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Trodelvy® (sacituzumab govitecan-hziy) Hypersensitivity and Infusion-Related Reactions

This document is in response to your request for information regarding hypersensitivity and infusion-related reactions with Trodelvy® (sacituzumab govitecan-hziy [SG]).

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The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Summary

Relevant Product Labeling[1]

Hypersensitivity and infusion-related reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with SG treatment. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions.

Hypersensitivity reactions within 24 hours of dosing occurred in 35% of patients treated with SG. Grade 3 to 4 hypersensitivity occurred in 2% of patients treated with SG. The incidence of hypersensitivity reactions leading to permanent discontinuation of SG was 0.2%. The incidence of anaphylactic reactions was 0.2%.

Premedication for infusion reactions in patients receiving SG is recommended. Have medications and emergency equipment to treat infusion-related reactions, including anaphylaxis, available for immediate use when administering SG.

Closely monitor patients for hypersensitivity and infusion-related reactions during each SG infusion and for at least 30 minutes after completion of each infusion.

Permanently discontinue SG for Grade 4 infusion-related reactions.

Dosage and administration: Administer the first infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose for signs or symptoms of infusion-related reactions.

Administer subsequent infusions over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.

Prior to each dose of SG, premedication for prevention of infusion reactions is recommended. Premedicate with antipyretics and histamine 1 (H1) and histamine 2 (H2) blockers prior to infusion; corticosteroids may be used for patients who had prior infusion reactions.

Slow or interrupt the infusion rate of SG if the patient develops an infusion-related reaction. Permanently discontinue SG for life-threatening infusion-related reactions.

Contraindications: SG is contraindicated in patients who have experienced a severe hypersensitivity reaction to SG.

Patient counseling information: Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, tongue, or throat swelling, urticaria, difficulty breathing, lightheadedness, dizziness, chills, rigors, wheezing, pruritus, flushing, rash, hypotension, or fever that occur during or within 24 hours following the infusion.

Incidence of Hypersensitivity Reported in SG Clinical Studies

- During the phase 3 ASCENT study in patients with metastatic triple-negative breast cancer (mTNBC),[2] hypersensitivity events of any grade and of Grade ≥3 occurring within 24 hours of dosing were reported in 34.1% and 1.7% of participants in the SG arm vs 20.5% and 1.3% in the chemotherapy treatment of physician's choice (TPC) [eribulin, vinorelbine, capecitabine or gemcitabine] arm, respectively.[3]
- During the phase 3 TROPiCS-02 study in participants with hormone receptor-positive (HR+)/HER2-negative (HER2-) metastatic breast cancer (mBC), hypersensitivity events occurring on the day of or 1 day after infusion were reported in 26.5% (n=71) of patients in the SG arm compared to 19.3% (n=48) of patients in the TPC arm.[4]
- During the TROPHY U-01 study in participants with locally advanced or metastatic urothelial cancer (mUC),[5] 39.8% of the participants in Cohort 1 of the study experienced hypersensitivity reactions within 24 hours of dosing. Grade ≥3 hypersensitivity occurred in 0.9% of the participants.[3]
- In the phase 1/2 basket study (IMMU-132-01) in participants with metastatic epithelial cancer, the incidence of hypersensitivity reactions within 24 hours of dosing of any grade was 37.6%.[6]

Hypersensitivity and Infusion-Related Reactions in SG Clinical Studies

ASCENT Study in mTNBC

ASCENT, a global, open-label, randomized, confirmatory, phase 3 study was conducted to investigate the efficacy and safety of SG in comparison with TPC in participants with refractory or relapsed mTNBC who had received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease.[2]

Participants with history of prior use of irinotecan were excluded from participation in the study. A total of 529 participants with mTNBC were enrolled and randomly assigned (ratio of 1:1) to receive either SG (n=267; 10 mg/kg IV on Days 1 and 8 of a 21-day cycle) or TPC (n=262). Participants received a median of 7 treatment cycles of SG, with a median treatment duration (range) of 4.4 (0.03–22.9) months.[2]

Prevention of hypersensitivity

Premedication with antipyretics and H1 and H2 blockers for prevention of infusion related reactions (IRR) was recommended. Corticosteroids (50 mg of hydrocortisone or its

equivalent orally or IV) could be added if needed.[7] No frequency data are available regarding pre-infusion medication use for prevention of IRRs.[2]

SG was administered as a slow IV infusion (Table 1).[8]

Table 1. Infusion Rate Guidelines in ASCENT[8]

Infusion Rate[a]	First Infusion	Subsequent Infusions
Initial rate (first 15 min)	≤50 mg/hr,	100–200 mg/hr
Incremental rate (advance every 15–30 min)	50 mg/hr	100–200 mg/hr
Maximum recommended rate	500 mg/hr	1000 mg/hr

[a]These suggested infusion rate guidelines were for participants who remained stable in the absence of hypersensitivity or infusion-related events.

Safety

The safety population consisted of the 482 participants who received ≥1 treatment dose (258 in the SG arm and 224 in the TPC arm).[2,9,10] Hypersensitivity within 24 hours of dosing of any grade was reported in 34.1% of participants in the SG arm vs 20.5% in the TPC arm (Table 2). Serious hypersensitivity occurred in 0.4% of participants in SG group vs 1.3% of participants in the TPC arm. No cases of anaphylactic reactions in either arm of the study were reported. Hypersensitivity did not lead to permanent discontinuation of study drug or to dose reduction in either study arm. Hypersensitivity led to treatment interruption in 1.2% of participants in the SG arm and in 0.4% of participants in the TPC arm. The most frequent hypersensitivity events in both arms were cough (7.4% in the SG arm and 6.7% in the TPC arm) and dyspnea (7% in the SG arm and 6.7% in the TPC arm).[3]

Table 2. Hypersensitivity in ASCENT[3]

	SG (n=258)			TPC (n=224)		
	All Grades, %	Grade 3, %	Grade 4, %	All Grades, %	Grade 3, %	Grade 4, %
Hypersensitivity[a]	34.1	1.7	0	20.5	1.3	0

[a]Hypersensitivity reactions within 24 hours of dosing.

Median time to the first event of hypersensitivity of any grade and of Grade ≥3 as well as median duration of hypersensitivity of any grade and of Grade ≥3 is available in Table 3.

Table 3. Time to Onset and Duration of Hypersensitivity in ASCENT[3]

	SG (n=258)	TPC (n=224)
Median time to first event of hypersensitivity of any grade,[a] days	42	25
Median time to first event of hypersensitivity of Grade ≥3,[a] days	110	15
Median duration of hypersensitivity of any grade,[b] days	18.5	13
Median duration of hypersensitivity of Grade ≥3,[b] days	5	4

[a]Defined as time from the first dose of study drug to the first event.
[b]Calculated as the last date of hypersensitivity event minus the first onset date +1.

Infusion-related reactions management[8]

In ASCENT, the permanent termination of infusion was advised for a serious infusion reaction that was considered severe or life threatening (Grade ≥3). The occurrence of Grade 3 infusion-related reactions also required permanent termination of the infusion. In instances of moderate infusion toxicity (Grade 2 events), the infusion was stopped for ≥15 minutes or until symptoms resolved for and then resumed at the slowed infusion rate, if the participant was stable. Recommended actions for mild toxicity (Grade 1 events) included

slowing the remaining infusion rate. Any infusion toxicity must have resolved to Grade ≤1 prior to a participant receiving the next scheduled infusion.

TROPiCS-02 Study in HR+/HER2- mBC

TROPiCS-02, a phase 3, open-label, randomized, multicenter study compared the safety and efficacy of SG with TPC in 543 patients with HR+/HER2- mBC who were previously treated with ≥1 endocrine therapy, a taxane, and a cyclin-dependent kinase 4/6 inhibitor in any setting and had received ≥2 and ≤4 prior chemotherapy regimens for metastatic disease. In the SG treated arm (n=268), participants received a mean of 8.2 SG treatment cycles (range: 1–35) over a median duration of 4.1 months (range 0.03–24.2).[11,12]

Safety

Patients were excluded for known hypersensitivity or intolerance to either of the study drugs or any of the excipients. In the SG group premedication for preventing infusion reactions, including antipyretics and H1 and H2 blockers, was recommended before SG infusion. Corticosteroids (50 mg hydrocortisone or equivalent orally or IV) could be administered prior to subsequent infusions as needed. In the TPC group, premedication (ie, antipyretics, H1 blockers, and H2 blockers) use for prevention of infusion reactions and medications for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea for patients in the chemotherapy arm was based on the investigator's discretion. IRRs were defined as symptoms that occurred within the first 6 hours after SG administration and could occur at any cycle.[13]

In TROPiCS-02, hypersensitivity adverse events (AEs) occurring on the of or 1 day after infusion were reported in 26.5% (n=71) of patients in the SG arm compared to 19.3% (n=48) of patients in the TPC arm. The median time to onset of the first event of hypersensitivity was 29 days in the SG group and 19 days in the TPC group. The median time to onset of the first event of Grade 3 or higher hypersensitivity was 51 days in the SG group and 26 days in the TPC group.[4]

TROPHY U-01 Study in mUC

TROPHY-U-01, a global, multicohort, open-label, phase 2 study, is investigating the efficacy and safety of SG in patients with unresectable locally advanced, or mUC.[5] All patients will receive SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle until loss of clinical benefit or unacceptable toxicity.[14-16]

Cohort 1 (n=113) included patients whose disease had progressed after previous treatment with a platinum (PLT)-based chemotherapy + checkpoint inhibitor (CPI) therapy. Median follow-up (range) was 10.5 months (0.3–40.9).[14]

Cohort 2 (n=38) included patients, in a first-line metastatic setting, who were ineligible for PLT-based chemotherapy and who had progressed after prior CPI-only therapy. Median follow-up (range) was 9.3 months (0.5–30.6).[15]

Cohort 3 (n=41) included CPI-naïve patients who had progressed after prior PLT-based chemotherapy. Patients were treated with SG + pembrolizumab 200 mg on Day 1 of 21-day cycle. Median follow-up (range) was 12.5 months (0.9–24.6).[16]

Safety

The incidence of hypersensitivity reactions within 24 hours of dosing was 39.8% in Cohort 1 of the study. The most frequent hypersensitivity events were dyspnea (12.4%), hypotension (6.2%), and cough (6.2%). Grade 3 hypersensitivity occurred in 1 participant (0.9%). No cases of Grade 4 or of serious hypersensitivity were reported. No cases of anaphylaxis were reported.[3] Primary analyses from Cohorts 2 and 3 of any-grade treatment-related AEs with an incidence >20% and ≥15%, respectively did not report an analysis of hypersensitivity.[17,18]

IMMU-132-01 Study in Metastatic Epithelial Cancer

A phase 1/2, single-arm, open-label multicenter basket study investigated SG in patients with metastatic epithelial cancers (including mTNBC, mUC, and HR+/HER2- mBC) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease. Patients received SG IV (8, 10,12, or 18 mg/kg) on days 1 and 8 of 21-day cycles.[6] Participants who had a history of anaphylactic reaction to irinotecan or Grade ≥ 3 gastrointestinal toxicity to prior irinotecan were excluded from the participation in the study.[19]

Safety

All participants who received ≥1 doses of SG were included in the overall safety population (OSP; N=495). During the study, pre-infusion medications were given at the discretion of the investigator. Of the 495 participants in the OSP, 85.7% (n=424) of participants received pre-infusion medications.[6] No data are available regarding the frequency of administration of pre-infusion medications for prevention of IRRs specifically. Hypersensitivity within 24 hours of infusion was seen in 37.6% of patients in the OSP. The most frequent hypersensitivity events were cough (11.3%), dyspnea (10.3%), and rash (9.3%). One case of anaphylactic reaction occurred in a participant treated with an initial SG dose of 10 mg/kg.[3]

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Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Follow-Up

For any additional questions, please contact Trodelvy Medical Information at:

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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