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Management of infusion-related reactions (IRRs) in patients receiving amivantamab in the CHRYSALIS study

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ABSTRACT

Background: Amivantamab, a fully humanized EGFR-MET bispecific antibody, has antitumor activity in diverse EGFR- and MET-driven non-small cell lung cancer (NSCLC) and a safety profile consistent with associated on-target activities. Infusion-related reaction(s) (IRR[s]) are reported commonly with amivantamab. We review IRR and subsequent management in amivantamab-treated patients.

Methods: Patients treated with the approved dose of intravenous amivantamab (1050 mg, <80 kg; 1400 mg, ≥80 kg) in CHRYSALIS—an ongoing, phase 1 study in advanced EGFR-mutated NSCLC—were included in this analysis. IRR mitigations included split first dose (350 mg, day 1 [D1]; remainder, D2), reduced initial infusion rates with proactive infusion interruption, and steroid premedication before initial dose. For all doses, pre-infusion antihistamines and antipyretics were required. Steroids were optional after the initial dose.

Results: As of 3/30/2021, 380 patients received amivantamab. IRRs were reported in 256 (67%) patients. Signs/symptoms of IRR included chills, dyspnea, flushing, nausea, chest discomfort, and vomiting. Most of the 279 IRRs were grade 1 or 2; grade 3 and 4 IRR occurred in 7 and 1 patients, respectively. Most (90%) IRRs occurred on cycle 1, D1 (C1D1); median time-to-first-IRR onset during C1D1 was 60 min; and first-infusion IRRs did not compromise subsequent infusions. Per protocol, IRR was mitigated on C1D1 with holding of infusion (56% [214/380]), reinitiating at reduced rate (53% [202/380]), and aborting infusion (14% [53/380]). C1D2 infusions were completed in 85% (45/53) of patients who had C1D1 infusions aborted. Four patients (1% [4/380]) discontinued treatment due to IRR. In studies aimed at elucidating the underlying mechanism(s) of IRR, no pattern was observed between patients with versus without IRR.

Conclusion: IRRs with amivantamab were predominantly low grade and limited to first infusion, and rarely occurred with subsequent dosing. Close monitoring for IRR with the initial amivantamab dose and early intervention at first IRR signs/symptoms should be part of routine amivantamab administration.

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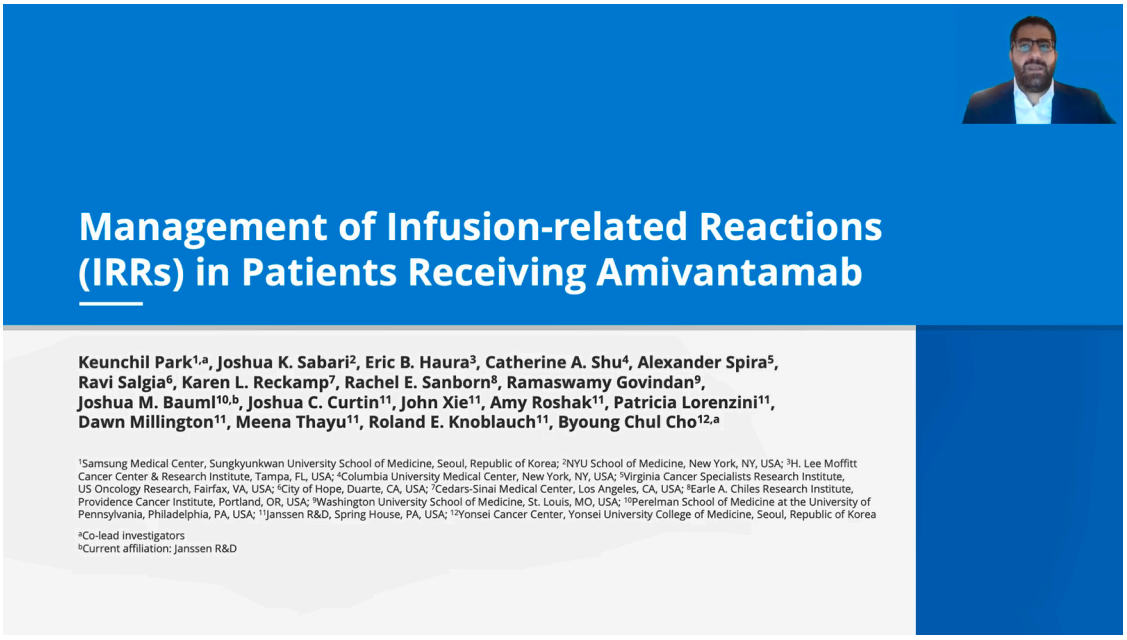
1. Introduction

Amivantamab (RYBREVANT®, Janssen Biotech, Inc) is a fully humanized, immunoglobulin (Ig) G1, epidermal growth factor receptor (EGFR)-MET bispecific antibody with multiple mechanisms of action, including immune cell-directing activity that was designed to simultaneously block 2 distinct driver pathways in NSCLC.[1–3] By binding to the extracellular domains of EGFR and MET with high affinity, amivantamab inhibits ligand binding, promotes receptor-antibody complex endocytosis and degradation, induces Fc-dependent trogocytosis by macrophages, and causes antibody-dependent cellular cytotoxicity by natural killer cells. Amivantamab has demonstrated antitumor activity in diverse EGFR- and MET-driven non-small cell lung cancer (NSCLC),[1–6] and the safety profile of amivantamab is consistent with associated on-target activities.

In CHRYSALIS—an ongoing, first-in-human, open-label, dose-escalation/-expansion, phase 1 study—the safety, pharmacokinetics, and efficacy of amivantamab are being evaluated in adults with advanced NSCLC as monotherapy and in combination with other therapies.[5] Efficacy benefits within the population of patients with NSCLC and EGFR exon 20 insertion mutations (ex20ins) who progressed on or after platinum-based chemotherapy included an overall response rate of 40 % and median duration of response of 11.1 months, with 63 % of patients having a duration of response of ≥ 6 months.[7] Based on these findings, amivantamab was the first targeted therapy approved for the treatment of these patients.[7,8].

Conventional cytotoxic drugs and therapeutic monoclonal antibodies, including amivantamab, have been associated with infusion-related reaction(s) IRR(s).[5,7] IRRs can range from presenting as mild-to-moderate signs and symptoms (eg, as chills, fever, mild hypotension, dyspnea, and rash) to causing death.[9,10] Systemic IRRs, which may occur with the introduction of a new protein therapeutic infusion, are frequently observed; however, the mechanism inducing the reactions vary.[9,10] The Common Terminology Criteria for Adverse Events (CTCAE) includes separate criteria and grades of severity for each type of reaction: allergic reaction versus IRR.[11] Though IRRs are a common complication of monoclonal antibodies, they typically can be managed.[10] The objectives of this analysis of data from the ongoing CHRYSALIS study were to characterize the incidence and symptomatology of IRR in patients treated with amivantamab and review subsequent management strategies employed for IRR mitigation.[5] To view a summary of the study presented by Dr Joshua K. Sabari, please **click on the image** or see the **Supplementary data** available online.



Video 1.

2. Methods

2.1. Study design and population

CHRYSALIS is an ongoing study (NCT02609776) that was designed to determine the recommended phase 2 dose (RP2D) of amivantamab, as well as its antitumor activity in patients with advanced NSCLC.[5] The study design, as well as findings from the population of patients with EGFR ex20ins NSCLC previously treated with platinum-based chemotherapy, have been reported.[5] The present analysis, which was conducted for descriptive purposes only, included all patients in CHRYSALIS who were treated at the RP2D of intravenous (IV) amivantamab (1050 mg for patients weighing < 80 kg; 1400 mg for patients weighing ≥ 80 kg) as of March 30, 2021. Where appropriate, data were summarized as numbers and corresponding percentages.

2.2. Infusion-related reactions and mitigation strategies

During cycle 1 (C1), a peripheral line rather than a central line was required to limit initial amivantamab exposure in the event the infusion needed to be stopped due to IRR. Use of a central line catheter was permitted for cycle 2, day 1 (C2D1) and all subsequent cycles. IV administration sets were primed with 15 to 25 mL of 5.0 % dextrose (glucose) solution or 0.9 % normal saline solution before infusing amivantamab. At the end of infusion, 10 mL of blood volume was drawn and discarded before flushing the catheter with dextrose/saline to avoid rapid infusion of residual amivantamab. Adverse events, including IRR, were graded according to CTCAE, version 4.03.[5,12].

Mitigation strategies were implemented to reduce the risks associated with IRR, including reducing the rate of initial infusion of amivantamab, and encouraging the temporary interruption of infusions at the first signs of IRR (Fig. 1; Table 1) were previously described in detail.[5] Patients had the first dose of amivantamab administered in a “split

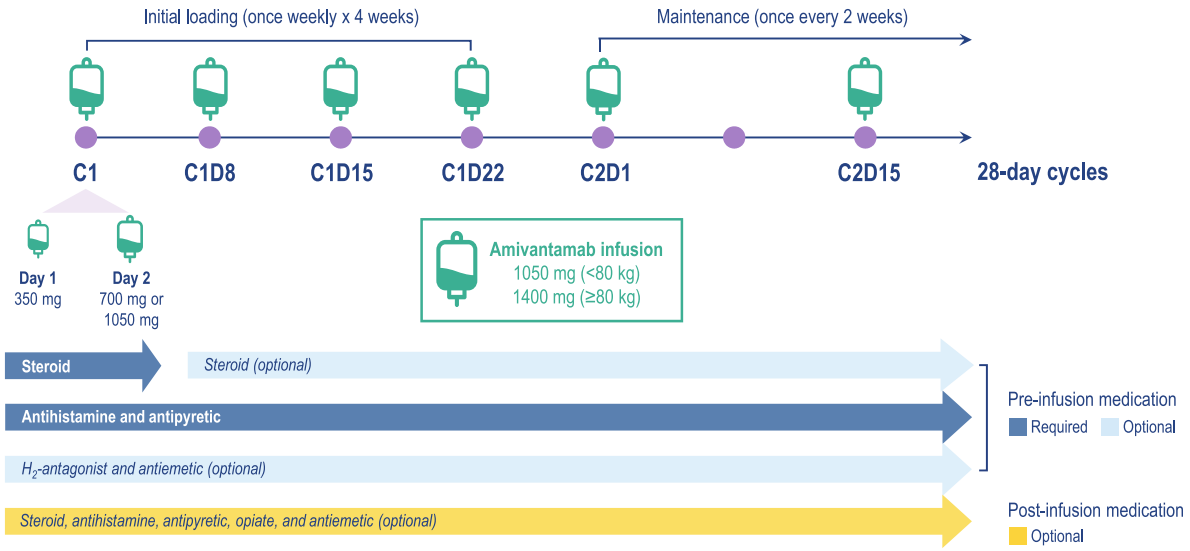


Fig 1. Amivantamab monotherapy dosing schema. Abbreviations: C, cycle 1; D, day.

Table 1
Guidelines for monitoring and management of infusion-related reactions in CHRYSALIS.

Toxicity grade	Treatment/intervention	Pre-medication and treatments at subsequent dosing
General	Patients were informed of the symptoms of IRR and instructed to alert site staff as soon as they were experienced	
Grade 1 *Mild reaction*	If occurring with initial dose, consider infusion interruption	Antihistamine, antipyretic, and steroid
Grade 2 *Mild-to-moderate reaction*	Interrupt infusion, monitor until symptoms recover First interruption: restart at 50 % the rate Second interruption: Restart at 50 % the rate at time of the second interruption or consider discontinuation at that visit If no evidence of recurring IRR symptoms after 30 min, rate can be increased to the prior rate Further rate escalation can resume after another 30 min if no evidence of recurring signs and symptoms	Antihistamine, antipyretic, and steroid Consider meperidine for chills and rigor
Grade 3 *Severe reaction*	Stop infusion	Based on the severity of symptoms, consider discontinuation of treatment with amivantamab Discontinue treatment with amivantamab for recurrent grade 3 IRR
Grade 4 *Life-threatening reaction*	Stop infusion	Discontinue treatment with amivantamab

Abbreviations: IRR, infusion-related reaction.

manner", with 350 mg administered on C1D1 and the remainder administered on C1D2. Per protocol, to prevent or mitigate IRR events, pre-treatment with corticosteroids, an antihistamine, and acetaminophen was implemented, along with an escalating infusion rate regimen, starting with the first dose. Patients were to report signs and symptoms of IRR early to allow for rapid interruption and to prevent worsening of the IRR.[5] For all doses, pre-infusion antihistamines and antipyretics were required. Steroids were optional after the initial dose.

2.3. Translational studies

During the conduct of the CHRYSALIS study, the protocol was amended to allow for the collection of serum samples for use in translational studies, which were performed to evaluate potential mechanisms of the IRR observed with amivantamab administration, such as cytokine release, tumor lysis syndrome, mast cell degranulation, and complement activation. Serum samples were collected on C1D1 (start of infusion, 2 h after start of infusion, and end of infusion), C1D2 (start of infusion and end of infusion), and at the onset of IRR from a subset of patients who received amivantamab (additional samples). Tumor necrosis factor-α, interferon-γ, and interleukin-6 levels were measured to assess cytokine release syndrome; calcium, potassium, urate, lactate dehydrogenase levels were measured to evaluate tumor lysis syndrome; and tryptase and histamine levels were measured to assess mast cell degranulation. Complement activation was assessed using the 50 % hemolytic complement assay (CH_{50}). Comparisons in marker levels were made between patients with and without IRR.

3. Results

3.1. Patients

As of the March 30, 2021 data cutoff, 380 patients had received the RP2D of amivantamab monotherapy in CHRYSALIS. IRRs were reported in 256 (67 %) of these patients. Overall, 279 IRRs were reported during the analysis period: 66 % (252/380) on C1D1, 3.5 % (13/371) on C1D2, 0.8 % (3/363) on C1D8, 0.8 % (3/353) on C1D15, 0.3 % (1/345) on C1D22, and 0.11 % (5/4518) on or after cycle 2.

Table 2
Most frequent (≥ 10 % of patients with infusion-related reactions) symptoms of infusion-related reactions.

Symptom of infusion-related reaction, n (%)	Total (n = 256)
Chills	94 (37)
Dyspnea	86 (34)
Flushing	68 (27)
Nausea	69 (27)
Chest discomfort	45 (18)
Vomiting	39 (15)

3.2. Infusion-related reactions and mitigation strategies

IRRs typically were experienced as a systemic reaction, with the most frequently experienced symptoms (≥ 10 % of patients with IRR) being chills (37 %) and dyspnea (34 %) (Table 2). Among the 380 patients included in this analysis: 39 (10 %) had grade 1 severity, 209 (55 %) had grade 2 severity, 7 (2 %) had grade 3 severity IRR events, and 1 (0.3 %)—who received the C1D1 dose with required premedication but without implementation of IRR mitigation strategies (ie, reduced infusion rate at first infusion)—had a grade 4 severity event (Fig. 2). No patient had a grade 5 severity IRR event. The predominance of grade 2 IRR (ie, infusion interruption indicated but responded promptly to symptomatic treatment) on C1D1 is consistent with protocol recommendations to hold an infusion at the first sign of an IRR, even for grade 1 events, to prevent more serious reactions. Most of the 279 IRR events (97 %) were grade 1 or 2 severity; the vast majority of events (90 %) occurred on C1D1; and these events did not compromise the ability to administer subsequent infusions. Only 5 events occurred on or after cycle 2. IRRs occurred early during infusion, with a median time to first IRR onset for C1D1 being 60 min (range: 1–1071).

All patients received pre-infusion steroids on C1D1 and C1D2 as required per protocol to reduce the risk of severe IRR. Approximately half (51 %) of patients received optional steroids on C1D8, and use of optional steroids decreased with subsequent cycles (Fig. 3). Most IRRs were managed by modifying the ongoing infusion (Table 3). C1D1 infusion was aborted for 53 IRRs (21 % of IRRs and 14 % of all patients); however, 45 (85 %) of the 53 patients completed the C1D2 infusion. Only 4 patients discontinued treatment due to IRR (1.1 % of all patients; 1.6 % of patients with an IRR); 3 patients discontinued after the C1D1 infusion, and 1 patient discontinued after the C16D1 infusion. All 4 of the IRRs that led to discontinued treatment were grade 4 severity, which led physicians to discontinue amivantamab monotherapy in accordance with the CHRYSALIS protocol recommendations (Table 1).

Medications to treat IRR were reported for 208 (55 %) patients and were used primarily on C1D1 (91 %) and C1D2 (5 %). The most commonly utilized medications to treat IRRs were antihistamines (36 %), steroids (33 %), analgesics (21 %), oxygen (12 %), and histamine H2-receptor antagonists (11 %).

3.3. Translational studies

Quantification of cytokine release markers, mast cell degranulation markers, tumor lysis syndrome markers, and complement activity over time in patients experiencing IRRs, as well as in comparison to patients who did not experienced IRRs, failed to identify any marker that was associated with amivantamab IRR. (Supplementary Fig. 1).

4. Discussion

In the CHRYSALIS study, treatment with amivantamab provided robust and durable efficacy in patients with ex20ins NSCLC who progressed on or after platinum-based chemotherapy, which is a population that typically has a poor prognosis and historically had few subsequent treatment options. IRRs frequently occur with the first exposure to amivantamab. Consequently, the IRR primarily occurs early in the first infusion on C1D1, with a median time to onset of 60 min. With the recommended mitigation strategies, and with early identification by healthcare providers, patients, or both, these reactions can be effectively managed. IRRs are generally low toxicity grade, and rarely prevent patients from having the opportunity to receive clinical benefit with amivantamab. Findings from this analysis indicate the management guidelines followed during the clinical trial, including the amivantamab

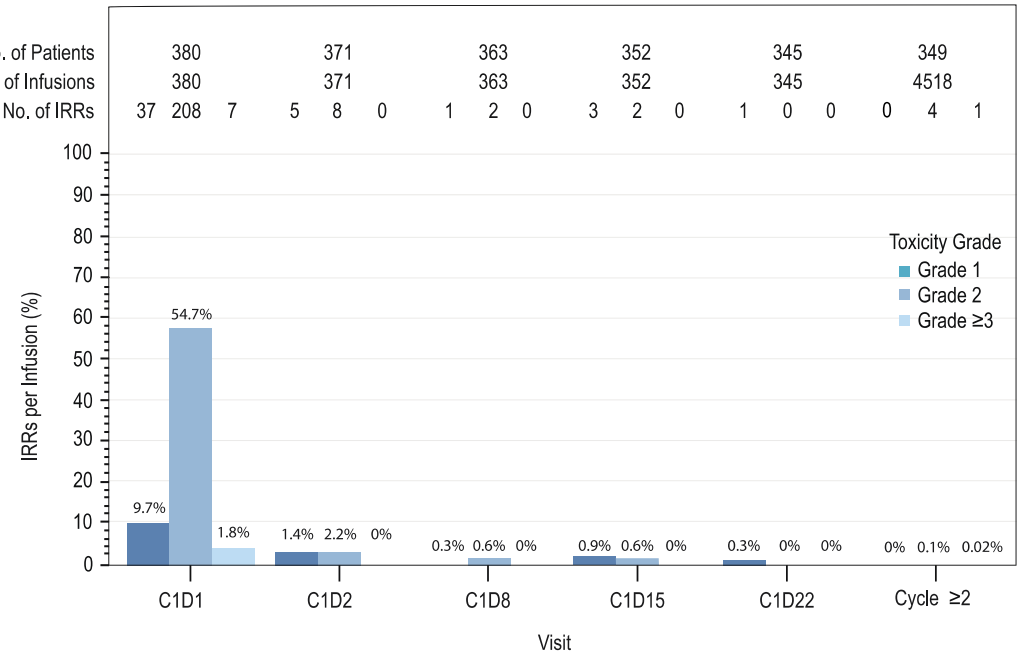


Fig 2. Infusion-related reactions per amivantamab infusion by toxicity grade. Infusion-related reactions were counted only once per visit (C1D1 and C1D2 were counted as separate infusion visits) per patient. The event with the worst toxicity experienced by the patient was used. Abbreviations: C, cycle; D, day; IRR; infusion-related reaction.

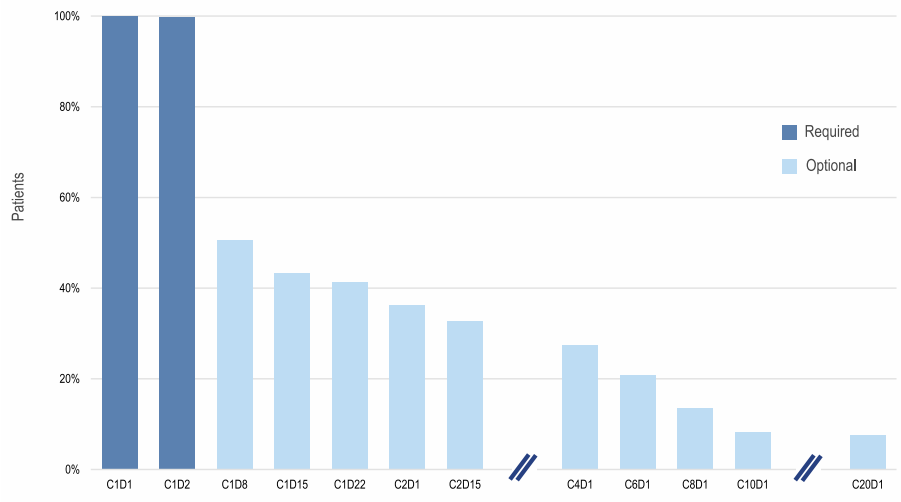


Fig 3. Receipt of pre-infusion steroid medications[a] by cycle. [a]An early protocol amendment required steroid premedication with each amivantamab dose, which was modified with subsequent protocol amendments when declining infusion-related reaction risk was recognized. Abbreviations: C, cycle; D, day.

Table 3
Treatment modifications due to infusion-related reactions.

	Total (n = 380)
Patients with infusion-related reactions, n (%)	256 (67)
Treatment modifications during the C1D1 infusion, n (%)	
Infusion interrupted	214 (56)
Infusion rate decreased	202 (53)
Infusion not completed	53 (14)[a]
Discontinued treatment, n (%)	4 (1)[b]

Abbreviations C, cycle D, day.
[a] C1D2 infusions were completed in 45 patients.
[b] Three patients discontinued after the C1D1 infusion, and 1 patient discontinued after the C16D1 infusion.

dosing schedule and pre-/post-infusion medications (Fig. 1; Table 1), were successful in managing amivantamab IRR. In the present analysis, only 5 events occurred after cycle 2, and few patients discontinued treatment due to IRR. Results of CHRYSALIS informed the recommendations for administering amivantamab and the guidance for monitoring and managing IRR that are provided in the US prescribing information [7] (summarized in Supplementary Table 1).

Signs and symptoms of IRR observed with amivantamab administration are consistent with IRRs described for other monoclonal antibody injectables.[9,10] However, amivantamab IRRs are different from those reported with administration of conventional cytotoxic drugs (IgE-mediated allergic reactions)[9] and some other monoclonal antibodies (cytokine-release reactions)[9] in that they are primarily a first-infusion (vs second-infusion or recurrent) event and do not affect subsequent treatments.

As mentioned, the most commonly experienced IRR symptoms experienced with amivantamab infusion are chills, dyspnea, flushing, nausea, chest discomfort, and vomiting. Healthcare providers should explain these symptoms to new (amivantamab-naïve) patients before their first infusion. Effective management of amivantamab-related IRRs can be accomplished with proactive patient-reporting of the onset of symptoms consistent with an IRR and temporary suspension of the infusion, except for grade 4 events.[7,8] Importantly, the vast majority of amivantamab-related IRRs will not preclude patients from continuing therapy; the risk of IRR drops substantially with continued therapy, including C1D2 dosing. When resuming amivantamab after a prolonged dose hold lasting over a month, consideration may be given to re-initiating with weekly dosing using the two-day split dose the patient received on C1D1 and C1D2.

As no correlation between IRR and cytokine release, mast cell degranulation, tumor lysis syndrome, or complement activation was observed, the underlying mechanism(s) of amivantamab IRR requires further evaluation. Although we were unable to characterize the exact mechanism of amivantamab-related IRRs, results suggest that cytokine release syndrome, mast cell degranulation, tumor lysis syndrome, and complement activation do not play a pathophysiologic role. Furthermore, the ability to successfully rechallenge patients with amivantamab after IRR in the vast number of cases strongly argues against IgE-mediated allergic reactions that have been observed with other monoclonal antibodies, such as cetuximab. Additional studies of subcutaneous formulation and administration, of amivantamab or the use of other premedication regimens, to reduce the incidence of amivantamab IRR are warranted and are underway.

5. Conclusion

In conclusion, although IRRs occur frequently with amivantamab treatment, they generally do not interfere with long-term therapy administration. Education and early intervention at the first signs or symptoms of IRR should be part of the routine administration of amivantamab.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Data-Sharing Statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to CHRYSALIS study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Previous presentations: Results from this study were presented at European Society for Medical Oncology 2021.

Submission declaration: The work reported within this manuscript is not under consideration for publication elsewhere; the manuscript is approved by all authors; and, if accepted, the work will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.02.008.

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