bispecific molecules were generated and retested in heterodimerized format, and amivantamab was selected based on the best multi-functional features mentioned previously. In addition, to reduce binding to healthy cells with normal EGFR expression and potentially improve tolerability, bispecifics with higher affinity to MET over EGFR were favored.

One advantage that arises from the unique binding properties of bispecific molecules is dual-receptor avidity. Here, the favored interaction between amivantamab and the tumor cell is through binding to the target with the highest affinity (eg, MET), enabling the second arm to come into closer proximity and bind to its target, albeit with weaker affinity (eg, EGFR). Amivantamab binds EGFR extracellular domain with K_D) of 1.4 nanomolar/liter and MET extracellular domain with K_D of 40 picomolar/liter.[21] This dual-arm binding of amivantamab

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results in an increase in overall binding affinity on cells expressing both targets, in this instance predominantly cancer cells because healthy cells rarely express concomitant high levels of these two receptors.[27, 34] Thus, this precision target binding design of amivantamab intrinsically favors cancer-specific simultaneous binding of EGFR and MET, leading to concomitant inhibition of these interacting signaling pathways.[27] Accordingly, *in vitro* studies comparing amivantamab to the combination of monovalent anti-EGFR and anti-MET mAbs showed that by simultaneously engaging EGFR and MET binding on the same cell, amivantamab promoted dual-receptor avidity and enhanced inhibition of receptor phosphorylation for the lower expressed receptor on the selected cell line.[27, 34]

Because it is derived from two parental mAbs produced in engineered cell lines that incorporate low levels of fucose into proteins, amivantamab also displays low levels of fucosylation. Low fucosylation enhances binding of the Fc region of amivantamab to FcgRIIIa on immune cells, thus enhancing engagement of immune cells and driving better immune cell–directing activity (including ADCC), compared with normally fucosylated antibodies.[30]

Efficacy and safety

Amivantamab's target selectivity and design features, as well as the compelling large body of preclinical anti-cancer activity, supported its clinical development as a first-in-class agent against EGFR-mutant NSCLC. In 2021, amivantamab was approved for the treatment of patients with advanced NSCLC with *EGFR* ex20ins whose disease had progressed on or after platinum-based chemotherapy. Amivantamab was the first bispecific molecule approved for the treatment of solid tumors. Prior approvals of bispecific molecules in blood cancer include two T-cell redirectors, blinatumomab and catumaxomab, the latter for which approval was later withdrawn.

Clinical efficacy and safety data from a cohort of patients with locally advanced or mNSCLC in the CHRYSALIS study (ClinicalTrials.gov Identifier: NCT02609776) were submitted to support FDA approval of amivantamab. The efficacy population included patients with *EGFR* ex20ins whose disease had progressed on or after platinum-based chemotherapy.[35] Of 81 patients, 3 confirmed complete responses and 29 partial responses were observed, for an overall response rate (ORR) of 40% (95% confidence interval [CI], 29-51) as assessed by blinded independent central review. The median duration of response for the 32 responders was 11.1 months (95% CI, 6.9-not reached). Antitumor responses were observed in patients across different *EGFR* ex20ins, regardless of the site or type of insertions.[36]

Safety was evaluated in 302 patients with any driver *EGFR* mutation who received ≥1 dose of amivantamab.[35] Because amivantamab treatment leads to EGFR and MET inhibition, adverse reactions known to occur upon inhibition of these pathways were observed in ≥20% of patients, including rash, paronychia, stomatitis, and edema.[35, 36] These adverse reactions, particularly rash, were similar to those documented with cetuximab and some TKIs, including erlotinib and afatinib.[37-39] Considering that amivantamab is delivered by infusion, it is not surprising that one of the most common adverse events was infusion-related reactions (IRRs). IRRs encompass a range of symptoms, including chills, dyspnea, flushing, nausea, chest discomfort, and vomiting.

Although IRRs occurred in 66% of the overall safety population, their overall incidence decreases in intensity and frequency upon subsequent infusions. For this reason, the initial administration of amivantamab was split over 2 days, which led to lower incidence and severity of IRRs and therefore better patient experience. Although 65% of these patients experienced IRRs on the first day of treatment, the incidence decreased to 3.4% on the second day of treatment and continued to decrease thereafter. In addition, these IRRs were generally well tolerated, with 97% being grade 1 (mild transient reaction; infusion interruption not indicated; no intervention needed) to 2 (moderate; infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours]).[40] Only 1.3% of patients permanently discontinued amivantamab treatment due to IRRs.[35] To mitigate IRRs, a subcutaneous (SC) formulation of amivantamab is currently being investigated. Preliminary data from PALOMA (ClinicalTrials.gov Identifier: NCT04606381) showed that SC administration was well-tolerated and reduced IRRs to 18.2% in 33 patients with advanced solid tumors.[41]

Although amivantamab was the first bispecific antibody approved for solid tumors, it entered a market offering several existing anti-EGFR mAb therapies (**Table 2**). Most notably, cetuximab (Erbitux®; Eli Lilly and Company, Indianapolis, IN 46285, USA), approved for squamous cell carcinoma of the head and neck and KRAS wild-type, EGFR-expressing, metastatic colorectal cancer, has also been investigated for the treatment of NSCLC in numerous clinical trials, including two phase 2 studies (FLEX[42] and BMS 099[42]) in which cetuximab was combined with chemotherapy for the treatment of EGFR-mutated mNSCLC. Because clinical benefits were marginal for the level of toxicity observed, neither study led to cetuximab approval for this indication.[3] The clinical benefit of amivantamab in broader aberrant EGFR signaling settings remains to be fully evaluated. However, amivantamab's preliminary success in *EGFR* ex20ins, considering the history of cetuximab and other anti-EGFR agents against NSCLC, poses an interesting question about the differentiating MOA of amivantamab compared with other agents. Several features of amivantamab, discussed throughout this review, could result in improved outcomes compared with previously evaluated anti-EGFR agents. These additional features include superior tumor-specificity due to the dual targeting of EGFR and MET, enhanced inhibition of oncogenic signaling pathways due to increased dual-receptor avidity, enhanced effector functions due to the low fucose Fc region, and reduced immunogenicity due to fully human antibody construction.

With the approval of amivantamab for previously treated patients with *EGFR* ex20ins advanced NSCLC and the demonstration of its broad activity in preclinical studies, various clinical trials further evaluating amivantamab efficacy in different EGFR-mutant settings are ongoing. In the frontline setting, amivantamab is being evaluated in combination with carboplatin/pemetrexed versus chemotherapy alone in patients with advanced or metastatic NSCLC harboring *EGFR* ex20ins in the ongoing phase 3 PAPILLON study (ClinicalTrials.gov identifier: NCT04538664).[43]

Amivantamab is also being evaluated in a regimen with lazertinib, a brain-penetrant third-generation EGFR TKI.[44] In CHRYSALIS-2 (ClinicalTrials.gov identifier: NCT04077463), the combination of amivantamab and lazertinib showed activity in patients with common *EGFR* exon 19 deletion or L858R mutations that progressed on osimertinib and platinum-based chemotherapy, including an ORR of 33% and clinical benefit rate (CBR) of 57%.[45] In this study, the amivantamab plus lazertinib regimen was also evaluated in combination with carboplatin/pemetrexed, resulting in an ORR of 50% and CBR of 80% for patients with advanced NSCLC who had progressed on prior TKI therapy, including those with baseline brain metastases. The safety profile was consistent with those of the individual therapies, and no new safety signals were identified.[46] The phase 3 MARIPOSA-2 study (ClinicalTrials.gov identifier: NCT04988295) is comparing the amivantamab/lazertinib/carboplatin/pemetrexed combination to amivantamab/carboplatin/pemetrexed or carboplatin/pemetrexed in patients with EGFR-mutated locally advanced or metastatic NSCLC after progression on prior osimertinib.[47]

Strikingly, for a group of 20 treatment-naive patients with advanced NSCLC harboring common *EGFR* exon 19 deletion or L858R mutations who were treated with amivantamab plus lazertinib in CHRYSALIS (ClinicalTrials.gov identifier: NCT02609776), ORR was 100%.[44] The combination of amivantamab plus lazertinib as frontline therapy is being compared to osimertinib in patients with locally advanced or metastatic exon 19 deletion or L858R NSCLC in the phase 3 MARIPOSA study (ClinicalTrials.gov identifier: NCT04487080).[48]

Amivantamab plus lazertinib continues to be evaluated in multiple EGFR NSCLC populations, and the safety profile is consistently similar to that of amivantamab monotherapy.[44, 49-51] Mechanistically, simultaneous treatment with amivantamab and lazertinib capitalizes on two structurally distinct mechanisms of EGFR inhibition, including amivantamab's extracellular inhibition of EGFR and lazertinib's intracellular EGFR TKI activity. This multi-pronged inhibition of EGFR combined with previously discussed anti-cancer features of amivantamab may provide alternative treatment for this patient population. Importantly, treatment with lazertinib may bring efficacy against brain metastases, which in many instances limits the efficacy of current therapies. Interestingly, in the CHRYSALIS study, documented CNS progression was lower (7%) with amivantamab plus lazertinib treatment than that with amivantamab monotherapy (17%) treatment.[50]

Table 2. Anti-EGFR Antibodies Approved for the Treatment of Cancer

Generic name	Amivantamab[35]	Necitumumab[52]	Panitumumab[53]	Cetuximab[54]
Brand name	Rybrevant™	Portrazza™	Vectibix®	Erbitux®
Owner	Janssen	Eli Lilly	Amgen	Eli Lilly
Initial US approval	2021	2015	2006	2004
Indication	Locally advanced or mNSCLC with	Metastatic squamous NSCLC: in	Metastatic CRC with disease progression on or	• SCCHN: in combination with radiation therapy,

	EGFR ex20ins and disease progression on or after platinum-based chemotherapy	combination with gemcitabine and cisplatin (first-line)	following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens *(Approval is based on progression-free survival; no data demonstrated an improvement in disease-related symptoms or increased survival)*	platinum-based therapy with fluorouracil, or after progression on platinum-based therapy • KRAS wild-type, EGFR-expressing, metastatic CRC: in combination with FOLFIRI for first-line treatment; in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; as single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan
Design (schematic)	Fully human anti-EGFR, anti-MET bispecific IgG1	Recombinant human IgG1 mAb	Recombinant human IgG2 mAb	Recombinant human/mouse chimeric IgG1 mAb
MOA	Ligand blocking, receptor degradation, ADCC, ADCP, ADCR, ADCT	Receptor degradation, ADCC	Ligand blocking	Ligand blocking, ADCC
Most common adverse events (30%), all grades	Among 129 patients: rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%)	Among 538 patients: hypomagnesemia (83%), hypocalcemia (45%), rash (44%), hypophosphatemia (31%)[a]	Among 229 patients: skin toxicity (90%), erythema (65%), hypomagnesemia (38%), dermatitis acneiform (57%), pruritus (57%)	Among 1,373 patients[b]: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, infection[c]
Efficacy	Among 81 patients: ORR: 40%; DOR: 11.1	Among 545 patients: OS: 11.5 months; PFS: 5.7 months	Among 231 patients: PFS: 96 days	Among 211 patients with SCCHN + radiation: • Locoregional

months				control: 24.4 months
				• OS: 49.0 months
				Among 222 patients with SCCHN + platinum-based therapy + fluorouracil:
				• OS: 10.1 months;
				• PFS: 5.5 months;
				• ORR: 35.6%
				Among 608 patients with CRC + FOLFIRI:
				• PFS: 8.9 months;
				• OS: 491 months;
				• ORR: 46%
				Among 387 patients with previously treated CRC:
				• OS: 6.1 months
				Among 329 patients with CRC + irinotecan
				• ORR: 23%;
				• DOR: 5.7 months

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADCR, antibody-dependent cytokine release; ADCT, antibody-dependent cellular trogocytosis; CRC, colorectal cancer; DOR, duration of response; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; FOLFIRI, folinic acid, fluorouracil, and irinotecan; IgG1, immunoglobulin G1; IgG2, immunoglobulin G2; IRR, infusion-related reaction; KRAS, kirsten rat sarcoma viral oncogene homolog; mAb, monoclonal antibody; MET, mesenchymal-epithelial transition factor; mNSCLC, metastatic non–small cell lung cancer; MOA, mechanism of action; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCCHN, squamous cell carcinoma of the head and neck.

Note: Because clinical trials are conducted under widely varying conditions, rates of response, survival, and adverse reactions observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

[a]Adverse events occurred at rate ≥2% higher than in the gemcitabine and cisplatin alone arm.
[b]Includes patients with SCCHN or CRC enrolled in clinical trials, treated at the recommended dosage for a median of 7 to 14 weeks.

[c]Adverse events occurring in ≥25% of patients.

Conclusions and future directions

Despite the improved treatment success of patients with EGFR-mutated NSCLC with EGFR TKIs, most patients will experience recurrence of disease through acquired treatment resistance mutations. Many of these resistance mutations are driven by mutations in EGFR or other gene alterations, such as *MET* amplification or increased expression of its ligand, HGF. To address these mechanisms of resistance and potentially prevent their occurrence in the first place, a better understanding of the driver determinants of cancer and mechanisms of resistance, coupled with improved medicines with increased safety profiles to permit combination regimens in earlier stages of cancer, even pre-malignancy, will be required to prevent and cure NSCLC.[55]

In this article we reviewed the design, MOAs, and clinical efficacy and safety profile of amivantamab. In summary, we discussed the three distinct MOAs of amivantamab, including ligand blocking, receptor degradation, and immune cell–directing activity, such as trogocytosis, leading to clinical efficacy in NSCLC with *EGFR* ex20ins. Although amivantamab is currently FDA approved as monotherapy, combination therapy strategies are currently being explored for patients with either *EGFR* ex20ins (with chemotherapy) or common *EGFR* mutations (with third-generation EGFR TKI, lazertinib). Capitalizing on the enhanced immune cell–directing activity of amivantamab through its low fucosylated Fc-region, amivantamab offers the potential for effective combination with checkpoint inhibitors or other immunologic enhancing agents for the treatment of cancer.

Although significant progress has been made in understanding the genetic landscape of NSCLC, including identification of EGFR and MET driver pathways and the advancement of medicines to treat tumors with these alterations, further research is needed to improve outcomes to address the unmet needs of patients with NSCLC.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–249. https://doi.org/10.3322/caac.21660
2. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. *Lancet.* 2021;398:535–554. https://doi.org/10.1016/S0140-6736(21)00312-3
3. Mazzarella L, Guida A, Curigliano G. Cetuximab for treating non-small cell lung cancer. *Expert Opin Biol Ther.* 2018;18:483–493. https://doi.org/10.1080/14712598.2018.1452906
4. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, Yang ZY, Mao C, Tang JL. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a

systematic review and meta-analysis. *Oncotarget.* 2016;7:78985–78993.
https://doi.org/10.18632/oncotarget.12587

5. Sholl LM, Aisner DL, Varella-Garcia M, Berry LD, Dias-Santagata D, Wistuba II, Chen H, Fujimoto J, Kugler K, Franklin WA, Iafrate AJ, Ladanyi M, Kris MG, Johnson BE, Bunn PA, Minna JD, Kwiatkowski DJ; LCMC Investigators, et al. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: the lung cancer mutation consortium experience. *J Thorac Oncol.* 2015;10:768–777. https://doi.org/10.1097/JTO.0000000000000516

6. Wee P, Wang Z. Epidermal growth factor receptor cell proliferation signaling pathways. *Cancers (Basel).* 2017;9:52. https://doi.org/10.3390/cancers9050052

7. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol.* 2020;61:167–179. https://doi.org/10.1016/j.semcancer.2019.09.015

8. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378:113–125. https://doi.org/10.1056/NEJMoa1713137

9. Zhou C, Ramalingam SS, Kim TM, Kim SW, Yang JC, Riely GJ, Mekhail T, Nguyen D, Garcia Campelo MR, Felip E, Vincent S, Jin S, Griffin C, Bunn V, Lin J, Lin HM, Mehta M, Jänne PA. Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion-positive metastatic non-small cell lung cancer: a phase 1/2 open-label nonrandomized clinical trial. *JAMA Oncol.* 2021;7:e214761.

10. Murray B, Pandey A, Roth B, Saxton T, Estes DJ, Agrawal H, Vishwakarma S, Hallur G, Ahmad I; Trivedi R, Jenkins H, Pearson PG. LNG-451 (BLU-451) is a potent, CNS-penetrant, wild-type EGFR sparing inhibitor of EGFR exon 20 insertion mutations. Poster presented at: AACR Meeting 2022, April 8-13, 2022; New Orleans, LA, USA. https://www.blueprintmedicines.com/wp-content/uploads/2022/04/Blueprint-Medicines-AACR-2022-BLU-451-EGFR-Exon-20-Insertions-Preclinical-Poster.pdf

11. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol.* 2018;29(suppl 1):i10–i19. https://doi.org/10.1093/annonc/mdx703

12. Passaro A, Janne PA, Mok T, Peters S. Overcoming therapy resistance in EGFR-mutant lung cancer. *Nat Cancer.* 2021;2:377–391. https://doi.org/10.1038/s43018-021-00195-8

13. Yano S, Yamada T, Takeuchi S, Tachibana K, Minami Y, Yatabe Y, Mitsudomi T, Tanaka H, Kimura T, Kudoh S, Nokihara H, Ohe Y, Yokota J, Uramoto H, Yasumoto K, Kiura K, Higashiyama M, Oda M, Saito H, Yoshida J, Kondoh K, Noguchi M. Hepatocyte growth factor expression in EGFR mutant lung cancer with intrinsic and acquired resistance to tyrosine kinase inhibitors in a Japanese cohort. *J Thorac Oncol.* 2011;6:2011–2017. https://doi.org/10.1097/JTO.0b013e31823ab0dd

14. Chu QS. Targeting non-small cell lung cancer: driver mutation beyond epidermal growth factor mutation and anaplastic lymphoma kinase fusion. *Ther Adv Med Oncol.* 2020;12:1758835919895756. https://doi.org/10.1177/1758835919895756

15. Migliore C, Morando E, Ghiso E, Anastasi S, Leoni VP, Apicella M, Cora' D, Sapino A, Pietrantonio F, De Braud F, Columbano A, Segatto O, Giordano S. miR-205 mediates

adaptive resistance to MET inhibition via ERRFI1 targeting and raised EGFR signaling. *EMBO Mol Med.* 2018;10:e8746. https://doi.org/10.15252/emmm.201708746.

16. Recondo G, Bahcall M, Sholl L, Leonardi G, Ricciuti B, Nguyen T, Venkatraman D, Lamberi G, Umeton R, Janne P. Mechanisms of resistance to MET tyrosine kinase inhibitors in patients with MET exon 14 mutant non-small cell lung cancer (meeting abstr). *J Thorac Oncol.* 2019;14:S285.

17. Jo M, Stolz DB, Esplen JE, Dorko K, Michalopoulos GK, Strom SC. Cross-talk between epidermal growth factor receptor and c-Met signal pathways in transformed cells. *J Biol Chem.* 2000;275:8806–8811. https://doi.org/10.1074/jbc.275.12.8806

18. Ortiz-Zapater E, Lee RW, Owen W, Weitsman G, Fruhwirth G, Dunn RG, Neat MJ, McCaughan F, Parker P, Ng T, Santis G. MET-EGFR dimerization in lung adenocarcinoma is dependent on EGFR mutations and altered by MET kinase inhibition. *PLoS One.* 2017;12:e0170798. https://doi.org/10.1371/journal.pone.0170798

19. Tang Z, Du R, Jiang S, Wu C, Barkauskas DS, Richey J, Molter J, Lam M, Flask C, Gerson S, Dowlati A, Liu L, Lee Z, Halmos B, Wang Y, Kern JA, Ma PC. Dual MET-EGFR combinatorial inhibition against T790M-EGFR-mediated erlotinib-resistant lung cancer. *Br J Cancer.* 2008;99:911–922. https://doi.org/10.1038/sj.bjc.6604559

20. Puri N, Salgia R. Synergism of EGFR and c-Met pathways, cross-talk and inhibition, in non-small cell lung cancer. *J Carcinog.* 2008;7:9. https://doi.org/10.4103/1477-3163.44372

21. Moores SL, Chiu ML, Bushey BS, Chevalier K, Luistro L, Dorn K, Brezski RJ, Haytko P, Kelly T, Wu SJ, Martin PL, Neijssen J, Parren PW, Schuurman J, Attar RM, Laquerre S, Lorenzi MV, Anderson GM. A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. *Cancer Res.* 2016;76:3942–3953. https://doi.org/10.1158/0008-5472.CAN-15-2833

22. Haura EB, Cho BC, Lee JS, Han J-Y, Lee KH, Sanborn RE, Govindan R, Cho EK, Kim S-W, Reckamp KL, Sabari JK, Thayu M, Bae K, Knoblauch RE, Curtin J, Haddish-Berhane N, Sherman LJ, Lorenzi MV, Park K, Bauml. JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC) (meeting abstr). *J Clin Oncol.* 2019;37:9009. https://doi.org/10.1200/JCO.2019.37.15_suppl.9009

23. Neijssen J, Cardoso RMF, Chevalier KM, , Wiegman L, Valerius T, Anderson GM, Moores SL, Schuurman J, Parren PWHI, Strohl WR, Chiu ML. Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. *J Biol Chem.* 2021;296:100641. https://doi.org/10.1016/j.jbc.2021.100641

24. Gramer MJ, van den Bremer ET, van Kampen MD, Kundu A, Kopfmann P, Etter E, Stinehelfer D, Long J, Lannom T, Noordergraaf EH, Gerritsen J, Labrijn AF, Schuurman J, van Berkel PH, Parren PW. Production of stable bispecific IgG1 by controlled Fab-arm exchange: scalability from bench to large-scale manufacturing by application of standard approaches. *MAbs.* 2013;5:962–973. https://doi.org/10.4161/mabs.26233

25. Labrijn AF, Meesters JI, de Goeij BE, van den Bremer ET, Neijssen J, van Kampen MD, Strumane K, Verploegen S, Kundu A, Gramer MJ, van Berkel PH, van de Winkel JG, Schuurman J, Parren PW. Efficient generation of stable bispecific IgG1 by controlled Fab-arm exchange. *Proc Natl Acad Sci U S A.* 2013;110:5145–5150. https://doi.org/10.1073/pnas.1220145110

26. Vijayaraghavan S, Lipfert L, Chevalier K, Bushey BS, Henley B, Lenhart R, Sendecki J, Beqiri M, Millar HJ, Packman K, Lorenzi MV, Laquerre S, Moores SL. Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor downmodulation and antitumor activity by monocyte/macrophage trogocytosis. *Mol Cancer Ther.* 2020;19:2044–2056. https://doi.org/10.1158/1535-7163.MCT-20-0071

27. Jarantow SW, Bushey BS, Pardinas JR, Boakye K, Lacy ER, Sanders R, Sepulveda MA, Moores SL, Chiu ML. Impact of cell-surface antigen expression on target engagement and function of an epidermal growth factor receptor x c-MET bispecific antibody. *J Biol Chem.* 2015;290:24689–24704. https://doi.org/10.1074/jbc.M115.651653

28. Castoldi R, Ecker V, Wiehle L, Majety M, Busl-Schuller R, Asmussen M, Nopora A, Jucknischke U, Osl F, Kobold S, Scheuer W, Venturi M, Klein C, Niederfellner G, Sustmann C. A novel bispecific EGFR/Met antibody blocks tumor-promoting phenotypic effects induced by resistance to EGFR inhibition and has potent antitumor activity. *Oncogene.* 2013;32:5593–5601. https://doi.org/10.1038/onc.2013.245

29. Stewart R, Hammond SA, Oberst M, Wilkinson RW. The role of Fc gamma receptors in the activity of immunomodulatory antibodies for cancer. *J Immunother Cancer.* 2014;2:29. https://doi.org/10.1186/s40425-014-0029-x

30. Grugan KD, Dorn K, Jarantow SW, Bushey BS, Pardinas JR, Laquerre S, Moores SL, Chiu ML. Fc-mediated activity of EGFR x c-Met bispecific antibody JNJ-61186372 enhanced killing of lung cancer cells. *mAbs.* 2017;9:114–126. https://doi.org/10.1080/19420862.2016.1249079

31. Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, Kolahian S, Javaheri T, Zare P. Tumor microenvironment complexity and therapeutic implications at a glance. *Cell Commun Signal.* 2020;18:59. https://doi.org/10.1186/s12964-020-0530-4

32. Charakidis M, Boyer M. Targeting MET and EGFR in NSCLC-what can we learn from the recently reported phase III trial of onartuzumab in combination with erlotinib in advanced non-small cell lung cancer? *Transl Lung Cancer Res.* 2014;3:395–396. https://doi.org/10.3978/j.issn.2218-6751.2014.09.03

33. Spigel DR, Ervin TJ, Ramlau RA, Daniel DB, Goldschmidt JH Jr, Blumenschein GR Jr, Krzakowski MJ, Robinet G, Godbert B, Barlesi F, Govindan R, Patel T, Orlov SV, Wertheim MS, Yu W, Zha J, Yauch RL, Patel PH, Phan SC, Peterson AC. Randomized phase II trial of onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2013;31:4105–4114. https://doi.org/10.1200/JCO.2012.47.4189

34. Zheng S, Moores S, Jarantow S, Pardinas J, Chiu M, Zhou H, Wang W. Cross-arm binding efficiency of an EGFR x c-Met bispecific antibody. *MAbs.* 2016;8(3):551–561. https://doi.org/10.1080/19420862.2015.1136762

35. RYBREVANT (amivantamab-vmjw) injection [package insert]. Horsham, PA: Janssen Biotech; July 2021.

36. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, Viteri S, Han JY, Kim SW, Lee CK, Sabari JK, Spira AI, Yang TY, Kim DW, Lee KH, Sanborn RE, Trigo J, Goto K, Lee JS, Yang JC, Govindan R, Bauml JM, Garrido P, Krebs MG, Reckamp KL, Xie J, Curtin JC, Haddish-Berhane N, Roshak A, Millington D, Lorenzini P, Thayu M, Knoblauch RE, Cho BC. Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the

CHRYSALIS phase I study. *J Clin Oncol.* 2021;39:3391–3402.
https://doi.org/10.1200/JCO.21.00662

37. Guo MZ, Marrone KA, Spira A, Freeman K, Scott SC. Amivantamab: a potent novel EGFR/c-MET bispecific antibody therapy for EGFR-mutated non-small cell lung cancer. *Oncol Haematol.* 2017;17:42–47. https://doi.org/10.17925/OHR.2021.17.1.42

38. Kainis I, Syrigos N, Kopitopoulou A, Gkiozos I, Filiou E, Nikolaou V, Papadavid E. Erlotinib-associated rash in advanced non-small cell lung cancer: relation to clinicopathological characteristics, treatment response, and survival. *Oncol Res.* 2018;26:59-69. https://doi.org/10.3727/096504017X14913452320194

39. Zhang Y, Miao S, Wang F, Fang W, Chen G, Chen X, Yan F, Huang X, Wu M, Huang Y, Zhang L. The efficacy and toxicity of afatinib in advanced EGFR-positive non-small-cell lung cancer patients after failure of first-generation tyrosine kinase inhibitors: a systematic review and meta-analysis. *J Thorac Dis.* 2017;9:1980-1987. https://doi.org/10.21037/jtd.2017.06.08

40. US Department of Health and Human Services. Common terminology for adverse events (CTCAE) Version 5.0 2017. Published November 27, 2017. Accessed May 17, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quic k_reference_5x7.pdf

41. Krebs MG, Johnson ML, Cho BC, Lee S-H, Kudgus-Lokken R, Zemlickis D, Mitselos A, Berkay E, Bauml JM, Knoblauch RE, Hellemans P, Minchom AR. Subcutaneous delivery of amivantamab in patients with advanced solid malignancies: initial safety and pharmacokinetic results from the PALOMA study. Presented at AACR Annual Meeting; April 8-13, 2022; New Orleans, LA. Abstract CT198.

42. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, Vynnychenko I, Park K, Yu CT, Ganul V, Roh JK, Bajetta E, O'Byrne K, de Marinis F, Eberhardt W, Goddemeier T, Emig M, Gatzemeier U; FLEX Study Team. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet.* 2009;373:1525–1531. https://doi.org/10.1016/S0140-6736(09)60569-9

43. ClinicalTrials.gov. 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 (PAPILLON). Accessed October 14, 2022. https://clinicaltrials.gov/ct2/show/NCT04538664.

44. Cho BC, Lee KH, Cho EK, Kim D, Lee J, Han J, Kim S, Spira A, Haura EB, Sabari JK, Sanborn RE, Bauml JM, Gomez JE, Lorenzini P, Infante JR, Xie J, Haddish-Berhane N, Thayu M, Knoblauch RE, Park K. Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation EGFR tyrosine kinase inhibitor, in advanced EGFR-mutant NSCLC. Presented at: ESMO Congress; September 20, 2020; Virtual. Abstract 12580.

45. Shu CA, Goto K, Ohe Y, Besse B, Lee S-H, Wang Y, Griesinger F, Yang J C-H, Felip E, Sanborn RE, Caro RB, Curtin JC, Chen J, Mahoney JM, Trani L, Bauml JM, Knoblauch RE, Thayu M, Cho BC. Amivantamab and lazertinib in patients with EGFR-mutant non–small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2. *J Clin Oncol.* 2022;40:9006. https://doi.org/10.1200/JCO.2022.40.16_suppl.9006

46. Marmarelis ME, Lee SH, Spira AI, Ou S-HI, Waqar S, Li S, Thayu M, Knoblauch RE, Bauml JM, Cho BC. Amivantamab and lazertinib in combination with platinum-based chemotherapy in relapsed/refractory EGFR-mutant NSCLC (meeting abstr). *J Thorac Oncol.* 2022;17:S68. https://doi.org/10.1016/j.jtho.2022.07.114

47. ClinicalTrials.gov. A study of amivantamab and lazertinib in combination with platinum-based chemotherapy compared with platinum-based chemotherapy in patients with epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic non-small cell lung cancer after osimertinib failure (MARIPOSA-2). Accessed November 1, 2022. https://clinicaltrials.gov/ct2/show/NCT04988295

48. ClinicalTrials.gov. A study of amivantamab and lazertinib combination therapy versus osimertinib in locally advanced or metastatic non-small cell lung cancer (MARIPOSA). Accessed October 31, 2022. https://clinicaltrials.gov/ct2/show/NCT04487080

49. Shu CA, Goto K, Ohe Y, Besse B, Park K, Wang Y, Griesinger F, Yang JC, Felip E, Sanborn RE, Bernabe Caro R, Bauml JM, Chen J, Fennema E, Mahoney J, Trani L, Knoblauch RE, Thayu M, Cho BC. Amivantamab plus lazertinib in post-osimertinib, post-platinum chemotherapy EGFR-mutant non-small cell lung cancer (NSCLC): preliminary results from CHRYSALIS-2. Presented at: ESMO Congress; September 16-21, 2021; Virtual. Abstract 1193MO.

50. Leighl NB, Shu CA, Minchom A, Felip E, Cousin S, Cho BC, Park K, Han J, Boyer M, Lee CK, Moreno Garcia V, Tomasini P, Viteri S, Xie J, Mertz J, Artis E, Schnepp RW, Knoblauch RE, Thayu M, rigo Perez JM. Amivantamab monotherapy and in combination with lazertinib in post osimertinib EGFR mutant NSCLC: analysis from the CHRYSALIS study. Oral presentation at: ESMO Congress; September 16-21, 2021; Virtual. Abstract 1192MO.

51. Bauml J, Cho BC, Park K, Lee KH, Cho EK, Kim D-W, Kim S-W, Haura EB, Sabari JK, Sanborn RE, Nagasaka M, Ou S-HI, Minchom AR, Gomez JE, Curtin JC, Gao G, Roshak A, Thayu M, Knoblauch RE, Spira AI. Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response (meeting abstr). *J Clin Oncol.* 2021;39:9006. https://doi.org/10.1200/JCO.2021.39.15_suppl.9006

52. PORTRAZZA (necitumumab) injection [package insert]. Indianapolis, IN: Eli Lilly and Company; November 2015.

53. VECTIBIX® (panitumumab) injection for intravenous infusion [package insert]. Thousand Oaks, CA: Amgen, Inc.

54. ERBITUX® (cetuximab) injection, for intravenous infusion [package insert]. Branchburg, NJ: ImClone LLC; 2016.

55. Emdal KB, Dittmann A, Reddy RJ, Lescarbeau RS, Moores SL, Laquerre S, White FM. Characterization of in vivo resistance to osimertinib and JNJ-61186372, an EGFR/met bispecific antibody, reveals unique and consensus mechanisms of resistance. *Mol Cancer Ther.* 2017;16:2572–2585. https://doi.org/10.1158/1535-7163.MCT-17-0413
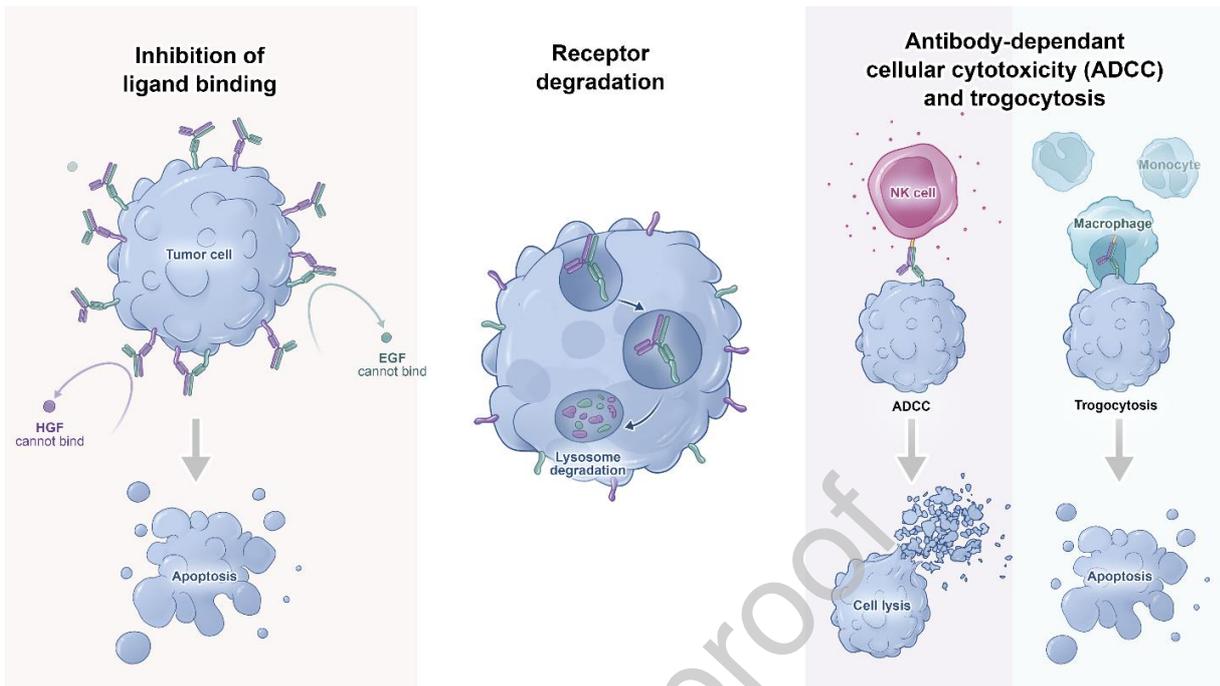
Figures

Figure 1. Engineered Fc mutations within EGFR and MET antibodies lead to bispecific amivantamab formation following controlled Fab-arm exchange process.
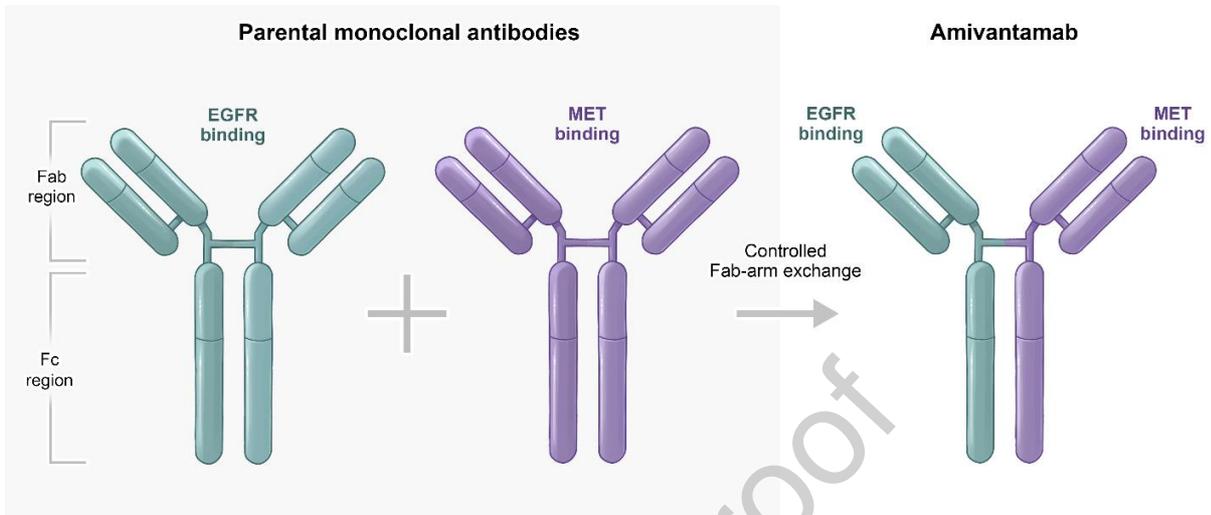
EGFR, epidermal growth factor receptor; Fab, antigen-binding fragment; Fc, crystallizable fragment; MET, mesenchymal-epithelial transition factor.

Figure 2. Schematic of amivantamab's three MOAs – ligand blocking, receptor degradation, and activation of immune-cell–directing activity.

MOA, mechanism of action.