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TROPiCS-04: A Randomized Phase 3 Study of Sacituzumab Govitecan vs Chemotherapy in Pretreated Advanced Urothelial Carcinoma

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Declaration of Interests

Petros Grivas

- Consulting/Advisory Role: Merck, Bristol Myers Squibb, AstraZeneca, EMD Serono, Pfizer, Janssen, Roche, Astellas Pharma, Gilead Sciences, Inc., Fresenius Kabi, CG Oncology, Strata Oncology, ImmunityBio, Asieris Pharmaceuticals, AbbVie, Bicycle Therapeutics, Replimune, Daiichi Sankyo
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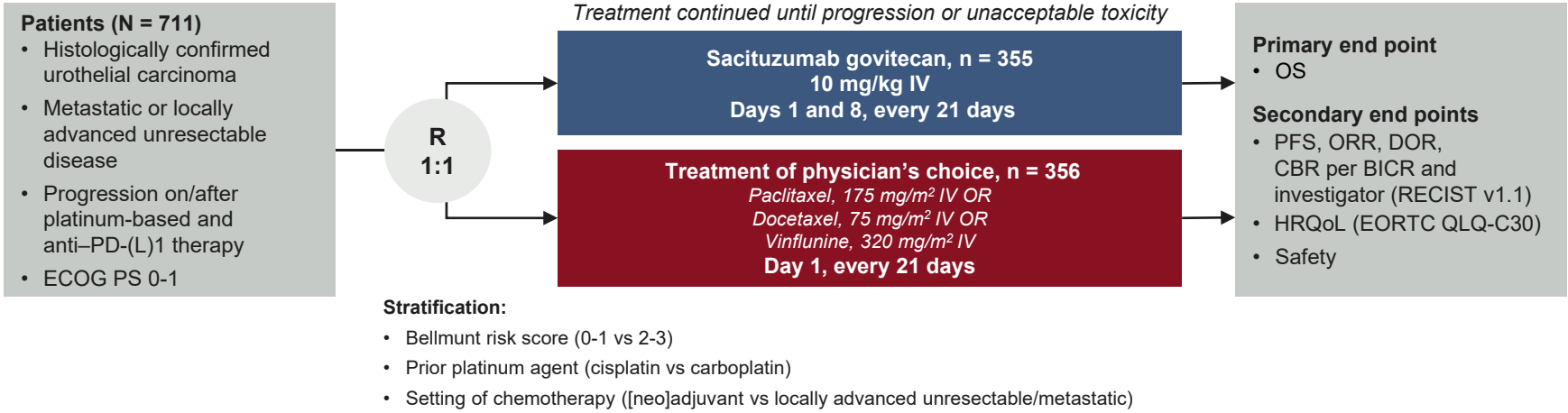
Introduction

- Historically, there have been limited treatment options for patients with locally advanced or metastatic UC following disease progression on first-line regimen[1]
- The treatment landscape for advanced UC has evolved considerably in the last few years; new first- and subsequent-line treatment options, especially ADCs and erdafitinib, have emerged that have improved survival outcomes in phase 3 trials[2-6]
- Despite the significant improvement in OS and PFS observed with these new regimens, there remains a need for more therapies for patients with disease progression on prior treatments
- SG, a Trop-2–directed antibody-drug conjugate, showed efficacy (ORR 28%-41%) and a manageable toxicity profile as single agent or in combination with pembrolizumab in the multicohort phase 2 TROPHY-U-01 study in pretreated patients with advanced UC[7-10]
  - SG is approved in many countries for the treatment of metastatic triple-negative breast cancer and HR+/HER2- metastatic breast cancer[11,12]
- We report results from the final analysis of the global, open-label, randomized phase 3 TROPiCS-04 study (NCT04527991) in patients with pretreated advanced UC

ADC, antibody-drug conjugate; **FGFR**, fibroblast growth factor receptor; **PFS**, progression-free survival; **ORR**, objective response rate; **OS**, overall survival; **SG**, sacituzumab govitecan; **Trop-2**, trophoblast cell surface antigen 2; **UC**, urothelial carcinoma.

1. Bellmunt J, et al. *N Engl J Med*. 2024;376:1015-26. 2. Powles T, et al. *N Engl J Med*. 2021;384:1125-35. 3. Balar AV, et al. *Ann Oncol*. 2023;34:289-99. 4. Loriot Y, et al. *N Engl J Med*. 2019;381:338-48. 5. Van der Heijden MS, et al. *N Eng J Med*. 2023;389:1778-1789. 6. Powles T, et al. *N Eng J Med*. 2024:390:875-88. 7. Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474-85. 8. Loriot Y, et al. *Ann Oncol*. 2024;35:392-401. 9. Grivas P, et al. *J Clin Oncol*. 2024;42:1415-25. 10. Petrylak DP, et al. *J Clin Oncol*. 2024;42:3410-20. 11. TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc., February 2023. 12. TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. County Cork, Ireland: Gilead Sciences Ireland UC, August 2023.

TROPiCS-04 Study Design



- G-CSF primary prophylactic use for neutropenia was not required per study protocol, but investigators were encouraged to consider prophylaxis in patients with risk factors for febrile neutropenia, per ASCO guidelines for use of growth factors[1]
  - Following IDMC recommendation, a memorandum sent to the participating sites in September 2022 strongly recommended primary prophylaxis with G-CSF starting in cycle 1 in patients at risk for developing febrile neutropenia
- At data cutoff (8 March 2024), **median follow-up was 9.2 months (range: 0-33.7)**

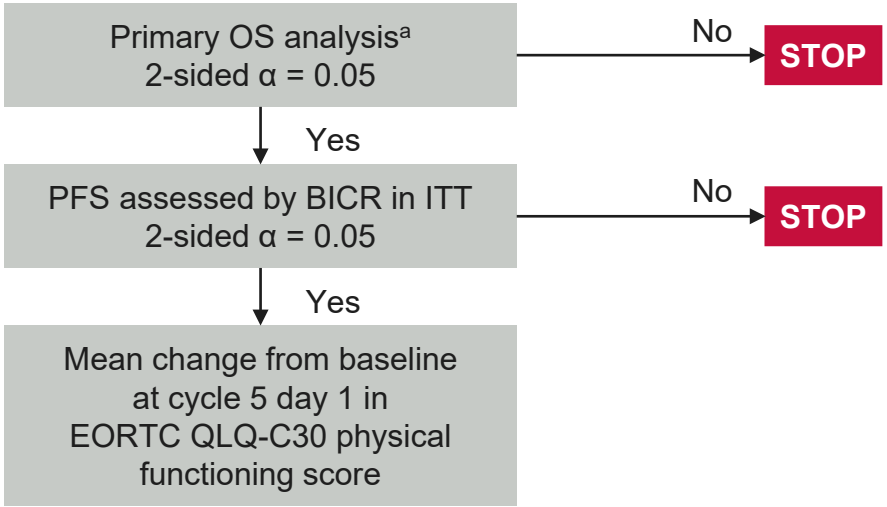
ASCO, American Society of Clinical Oncology; **BICR**, blinded independent central review; **CBR**, clinical benefit rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EORTC QLQ-C30**, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **G-CSF**, granulocyte colony stimulating factor; **HRQoL**, health-related quality of life; **IDMC**, independent data monitoring committee; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD-(L)1**, programmed death (ligand) 1; **PFS**, progression-free survival; **R**, randomized; **RECIST**, Response Evaluation Criteria in Solid Tumors.

1. Smith TJ, et al. *J Clin Oncol*. 2015;33:3199-212.

Statistical Analysis: Final Planned Analysis

- Estimated sample size was ~696 patients
- Final OS analysis was planned after accrual of 536 events, which was projected to provide 90% power to demonstrate an HR of 0.755 at a 2-sided alpha of 5%

Hierarchical testing to ensure the overall Type I error rate is strictly controlled at a 2-sided alpha of 0.05 for comparison between SG and TPC groups



[a]The efficacy boundaries for OS at the interim and final analyses were determined using the Lan-DeMets spending function that approximates O'Brien/Fleming boundaries.
BICR, blinded independent central review; **EORTC QLQ-C30**, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **HR**, hazard ratio; **ITT**, intent-to-treat; **OS**, overall survival; **PFS**, progression-free survival; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice.

Demographics and Baseline Characteristics

Characteristic	SG n = 355	TPC n = 356
Median age (range), years	67 (41-89)	68 (30-85)
< 65, n (%)	133 (37)	131 (37)
65-74, n (%)	154 (43)	138 (39)
≥ 75, n (%)	68 (19)	87 (24)
Sex, n (%)		
Male	284 (80)	279 (78)
Geographic region, n (%)		
North America	20 (6)	9 (3)
Europe	230 (65)	260 (73)
Rest of the world[a]	105 (30)	87 (24)
ECOG PS,[b] n (%)		
0	131 (37)	132 (37)
1	224 (63)	220 (62)
Bellmunt risk score[c]		
0-1	262 (74)	267 (75)
2-3	93 (26)	89 (25)

Characteristic	SG n = 355	TPC n = 356
State of cancer at enrollment, n (%)		
Metastatic	330 (93)	320 (90)
Locally advanced unresectable	25 (7)	36 (10)
Site of primary tumor,[d] n (%)		
Upper urinary tract	134 (38)	119 (33)
Lower urinary tract	220 (62)	233 (65)
Metastatic sites, n (%)		
Lymph node only	50 (14)	37 (10)
Liver	105 (30)	104 (29)
Brain	6 (2)	5 (1)
Number of prior anticancer regimens, n (%)		
1-2	243 (68)	252 (71)
≥ 3	112 (32)	104 (29)
Most recent prior platinum-based therapy, n (%)		
Cisplatin	212 (60)	203 (57)
Carboplatin	143 (40)	153 (43)
Setting of most recent prior platinum-based therapy, n (%)		
Neoadjuvant/adjuvant	62 (17)	60 (17)
Locally advanced unresectable/metastatic	293 (83)	296 (83)

[a]Includes China, Korea, Australia, Taiwan, Singapore, and Hong Kong. [b]In the TPC group, 3 patients had an ECOG PS of 2 and 1 patient an ECOG PS of 3. [c]Bellmunt risk scores range from 0 to 3 according to the presence of the following risk factors: a hemoglobin level of < 10 g per deciliter, an ECOG PS score of greater than 0, and liver metastases. [d]1 patient in the SG group and 4 patients in the TPC group had missing data.
ECOG PS, Eastern Cooperative Oncology Group performance status; **SG**, sacituzumab govitecan; **TPC**, treatment of physicians' choice.

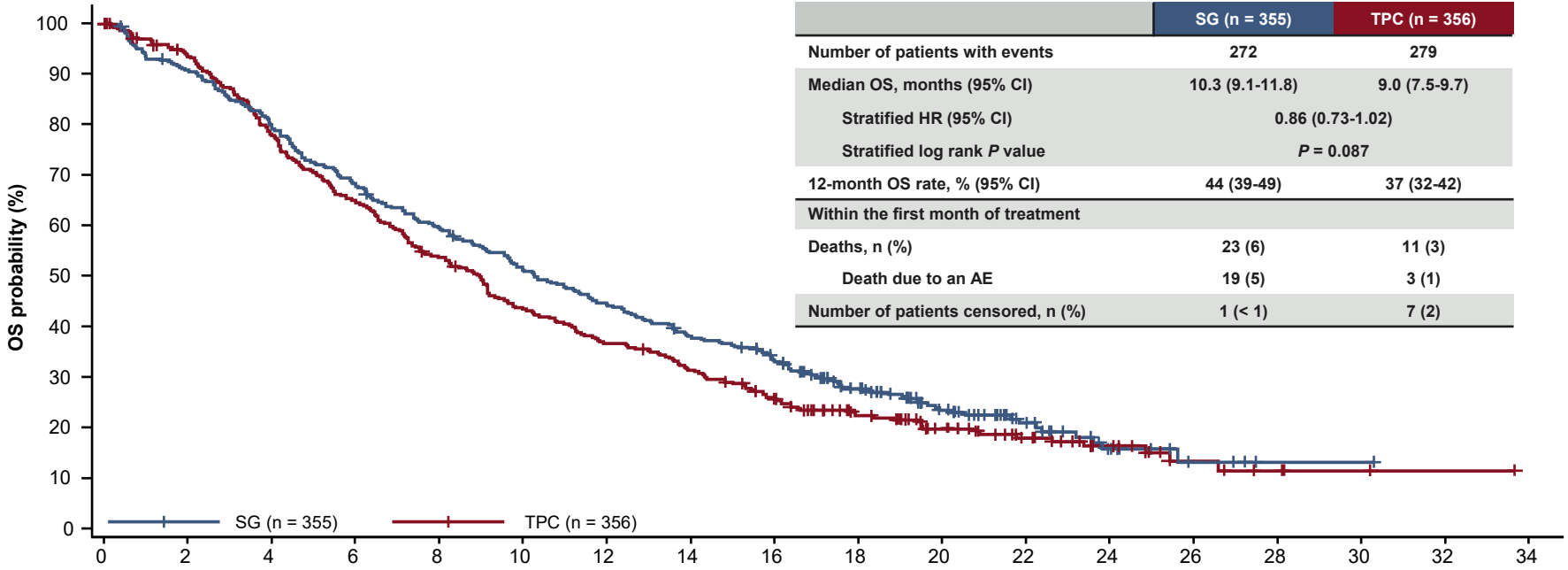
Exposure and Disposition

ITT Population	SG n = 355	TPC n = 356
All treated patients,[a] n (%)	349 (98)	337[b] (95)
Median duration of treatment, months (range)	3.0 (0-26.6)	2.1 (0-20.7)
Median number of cycles received (range)	5 (1-33)	4 (1-30)
Discontinued treatment, n (%)	340 (96)	334 (94)
Primary reason for treatment discontinuation, n (%)		
Disease progression	244 (69)	231 (65)
Adverse event	56 (16)	52 (15)
Withdrawal of consent	20 (6)	21 (6)
More than a 5-week dose delay from the last dose	11 (3)	16 (5)
Other[c]	9 (3)	14 (4)

- 179 (50%) patients randomized to SG and 174 (49%) to TPC received any SACT
  - **Subsequent EV was received by 67 (19%) patients in the SG group and 74 (21%) in the TPC group**

[a]6 (2%) patients in the SG group and 19 (5%) in the TPC group were randomized but did not receive treatment. [b]Paclitaxel (n = 157, 47%), docetaxel (n = 137, 41%), and vinflunine (n = 43, 13%). [c]Other reasons include failure to resolve a toxicity within 3 weeks of the last dose of study drug, patient noncompliance, COVID-19, and other.
EV, enfortumab vedotin; **ITT**, intent-to-treat; **SACT**, subsequent anticancer therapy; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice.

Primary End Point: Overall Survival



	SG (n = 355)	TPC (n = 356)
Number of patients with events	272	279
Median OS, months (95% CI)	10.3 (9.1-11.8)	9.0 (7.5-9.7)
Stratified HR (95% CI)	0.86 (0.73-1.02)	
Stratified log rank *P* value	*P* = 0.087	
12-month OS rate, % (95% CI)	44 (39-49)	37 (32-42)
Within the first month of treatment		
Deaths, n (%)	23 (6)	11 (3)
Death due to an AE	19 (5)	3 (1)
Number of patients censored, n (%)	1 (< 1)	7 (2)

Number at risk (events)

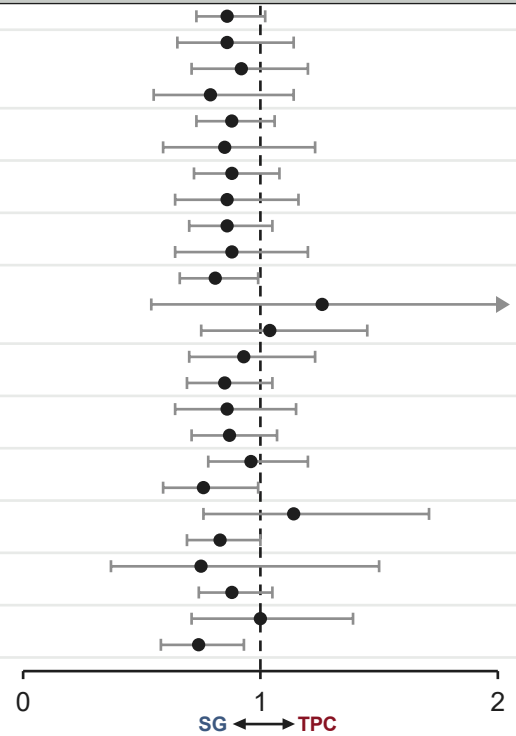
SG	355 (0)	320 (33)	282 (71)	241 (112)	209 (143)	179 (172)	155 (196)	132 (218)	112 (235)	78 (252)	49 (262)	26 (266)	12 (271)	4 (272)	1 (272)	1 (272)	0 (272)
TPC	356 (0)	323 (22)	269 (76)	224 (121)	184 (160)	148 (195)	125 (218)	106 (236)	84 (255)	59 (265)	41 (271)	26 (274)	16 (276)	7 (278)	4 (279)	2 (279)	1 (279)	0 (279)

- While there was a trend toward favorable OS with SG, the primary end point of improved OS with SG vs TPC was not met

HR, hazard ratio; **OS**, overall survival; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice.

Overall Survival: Subgroup Analysis

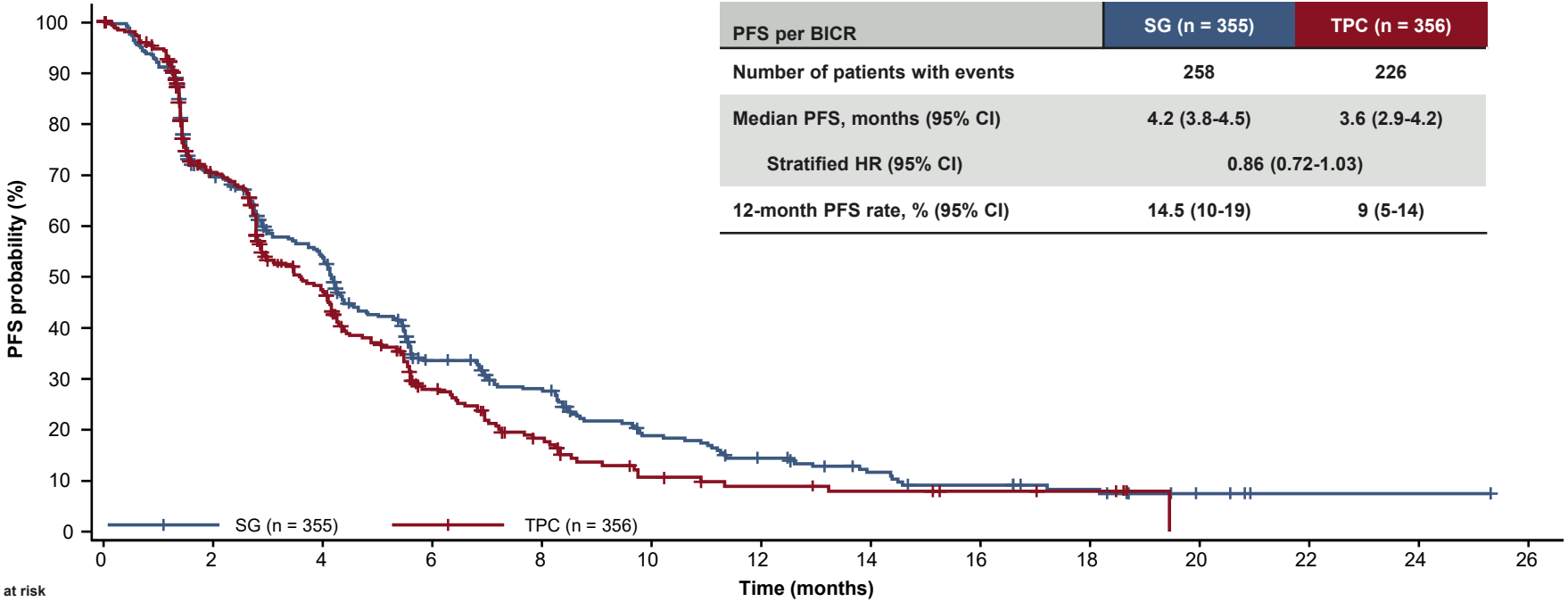
Category (ITT Population)	Subgroup	Median OS (95% CI), Months		HR (95% CI)
		SG	TPC	
Overall (SG, n = 355; TPC, n = 356)		10.3 (9.1-11.8)	9.0 (7.5-9.7)	0.86 (0.73-1.02)
Age, years	< 65 (SG, n = 133; TPC, n = 131)	11.2 (9.1-13.6)	9.6 (8.1-11.5)	0.86 (0.65-1.14)
	65-74 (SG, n = 154; TPC, n = 138)	9.6 (6.7-11.0)	8.3 (6.5-9.3)	0.92 (0.71-1.20)
	≥ 75 (SG, n = 68; TPC, n = 87)	12.5 (7.4-15.9)	7.6 (6.4-10.8)	0.79 (0.55-1.14)
Sex	Male (SG, n = 284; TPC, n = 279)	10.2 (8.6-11.6)	9.0 (7.4-9.8)	0.88 (0.73-1.06)
	Female (SG, n = 71; TPC, n = 77)	12.0 (7.4-16.0)	8.8 (6.5-11.7)	0.85 (0.59-1.23)
Number of prior anticancer regimens	1-2 (SG, n = 243; TPC, n = 252)	11.4 (9.8-12.8)	9.2 (7.5-10.8)	0.88 (0.72-1.08)
	> 2 (SG, n = 112; TPC, n = 104)	8.2 (6.2-10.3)	8.6 (5.8-9.4)	0.86 (0.64-1.16)
Bellmunt risk factors[a]	0-1 (SG, n = 262; TPC, n = 267)	11.7 (10.0-13.6)	9.7 (8.8-11.5)	0.86 (0.70-1.05)
	2-3 (SG, n = 93; TPC, n = 89)	7.2 (5.3-9.6)	5.4 (3.7-7.2)	0.88 (0.64-1.20)
Geographic region	Europe (SG, n = 230; TPC, n = 260)	10.7 (8.8-12.0)	8.1 (6.7-9.2)	0.81 (0.66-0.99)
	North America (SG, n = 20; TPC, n = 9)	10.2 (5.6-18.3)	10.8 (0.6-23.4)	1.26 (0.54-2.94)
	Rest of world (SG, n = 105; TPC, n = 87)	10.0 (7.4-13.6)	10.6 (8.1-13.9)	1.04 (0.75-1.45)
Site of primary tumor	Upper urinary tract (SG, n = 134; TPC, n = 119)	11.2 (9.6-12.5)	9.8 (8.1-12.5)	0.93 (0.70-1.23)
	Lower urinary tract (SG, n = 220; TPC, n = 233)	9.8 (8.2-12.4)	8.2 (6.5-9.2)	0.85 (0.69-1.05)
Liver metastases	Yes (SG, n = 105; TPC, n = 104)	7.4 (5.5-9.6)	7.1 (4.6-8.5)	0.86 (0.64-1.15)
	No (SG, n = 250; TPC, n = 252)	12.0 (10.0-13.9)	9.7 (8.3-11.7)	0.87 (0.71-1.07)
Type of most recent prior platinum therapy[a]	Cisplatin (SG, n = 212; TPC, n = 203)	9.7 (7.5-11.0)	9.2 (7.8-11.1)	0.96 (0.78-1.20)
	Carboplatin (SG, n = 143; TPC, n = 153)	12.5 (9.6-14.0)	7.6 (6.5-9.2)	0.76 (0.59-0.99)
Setting of most recent prior platinum therapy[a]	(Neo)adjuvant (SG, n = 62; TPC, n = 60)	7.7 (5.5-10.3)	8.8 (7.2-13.0)	1.14 (0.76-1.71)
	Metastatic (SG, n = 293; TPC, n = 296)	11.2 (9.7-12.9)	9.0 (7.3-9.8)	0.83 (0.69-1.00)
Prior use of enfortumab vedotin	Yes (SG, n = 24; TPC, n = 15)	10.2 (6.4-13.6)	8.0 (3.4-13.7)	0.75 (0.37-1.50)
	No (SG, n = 331; TPC, n = 341)	10.3 (9.0-12.0)	9.0 (7.6-9.7)	0.88 (0.74-1.05)
Best response to the most recent prior regimen	Response (SG, n = 97; TPC, n = 96)	13.0 (10.3-16.2)	11.8 (9.0-15.3)	1.00 (0.71-1.39)
	No response (SG, n = 173; TPC, n = 192)	9.0 (7.1-11.6)	7.4 (6.3-9.1)	0.74 (0.58-0.93)



- HRs of OS consistently favored SG vs TPC in most prespecified subgroups

[a]Stratification factors.
HR, hazard ratio; **ITT**, intent-to-treat; **OS**, overall survival; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice.

Secondary End Point: Progression-Free Survival



PFS per BICR	SG (n = 355)	TPC (n = 356)
Number of patients with events	258	226
Median PFS, months (95% CI)	4.2 (3.8-4.5)	3.6 (2.9-4.2)
Stratified HR (95% CI)	0.86 (0.72-1.03)	
12-month PFS rate, % (95% CI)	14.5 (10-19)	9 (5-14)

Number at risk (events)														
SG	355 (0)	221 (100)	160 (148)	82 (205)	64 (218)	39 (238)	28 (247)	19 (252)	14 (256)	10 (257)	4 (258)	1 (258)	1 (258)	0 (258)
TPC	356 (0)	196 (90)	116 (151)	52 (194)	29 (211)	14 (222)	10 (224)	8 (225)	6 (225)	5 (225)	0 (226)			

- No significant PFS benefit was observed with SG vs TPC

BICR, blinded independent central review; **HR**, hazard ratio; **PFS**, progression-free survival; **TPC**, treatment of physician's choice.

Secondary End Point: Best Overall Response

Response per BICR	SG n = 355	TPC n = 356
Objective response rate (CR + PR), n (%) [95% CI]	80 (23) [18-27]	49 (14) [10-18]
Stratified odds ratio (95% CI)	1.84 (1.24-2.73)	
Best overall response, n (%)		
CR	19 (5)	9 (3)
PR	61 (17)	40 (11)
SD	151 (43)	170 (48)
SD ≥ 6 months	26 (7)	24 (7)
PD	75 (21)	77 (22)
Not evaluable	49 (14)	60 (17)
Median DOR (95% CI), months	7.2 (6.3-8.4)	6.5 (5.2-8.3)
Clinical benefit rate (CR + PR + SD ≥ 6 months), n (%) [95% CI]	106 (30) [25-35]	73 (21) [16-25]
Stratified odds ratio (95% CI)	1.68 (1.19-2.37)	

- **A higher ORR was observed with SG vs TPC, and SG response rates were consistent with previous results from the phase 2 TROPHY-U-01 study[1,2]**

BICR, blinded independent central review; **CR**, complete response; **DOR**, duration of response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SG**, sacituzumab govitecan; **SD**, stable disease; **TPC**, treatment of physicians' choice.

1. Tagawa ST, et al. *J Clin Oncol.* 2021;39:2474-85. 2. Loriot Y, et al. *Ann Oncol.* 2024;35:392-401.

Safety Summary

Safety-Evaluable Patients, n (%)	SG n = 349	TPC n = 337
Any-grade TEAEs	347 (99)	320 (95)
Treatment-related	339 (97)	296 (88)
Grade ≥ 3 TEAEs	269 (77)	171 (51)
Treatment-related	233 (67)	119 (35)
Serious TEAEs	183 (52)	110 (33)
Treatment-related	120 (34)	60 (18)
TEAEs leading to discontinuation	54 (15)	50 (15)
Treatment-related	39 (11)	42 (12)
TEAEs leading to death	25 (7)	7 (2)
Treatment-related	15 (4)	5 (1)

- Grade 5 TEAEs were observed in 7% of patients in the SG group vs 2% of patients in the TPC group
  - 16 (5%) events with SG were infections in the setting of neutropenia, of which 14 occurred within the first month of treatment
  - Patients who experienced fatal infections with neutropenia had a higher burden of risk factors for medical complications compared with the overall SG group
    - Age ≥ 65 years, 81%; prior cystectomy, 56%; prior major urinary tract procedure, 81%; prior radiotherapy, 50%; at least 3 prior anticancer regimens, 50%

SG, sacituzumab govitecan; **TEAE**, treatment-emergent adverse event; **TPC**, treatment of physician's choice.

Most Common TRAEs

Most Common TRAEs, n (%)	SG n = 349		TPC n = 337	
	Any Grade (≥ 15%)[a]	Grade ≥ 3 (≥ 5%)[b]	Any Grade (≥ 15%)[a]	Grade ≥ 3 (≥ 5%)[b]
Fatigue[c]	187 (54)	41 (12)	132 (39)	18 (5)
Anemia[d]	161 (46)	46 (13)	97 (29)	23 (7)
Alopecia	134 (38)	0	110 (33)	2 (1)
Diarrhea	182 (52)	51 (15)	47 (14)	9 (3)
Neutropenia[e]	166 (48)	122 (35)	51 (15)	35 (10)
Nausea	143 (41)	11 (3)	49 (15)	2 (1)
Decreased appetite	79 (23)	9 (3)	39 (12)	1 (< 1)
Vomiting	77 (22)	10 (3)	18 (5)	2 (1)
Leukopenia[f]	68 (19)	36 (10)	20 (6)	9 (3)
Neuropathy peripheral	9 (3)	0	56 (17)	8 (2)
Febrile neutropenia	41 (12)	41 (12)	15 (4)	15 (4)

All adverse events occurring after the first dose of study drug until 30 days after the last dose of study drug were recorded.
[a]Occurring in ≥ 15% of patients in any treatment group. [b]Includes grade ≥ 3 events occurring in ≥ 5% of patients, and any grade events occurring in ≥ 15% of patients in any treatment group. [c]Includes fatigue and asthenia. [d]Includes anemia, hemoglobin decreased, and red blood cell count decreased. [e]Includes neutropenia and neutrophil count decreased. [f]Includes leukopenia and white blood cell count decreased.
SG, sacituzumab govitecan; **TPC**, treatment of physician's choice; **TRAE**, treatment-related adverse event.

G-CSF Use and Impact on AEs

Safety-Evaluable Patients, n (%)	SG n = 349	TPC n = 337
Any prophylaxis	128 (37)	87 (26)
Primary prophylaxis	74 (21)	73 (22)
Secondary prophylaxis	54 (15)	14 (4)
Therapeutic	106 (30)	33 (10)

- Primary prophylaxis was defined as G-CSF use on or after cycle 1 day 1 and prior to the onset of the first occurrence of neutropenia or no event of neutropenia
- Secondary prophylaxis was defined as G-CSF use after resolution of grade ≥ 2 neutropenia (to grade ≤ 1) or after occurrence of grade 1 neutropenia; and prior to any subsequent grade ≥ 2 neutropenia or no occurrence of subsequent grade ≥ 2
- G-CSF use was considered therapeutic if administered during grade ≥ 2 neutropenia

Patients Receiving SG, n (%)	With Primary Prophylactic G-CSF n = 74	Without Primary Prophylactic G-CSF n = 275
AESI neutropenia[a]	32 (43)	162 (59)
AESI neutropenia grade ≥ 3[a]	24 (32)	131 (48)
Febrile neutropenia	7 (9)	33 (12)
AESI serious infections secondary to neutropenia after the first AESI neutropenia[b]	1 (1)	22 (8)
Fatal infection secondary to neutropenia	2 (3)[c,d]	14 (5)

- **G-CSF primary prophylactic use was 21% and 22% with SG and TPC, respectively, in this population at high risk for febrile neutropenia**
- **Incidence of grade ≥ 3 neutropenia with or without primary prophylactic G-CSF was 32% and 48%, respectively**

[a]AESI neutropenia includes preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia. [b]AESI serious infections secondary to neutropenia includes an AE with a preferred term from System Organ Class Infections and Infestations that was assessed as serious by the investigator and started on or within 11 days after start date of AESI neutropenia. [c]1 patient had a preexisting open wound/ulceration, underwent an invasive procedure without adequate (per protocol) healing before next SG, and did not receive prophylactic G-CSF with their last SG dose; the patient died of sepsis. Another patient had rapid tumor progression with kidney damage resulting on the placement of a nephrostomy tube without adequate healing before next SG (per protocol); the patient died of septic shock. [d]Includes 1 patient with serious infection occurring on 15 days after neutropenia, therefore outside the window of AESIs of serious infection secondary to neutropenia.
AE, adverse event; **AESI**, adverse event of special interest; **G-CSF**, granulocyte colony stimulating factor; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice.

Conclusions

- SG did not result in a significant improvement in OS or PFS vs TPC in pretreated advanced UC, although SG activity was demonstrated by a higher ORR
- Safety data were consistent with the known toxicity profile of SG across tumor types, except for increased rates of neutropenic complications in this high-risk population
  - Increased incidences of grade ≥ 3 neutropenic events, infections secondary to neutropenia, and grade 5 TEAEs were observed with SG vs TPC
  - Low usage of G-CSF prophylaxis may have resulted in higher rates of neutropenic complications
- TROPiCS-04 showed that SG is active in advanced UC but did not demonstrate significant improvement over TPC
  - Several reasons may have contributed to the results beyond efficacy, e.g. early deaths due to toxicity with SG, higher number of patients randomized but not treated with TPC, subsequent therapies, including EV

EV, enfortumab vedotin; **G-CSF**, granulocyte colony stimulating factor; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **SACT**, subsequent anticancer therapy; **SG**, sacituzumab govitecan; **TPC**, treatment of physician's choice; **UC**, urothelial carcinoma.

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