

4 Innovation

4.1 RYBREVANT® – a breakthrough drug for NSCLC

On March 10, 2020, the FDA granted breakthrough therapy designation for amivantamab for the treatment of patients with metastatic NSCLC with EGFR ex20ins whose disease had progressed on or after platinum-based chemotherapy. At that time, there were no FDA-approved targeted therapies for patients harboring EGFR ex20ins. FDA breakthrough therapy designation is granted to expedite the development and regulatory review of investigational therapies for serious or life-threatening diseases.⁵⁶

On May 21, 2021, amivantamab became the first targeted therapy approved for adult patients with NSCLC harboring EGFR ex20ins and the first bispecific antibody in NSCLC.⁴³ This approval was based on data from the phase 1 CHRYSALIS study.

4.2 RYBREVANT® – a novel approach for NSCLC therapy with paradigm changing efficacy for NSCLC patients harboring EGFR ex20ins mutations

The novel design and multicomponent mechanism of action for amivantamab has led to a paradigm shift in the treatment of these patients. Furthermore, the availability of this safe and effective targeted therapy makes the identification of patients with these mutations even more critical.

4.2.1 *First targeted therapy to be approved for NSCLC patients harboring EGFR ex20ins mutations following progression on chemotherapy*

Amivantamab is the first targeted therapy to be approved for use in patients with NSCLC harboring EGFR ex20ins, improving the prognosis of this patient population who previously had limited effective options after progression on chemotherapy. The proven efficacy of amivantamab in this patient population, including an ORR of 40% (95% CI, 29-51), along with its tolerable safety profile (which is consistent with on-target inhibition of EGFR and MET pathways), led to its approval.²⁶

4.2.2 *First fully human, bispecific antibody approved for the treatment of patients with NSCLC that targets EGFR ex20ins mutations*

Amivantamab has demonstrated clinically meaningful efficacy in patients with EGFR ex20ins NSCLC. Although the role of MET expression and/or activation in patients with EGFR ex20ins NSCLC has not been established, the proven effectiveness of this bispecific antibody suggests that the specificity of antibody-based therapies can be broadened while maintaining efficacy.²⁶ The bispecific nature of amivantamab provides potential to treat other EGFR-driven and/or MET-driven tumors; research is ongoing to determine its efficacy and safety in a number of these patient populations. The tolerable safety profile of amivantamab may prove to be critical in its continued use in the EGFR ex20ins as well as its potential use in numerous other populations.⁵⁷

4.3 RYBREVANT® offers a unique multilayered mechanism of action, which suggests it may be effective in a broader range of patients and in combination with different therapies

Amivantamab's mechanisms of action, which include ligand blocking, receptor degradation, and immune cell-mediated activity, provide great potential for innovative use. As research continues, the importance of each component and its effect in different mutations and patient populations will be further elucidated.

4.3.1 Ligand blocking

The EGFR and MET signaling pathways lead to cell proliferation; hence, blocking ligand-induced receptor phosphorylation/activation slows cell proliferation and cancer growth.⁵² However, given that patients with NSCLC harboring EGFR ex20ins and other activating mutations possess tyrosine kinase receptors whose equilibrium is shifted toward the active state^{58,59} and in light of tumor heterogeneity, much of the cell proliferation due to activated TKI signaling pathways is independent of ligand binding to the TKI receptors.²² Although other components of amivantamab's mechanisms of action discussed below work independent of ligand-induced activation, the combination of amivantamab with a treatment that blocks ligand-independent signaling may provide additional benefit in patients with activating mutations. Studies of such treatment combinations are ongoing, including CHRYSALIS-2, MARIPOSA, and MARIPOSA-2, which are evaluating the efficacy and safety of amivantamab plus lazertinib,⁵⁷ a brain-penetrant third-generation EGFR TKI with activity against T790M mutations,⁶⁰ in patients with common and uncommon EGFR mutations. A waterfall plot showing the promising preliminary results from Cohort A of CHRYSALIS-2, which is evaluating patients with NSCLC harboring ex19del or L858R deletion post-osimertinib and platinum-based chemotherapy, is shown below.

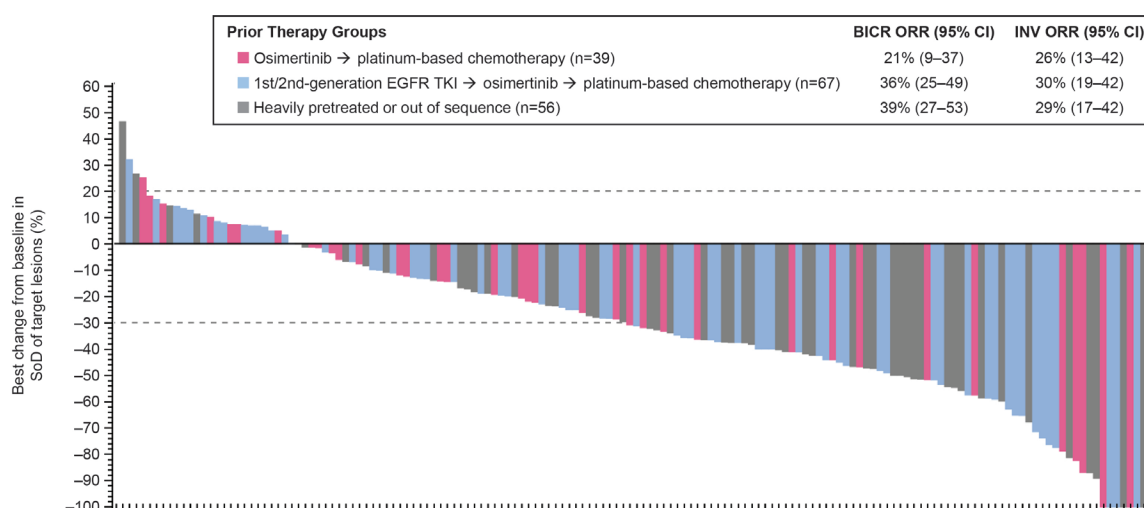


Figure 12. Best change from baseline in sum of diameters (SoD) of target lesions.⁵⁴

4.3.2 Receptor degradation

Removing receptors from the cell membrane prevents ligand-dependent and ligand-independent activation of the pro-proliferation pathways and thus inhibits cell proliferation and tumor growth.¹⁴ This mechanism may be of particular benefit in patients with EGFR and/or MET amplification mutations, as they have an overabundance of receptors with the potential to trigger cell proliferation. Further research and biomarker analysis are needed for this assessment.

4.3.3 Immune cell-directing functions

The low-fucose FC domain of amivantamab triggers immune cell-directed activity against tumor cells with mutated EGFR and MET receptors.³⁹ Monocytes, macrophages, and natural killer cells act through various mechanisms, as detailed in section 3, to reduce tumor cell proliferation and/or cause tumor cell death.³⁹ The role of the immune cell-directing activity in amivantamab's mechanism of action suggests that combining amivantamab with ICIs or other immunotherapy may be effective, providing an area of future research.

4.3.4 Dual-receptor action

By targeting the extracellular portion of EGFR and mesenchymal-epithelial transition factor (MET) receptor, amivantamab bypasses intracellular resistance mechanisms. Moreover, as many patients will have mutations in both receptors due to the overlapping signaling pathways of EGFR and MET and the compensatory changes which occur in one pathway when the other is inhibited, targeting both receptors rather than just one provides additional benefit.¹⁵ These mechanisms of action suggest that, in addition to efficacy in EGFR ex20ins mutations, amivantamab may prove efficacious as monotherapy or in combination with other therapies in patients with NSCLC harboring various primary and secondary EGFR and MET mutations, including those with common EGFR mutations (such as those who have relapsed after TKIs) and MET exon 14 skipping mutations.

Due to this potential efficacy, various trials are ongoing to determine the efficacy of amivantamab monotherapy and combination therapy in different patient populations, many of which are detailed in section 3. Cohorts in CHRYSLIS are evaluating amivantamab monotherapy in patients with different primary and secondary EGFR and MET mutations. For example, the MET-2 cohort of the CHRYSLIS trial is evaluating amivantamab monotherapy in both treatment-naïve and previously treated patients with advanced or metastatic NSCLC MET exon 14 skipping mutations, with encouraging preliminary results.⁶¹ CHRYSLIS-2, MARIPOSA, MARIPOSA-2, and PAPILLON trials are also evaluating amivantamab combination therapy in various patient populations, as discussed in section 3.

4.4 Improving patient convenience with RYBREVANT®

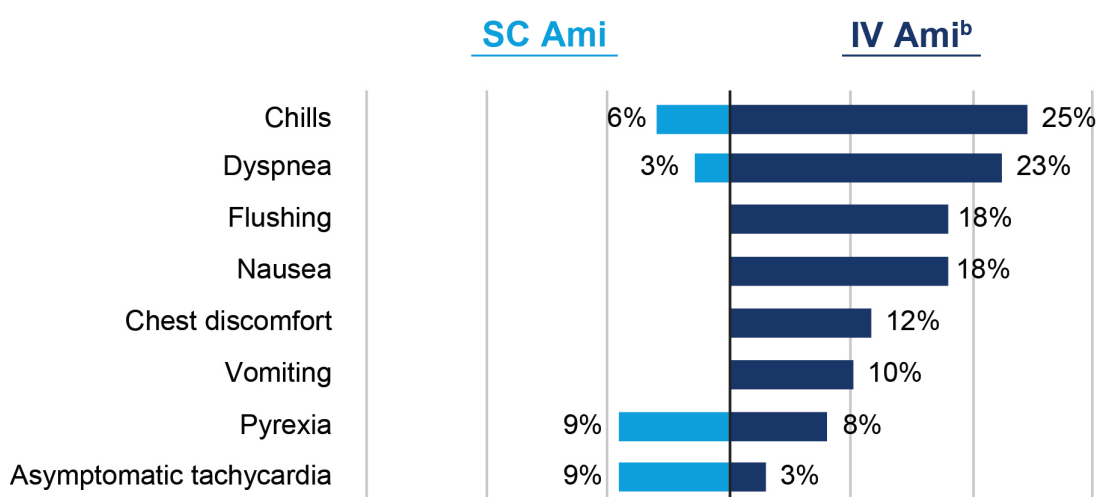
Although studies have demonstrated the safety profile of amivantamab, intravenous (IV) delivery of amivantamab leads to IRRs among 67% of patients, resulting in dose interruptions and slower infusion restart rates, and necessitates splitting of the first dose over 2 days.⁵⁵ Subcutaneous (SC) administration of amivantamab could

simplify and accelerate administration, reduce patient morbidity, and improve the overall patient and health care provider experience. Investigational SC formulations of amivantamab have been developed and are currently being studied.

4.4.1 SC formulation

4.4.1.1 PALOMA (amivantamab SC in advanced solid malignancies)⁶²

The ongoing phase 1 PALOMA study, with an estimated enrollment of 196 participants, is investigating SC administration of amivantamab to assess the feasibility, safety, and pharmacokinetics of SC formulations of amivantamab ± recombinant human hyaluronidase. Preliminary results show that, compared with IV administration, SC administration of amivantamab reduced delivery time, did not require split dosing, and reduced the incidence and severity of IRRs. The AE profile, outside of IRRs, was comparable to IV amivantamab. IRRs were observed with 18.2% of patients in PALOMA as compared to 67.3% of patients in CHRYSALIS.⁵⁵



^aAll IRR symptoms with SC administration; IRR symptoms ≥10% for IV administration.

^bIRR symptoms reported in all patients treated at the RP2D in the CHRYSALIS study based on a March 2021 data cutoff.^{44,55}

Figure 13. IRR symptoms^a with SC administration as compared to historical IRR symptoms with IV administration of amivantamab.

4.4.1.2 PALOMA-3 (amivantamab SC + lazertinib in NSCLC post-OSI and platinum-based chemotherapy)⁶³

The primary objective of the ongoing phase 3 PALOMA-3 trial, which has an estimated enrollment of 604, is to assess the noninferiority of SC amivantamab as a co-formulation with human hyaluronidase (SC-CF) plus lazertinib versus amivantamab IV in patients with NSCLC who have progressed on or after osimertinib and chemotherapy. The rationale for conducting this study in this setting is based on 2 factors. First, previously treated NSCLCs harboring an EGFR ex19del or exon 21 L858R mutation represent a large patient population with profound unmet medical needs. Second, to identify the impact of changing amivantamab from an IV

administration to a SC route of administration, the ideal clinical setting is one where amivantamab is anticipated to be the major contributor to the observed antitumor activity. Among patients who have already experienced disease progression on the third-generation EGFR TKI osimertinib, it is unlikely that the third-generation EGFR TKI lazertinib alone would have significant activity. Therefore, the ORR in this setting more closely reflects the clinical activity of amivantamab and is therefore the most appropriate clinical setting to demonstrate the noninferiority of amivantamab SC versus amivantamab IV combinations.

4.5 Ongoing innovation: RYBREVANT®, a revolution in NSCLC and beyond

While the CHRYSALIS study helped establish amivantamab as the first targeted therapy for NSCLC patients harboring EGFR ex20ins on or after progression with platinum-based chemotherapy, studies are ongoing to demonstrate that amivantamab can revolutionize treatment in other settings beyond NSCLC.

4.5.1 RYBREVANT® in gastric or esophageal cancer⁶⁴

Amivantamab is being evaluated in a phase 2 study enrolling patients with gastric or esophageal cancer. Patients must be refractory to ≥ 2 or ≥ 1 prior lines of therapy for gastric and esophageal cancer, respectively, which must include fluoropyrimidine- and platinum-based chemotherapies. Patients will be excluded for prior EGFR or cMET therapies and the presence of untreated brain metastases. The primary endpoint being evaluated is ORR. This study is currently recruiting and is expected to enroll 60 patients. The estimated study completion date is June 30, 2023.

4.5.2 RYBREVANT® in advanced or metastatic colorectal cancer⁶⁵

A phase 1b/2 study will evaluate amivantamab monotherapy and amivantamab in combination with standard of care chemotherapy in patients with advanced or metastatic colorectal cancer. Two anti-EGFR antibodies are currently considered standard of care for colorectal cancer; however, MET is highly expressed in certain subsets of patients with CRC and may confer resistance to anti-EGFR therapies. The primary outcome measures will include ORR, number of patients with dose-limiting toxicities, AEs, and laboratory or vital sign abnormalities. This study is not yet recruiting and is expected to enroll 225 patients. The estimated study completion date is October 30, 2026.

4.6 Conclusion

With the discovery of numerous genetic mutations that contribute to lung cancer, finding therapies to target these mutations and improve survival has become a focus of lung cancer research. Various therapies have been developed, including treatments developed to combat acquired mutations that have created resistance to previous treatments. Therefore, finding therapies that can treat resistance mutations is an area of high unmet need. The bispecific nature of amivantamab as well as its multimodal mechanism of action enables it to treat common and

uncommon primary and resistance mutations in NSCLC. In doing so, it has broadened the scope of patients for whom targeted therapy is available and effective. In its first approved indication, it improved survival for patients with NSCLC harboring EGFR ex20ins who previously had limited therapy options beyond chemotherapy and whose prognosis was significantly worse than those with the common EGFR mutations, for whom EGFR TKIs are, at least initially, effective. As research continues to explore the use of amivantamab in several other patient populations with NSCLC as well as in patients with other types of cancer, there is potential to greatly expand the reach and benefit of this novel therapy.