GILEAD | Medical Information

Trodelvy® (sacituzumab govitecan-hziy) Impact of UGT1A1 Status on Safety Profile in Patients With mUC

This document is in response to your request for information regarding the impact of uridine diphosphate glucuronosyl transferase family 1 member A1 (UGT1A1) status on the safety profile of Trodelvy® (sacituzumab govitecan-hziy [SG]) in patients with metastatic urothelial cancer (mUC).

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 causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

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.

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

Clinical Data

In TROPHY-U-01 Cohort 1, in patients (n=113) with locally advanced or metastatic urothelial cancer (mUC), any grade treatment-related adverse events (TRAEs) occurred in 93%, 94%, and 100% of patients with *1/*1, *1/*28, and *28/*28 genotypes (GT), respectively. Safety outcome data by UGT1A1 GT is only available for Cohort 1.[1]

- Neutropenia occurred more frequently among those with the **28/*28* alleles (50%) or **1/*28* alleles (55%) vs the wild-type (WT) **1/*1* allele (38%),[1,2] and the rate of Grade ≥3 neutropenia was higher among patients with the **28/*28* allele (54%) vs those with the **1/*28* (34%) or **1/*1* (31%) alleles.[2]
- Diarrhea occurred more frequently among those with the **28/*28* alleles (71%) or **1/*28* alleles (72%) vs the WT **1/*1* allele (53%).[1]

In IMMU-132-01, in patients (N=495) with metastatic epithelial cancers (including mUC), patients with the homozygous *UGT1A1*28* polymorphism (**28/*28*) had higher rates of neutropenia (61%) vs patients with the heterozygous *UGT1A1 (*1/*28;* 38%) or the WT (**1/*1;* 33%) alleles. Higher rates of diarrhea were also observed in the patients with the **28/*28* allele (61%) vs patients with the heterozygous *UGT1A1 (*1/*28;* 52%) or the WT (**1/*1;* 55%) alleles.[3]

TROPiCS-04 is an open-label, global, multicenter, randomized, phase 3 study comparing the efficacy and safety of SG vs TPC in patients with locally advanced unresectable or mUC who progressed after prior PLT-based chemotherapy and CPI therapies. Safety data specific to UGT1A1 status was not reported in this study.[4]

Clinical Data

TROPHY-U-01 Cohort 1 in mUC

TROPHY-U-01 is an ongoing global, open-label, phase 2, multi-cohort study investigating the safety and efficacy of SG 10 mg/kg IV on days 1 and 8 of 21 day treatment cycles, in patients with unresectable locally advanced/mUC.[5] Safety outcome data by UGT1A1 GT is only available for Cohort 1. The overall safety population (OSP; n=113) included patients with locally advanced, unresectable or mUC whose disease had progressed after previous treatment with a platinum-based and checkpoint inhibitor therapy, who received a median of 6 treatment cycles, with a median (range) treatment duration of 3.7 (0–20) months.[2,6] In an updated safety and efficacy analysis the median (range) follow-up extended to 10.5 (0.3-40.9) months.[1]

UGT1A1 GT status was evaluable for 106 (94%) patients (**1/*1*, n=45 [40%]; **1/*28*, n=47 [42%]; **28/*28*, n=14 [12%]) and missing for 7 patients (6%). In those with *1/*1, *1/*28, and *28/*28 GT, any grade TRAEs occurred in 93%, 94%, and 100% of patients. Additional safety outcomes according to UGT1A1 GT are presented in Table 1.[1]

Table 1. TROPHY-U-01 Cohort 1: Safety Outcomes by UGT1A1 GT[1]

Safety Outcomes		UGT1A1 Status		
		****1/*1*** **(n=45)**	****1/*28*** **(n=47)**	****28/*28*** **(n=14)**
Any grade TEAE, n (%)		44 (98)	46 (98)	14 (100)
Grade ≥3 TEAE, n (%)		40 (89)	24 (72)	14 (100)
Serious AE, n (%)		23 (51)	17 (36)	10 (71)
Death, n (%)		2 (4)	1 (2)	0
Any grade TRAE, n (%)		42 (93)	44 (94)	14 (100)
Grade ≥3 TRAE, n (%)		28 (62)	28 (60)	11 (79)
Treatment-related death, n (%)		1 (2)	0	0
TRAE that led to discontinuation of SG, n (%)		3 (7)	3 (6)	2 (14)
TRAE that led to dose reduction, n (%)		17 (38)	16 (34)	6 (43)
TRAE that led to dose interruption, n (%)		19 (42)	20 (43)	10 (71)
Most common TRAEs (≥20% of patients in any UGT1A1 status group), %	Diarrhea	53	72	71
	Nausea	58	53	79
	Fatigue	53	57	50
	Alopecia	44	47	57
	Neutropenia	38	55	50
	Decreased Appetite	40	34	36
	Anemia	38	32	29
	Vomiting	36	28	14
	Leukopenia	22	23	50
	Abdominal pain	7	19	21
	Asthenia	13	11	29
	Pruritis	9	21	7
	Chills	4	13	29

Safety Outcomes		UGT1A1 Status		
		*1/*1 (n=45)	*1/*28 (n=47)	*28/*28 (n=14)
	Hypotension	4	11	21
	Hyponatremia	4	2	21
	Peripheral neuropathy	2	2	29

Abbreviation: TEAE=treatment-emergent adverse event

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 in patients with metastatic epithelial cancers (including mUC) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease. UGT1A1 testing was performed in all patients.[3]

Impact of UGT1A1 status on safety

The OSP (N=495) included all patients who received ≥1 dose of SG. Descriptive analysis was performed to analyze the incidence of AEs in 81.4% of patients in the OSP who had UGT1A1 GT data available (n=403).[3]

The pattern and incidence of AEs were broadly similar between patients who were heterozygous (**1/*28*) and those who had the WT allele. Safety outcomes according to UGT1A1 status can be found in Table 2.[7]

Table 2. IMMU-132-01: Safety Outcomes According to UGT1A1 Status[7]

Safety Outcomes, n (%)		UGT1A1 Status		
		*1/*1 (n=177)	*1/*28 (n=180)	*28/*28 (n=46)
Any grade TEAE		177 (100)	179 (99.4)	46 (100)
Grade ≥3 TEAE		121 (68.4)	141 (78.3)	41 (89.1)
Any grade TRAE		175 (98.9)	173 (96.1)	44 (95.7)
Grade ≥3 TRAE		95 (53.7)	110 (61.1)	38 (82.6)
SAE		64 (36.2)	66 (36.7)	27 (58.7)
Treatment-related SAE		25 (14.1)	18 (10)	19 (41.3)
TEAE that led to discontinuation of SG		12 (6.8)	12 (6.7)	2 (4.3)
TEAE that led to dose interruption		82 (46.3)	87 (48.3)	33 (71.7)
TEAE that led to on-treatment death[a]		5 (2.8)	8 (4.4)	1 (2.2)
Most common TRAEs (≥30% of patients in any UGT1A1 status group)	Nausea	112 (63.3)	103 (57.2)	31 (67.4)
	Diarrhea	97 (54.8)	93 (51.7)	28 (60.9)
	Fatigue	80 (45.2)	80 (44.4)	21 (45.7)
	Alopecia	74 (41.8)	73 (40.6)	15 (32.6)
	Vomiting	72 (40.7)	56 (31.1)	23 (50)
	Anemia	66 (37.3)	57 (31.7)	23 (50)
	Neutropenia	59 (33.3)	69 (38.3)	28 (60.9)
	Decreased appetite	39 (22)	50 (27.8)	18 (39.1)

Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event
[a]Defined as death that occurred between the start of SG treatment and 30 days after the last dose.

TROPiCS-04 Study in mUC

TROPiCS-04 is an open-label, global, multicenter, randomized, phase 3 study comparing the efficacy and safety of SG vs TPC in patients with locally advanced unresectable or mUC who progressed after prior PLT-based chemotherapy and CPI therapies. Safety data specific to UGT1A1 status was not reported in this study.[4]

References

1. Loriot Y, Petrylak DP, Kalebasty AR, et al. TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: updated safety and efficacy outcomes. *Ann Oncol.* 2024;35(4):392-401.
2. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol.* 2021;39(22):2474-2485.
3. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol.* 2021;32(6):746-756.
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5. ClinicalTrials.gov. Study of Sacituzumab Govitecan-hziy in Metastatic Urothelial Cancer (TROPHY U-01). ClinicalTrials.gov Identifier: NCT03547973. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03547973?term=NCT03547973&draw=2&rank=1.
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7. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial [Supplementary Appendix]. *Ann Oncol.* 2021;32(6):746-756.

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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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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