TROPHY-U-01 Cohort 4 (C4): Sacituzumab Govitecan (SG) in Combination With Cisplatin (cis) as First-Line (1L) Therapy, Followed by Maintenance Avelumab Plus (+) SG or Zimberelimab (zim) + SG in Patients With Treatment (Tx)-Naïve Metastatic Urothelial Cancer (mUC)

Poster TPS4611

TROPHY-U-01

Chethan Ramamurthy,[1] Alejandro Recio-Boiles,[2] Petros Grivas,[3] Umang Swami,[4] Yohann Loriot,[5] Julia Tonelli,[6] Mitch Sierecki,[6] Philippe Barthélémy[7]

[1]University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; [2]University of Arizona Cancer Center, Tucson, AZ, USA; [3]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]Institut de Cancérologie Gustave Roussy, Université Paris-Saclay, Villejuif, France; [6]Gilead Sciences, Inc., Foster City, CA, USA; [7]Institut de Cancérologie Strasbourg Europe, Strasbourg, France

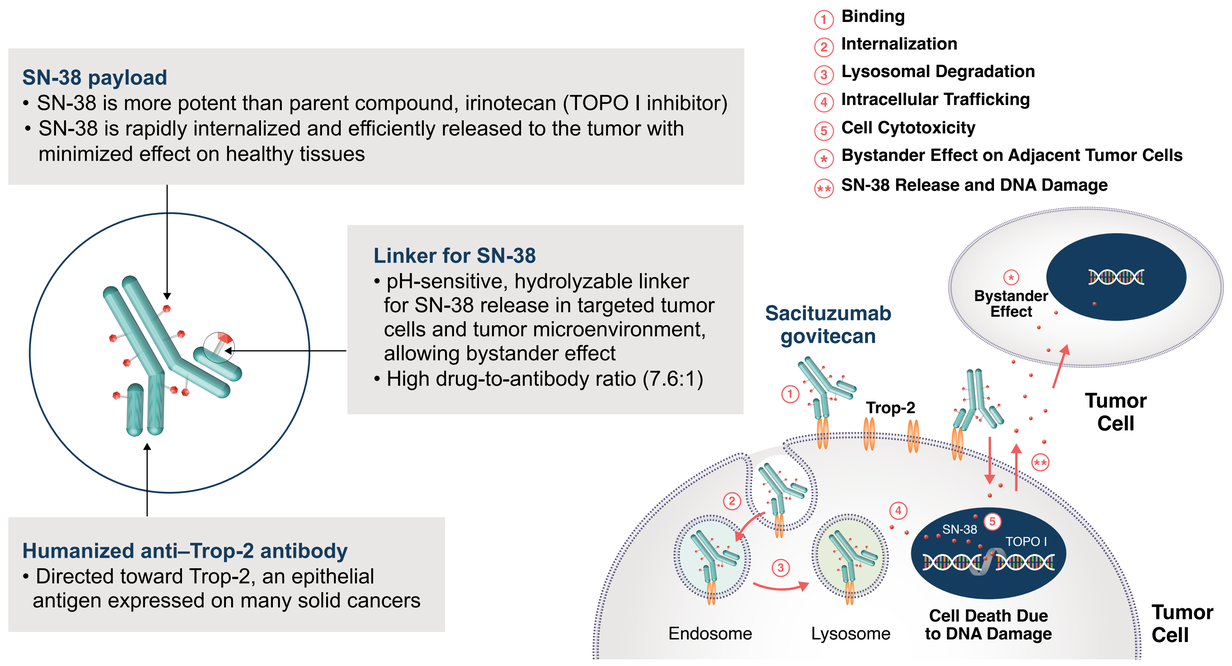
Introduction

- The current gold standard for first-line cisplatin-eligible patients with metastatic urothelial carcinoma (mUC) is cisplatin-based chemotherapy, followed by switch maintenance with avelumab in patients with non-progressive disease based on results from the JAVELIN study.[1-3] Although response rates are high with these regimens,[3] responses are not durable without avelumab maintenance and more effective treatments are needed
- Sacituzumab govitecan (SG) is a novel Trop-2–directed antibody-drug conjugate carrying a cytotoxic SN-38 payload (Figure 1)[4-7]
  - In the TROPHY-U-01 Cohort 1 of 113 patients with locally advanced or mUC who previously received platinum-based therapy and a checkpoint inhibitor (CPI), SG demonstrated an objective response rate (ORR) of 28% per central review,[8] median overall survival (OS) 10.9 months, and a manageable safety profile leading to accelerated FDA approval in the United States in this patient population[9,10]
  - In the TROPHY-U-01 Cohort 3 of 41 patients, interim efficacy and safety results for checkpoint-inhibitor–naïve patients with mUC who progressed after platinum-based chemotherapy demonstrated an ORR of 41% based on central review, and a manageable safety profile after treatment with SG and pembrolizumab combination therapy[11]
- The clinical activity and safety profile of SG suggest that it could be combined with cisplatin, with the potential for improved clinical outcomes if used as first-line induction chemotherapy in locally advanced or mUC[12,13]
- This study will also evaluate whether SG in combination with avelumab (anti–programmed death ligand 1) or zimberelimab (anti–programmed death-1) during first-line maintenance treatment would provide progression-free survival (PFS) and overall survival (OS) benefit compared with avelumab or zimberelimab alone

Study Objective

- Cohort 4 of TROPHY-U-01 study is evaluating the safety, tolerability and clinical activity of SG + cisplatin as induction therapy followed by maintenance therapy with SG + avelumab or zimberelimab in cisplatin-eligible patients with mUC or unresectable locally advanced disease

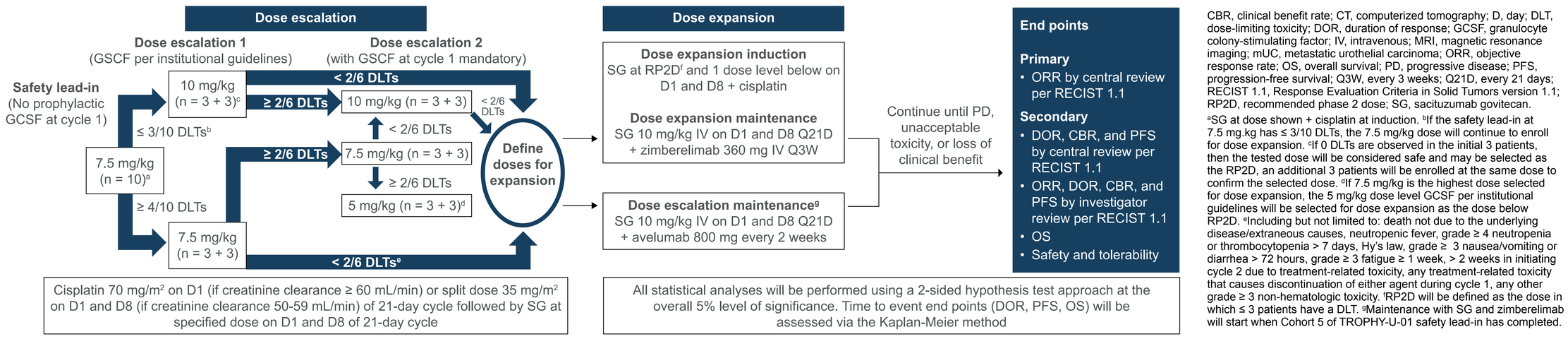
Figure 1. Sacituzumab govitecan: a novel antibody-drug conjugate[5-8]



TOPO I, topoisomerase I; Trop-2, trophoblast cell surface antigen 2. Adapted from Rugo HS, et al. TROPiCS-02: a phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncol*. 2020;16:705-715. Complete licensing info can be found here: http://creativecommons.org/licenses/by-nc-nd/4.0/.

Study Design

Figure 2. Cohort 4 study design in TROPHY-U-01, a phase 2, open-label study of sacituzumab govitecan in unresectable locally advanced/metastatic urothelial cancer (NCT03547973)



CBR, clinical benefit rate; CT, computerized tomography; D, day; DLT, dose-limiting toxicity; DOR, duration of response; GCSF, granulocyte colony-stimulating factor; IV, intravenous; MRI, magnetic resonance imaging; mUC, metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; Q21D, every 21 days; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; SG, sacituzumab govitecan.

[a]SG at dose shown + cisplatin at induction. [b]If the safety lead-in at 7.5 mg.kg has ≤ 3/10 DLTs, the 7.5 mg/kg dose will continue to enroll for dose expansion. [c]If 0 DLTs are observed in the initial 3 patients, then the tested dose will be considered safe and may be selected as the RP2D, an additional 3 patients will be enrolled at the same dose to confirm the selected dose. [d]If 7.5 mg/kg is the highest dose selected for dose expansion, the 5 mg/kg dose level GCSF per institutional guidelines will be selected for dose expansion as the dose below RP2D. [e]Including but not limited to: death not due to the underlying disease/extraneous causes, neutropenic fever, grade ≥ 4 neutropenia or thrombocytopenia > 7 days, Hy's law, grade ≥ 3 nausea/vomiting or diarrhea > 72 hours, grade ≥ 3 fatigue ≥ 1 week, > 2 weeks in initiating cycle 2 due to treatment-related toxicity, any treatment-related toxicity that causes discontinuation of either agent during cycle 1, any other grade ≥ 3 non-hematologic toxicity. [f]RP2D will be defined as the dose in which ≤ 3 patients have a DLT. [g]Maintenance with SG and zimberelimab will start when Cohort 5 of TROPHY-U-01 safety lead-in has completed.

Key Eligibility Criteria

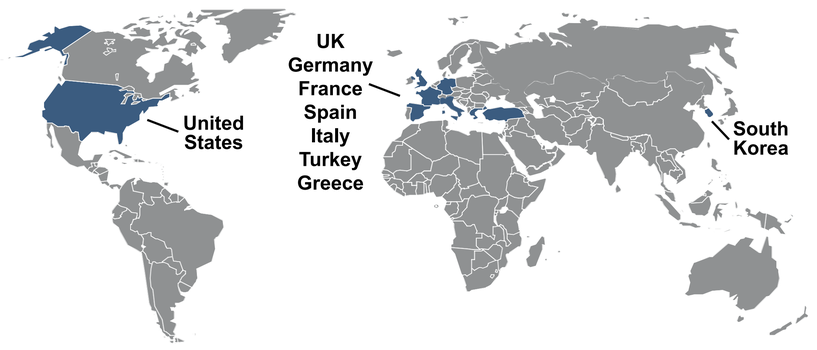
Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
Age ≥ 18 years, with 3-month life expectancy	Refractory to platinum (ie, relapse ≤ 12 months after completion of chemotherapy) in neoadjuvant/adjuvant setting
Histologically documented locally advanced or mUC — Measurable disease by CT or MRI per RECIST 1.1	Prior anticancer monoclonal antibody within 4 weeks of study drug initiation
Archival tumor tissue comprising muscle-invasive or mUC, or biopsy of mUC	Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of study drug initiation
Cisplatin-eligible with no prior therapy, including platinum-based chemotherapy in metastatic or unresectable locally advanced setting	Active autoimmune disease that required systemic treatment within 2 years of study drug initiation
CrCl[a] of ≥ 50 mL/min. Cisplatin 70 mg/m^2 option on day 1 for CrCl ≥ 60 mL/min and split dose of 35 mg/m^2 option on days 1 and 8 for CrCl 50-59 mL/min	History or evidence of interstitial lung disease or non-infectious pneumonitis
Adequate blood counts without transfusion or growth factor support within 2 weeks of study drug initiation	Active CNS metastases and/or carcinomatous meningitis
Adequate hepatic function, ECOG PS 0-1	Grade ≥ 2 hearing loss
	Grade ≥ 2 peripheral neuropathy
	Active cardiac disease
	Active chronic inflammatory bowel disease or GI perforation within 6 months of enrollment

CNS, central nervous system; CrCl, creatinine clearance; CT, computerized tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; MRI, magnetic resonance imaging; mUC, metastatic urothelial carcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
[a]Creatinine clearance calculated by Cockcroft-Gault formula or another validated tool.

Study Sites/Enrollment

Figure 3. TROPHY-U-01 study sites and contacts



Study enrollment for TROPHY-U-01 (NCT03547973) Cohort 4 began in February 2021 and is currently ongoing.

Overall, enrollment will occur at ~120 sites globally.

For more information, please visit https://clinicaltrials.gov/ct2/show/NCT03547973

Contact email: GileadClinicalTrials@gilead.com

References: **1.** National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 1.2023. **2.** Powles T, et al. *N Engl J Med*. 2020; 383:1218-1230. **3.** Powles T, et al. *J Clin Oncol*. 2023 Apr 18:JCO2201792. doi: 10.1200/JCO.22.01792. **4.** Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. **5.** Avellini C, et al. *Oncotarget*. 2017;8:58642-58653. **6.** Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885. **7.** Rugo HE, et al. *Future Oncol*. 2020;16:705-715. **8.** Tagawa ST, et al. *J Clin Oncol*. 2023;41(6_suppl):526. **9.** Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474-2485. **10.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Gilead Sciences, Inc., Foster City, CA; February 2023. **11.** Grivas P, et al. *J Clin Oncol*. 2023;41(6_suppl):518. **12.** BAVENCIO® (avelumab) [prescribing information]. EMD Serono Inc., Rockland, MA; July 2022. **13.** Johnson ML, et al. *J Clin Oncol*. 2022;40(suppl 36):397600.

Acknowledgments: We thank the patients and their caregivers for helping us realize the possibilities of this research. We thank the dedicated study investigators and their devoted team members for participating in the TROPHY-U-01 study. This study is sponsored by Gilead Sciences, Inc. Editorial support was provided by Sonal Joshi, PhD, of Parexel and funded by Gilead Sciences, Inc.
Correspondence: p.barthelemy@icans.eu

Presented at American Society of Clinical Oncology (ASCO); June 2-6, 2023; Chicago, IL & Online