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Trodelvy® (sacituzumab govitecan-hziy) Dose Modifications in mUC Studies

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and dose modifications in metastatic urothelial cancer (mUC) clinical studies.

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Trodelvy is not indicated for use in patients with mUC. 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

Dose Modifications During SG mUC Clinical Studies

In TROPiCS-04, a study in patients with locally advanced and unresectable or UC, treatment-related adverse events (TRAEs) led to dose reduction in 37% and 26% of patients in the SG and chemotherapy treatment of physician's choice (TPC) groups, respectively. TRAEs led to dose interruption in 52% and 18% of patients, respectively.[1]

In TROPHY-U-01, a study in patients with locally advanced or mUC, 40% of patients in Cohort 1 required dose reductions, and 47% required dose interruptions of SG due to TRAEs.[2] In Cohort 2, TEAEs led to dose interruption and reduction in 61% and 37% of patients, respectively.[3] In Cohort 3, TRAEs led to SG dose interruptions, reductions, and discontinuation in 46%, 39%, and 15% of patients, respectively.[4]

In IMMU-132-01, adverse events (AEs) led to treatment interruption and dose reduction in 51.7% and 32.3% of patients, respectively, with metastatic epithelial cancer.[5]

Dose Modifications During SG mUC Clinical Studies

Adverse reactions were managed with established supportive care measures and included dose modifications.[5,6]

TROPiCS-04 Study in Locally Advanced Unresectable or mUC

TROPiCS-04, a global, open-label, multicenter, randomized, phase 3 study, investigated the efficacy and safety of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle vs single-agent chemotherapy TPC (paclitaxel, docetaxel, or vinflunine) IV on Day 1 of a 21-day cycle in patients with locally advanced and unresectable or UC. Delays or modifications in study drug doses were permitted according to the study protocol.[1]

The safety analysis set was composed of all patients who received ≥1 dose of SG (n=349) or TPC (n=337). Eligible patients had histologically confirmed, locally advanced and unresectable or mUC and had previously received platinum (PLT)-based chemotherapy and anti-programmed death (ligand)-1 therapy in the advanced setting. Prior treatment with erdafitinib, enfortumab vedotin, and investigational agents was permitted. Patients received a median of 3 months of SG and 2.1 months of TPC and had a median (range) duration of follow-up of 9.2 (0–33.7) months.[1]

Efficacy and safety

Efficacy outcomes data specific to the patients who required dose interruption(s) or reduction(s) were not reported.[1]

TRAEs and treatment-emergent adverse events (TEAEs) that led to dose reduction or interruption are shown in Table 1. In the SG and TPC groups, 11 and 16 patients, respectively, required a delay in study drug dosing that led to treatment discontinuation, though no reason was provided.[7]

Table 1. TROPiCS-04: TRAEs and TEAEs That Led to Dose Reduction or Dose Interruption (Safety Analysis Set)[1,7]

Safety Parameters, n (%)		SG (n=349)	TPC (n=337)
TRAEs	Led to dose reduction	129 (37)	86 (26)
	Led to dose interruption	183 (52)	61 (18)
TEAEs	Led to dose reduction	132 (38)	94 (28)
	Led to dose interruption	232 (66)	105 (31)

TROPHY-U-01 Study in mUC

TROPHY-U-01, an ongoing, global, open-label, multicohort, phase 2 study (NCT03547973), is investigating the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle.[8] Data are only available for Cohorts 1 through 3.

The overall safety population (OSP) in Cohort 1 (N=113) included patients who received treatment and had locally advanced and unresectable or mUC whose disease had progressed after previous treatment with a PLT-based regimen and checkpoint inhibitor (CPI) therapy.[2] In the primary analysis, patients received a median of 6 treatment cycles with a median (range) treatment duration of 3.7 (0–20) months, with a median (range) follow-up of 9.1 (0–19.9) months.[6] In the updated analysis, the median (range) follow-up duration was 10.5 (0.3–40.9) months.[2]

Data from primary analysis of Cohort 2 (N=38; patients with locally advanced or mUC who progressed after CPI therapy and were cisplatin-ineligible at the start of the study) are presented below. Patients in Cohort 2 received a median (range) of 6 (1–27) cycles and 11.5 (1–54) doses of SG; the median (range) treatment duration was 4.4 (0–19) months and patients were followed for a median (range) 9.3 (0.5–30.6) months.[3]

Data from primary analysis of Cohort 3 (N=41; patients with locally advanced or mUC who were CPI-naïve and had progressed after prior PLT-based therapies) are presented below. Patients received a median (range) of 8 (1–32) cycles and 15 (2–63) doses of SG. The median (range) treatment duration of SG was 5.1 (0–23) months; patients were followed for a median (95% CI) of 14.8 (12.6–16.8) months.[4]

Efficacy and safety

Efficacy outcomes data specific to the patients who required dose interruption(s) or reduction(s) were not reported.[2,9]

In Cohort 1, 40% of patients had dose reductions due to TRAEs (Table 2)[2]; these reductions were most commonly due to neutropenia, diarrhea, and fatigue. A single dose reduction was reported in 31% of patients.[6]

Dose interruption due to TRAEs occurred in 47% of patients (Table 2)[2]; these were most commonly due to neutropenia, leukopenia, and anemia.[6]

Treatment interruption(s) were assessed in the safety subpopulation of patients in Cohort 1 with uridine diphosphate-glucuronosyl transferase 1A1 (*UGT1A1)* genotype (n=106) and are summarized in Table 2.[2]

Table 2. TROPHY-U-01 Study Cohort 1: TRAEs That Led to SG Dose Reduction and Dose Interruption[2]

TRAEs, n (%)	Cohort 1 (N=113)	*UGT1A1* Status Available (n=106)		
		WT (**1/*1*; n=45)	Heterozygous (**1/*28*; n=47)	Homozygous (**28/*28*; n=14)
Led to dose reduction	45 (40)	17 (38)	16 (34)	6 (43)
Led to dose interruption	53 (47)	19 (42)	20 (43)	10 (71)

Abbreviation: WT=wild type.

In Cohort 2, TEAEs led to dose interruption and reduction in 61% and 37% of patients, respectively; 2 patients (5%) required an interruption in SG infusion. At the time of data cutoff, 1 patient discontinued SG due to a treatment delay of >3 weeks within the first 6 SG cycles, and 1 patient due to a treatment delay of >5 weeks for any reason.[3]

In Cohort 3, the median (range) dose intensity was 92% (57–102%); 44% of patients required ≥1 dose reduction for any reason. No patients required a treatment delay for >3 weeks during the first 6 cycles; however, 4 patients required a treatment delay of >5 weeks for any reason. TRAEs led to dose interruptions in 46% of patients, dose reduction in 39% of patients, and discontinuations of SG in 15%.[4]

IMMU-132-01 Study in Metastatic Epithelial Cancer

IMMU-132-01, a phase 1/2, single-arm, open-label basket study, investigated the efficacy and safety of SG as an IV infusion on Days 1 and 8 of a 21-day treatment cycle in patients with metastatic epithelial cancers (including patients with mUC) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease. During the dose-escalation phase of this study, SG was administered at doses of 8 (n=81), 10 (n=402), 12 (n=9), or 18 (n=3) mg/kg. *UGT1A1* testing was performed in all patients.[5]

Efficacy and safety

Efficacy data specific to patients who required dose interruption(s) or reduction(s) were not reported.[5]

All patients who received ≥1 dose of SG were included in the OSP (N=495). AEs that led to treatment interruption occurred in 51.7% of patients (n=256) and included neutropenia (21%), decreased neutrophil count (9.5%), and anemia (5.3%). One or more dose reductions were required in 160 patients (32.3%); 130 patients (26.3%) required a single

dose reduction. The median (range) time to first dose reduction was 33 (7–609) days after the first dose of SG.[5]

Dose interruption(s) due to TEAEs were assessed in the safety subpopulation of patients with *UGT1A1* genotype (n=403) and were observed in 82 (46.3%), 87 (48.3%), and 33 (71.7%) patients with the **1/*1* (WT), **1/*28* (heterozygous), and **28/*28* (homozygous) genotypes, respectively.[10]

References

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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

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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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