Section Editors: Theresa Wicklin Gillespie and Constance Visovsky

ORIGINAL RESEARCH

Infusion-Related Reaction Management With Amivantamab for *EGFR* Exon 20 Insertion Mutation NSCLC: A Practical Guide for Advanced Practitioners

LINDSAY DOUGHERTY,[1] CRNP, DNP, WHITNEY E. LEWIS,[2] PharmD, BCOP, MEGHAN O'NEILL,[1] CRNP, MSN, AMITABHA BHAUMIK,[3] PhD, DENISE D'ANDREA,[3] MD, and ANDY L. JOHNSON,[3] PhD

From [1]Abramson Cancer Center, University of Pennsylvania Health System, Philadelphia, Pennsylvania; [2]The University of Texas MD Anderson Cancer Center, Houston, Texas; [3]Janssen Scientific Affairs, LLC, Horsham, Pennsylvania

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Lindsay Dougherty, CRNP, DNP, Abramson Cancer Center, University of Pennsylvania Health System, Perelman Center for Advanced Medicine, 2nd floor West Pavilion, 3400 Civic Center Boulevard, Philadelphia, PA 19104
E-mail: lindsay.dougherty@pennmedicine.upenn.edu

https://doi.org/10.6004/jadpro.2024.15.4.2

Abstract

Many targeted therapies to treat genetic mutations in non–small cell lung cancer (NSCLC) have been developed. Amivantamab (Rybrevant), a bispecific antibody targeting the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor, was approved by the US Food and Drug Administration in 2021 for the treatment of adult patients with locally advanced or metastatic NSCLC *EGFR* exon 20 insertions, whose disease progressed on or after platinum-based chemotherapy. Amivantamab is administered intravenously weekly for 4 weeks, then every 2 weeks starting at Week 5, as 1,050 mg (body weight [BW] < 80 kg) or 1,400 mg (BW ≥ 80 kg), with the first dose split over 2 days. Infusion-related reactions (IRRs) are common with amivantamab and may present as chills, dyspnea, nausea, chest discomfort, and vomiting. To aid in the prevention, diagnosis, and treatment of IRRs, we evaluated infusion duration, IRR timing, and IRR severity in this post hoc analysis of patients who received amivantamab in CHRYSALIS. Infusion duration decreased over time, with a median infusion time at Cycle 1 Day 1 (C1D1) of 4.70 hours (1,050 mg) and 5.08 hours (1,400 mg), decreasing to 2.20 and 2.25 hours, respectively, by C1D22. Of the 273 IRRs, 98% occurred on C1D1 or C1D2, with median onset and time to resolution of 60 minutes. Most IRRs occurred during the infusion, were low grade, and were manageable with intervention strategies or treatment modifications. Advanced practitioners are critical in preventing, diagnosing, and managing IRRs, including educating patients and families, accurately administering infusions, prescribing premedications, and closely monitoring for IRRs.

J Adv Pract Oncol 2024;15(4):245–252

Lung cancer is the second most common cancer in the world and the leading cause of cancer deaths (GLOBOCAN, 2020). Non–small cell lung cancer (NSCLC) makes up approximately 85% of all new lung cancer diagnoses (Minguet et al., 2016). Although patients with early-stage NSCLC can benefit from localized treatments (surgery, radiotherapy, and other adjuvant therapies), patients with late-stage disease require systemic treatment such as chemotherapy, targeted therapies, and immunotherapies (Shokoohi et al., 2022). The 5-year overall survival rates with frontline chemotherapy remain low (7%–16%) despite recent advances in targeted and immunotherapies (Brahmer et al., 2023; Reck et al., 2021). Targeted therapies have improved survival for patients with identifiable mutations (Tan & Tan, 2022); however, clinical benefit is transient due to resistance mutations that often lead to disease progression. Amivantamab (Rybrevant), a bispecific antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET), was approved by the US Food and Drug Administration in 2021 for the treatment of adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion (ex20ins) mutations whose disease has progressed on or after platinum-based chemotherapy, based on results from the phase I, open-label, dose-escalation and dose-expansion CHRYSALIS study (Park et al., 2021a; Janssen Biotech, Inc., 2024). In the cohort of patients with *EGFR* ex20ins, an overall response rate of 40%, clinical benefit rate of 74%, median progression-free survival of 8.3 months, and median duration of response of 11.1 months were observed with amivantamab therapy (Park et al., 2021a).

An infusion-related reaction (IRR) is a common adverse reaction that occurs with the infusion of amivantamab. In the overall CHRYSALIS study population, IRRs were reported in 67% of the 380 patients who received amivantamab monotherapy at the recommended phase II dose (RP2D; data cutoff March 30, 2021), despite prophylaxis (Park et al., 2021b). The most common symptoms of these reactions included chills (25%), dyspnea (23%), flushing (18%), nausea (18%), chest discomfort (12%), and vomiting (10%; Park et al., 2021b). Markers of cytokine release, complement activation, mast cell degranulation, or tumor lysis syndrome were not associated with the IRRs (Park et al., 2021b).

Nurses and advanced practitioners (APs), such as pharmacists, nurse practitioners, and physician assistants, play a key role in the prevention, identification, and management of IRRs. While nurses and APs administer the infusion and monitor the patient throughout its duration, pharmacists are available, as needed, to triage symptoms, answer questions, and educate nurses and other APs who are treating patients with amivantamab. Nurses and APs prepare patients for amivantamab administration by educating them on signs and symptoms to expect before, during, and after their infusion. This is critical, as patients can often identify IRR symptoms prior to objective indicators, such as changes in vital signs. Nurses and pharmacists must carefully communicate orders to ensure the accuracy of the dose and administration rate of amivantamab, as well as the necessary pre- and postinfusion medications. Upon initiation of the infusion, it is important for nurses to identify and manage IRRs early to limit the severity and duration (Caceres et al., 2019).

This post hoc analysis evaluated the incidence, timing, type, and severity of IRRs from the CHRYSALIS trial (data cutoff of October 8, 2020; ClinicalTrials.gov Identifier: NCT02609776).

METHODS

This is a post hoc analysis of data from the CHRYSALIS trial (data cutoff of October 8, 2020) in which patients were treated at the RP2D of intravenous (IV) amivantamab (1,050 mg for body weight [BW] < 80 kg; 1,400 mg for BW ≥ 80 kg) once weekly for 4 weeks and once every 2 weeks thereafter, beginning at Week 5 (Figure 1). To minimize the risk of IRRs, the first dose was split over 2 days (350 mg on Cycle 1 Day 1 [C1D1] and the remainder of the dose on C1D2; Park et al., 2021b). Descriptive summary statistics (mean, median, interquartile range [IQR], and range) were generated to evaluate infusion duration, time to onset, and time to resolution of IRRs. Grade and severity of the reactions were also documented and analyzed. Further details were specified in the trial protocol and may be found in the US Prescribing Information (USPI) for amivantamab (Janssen Biotech, Inc., 2024).

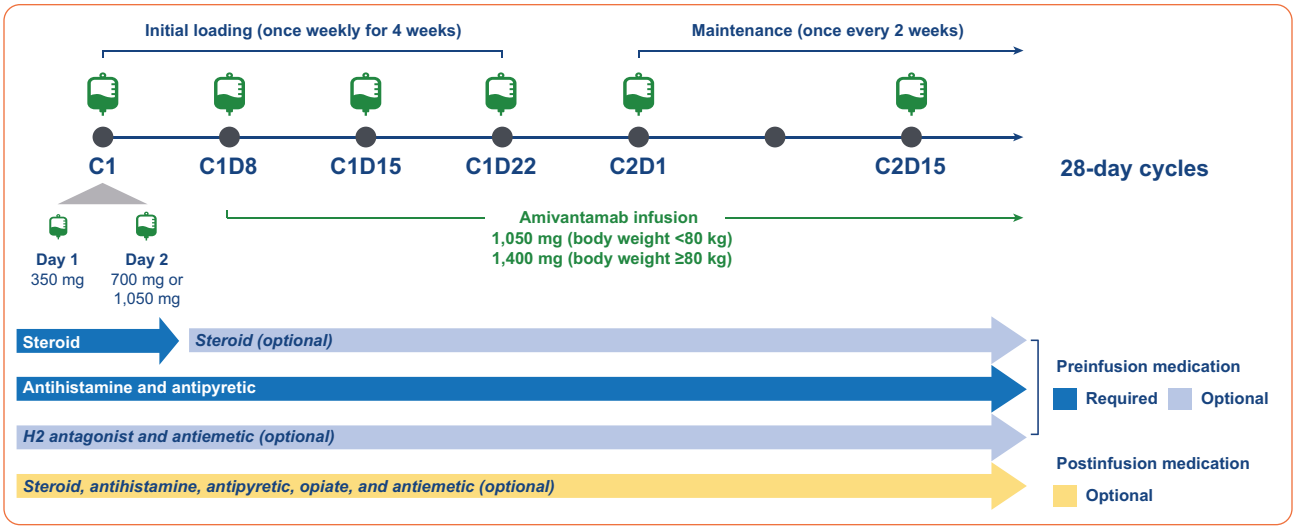


Figure 1. Amivantamab dosing schema. C = Cycle; D = Day. Information from Park et al. (2021b).

RESULTS

Infusion Duration

Of the 4,734 infusions administered to the 302 safety-evaluable patients who received the RP2D, the median infusion duration was 4.70 hours for the 1,050-mg dose and 5.08 hours for the 1,400-mg dose at C1D1 and 4.42 and 6.03 hours, respectively, at C1D2. The longer infusion duration may be explained by the reduced infusion rate and management of IRRs. The infusion duration decreased throughout the remainder of the cycle, with durations at C1D22 of 2.20 and 2.25 hours for the 1,050-mg and 1,400-mg doses, respectively (Figure 2). From Cycle 2 onward, the median infusion duration was 2.37 hours (mean, 2.50; range, 1.6–2.84; IQR, 2.20–2.50) for the 1,050-mg dose and 2.34 hours (mean, 2.36; range, 2.0–3.0; IQR, 2.18–2.54) for the 1,400-mg dose.

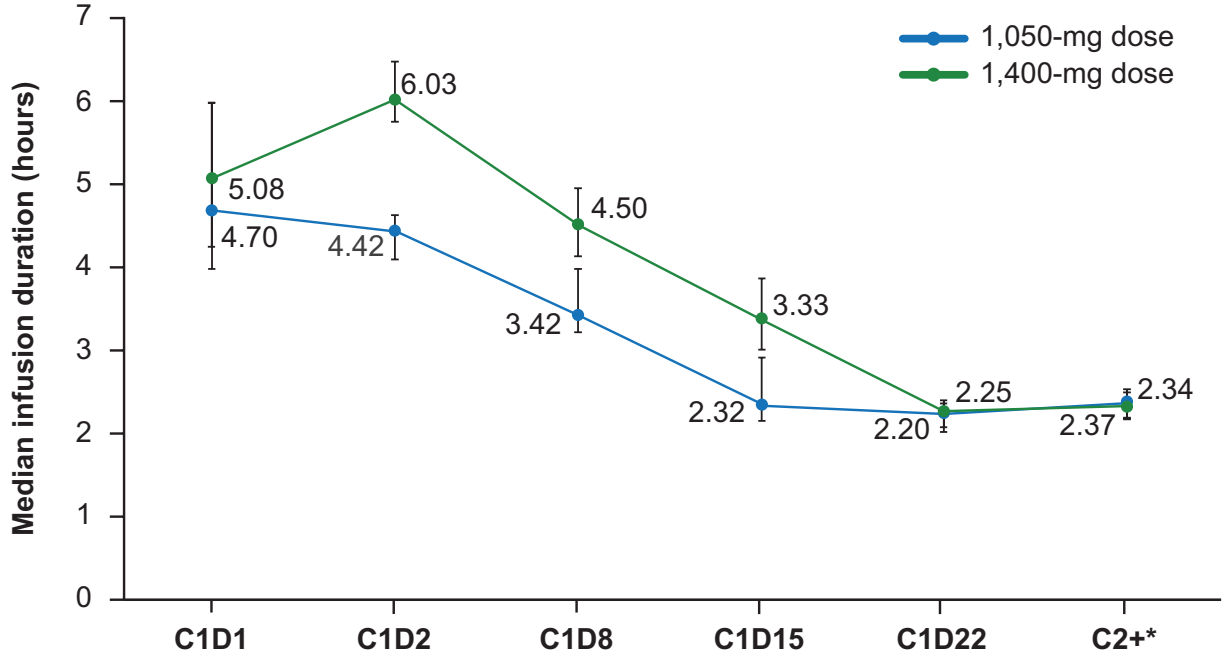
IRR Frequency and Timing

A total of 273 IRRs were experienced by 199 (66%) patients. The baseline characteristics of the patients who experienced IRRs were similar to those of the full safety population. Research is ongoing to identify characteristics of the few patients who experienced recurrent IRRs. Almost all IRRs (268 [98%]) occurred with the first infusion (258 [95%] with the C1D1 infusion and 10 [4%] occurred with the C1D2 infusion; Figure 3); of the patients with IRRs on C1D1, 141 had one IRR, 44 had two IRRs, 10 had three IRRs, and 3 had four IRRs. Of the 273 IRRs, the median time from infusion initiation to the onset of IRRs was 60 minutes (mean, 87.5; range, 7–1,108; IQR, 35–99), and the median time to IRR resolution was 60 minutes (mean, 189.6; range, 1–5,033; IQR, 30–118).

Almost all IRRs occurred during the infusion (266/273 [97%]), with a median IRR onset of 55 minutes (mean, 78.2; range, 7–376; IQR, 34–98). Notably, only seven IRRs occurred after infusion (median, 28 minutes; range, 12–906). Five of these IRRs occurred in three patients at 12 to 29 minutes after infusion, and two occurred in two patients at ≥ 30 minutes after infusion. One of the patients who experienced an IRR at ≥ 30 minutes after infusion had nonserious grade 1 pyrexia that began 906 minutes (15.10 hours) after stopping the infusion on C1D8 and lasted 202 minutes (3.4 hours). The other patient had nonserious grade 2 chills and pyrexia that began 546 minutes (9.1 hours) after stopping the infusion on C1D1 and lasted 525 minutes (8.8 hours).

Grade/Severity of IRRs

In total, 97% of amivantamab IRRs were grade 1 (mild transient reaction; infusion interruption not indicated) to 2 (moderate; infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids]; prophylactic medications indicated for ≤ 24 hours; Janssen Biotech, Inc., 2024; US Department of Health and Human Services, 2017). Symptoms of IRRs were variable and included



Duration of infusion (hours; 1,050-mg dose)						
Mean (SD)	4.97 (1.623)	4.39 (0.567)	3.59 (0.642)	2.51 (0.516)	2.26 (0.318)	2.50 (1.773)
Median	4.70	4.42	3.42	2.32	2.20	2.37
IQR	(4.25–6.00)	(4.10–4.63)	(3.23–4.00)	(2.17–2.93)	(2.08–2.37)	(2.20–2.50)
Range	(0.5–9.7)	(1.5–6.3)	(2.9–8.2)	(1.8–4.8)	(1.9–4.7)	(1.6–28.4)

Duration of infusion (hours; 1,400-mg dose)						
Mean (SD)	4.80 (2.154)	6.05 (0.742)	4.58 (0.585)	3.45 (0.585)	2.37 (0.445)	2.36 (0.234)
Median	5.08	6.03	4.50	3.33	2.25	2.34
IQR	(4.00–6.00)	(5.77–6.49)	(4.15–4.97)	(3.03–3.87)	(2.03–2.42)	(2.18–2.54)
Range	(0.5–9.7)	(4.0–8.0)	(3.0–6.1)	(2.1–5.0)	(1.9–3.9)	(2.0–3.0)

Figure 2. Duration of amivantamab infusion. C = Cycle; D = Day; IQR = interquartile range; SD = standard deviation. Error bars indicate IQRs. *For C2+, the maximum infusion duration was used per patient (as study patients may have received multiple infusions).

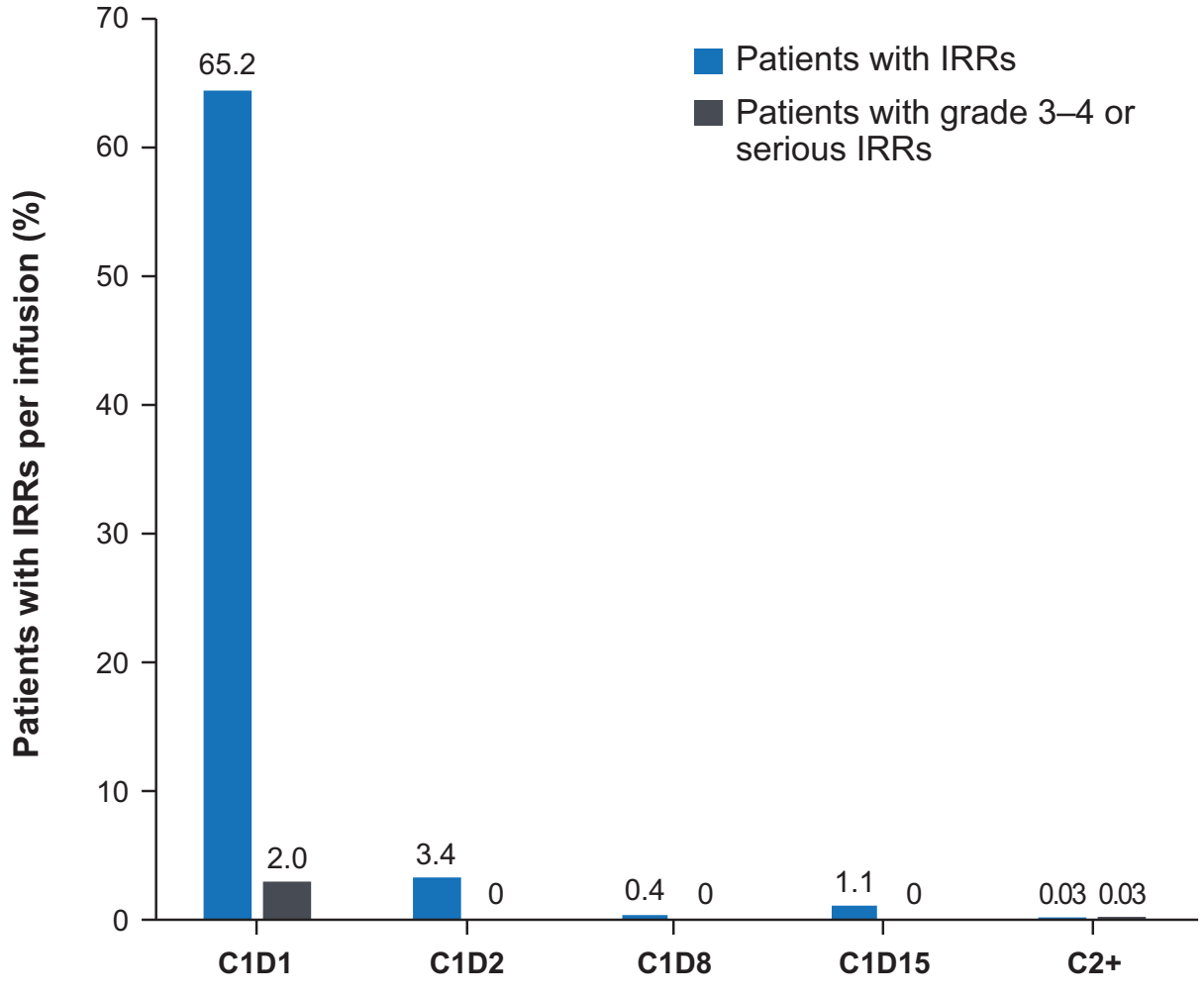
chills, dyspnea, flushing, nausea, chest discomfort, and vomiting. Only 3% of IRRs were grades 3 and 4 (Figure 3). These symptoms included dyspnea, hypoxia, hypertension, hypotension, and, in one patient, loss of consciousness.

Management of IRRs

Most IRRs were manageable with intervention strategies or treatment modifications, including dose interruptions in 56% of patients and infusion rate reductions in 53% of patients. Permanent discontinuation of amivantamab due to IRRs was rare, occurring in only 1.3% of patients. Infusion-related reactions during readministration following a dose interruption of ≥ 28 days were also rare, as only one patient experienced an IRR after a ≥ 28-day dose interruption (n = 86).

DISCUSSION

Discontinuations due to IRRs were rare (1.3% of patients), which in part reflects the critical role nurses and other medical professionals play in preventing,



	C1D1	C1D2	C1D8	C1D15	C2+
Patients with IRRs per infusion (frequency)	197	10	1	3	1
Patients with grade 3–4 or serious IRRs (frequency)	6	0	0	0	1

Figure 3. Patients with IRRs per infusion. C = Cycle; D = Day; IRR = infusion-related reaction.

diagnosing, and managing IRRs. Clinical providers must understand the characteristics of IRRs to provide this high level of care, which not only allows patients to continue their treatment but also maximizes their comfort during treatment. This post hoc analysis demonstrated important features of amivantamab IRRs—notably, that most IRRs associated with amivantamab are low grade, can be treated effectively with dose interruption/modification, and are primarily limited to the first infusion (split on C1D1 and C1D2). Recurrence of IRRs following a dose interruption of ≥ 28 days was rare. The decrease in infusion duration over the course of the treatment cycle is likely explained by the more rapid recommended infusion rate and decreased incidence of IRRs. As the number of IRRs decreases,

the management of any remaining adverse events (AEs) is important to address. Advanced practitioners should distinguish IRRs, which are primarily confined to C1D1, from AEs that may be seen throughout the course of treatment.

Knowledge of the timing, duration, type, and severity of amivantamab IRRs can guide the APs who play crucial, interconnected roles in the care of patients receiving amivantamab infusions. Additionally, nurses, pharmacists, and others involved in patient care can use this information to educate patients and family members on what symptoms to expect with IRRs and on the anticipated frequency and length of clinic visits, thus helping them prepare physically and mentally for their treatment. Knowing what to expect with an IRR and how it will be managed may calm patients' fears. Nurses should partner closely with patients and check on them often during the infusion to ensure symptoms of an IRR are identified and reported early, thus allowing for rapid interruption of the infusion and preventing the IRR from worsening. Education provided by pharmacists regarding amivantamab therapy and expected short- and long-term side effects helps nurses and APs prepare patients for treatment. Clear communication between nurses and APs ensures that each step of the infusion, from order execution to discharge instructions, is performed accurately, reducing the risk of IRRs and other complications of the infusion, such as extravasation at the infusion site and development of infection.

Several steps should be taken to minimize the risk and severity of IRRs should they occur (Table 1). Premedications should be administered, including antihistamines and antipyretics for every dose and steroids for C1D1 and C1D2 (optional thereafter). A peripheral line, rather than a central line, is recommended for the C1D1, C1D2, and C1D8 infusions to reduce drug exposure in the event of an IRR (Park et al., 2021b; Janssen Biotech, Inc., 2024). However, nurses may utilize central lines starting on C1D15. Additionally, IV administration sets should be primed with 15 to 25 mL of 5% dextrose or 0.9% sodium chloride solution prior to infusing amivantamab (Park et al., 2021b). At the end of the infusion, 10 mL of blood volume should be withdrawn prior to flushing the catheter with the 5% dextrose or 0.9% sodium chloride solution to avoid rapid infusion of residual amivantamab (Park et al., 2021b). Given that some patients had an IRR after completion of the infusion (most within 30 minutes) and that most of the IRRs occurred on C1D1, an observation period of 30 to 60 minutes following the infusion on C1D1 may be warranted.

When a patient reports signs and symptoms of an IRR, the infusion nurse should collaborate with APs to carefully evaluate the patient and determine what grade of IRR is occurring by assessing the patient's vital signs and performing a history and physical exam on the patient. The clinical care team can then adjust, or temporarily interrupt, the dose and administer supportive medications as appropriate depending on the grade of the reaction.

Table 1. Strategies to Prevent and Manage IRRs With Amivantamab

Split first dose	• Administer 350 mg on Cycle 1 Day 1 and the remainder of the dose on Cycle 1 Day 2
Premedications	• Administer premedications prior to amivantamab infusions as recommended » Antihistamines and antipyretics should be administered prior to all infusions » Glucocorticoids are required for Cycle 1 Day 1/Day 2 doses only and are administered as necessary for subsequent infusions
Infusion management	• Use a peripheral line rather than a central line during Week 1 and Week 2 to minimize drug exposure in the event of an IRR; a central line can be used for subsequent infusions • Reduce the rate of infusions (refer to the amivantamab prescribing information for details on infusion rate reductions)
Dose management	• Interrupt or reduce the amivantamab dose (refer to the amivantamab prescribing information for details on dose modifications or interruptions)
Patient communication	• Partner with patients to report symptoms of IRRs early to allow for rapid interruption of the infusion and prevent worsening of the IRR

Note. IRR = infusion-related reaction. Information from Park et al. (2021b); Janssen Biotech, Inc. (2024).

Please see Table 2 and the USPI for amivantamab for more details.

The mechanism of IRRs with amivantamab requires further investigation. Importantly though, permanent discontinuation of amivantamab is not usually required to manage IRRs as is commonly done for anaphylactic or allergic reactions to other oncology treatments (e.g., paclitaxel [taxol], carboplatin [Paraplatin], cetuximab [Erbitux]; LaCasce et al., 2022; Janssen Biotech, Inc., 2024). A thorough history and physical exam, not only at the time of the reaction but also prior to resuming administration of the infusion, is necessary. History of anaphylaxis, medication use, medication allergies, and comorbidities are among the patient characteristics that should be considered as nurses, APs, and the entire patient care team work closely together to provide optimal care to the patient.

Further research into the roles and interdependence of nurses, APs, and pharmacists in the care of patients receiving amivantamab has the potential not only to improve the incidence and outcomes of IRRs, but also to reduce the frequency and/or severity of other AEs reported with the infusion, ensure accurate administration of the infusion, and improve the overall patient experience.

Although this study provides essential information regarding IRRs, additional data would be helpful. Information on subgroups of patients, such as those with comorbidities, a history of allergic and/or infusion reactions, use of supportive therapies (e.g., montelukast [Singulair],

Table 2. Grading and Management of Infusion-Related Reactions

Reaction grade	Definition	Management
1	Mild reaction	• Monitor patient until reaction symptoms resolve • If occurring with initial dose, consider interrupting the infusion • Resume the infusion at 50% of the infusion rate at which the reaction occurred • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated • Include corticosteroid with premedications for subsequent dose
2	Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment	• Interrupt infusion • If clinically indicated, start IV fluids and give diphenhydramine 50 mg (or equivalent) IV and/or acetaminophen 650–1,000 mg; consider corticosteroids and bronchodilator therapy • Monitor patient closely until recovery from symptoms • Resume the infusion at 50% of the infusion rate at which the reaction occurred • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated • Include corticosteroid with premedications for subsequent dose
3	Severe or prolonged reaction (does not rapidly respond to symptomatic medication and/or brief interruption of the infusion); recurrence of symptoms following improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	• Interrupt infusion • Administer IV saline infusion • Recommend bronchodilators, supplemental oxygen, epinephrine 0.2–1 mg of a 1:1,000 solution for subcutaneous administration or 0.1–0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate) • Monitor patient closely until recovery from symptoms • Resume the infusion at 50% of the infusion rate at which the reaction occurred • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated • Include corticosteroid with premedications for subsequent dose • For recurrent grade 3 reactions, permanently discontinue treatment
4	Severe or life-threatening reaction; pressor or ventilator support indicated	• Interrupt and permanently discontinue treatment

Note. IV = intravenous. Information from Janssen Biotech, Inc. (2024); Park et al. (2021a, 2021b); US Department of Health and Human Services (2017).

benzodiazepines), and other demographic and clinical characteristics may further improve the care of patients being treated with amivantamab.

Strengths of this study include the sizable patient population, detailed analyses performed, and the incorporation of valuable input from nurses and APs who have experience treating IRRs related to amivantamab therapy. Limitations of this study include the lack of a control arm and subgroups.

CONCLUSIONS

Infusion-related reactions may occur with amivantamab infusion, as with other monoclonal antibody infusions. Importantly, IRRs with amivantamab are distinct in that they are not associated with markers of cytokine release, complement activation, mast cell degranulation, or tumor lysis syndrome. Amivantamab infusion may be resumed upon resolution of IRR symptoms with the appropriate rate modification and premedications. Permanent discontinuation of amivantamab due to IRRs was rare. Nurses and APs play critical roles in the care of patients receiving amivantamab infusions; thus, it is essential that they are properly educated and trained to best prevent, diagnose, and manage IRRs. Incorporation of the results of this post hoc analysis into clinical practice will augment the education and training of APs and thus improve patient care.

Disclosure

Andy L. Johnson, Denise D'Andrea, and Amitabha Bhauik are employees of Janssen Scientific Affairs, LLC. Stock or stock options: Denise D'Andrea, Andy L. Johnson. Payment or honoraria: Whitney E. Lewis, Lindsay Dougherty. Meeting and/or travel support: Whitney E. Lewis. Data Safety Monitoring Board or Advisory Board Participation: Whitney E. Lewis, Meghan O'Neill.

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