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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 (IRRs) with Trodelvy® (sacituzumab govitecan-hziy [SG]).

Gilead continually assesses safety data from all sources for unidentified drug reactions and updates the product label information accordingly to reflect the safety profile of SG. Because case reports of potential adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

Information summarized in this document includes data for SG monotherapy (10 mg/kg IV on Days 1 and 8 of a 21-day treatment cycle) from phase 2 and 3 clinical studies that constitute the largest pooled safety population of SG.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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]

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 IRRs.

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, and corticosteroids may be used for patients who had prior infusion reactions.

The recommended dosage modifications for IRRs are provided in Table 1.

Table 1. Dose Modifications for IRRs[1]

Severity	Dose Modification
Grade 1–3 IRRs	Slow infusion rate or interrupt the infusion
Grade 4 IRRs	Discontinue SG

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

SG can cause serious hypersensitivity reactions including life-threatening anaphylactic reactions. 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 IRRs.

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 and IRRs in SG Clinical Studies

A pooled safety analysis examined exposure to SG 10 mg/kg IV as monotherapy in 1063 patients from four studies of multiple epithelial tumors (IMMU-132-01,[2] ASCENT,[3] TROPiCS-02,[4] and TROPHY-U-01[5-7]). These studies included patients with metastatic triple negative breast cancer (mTNBC), hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (HR+/HER2- mBC), and metastatic urothelial cancer (mUC).[8] The median (range) duration of treatment with SG in this population was 4.1 (0–63) months.[1] Any-grade and Grade ≥3 hypersensitivity was reported in 35% (n=369) and 2% (n=17) of patients treated with SG, respectively.[8]

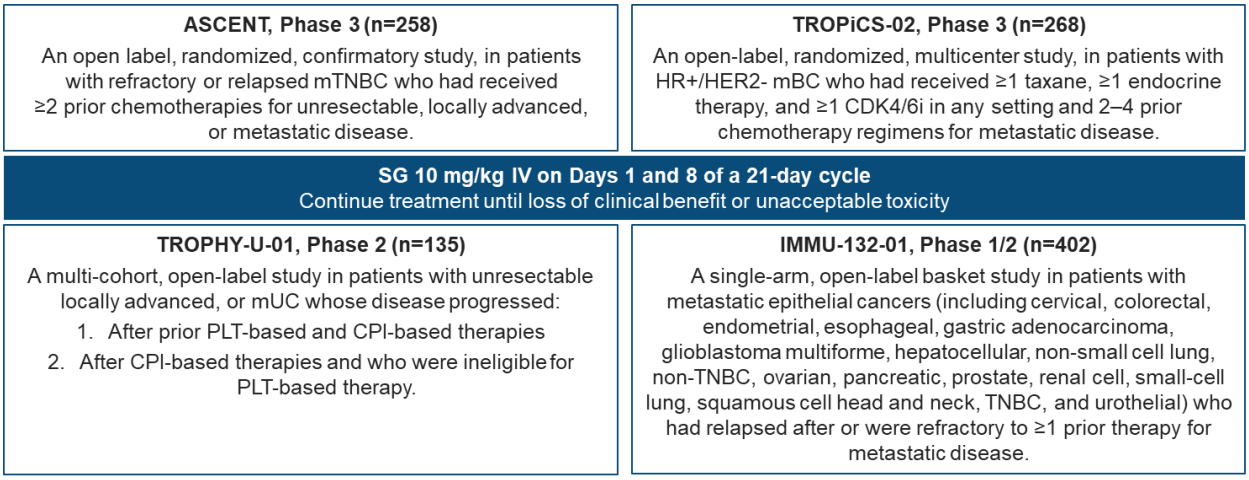
- In ASCENT, in patients with mTNBC,[3] any-grade and Grade ≥3 hypersensitivity events occurring within 24 hours of dosing were reported in 34.1% and 1.7% of patients in the SG arm vs 20.5% and 1.3% of patients in the arm that received chemotherapy treatment of physician's choice (TPC), respectively.[9]
- In TROPiCS-02, in patients with HR+/HER2- 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 vs 19.3% (n=48) of patients in the TPC arm.[10]
- In Cohort 1 of TROPHY U-01, in patients with locally advanced or mUC,[5] 39.8% of the patients the study experienced hypersensitivity reactions within 24 hours of dosing. Grade ≥3 hypersensitivity occurred in 0.9% of the patients.[9]
- In IMMU-132-01, in patients with metastatic epithelial cancer, the incidence of hypersensitivity reactions of any grade within 24 hours of dosing was 37.6%.[2]

Incidence of Hypersensitivity and IRRs in SG Clinical Studies

Pooled Safety Analysis

A pooled safety analysis (Figure 1) examined exposure to SG 10 mg/kg IV as monotherapy in 1063 patients from four studies of multiple epithelial tumors (IMMU-132-01,[2] ASCENT,[3] TROPiCS-02,[4] and TROPHY-U-01[5-7]). These studies included patients with mTNBC, HR+/HER2- mBC, and mUC.[8] The median treatment duration of SG in this population was 4.1 (range: 0–63) months.[1]

Figure 1. Pooled Clinical Studies[8]



Abbreviations: CDK4/6i=cyclin-dependent 4/6 inhibitor; CPI=checkpoint inhibitor therapies; PLT=platinum; TNBC=triple-negative breast cancer.

Hypersensitivity and IRRs[8]

Hypersensitivity was defined as hypersensitivity or anaphylactic reaction that occurred on the day of or 1 day after SG administration. Any-grade and Grade ≥3 hypersensitivity was reported in 35% (n=369) and 2% (n=17) of patients treated with SG, respectively. The times to onset and resolution of any-grade and Grade ≥3 hypersensitivity are shown in Table 2.

Table 2. Pooled Safety: Time to Onset and Resolution of Hypersensitivity (N=1063)[8]

	Time to Onset		Time to Resolution	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypersensitivity, median (range), weeks	4.1 (0.1–122)	9.9 (0.1–45.3)	2.1 (0.1–47.6)	1.3 (1–12)

ASCENT Study in mTNBC

Patients received a median of seven treatment cycles of SG, with a median treatment duration (range) of 4.4 (0.03–22.9) months.[11] Premedication with antipyretics and H1 and H2 blockers for prevention of IRRs was recommended. Corticosteroids (50 mg of hydrocortisone or its equivalent orally or IV) could be added if needed.[11] No frequency data are available regarding pre-infusion medication use for prevention of IRRs.[3] SG was administered as a slow IV infusion (Table 3).[12]

Table 3. ASCENT: Infusion Rate Guidelines[12]

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

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

Permanent termination of infusion was advised for Grade ≥3 IRRs. In instances of moderate (Grade 2) infusion toxicity, the infusion was stopped for ≥15 minutes or until symptoms resolved and then resumed at a slower infusion rate, if the patient was stable. For mild (Grade 1) toxicity, the remaining infusion rate was slowed. Infusion toxicity must have resolved to Grade ≤1 prior to a patient receiving the next scheduled infusion.[12]

Hypersensitivity and IRRs[9]

In the SG vs TPC arms, any-grade hypersensitivity that occurred within 24 hours of dosing was reported by 34.1% vs 20.5% of patients in the safety population, respectively (Table 4Table 4), and serious hypersensitivity occurred in 0.4% vs 1.3% of patients. 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 patients in the SG arm and 0.4% of patients in the TPC arm. The most frequent hypersensitivity events were cough (SG, 7.4%; TPC, 6.7%) and dyspnea (SG, 7%; TPC, 6.7%). No cases of anaphylactic reactions were reported.

Table 4. ASCENT: Incidence of Hypersensitivity[9]

Incidence, %	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 occurred within 24 hours of dosing.

See Table 5 for time to onset and duration of hypersensitivity.

Table 5. ASCENT: Time to Onset and Duration of Hypersensitivity[9]

	SG (n=258)		TPC (n=224)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Time to first event of hypersensitivity, median, days[a]	42	110	25	15
Duration of hypersensitivity, median, days[b]	18.5	5	13	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 onset date +1.

TROPiCS-02 Study in HR+/HER2- mBC

In the SG arm (n=268), patients received a mean (range) of 8.2 (1–35) treatment cycles over a median (range) duration of 4.1 (0.03–24.2) months.[4]

Patients were excluded for known hypersensitivity to or intolerance of either of the study drugs or any of the excipients. Premedication to prevent 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, use of premedication (ie, antipyretics, H1 blockers, and H2 blockers) for prevention of IRRs and medications for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea for patients 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]

Hypersensitivity adverse events that occurred on the day of or 1 day after infusion were reported by 26.5% (n=71) vs 19.3% (n=48) of patients in the SG vs TPC arms, respectively. The median time to onset of the first event of hypersensitivity was 29 days vs 19 days in the SG vs TPC arms, respectively; median time to onset of the first event of Grade ≥3 hypersensitivity was 51 days vs 26 days.[10]

TROPHY U-01 Study in mUC

In Cohort 1 (n=113), the median (range) follow-up was 10.5 (0.3–40.9) months.[14] The incidence of hypersensitivity reactions within 24 hours of dosing was 39.8%; the most frequent were dyspnea (12.4%), hypotension (6.2%), and cough (6.2%). Grade 3 hypersensitivity occurred in 1 patient (0.9%). No cases of Grade 4 or of serious hypersensitivity were reported. No cases of anaphylaxis were reported.[9]

In Cohort 2 (n=38), the median (range) duration of follow-up was 9.3 (0.5–30.6) months. Primary analysis from Cohort 2 of any-grade treatment-related adverse events with an incidence >20% did not include any reports of hypersensitivity.[15]

IMMU-132-01 Study in Metastatic Epithelial Cancer

Patients who had a history of anaphylactic reaction to irinotecan or Grade ≥3 gastrointestinal toxicity to prior irinotecan were excluded from the study.[16]

All patients who received ≥1 dose 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. In the OSP, 85.7% (n=424) of patients received pre-infusion medications.[2] No data are available regarding the frequency of administration of pre-infusion medications for prevention of IRRs specifically. Within 24 hours of infusion, hypersensitivity reactions were reported in 37.6% of patients. The most frequent hypersensitivity events were cough (11.3%), dyspnea (10.3%), and rash (9.3%). One case of anaphylactic reaction occurred in a patient treated with SG 10 mg/kg.[9]

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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:

☎1-888-983-4668 or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

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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