

3 History of the development of RYBREVANT®

3.1 Rationale for development of RYBREVANT®

Amivantamab is a low-fucose, fully human, IgG1-based bispecific antibody directed against the EGFR and MET receptors, with demonstrated preclinical activity against tumors with the primary activating EGFR mutations, the T790M and C797S second-site resistance EGFR mutations, overexpressed wild-type EGFR, and activation of the MET pathway.¹⁵ By inhibiting EGFR and MET signaling functions, either by blocking ligand-induced activation and/or inducing receptor degradation, amivantamab may disrupt these signaling pathways and prevent tumor growth and progression. Furthermore, the presence of EGFR and MET on the surface of tumor cells allows amivantamab to target these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

Amivantamab was developed for the treatment of EGFR-mutated NSCLC, based on the hypothesis that, by targeting the extracellular domain (ECD) of each receptor (EGFR and MET), this bispecific antibody would demonstrate activity against tumors driven through the EGFR pathway, either through primary, TKI-sensitive mutations (eg, ex19del and L858R), as well as those tumors that are resistant to EGFR TKIs, either through primary resistance, or via the two most frequent mechanisms of resistance to current EGFR therapies: (1) secondary/tertiary mutations in EGFR (such as T790M and C797S) and (2) MET amplification or mutation.

Preclinical proof of concept for the bispecific action of amivantamab and the broad applicability of its action was achieved prior to clinical development; amivantamab inhibits human tumor growth in multiple xenograft mouse models, including tumors initiated from cell lines and patient explant material. Efficacy with amivantamab is observed in models with either wild-type EGFR or with EGFR mutations (eg, ex20ins, T790M, C797S), as well as in models with MET pathway activation due to either overexpression of HGF or MET gene amplification.

Amivantamab was assembled from parental antibodies produced in an engineered Chinese hamster ovary cell line that incorporates low levels of fucose into carbohydrate chains, including those attached to antibodies. It was deliberately engineered to have tighter binding affinity to the MET receptor than the EGFR.^{15,16} The human FcγIIIa receptor on natural killer cells, critical for ADCC, binds low-fucose antibodies more tightly and consequently mediates more potent and effective ADCC killing of target cancer cells.³⁷

3.2 RYBREVANT® mechanism of action

Amivantamab binds the EGFR ECD with affinity (K_D) of 1.4 nM and MET-ECD with stronger K_D of 40 pM. By binding to the ECD, amivantamab is not affected by co-mutations in the EGFR TKI binding pocket.¹⁵ Both pathways may be inhibited despite any intracellular tumor-causing or acquired mutations from prior therapies. Amivantamab has 3 mechanisms of action: ligand blocking, receptor degradation, and immune cell-directing functions. Notably, all 3 mechanisms of action are not required to occur simultaneously for amivantamab to be efficacious, broadening its use for diverse antitumor mechanisms. Preclinical studies have demonstrated in vitro and in vivo efficacy and safety using various models.

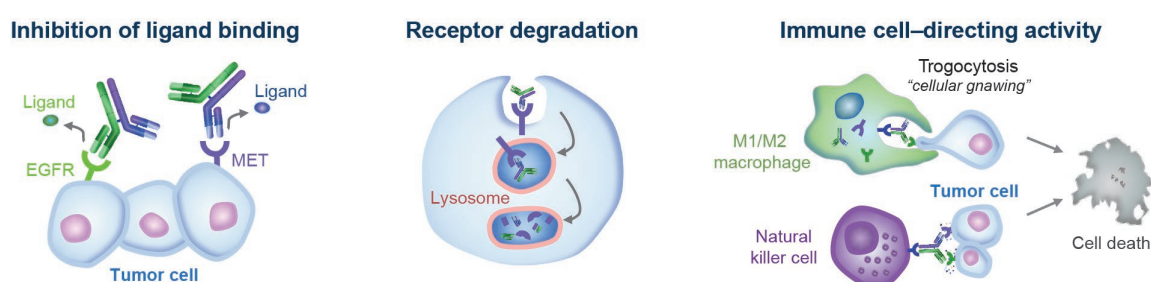


Figure 4. Amivantamab's 3 mechanisms of action.

3.2.1 Ligand blocking

Amivantamab prevents the binding of EGF to EGFR and/or of HGF to MET, which inhibits activation of these respective receptors and subsequent downstream signaling. Preclinical studies have shown that amivantamab inhibits ligand binding to EGFR and MET with similar potency as the parental bivalent monoclonal antibodies¹⁵. Amivantamab reduces ligand-induced receptor activation, which is measured by the inhibition of receptor phosphorylation and downstream signaling.¹⁵ Amivantamab inhibited EGFR and MET phosphorylation in cell lines with EGFR primary activating mutations, such as L858R, as well as acquired resistance mutations, such as T790M, and MET amplification.¹⁵ Additionally, in vitro studies showed that amivantamab as a bispecific antibody can inhibit receptor phosphorylation more potently than the combination of individual monovalent antibodies that target EGFR and MET, respectively. Amivantamab may be able to block downstream signaling more potently due to cross-arm binding of EGFR and MET on the same tumor cell.^{15,16,38}

3.2.2 Receptor degradation

Amivantamab can also inhibit tumor cell growth and proliferation through endocytosis and receptor downregulation. Amivantamab triggers receptor internalization and degradation by binding to EGFR and/or MET on the surface of tumor cells. Receptors bound to the antibody are engulfed by the cell membrane, internalized, and transported to lysosomes, where the antibody-receptor complex is degraded.¹⁴ In preclinical models, EGFR and MET protein levels were significantly

reduced in tumors treated with amivantamab.¹⁵ Amivantamab-Fc binding to immune cells in vitro was determined to further enhance the loss of receptors from the cell surface.³⁹

3.2.3 Immune cell-directing functions

Upon amivantamab binding to EGFR and MET on the cancer cell surface, the Fc domain of the antibody binds to FcγIIIa receptors on macrophages, monocytes, and natural killer cells triggering a range of immune effector cell functions.⁴⁰ These include ADCC, antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cytokine release (ADCR), and antibody-dependent cellular trogocytosis (ADCT).^{15,39} Amivantamab was designed to have low levels of fucose in the Fc region for enhanced FcR binding on immune effector cells to promote these activities.¹⁵ Notably, amivantamab was able to induce ADCC, ADCT, and ADCR more potently than cetuximab.³⁹

Preclinical models have evaluated the impact of these effector functions on amivantamab's efficacy by comparing it to the efficacy of an EGFR- and MET-bispecific Fc-silent antibody. Amivantamab demonstrated nearly 80% tumor growth inhibition versus <10% with the Fc-silent antibody. The Fc-silent antibody also inhibited receptor phosphorylation to a lesser extent than amivantamab, which indicated that amivantamab-Fc binding to immune cells plays a significant role in receptor downmodulation. This Fc interaction is also important for innate cell effector functions.⁴¹

Activation of natural killer cells leads to ADCC, a process by which the effector cell releases cytotoxic factors triggering tumor cell lysis.³⁹ The binding of monocytes and macrophages leads to trogocytosis, an Fc-mediated process in which cell surface proteins from the tumor cell membrane are removed by immune effector cells, such as monocytes, macrophages, and neutrophils.³⁹ This gnawing of the tumor cell membrane, as well as the removal of EGFR and MET receptors, eventually results in apoptosis.³⁹

3.3 RYBREVANT® clinical study program

Given its mechanisms of action and clinical targets, amivantamab is being developed across a wide range of disease and treatment settings. The clinical development program (**Figure 5**) includes studies of amivantamab as both monotherapy and combination therapy. Amivantamab is being studied in combination with the third-generation TKI lazertinib (LAZ) for atypical EGFR mutations and, in the frontline and third-line post-osimertinib, post-chemotherapy setting for common EGFR mutations (L858R and ex19del). Amivantamab is also being evaluated in combination with chemotherapy in MARIPOSA-2 in the second-line, post-osimertinib setting. Clinical trial enrollment has been robust, reflecting the enthusiasm for amivantamab among the clinical community.

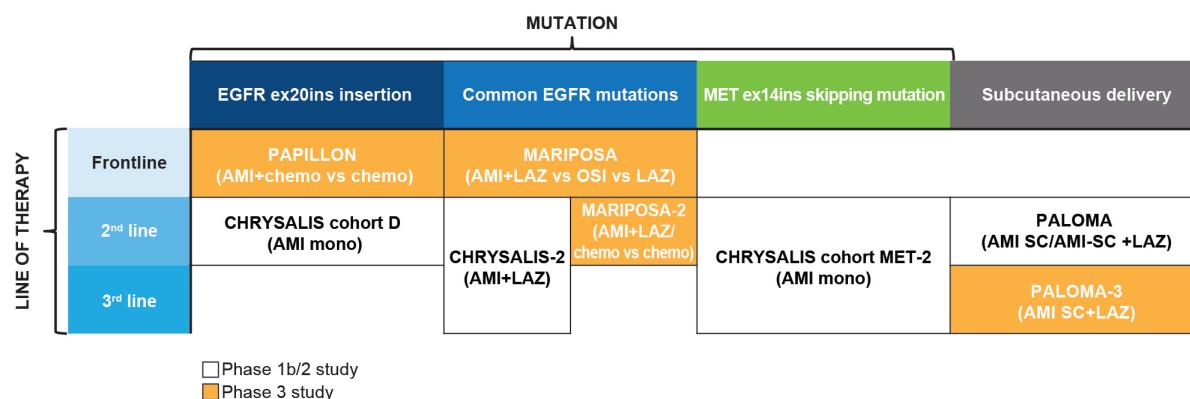


Figure 5. Clinical development program for amivantamab.

3.3.1 NSCLC: EGFR ex20ins mutations

3.3.1.1 Second-line: CHRYSLIS Cohort D (amivantamab monotherapy)

Amivantamab was approved by the FDA in May 2021 for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR ex20ins mutations as detected by an FDA-approved test whose disease has progressed on or after platinum-based chemotherapy based on the results of Cohort D of the CHRYSLIS trial.^{42,43}

CHRYSLIS is a first-in-human, open-label, dose-escalation and dose-expansion, phase 1 study of amivantamab in patients with advanced NSCLC.²⁶ Cohort D included patients who progressed on platinum-based chemotherapy who harbored a EGFR ex20ins mutation. The primary objective of the dose-escalation phase was to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) of amivantamab, and the primary objectives of the dose-expansion phase were to evaluate the safety, tolerability, and antitumor activity of amivantamab at the RP2D²⁶.

In the efficacy population (n = 81), the ORR by blinded independent central review (BICR) was 40% (95% confidence interval [CI], 29-51), including 3 complete responses and 29 (36%) partial responses (PR), with a median DOR of 11.1 months (95% CI, 6.9-not reached). As shown in the figure below, efficacy was observed across all key regions of ex20. The median PFS by BICR was 8.3 months (95% CI, 6.5-10.9) and the median OS was 22.8 months (95% CI, 14.6-not reached).²⁶ In addition, amivantamab also demonstrated a safety profile consistent with on target anti-EGFR and anti-MET activity. In the safety population (n = 114), the most common adverse events (AEs) were rash in 98 patients (86%), infusion-related reactions (IRRs) in 75 (66%), and paronychia in 51 (45%).²⁶ AEs observed with the inhibition of EGFR included rash, paronychia, stomatitis, pruritis, and diarrhea and those associated with MET inhibition included hypoalbuminemia and peripheral edema. A high percentage of patients experienced IRRs (66%); however, these reactions were primarily limited to Cycle 1 Day 1 and were managed with dose and rate modifications.^{26,44}

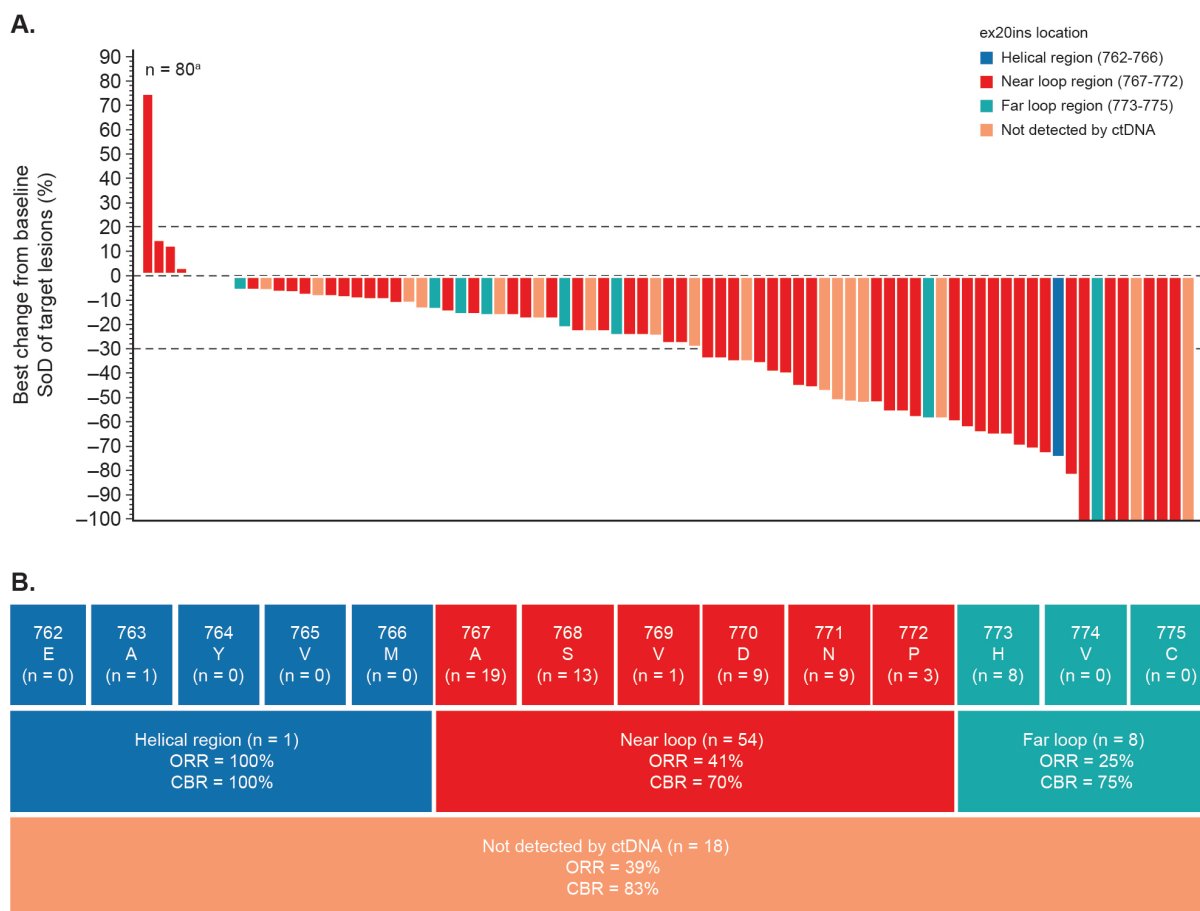


Figure 6. Tumor reduction and responses in the efficacy population.

External control analysis, using 3 US-based databases (ConcertAI, COTA, and Flatiron), was conducted to evaluate the effectiveness of amivantamab versus physicians' choice of cancer therapy in the real-world setting in patients with advanced NSCLC with EGFR ex20ins. Amivantamab-treated patients had an ORR of 40% (95% CI, 29.5-50.5) versus 16% (95% CI, 11.2-22.0) among external controls.⁴⁵ Patients treated with amivantamab also experienced longer median PFS (8.3 vs 2.9 months; hazard ratio [HR; 95% CI]: 0.47 [0.34-0.65]), time to next therapy (median 14.8 vs 4.8 months; HR [95% CI]: 0.40 [0.28-0.57]), and overall survival (median 22.8 vs 12.8 months; HR [95% CI]: 0.49 [0.31-0.77]) than external controls.⁴⁵ This analysis demonstrated that amivantamab improved outcomes versus external controls.⁴⁵

3.3.1.2 Second-line: CHRYSLIS-2 Cohort B (amivantamab + lazertinib)^{46,47}

Cohort B of the phase 1 CHRYSLIS-2 study is evaluating amivantamab in combination with lazertinib in patients with EGFR ex20ins. The primary objective is to evaluate the antitumor activity of the combination of amivantamab and lazertinib at the recommended phase 2 combined dose. This study is currently recruiting, with an estimated study completion date of December 2024.

3.3.1.3 First-line: PAPILLON (amivantamab + chemotherapy vs chemotherapy)^{48,49}

The phase 3, randomized, open-label PAPILLON study is evaluating amivantamab in combination with carboplatin-pemetrexed versus carboplatin-pemetrexed in patients with advanced or metastatic NSCLC with EGFR ex20ins. The primary objective is to evaluate PFS in the frontline setting. This study is currently recruiting, with an estimated enrollment of 300 patients. The estimated completion date is January 2025.

3.3.2 NSCLC: EGFR common mutations

3.3.2.1 First-line: MARIPOSA ([amivantamab + lazertinib] vs osimertinib vs lazertinib)^{50,51}

The phase 3 randomized MARIPOSA study is evaluating amivantamab in combination with lazertinib versus osimertinib versus lazertinib in patients with advanced or metastatic NSCLC with common EGFR mutations (ex19del or exon 21 L858R substitution). The primary objective is to evaluate PFS in the frontline setting. This study is currently recruiting, with an estimated enrollment of 1000 patients. The estimated study completion date is March 2026.

3.3.2.2 Second-line: MARIPOSA-2 ([amivantamab + lazertinib + chemotherapy] vs chemotherapy)⁴⁸

The phase 3, randomized, open-label MARIPOSA-2 study is evaluating amivantamab in combination with lazertinib and pemetrexed-carboplatin versus pemetrexed-carboplatin in patients with locally advanced or metastatic NSCLC with common EGFR mutations (ex19del or exon 21 L858R substitution). The primary objective is to evaluate PFS in the second-line setting in patients who have progressed on osimertinib. This study is currently recruiting, with an estimated enrollment of 500 patients. The estimated study completion date is November 2025.

3.3.2.3 Second-line: CHRYSALIS Cohort E (amivantamab + lazertinib)

Cohort E in the phase 1 CHRYSALIS study evaluated amivantamab in combination with lazertinib in chemotherapy-naïve, osimertinib-resistant patients and in frontline patients. As previously reported at ESMO 2020, of 20 treatment-naïve patients, a 100% ORR was observed (95% CI, 83-100) with 20 PRs.⁵² Median follow-up and median treatment duration was 7 months (4-10). A rapid time to first response was observed of 1.5 months (95% CI, 1.2-2.6). Of the patients in the osimertinib-resistant, chemotherapy-naïve cohort (n = 45), a 36% ORR was observed (95% CI, 22-51) with 1 complete response and 15 PRs (1 pending confirmation).⁵² Median follow-up was 4 months (1-7). Additionally, the combination therapy was well tolerated with low rates of treatment discontinuation (6%).⁵² IRRs were commonly observed (65% of patients); however, IRRs were all grade 1 or 2 and confined to the first infusion.⁵²

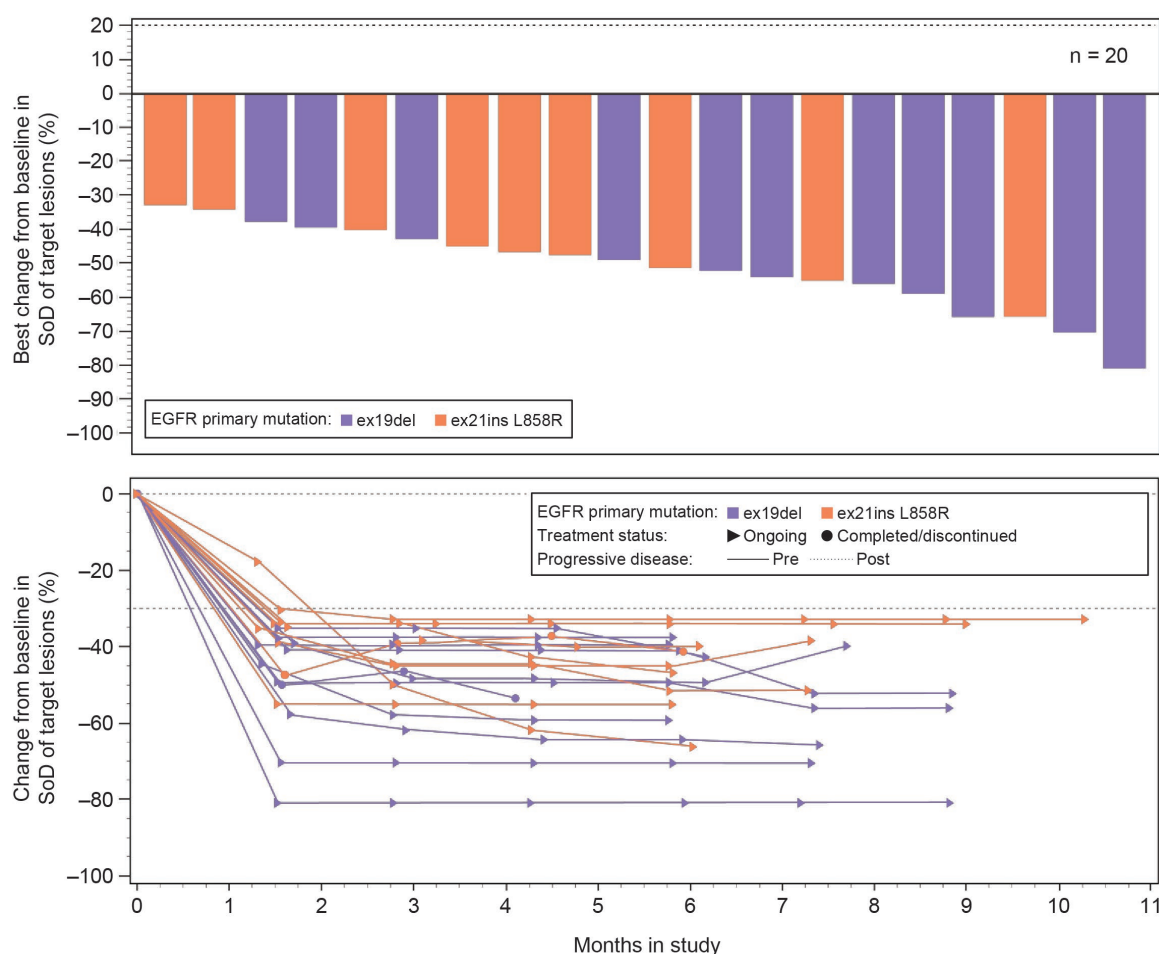


Figure 7. Antitumor activity of amivantamab + lazertinib in treatment-naïve patients.

At ASCO 2021, biomarker analyses were presented on the osimertinib-relapsed, chemotherapy-naïve cohort from CHRYSALIS with EGFR ex19del or L858R substitution (n = 45). Durable responses were observed with amivantamab plus lazertinib therapy with a 36% ORR (95% CI, 22-51), 64% median CBR (95% CI, 49-78), median PFS of 4.9 months (95% CI, 3.7-9.5), and median DOR of 9.6 months (95% CI, 5.3-not reached).⁵³ Of patients with EGFR/MET expression identified by immunohistochemistry staining (n = 10), a 90% ORR was observed, indicating that high EGFR or MET expression may be an alternative approach to identify potential responders to therapy.⁵³ Additionally, next-generation sequencing (NGS) identified a subgroup (those with EGFR/MET-based resistance) that is more likely to respond. ORR was 47% versus 29% for those without identified EGFR/MET-based resistance.⁵³ However, NGS missed half of confirmed responders with EGFR/MET-based resistance.

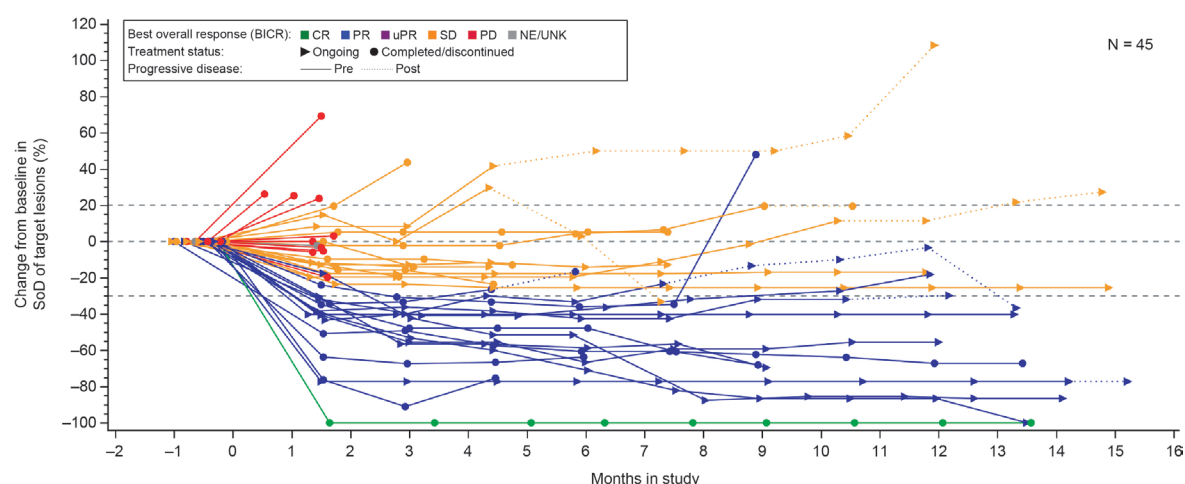


Figure 8. Best change from baseline of target lesions with amivantamab plus lazertinib therapy.

3.3.2.4 Second-line or higher: CHRYSALIS-2 Cohort A (amivantamab + lazertinib)

Cohort A of the CHRYSALIS-2 study evaluated amivantamab in combination with lazertinib in patients with EGFR exon19del or L8585R substitution who have progressed on osimertinib and platinum-based chemotherapy (n=162). Amivantamab plus lazertinib demonstrated durable antitumor activity with 33% BICR-assessed ORR (95% CI, 26-41) and 28% investigator-assessed ORR (95% CI, 22-36). Median DOR was 9.6 months (95% CI, 7.0-not evaluable [NE]) and 8.4 months (95% CI, 5.6-NE) for BICR- and investigator-assessments, respectively.⁵⁴ Median PFS was 5.1 months (95% CI, 4.2-6.9), and median OS was 14.8 months (95% CI, 12.1-NE).⁵⁴ Additionally, due to brain-penetrant features of lazertinib, central nervous system (CNS) activity was also explored with complete clearance of CNS lesions in 7 (26%) patients and progressive disease in 0 patients.⁵⁴ No new safety signals were identified with the combination therapy, and all individual AEs were mostly grades 1 and 2.⁵⁴ This cohort is currently full enrolled. These results are comparable to those previously reported for the post-osimertinib, chemotherapy-naïve population, suggesting that intervening chemotherapy does not interfere with amivantamab-lazertinib combination therapy.⁵³

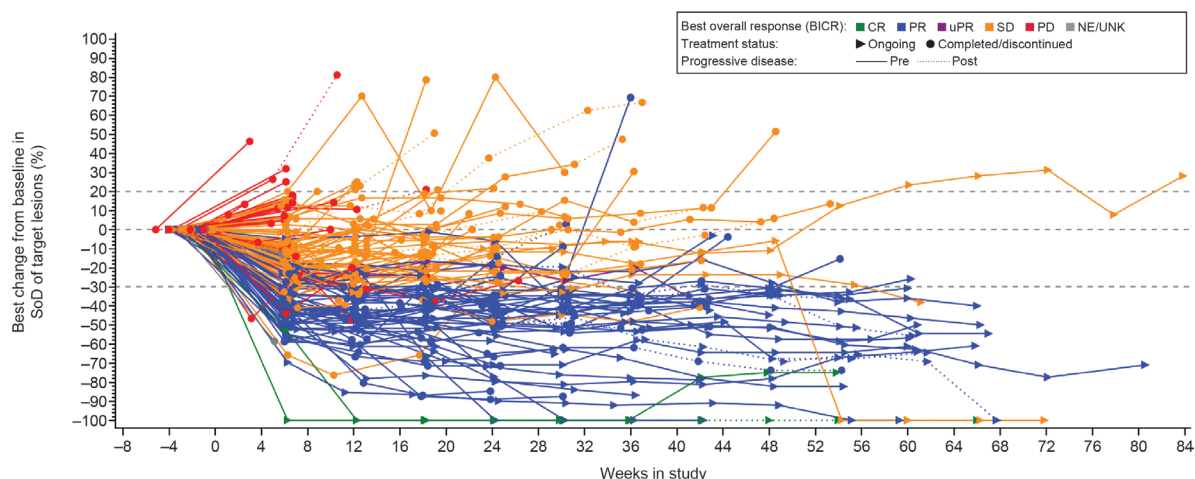


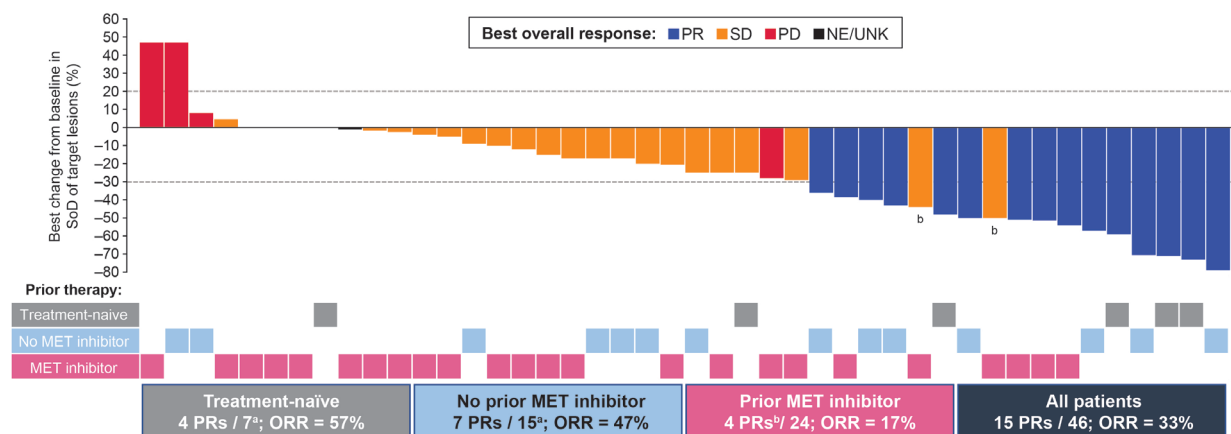
Figure 9. Best change from baseline of target lesions with amivantamab plus lazertinib therapy.

Among the 54 patients who responded to treatment, 30 were ongoing at the time of clinical cutoff. A response duration of ≥ 6 months was observed in 27 patients. Additionally, median time to response was 6.4 weeks (range, 5-54 weeks). For 69 patients with best response of stable disease (SD), 8 remained on treatment and 15 with SD duration ≥ 6 months.

3.3.3 NSCLC: MET mutations

3.3.3.1 CHRYSALIS MET exon 14 skipping cohort (amivantamab monotherapy)⁵⁵

The MET-2 cohort of the CHRYSALIS study evaluated amivantamab monotherapy in patients with advanced or metastatic NSCLC MET exon 14 skipping mutations (N = 55). Of these patients, 28 had prior MET inhibitor therapy and 46 were efficacy evaluable. At the time of presentation at ASCO 2022, median DOR was not estimable and 11 of 15 patients who responded were still receiving treatment. Of the treatment-naïve patients, a 71% clinical benefit objective response rate (CBR) was observed and median PFS was NE (95% CI, 2.6-NE). PRs were observed in 4 patients, and ORR was 57%. For patients with no prior MET therapy, 53% CBR and median PFS of 8.3 months was observed (95% CI, 1.5-15.3). PRs were observed in 7 patients, and ORR was 47%. For patients with prior MET therapy, 58% CBR and median PFS of 4.2 months was observed (95% CI, 2.9-NE). PRs were observed in 4 patients, and ORR was 17%. Median time to response was 1.6 months (range, 1.2-9.9). Overall, 15 PRs were observed, and ORR was 33%. Additionally, the safety profile of amivantamab in patients with MET exon 14 mutations is consistent with the overall safety profile. Treatment interruptions in 21%, reductions in 12%, and discontinuations in 5% of patients were reported. Enrollment in the MET exon 14 cohort of CHRYSALIS is ongoing; however, these preliminary results confirm the independent targeting action of the MET arm of amivantamab. The MET-TKI naïve cohort results are consistent with currently approved MET TKIs.



^aTwo patients discontinued prior to completing their 2nd postbaseline disease assessment (1 in treatment-naïve group and 1 in no prior MET inhibitor group).

^bTwo additional patients had a best timepoint response of PR but did not confirm

Figure 10. Antitumor activity of amivantamab monotherapy.

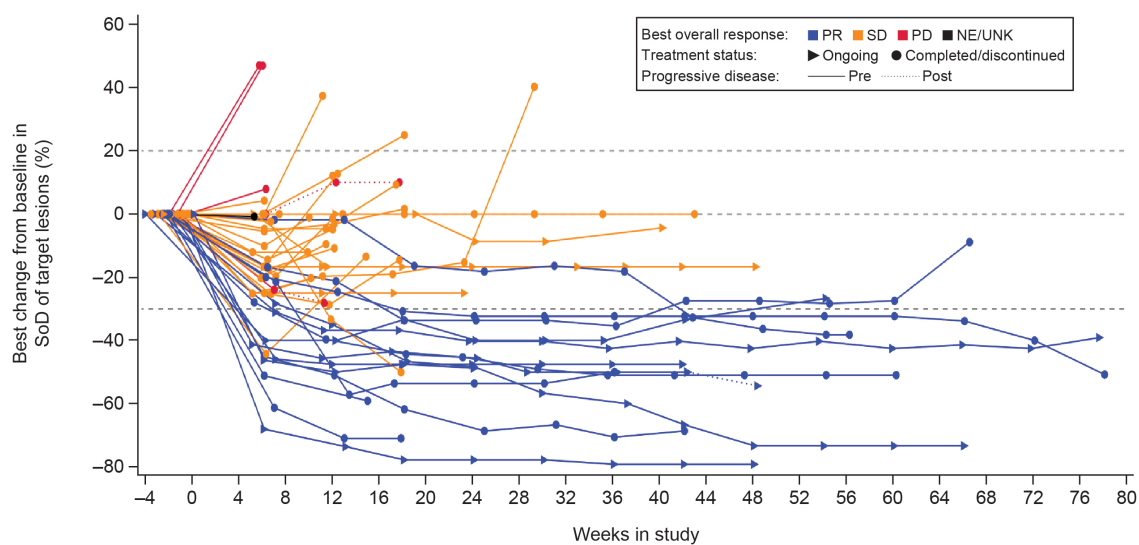


Figure 11. Best change from baseline of target lesions with amivantamab therapy.