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Trodelvy® (sacituzumab govitecan-hziy) Efficacy by Trop-2 Expression in Metastatic Urothelial Carcinoma

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and its efficacy by trophoblast cell-surface antigen 2 (Trop-2) expression in patients with metastatic urothelial carcinoma (mUC).

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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

Efficacy by Trop-2 Expression in SG Treated Patients with mUC

SG is a Trop-2–directed antibody-drug conjugate. Sacituzumab is a humanized antibody that recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that SG binds to Trop-2–expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.[1] An analysis of SG efficacy by Trop-2 expression was performed in a subgroup of patients from Cohorts 1 through 3 of the TROPHY-U-01 study in patients with mUC[2,3], further details below.

TROPHY-U-01

Study design

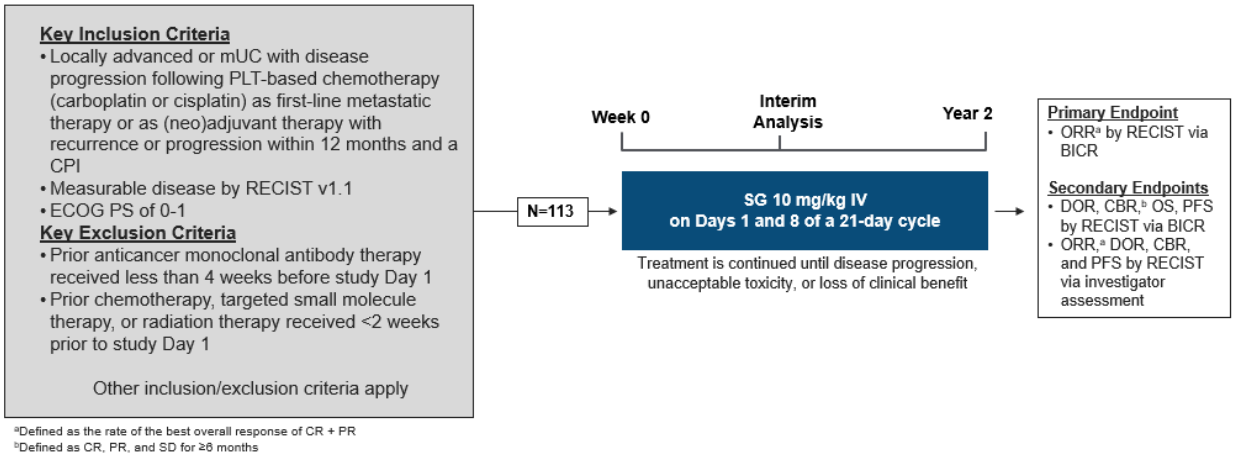
TROPHY-U-01 (NCT03547973), is an ongoing global, open-label phase 2, multi-cohort study of SG in patients with unresectable locally advanced/mUC. Approximately 827 patients are anticipated to be enrolled.[3] An analysis of efficacy by Trop-2 expression was performed on archival tumor samples collected from patients enrolled in Cohorts 1 through 3 (n=192 at data cutoff).[2] Further details of specific cohorts included in this analysis, including patient populations and treatment regimens are briefly described below.

Cohort 1[3,4]

Cohort 1 investigated the safety and efficacy of SG in patients with mUC who were previously treated with PLT-based therapy ± CPIs (

Figure 1).

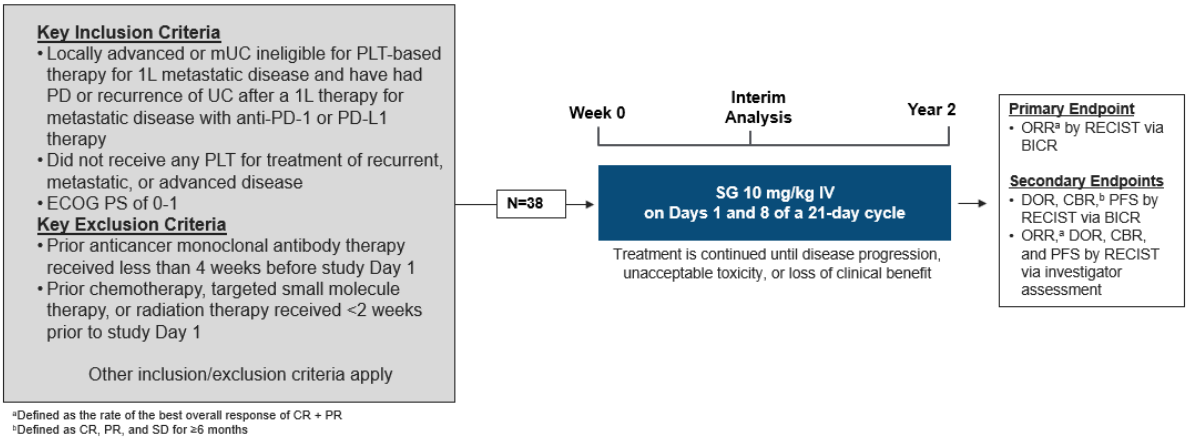
Figure 1. TROPHY-U-01: Study Design Cohort 1 (2L+)[3,4]



Cohort 2[3,5]

Cohort 2 is investigating the safety and efficacy of SG in PLT-ineligible patients with mUC who had progressed after CPI-only therapy (Figure 2).

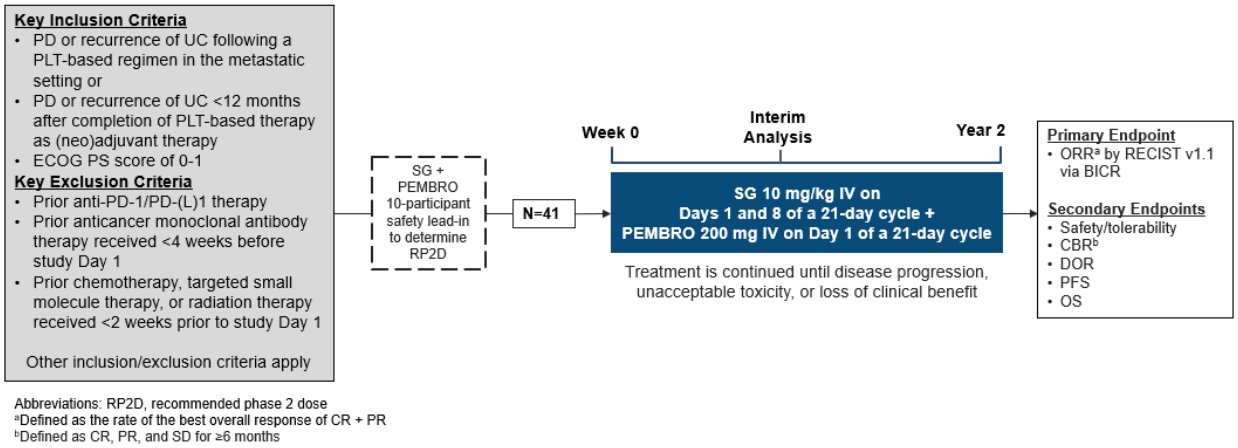
Figure 2. TROPHY-U-01: Study Design Cohort 2 (2L+)[3,5]



Cohort 3[3,6]

Cohort 3 was a single-arm design investigating the safety and efficacy of SG + PEMBRO in CPI-naïve patients who had progression of urothelial cancer after PLT-based chemotherapy in the metastatic setting or ≤12 months after completion of PLT in the (neo)adjuvant setting (Figure 3).

Figure 3. TROPHY-U-01: Study Design Cohort 3 (2L)[3,6]



Abbreviations: RP2D, recommended phase 2 dose
[a]Defined as the rate of the best overall response of CR + PR
[b]Defined as CR, PR, and SD for ≥6 months

Of those patients enrolled in Cohorts 1 through 3 of TROPHY-U-01, 144 patients (75%) had tumor tissue samples evaluable for Trop-2 testing, and 139 patients (72%) were evaluable for efficacy analysis based on Trop-2 expression. Baseline characteristics for patients with evaluable samples were consistent with the overall population.

Trop-2 protein was highly expressed in tumor tissue samples of patients across Cohorts 1 through 3. Median (IQR) Trop-2 H-score and percentage of Trop-2 membrane-positive tumor cells for evaluable patient samples were 215 (180–247) and 92% (75–98), respectively (ρ=0.82, P<0.001).

All Trop-2 expression groups exhibited a response to SG, and no difference was observed in ORR with different Trop-2 expression when categorized by median or tertile cut.

Cohort 1

ORRs for Cohort 1 samples with below (n=42) and above (n=45) median Trop-2 H-scores were 29% and 36%, respectively (P=0.49); median PFS was 3.4 and 6.7 months, respectively (HR, 0.77; 95% CI: 0.48–1.22; P=0.26); and median OS was 9.9 and 10.9 months, respectively (HR, 0.98; 95% CI: 0.61–1.58; P=0.93).

Tertile categorization groups were determined by stratifying patients into three similarly sized groups (T1, n=28; T2, n=29; and T3, n=30) based off Trop-2 H-scores.

- Median PFS for T1, T2, and T3 was 3.9, 6.9, and 5.5 months, respectively;
  - T2 vs T1: HR, 1.06; 95% CI: 0.59–1.9; P=0.85;
  - T3 vs T2: HR, 1.04; 95% CI: 0.58–1.87; P=0.89.
- Median OS for T1, T2, and T3 was 11, 10.6, and 10.4 months, respectively;
  - T2 vs T1: HR, 1.18; 95% CI: 0.65–2.13; P=0.59;
  - T3 vs T2: HR, 1.11; 95% CI: 0.61–2.01; P=0.73.

Cohort 2

ORRs for Cohort 2 samples with below (n=8) and above (n=8) median Trop-2 H-scores were 38% and 38%, respectively (*P*=1); median PFS was 5.5 and 6.9 months, respectively (HR, 0.74; 95% CI: 0.23–2.34; *P*=0.6); and median OS was 14 and 15.6 months, respectively (HR, 0.34; 95% CI: 0.06–1.79; *P*=0.2).

Cohort 3

ORRs for Cohort 3 samples with below (n=21) and above (n=15) median Trop-2 H-scores were 48% and 40%, respectively (*P*=0.65); median PFS was 5.5 and 4 months, respectively (HR, 1.16; 95% CI: 0.52–2.57; *P*=0.71); and median OS was 12.5 and 16.6 months, respectively (HR, 0.94; 95% CI: 0.36–2.48, *P*=0.9).

References

1. TRODELVY® Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Loriot Y, Balar AV, Petrylak DP, et al. Efficacy of sacituzumab govitecan (SG) in locally advanced (LA) or metastatic urothelial cancer (mUC) by trophoblast cell surface antigen 2 (Trop-2) expression. [Abstract 4579]. Paper presented at: American Society of Clinical Oncology (ASCO); June 2-6, 2023; Chicago, Illinois.
3. ClinicalTrials.gov. Phase II Open Label Study of IMMU-132 in Metastatic Urothelial Cancer. ClinicalTrials.gov Identifier: NCT03547973. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03547973. Accessed: 31 October 2024. Last Updated 16 October 2024.
4. Tagawa ST, Balar AV, Petrylak DP, et al. Updated outcomes in TROPHY-U-01 cohort 1, a phase 2 study of sacituzumab govitecan in patients with metastatic urothelial cancer who progressed after platinum-based chemotherapy and a checkpoint inhibitor [Poster 526]. Paper presented at: American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium; 16-18 February, 2023; San Francisco, CA.
5. Petrylak DP, Tagawa ST, Jain RK, et al. Primary analysis of TROPHY-U-01 cohort 2, a phase 2 study of sacituzumab govitecan in platinum-ineligible patients with metastatic urothelial cancer who progressed after prior checkpoint inhibitor therapy [Poster 520]. Paper presented at: American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium; 16-18 February, 2023; San Francisco, CA.
6. Grivas P, Pouessel D, Park C H, et al. TROPHY-U-01 Cohort 3: Sacituzumab Govitecan (SG) in Combination With Pembrolizumab (Pembro) in Patients (pts) With Metastatic Urothelial Cancer (mUC) Who Progressed After Platinum (PLT)-Based Regimens [Presentation]. Paper presented at: ASCO Genitourinary Cancers Symposium; 16 February, 2022; San Francisco, CA and Online.

Abbreviations

1L= first line
2L+=second-line and later
BICR=blinded independent central review
CBR=clinical benefit rate
CPIs=checkpoint inhibitors
DOR=duration of response
ECOG PS= Eastern Cooperative Oncology Group Performance Status
H-score=histological score
HR=hazard ratio
mUC=metastatic urothelial carcinoma
ORR=objective response rate
OS=overall survival
PD-1=programmed cell death protein 1
PD-L1=protein cell death ligand 1
PFS=progression-free survival
PLT=platinum
PR=partial response
RECIST=Response Evaluation Criteria in Solid Tumors v1.1
SD=stable disease
SG=sacituzumab govitecan-

hziy	surface antigen 2
Trop-2=trophoblast cell	UC=urothelial cancer

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.

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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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