Safety Analysis by *UGT1A1* Status of TROPHY-U-01 Cohort 1, a Phase 2 Study of Sacituzumab Govitecan (SG) in Patients (pts) With Metastatic Urothelial Cancer (mUC) Who Progressed After Platinum (PT)-Based Chemotherapy and a Checkpoint Inhibitor (CPI)

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Supplemental materials

Key Findings

- The safety profile of SG is manageable, with low discontinuation rates (7%)
- Among TRAEs of any grade, the most common were diarrhea, nausea, and fatigue both in the overall population of patients and those homozygous for the wild-type allele
- The most frequent TRAEs in patients heterozygous and homozygous, respectively, for the *UGT1A1**28 allele were diarrhea, fatigue, and neutropenia; and nausea, diarrhea, and alopecia
- The frequency of dose reductions or interruptions of SG, and the type and grade of AEs, depended on *UGT1A1* status

Conclusions

With longer follow-up, safety data were consistent with the known SG safety profile

AE incidence varied across *UGT1A1* subgroups, with numerically higher dose interruptions observed in patients homozygous for the *UGT1A1**28 allele

Sample sizes in this study were small; other cohorts of the TROPHY-U-01 and TROPiCS-04 trials in patients with mUC, as well as breast cancer trials, will further inform the impact of *UGT1A1* status on safety outcomes with SG and subsequent management strategies

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Background

Metastatic urothelial carcinoma

- The prognosis for patients with metastatic urothelial carcinoma (mUC) is poor, with an average 5-year survival < 10% for patients in the United States[1]
- Patients with locally advanced or mUC who progressed on or after platinum-based and checkpoint inhibitor (CPI) therapies have limited treatment options,[2,3] and additional safe and effective therapies are needed

Sacituzumab govitecan (SG)

- SG is a novel antibody-drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2) coupled to cytotoxic SN-38 payload via a hydrolyzable linker[4-7]
  - SG was granted FDA accelerated approval in the US for the treatment of patients with locally advanced or mUC who previously received PT-based chemotherapy and a CPI[8]
  - In an updated efficacy analysis of the pivotal TROPHY-U-01 Cohort 1 study of 113 patients, SG demonstrated an objective response rate (ORR) of 28%, a median overall survival (OS) of 10.9 months, and a manageable safety profile after median follow-up of 10.5 months[9]
  - A confirmatory randomized phase 3 trial, TROPiCS-04, is ongoing (NCT04527991)

UGT1A1 gene polymorphism

- SN-38, the cytotoxic payload in SG, is inactivated by uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) into SN-38G, which is excreted with bile[10]
  - Mutations in the *UGT1A1* gene, including the *UGT1A1**28 and *UGT1A1**6 polymorphisms, have been reported to be associated with toxicities in patients treated with SN-38–based chemotherapy; therefore, patients homozygous for the *UGT1A1**28 allele may be at an increased risk for adverse events (AEs)

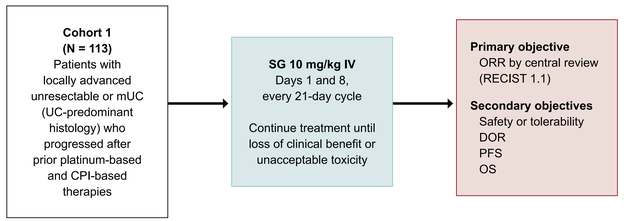
Objective

- Here, we report updated safety outcomes from the overall Cohort 1 of TROPHY-U-01 and by *UGT1A1* status

Methods

- TROPHY-U-01 is an international, multicohort, open-label, phase 2 study of SG in patients with unresectable locally advanced or mUC:
  - Patients in Cohort 1 of the TROPHY-U-01 study were aged ≥ 18 years with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1
  - The patient population, study drug dose, and objectives for Cohort 1 are presented in Figure 1
  - All patients who received ≥ 1 dose of SG were included in the evaluation of safety
  - The frequency and severity of AEs were classified using Medical Directory for Regulatory Activities (MedDRA) Version 22 or greater
  - Post hoc safety analyses were exploratory with descriptive statistics provided

Figure 1. TROPHY-U-01 Cohort 1 study design



CPI, checkpoint inhibitor; DOR, duration of response; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan.
ClinicalTrials.gov identifier: NCT03547973; IMMU-132-06 study.

Results

Patients

- As of July 26, 2022, the median follow-up was extended to 10.5 months (range, 0.3-40.9 months) for a total of 113 patients treated in Cohort 1; patient baseline characteristics are presented in Table 1

Table 1. Demographics and baseline characteristics

	Cohort 1 (N = 113)
Median age at study entry, y (range)	66 (33-90)
Sex, n (%)	
Female	25 (22)
Male	88 (78)
ECOG performance status, n (%)	
0	32 (28)
1	81 (72)
***UGT1A1* status, n (%)**	
Wild-type *1|*1	45 (40)
Heterozygous *1|*28	47 (42)
Homozygous *28|*28	14 (12)
Missing	7 (6)
Median prior anticancer regimens, n (range)	3 (1-8)
Known baseline comorbidities, n (%)	
Hypertension	59 (52)
Chronic kidney disease	14 (12)
Coronary artery disease	11 (10)
Diabetes mellitus II	9 (8)
Myocardial infarction	9 (8)

ECOG, Eastern Cooperative Oncology Group; *UGT1A1*, uridine diphosphate-glucuronosyltransferase 1A1.

Updated safety outcomes

- Treatment-related AEs (TRAEs) of any grade occurred in 95% (n = 107) of patients
- Serious AEs were observed in 45% of patients
  - 43% of patients required inpatient hospitalization or prolongation of existing hospitalization
- Consistent with prior reports, TRAEs led to SG discontinuation in 7%, dose reduction in 40%, and dose interruption in 47% of patients in the overall Cohort 1 population
- There was 1 treatment-related death due to febrile neutropenia–related sepsis in a 65-year-old male patient with mUC, stage III chronic kidney disease, and prior history of lung cancer
  - No new treatment-related deaths have occurred since the previous data cut (median follow-up, 9.1 months)
- TRAEs of any grade in ≥ 20% and grade ≥ 3 in ≥ 10% of all patients are presented in Tables 2 and 3, respectively

Table 2. Summary of TRAEs of any grade in ≥ 20% of all patients

n (%)	Cohort 1 (N = 113)
Diarrhea	73 (65)
Nausea	68 (60)
Fatigue	59 (52)
Neutropenia[a]	53 (47)
Alopecia	53 (47)
Decreased appetite	41 (36)
Anemia	38 (34)
Vomiting	34 (30)
Leukopenia	29 (26)

[a]Neutropenia includes neutrophil count decreased.

Table 3. Summary of TRAEs of grade 3 or higher in ≥ 10% of all patients

n (%)	Cohort 1 (N = 113)
Neutropenia[a]	39 (34)
Leukopenia	20 (18)
Anemia	16 (14)
Diarrhea	11 (10)
Febrile neutropenia	11 (10)

[a]Neutropenia includes neutrophil count decreased.

Safety outcomes by *UGT1A1* status

- A summary of safety outcomes is presented in Table 4
- Incidence of the most frequent TRAEs is shown in Table 5

Table 4. Summary of AEs by *UGT1A1* status

	UGT1A1 status		
n (%)	WT *1|*1 (n = 45)	Heterozygous *1|*28 (n = 47)	Homozygous *28|*28 (n = 14)
Any AEs	44 (98)	46 (98)	14 (100)
AEs grade ≥ 3	40 (89)	34 (72)	14 (100)
Serious AEs	23 (51)	17 (36)	10 (71)
Deaths	2 (4)	1 (2)	0 (0)
Any TRAEs	42 (93)	44 (94)	14 (100)
TRAEs grade ≥ 3	28 (62)	28 (60)	11 (79)
Treatment-related deaths	1 (2)	0 (0)	0 (0)

AE, adverse event; TRAE, treatment-related AE; *UGT1A1*, uridine diphosphate glucuronosyltransferase 1A1; WT, wild type.

Table 5. Summary of TRAEs of any grade in ≥ 20% of patients by *UGT1A1* status

	UGT1A1 status		
n (%)	WT *1|*1 (n = 45)	Heterozygous *1|*28 (n = 47)	Homozygous *28|*28 (n = 14)
Nausea	26 (58)	25 (53)	11 (79)
Diarrhea	24 (53)	34 (72)	10 (71)
Fatigue	24 (53)	27 (57)	7 (50)
Alopecia	20 (44)	22 (47)	8 (57)
Decreased appetite	18 (40)	16 (34)	5 (36)
Neutropenia[a]	17 (38)	26 (55)	7 (50)
Anemia	17 (38)	15 (32)	4 (29)
Vomiting	16 (36)	13 (28)	2 (14)
Leukopenia	10 (22)	11 (23)	7 (50)
Asthenia	6 (13)	5 (11)	4 (29)
Pruritis	4 (9)	10 (21)	1 (7)
Abdominal pain	3 (7)	9 (19)	3 (21)
Chills	2 (4)	6 (13)	4 (29)
Hyponatremia	2 (4)	1 (2)	3 (21)
Hypotension	2 (4)	5 (11)	3 (21)
Peripheral neuropathy	1 (2)	1 (2)	4 (29)

UGT1A1, uridine diphosphate glucuronosyltransferase 1A1; WT, wild type.
[a]Neutropenia includes neutrophil count decreased.

SG drug dose adjustments

- TRAEs leading to SG dose adjustments are presented in Table 6

Table 6. Summary of TRAEs leading to study drug dose adjustment by *UGT1A1* status

	UGT1A1 status		
n (%)	WT *1|*1 (n = 45)	Heterozygous *1|*28 (n = 47)	Homozygous *28|*28 (n = 14)
TRAEs leading to study drug			
Discontinuation	3 (7)	3 (6)	2 (14)
Dose reduction	17 (38)	16 (34)	6 (43)
Interruption	19 (42)	20 (43)	10 (71)

TRAE, treatment-related AE; *UGT1A1*, uridine diphosphate glucuronosyltransferase 1A1; WT, wild type.

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