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ORIGINAL ARTICLE

Sacituzumab govitecan in advanced urothelial carcinoma: TROPiCS-04, a phase III randomized trial

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Background: Sacituzumab govitecan (SG), a Trop-2-directed antibody–drug conjugate, demonstrated efficacy and manageable toxicity in the phase II TROPHY-U-01 study in pretreated advanced urothelial carcinoma (aUC). We report the results from final analysis of the global open-label randomized phase III TROPiCS-04 study (NCT04527991) in pretreated aUC.

Patients and methods: Patients with aUC whose disease had progressed on prior platinum-based chemotherapy and checkpoint inhibitor therapy were randomized 1 : 1 to receive SG or treatment of physician's choice (TPC; paclitaxel, docetaxel, or vinflunine). The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) by investigator and blinded independent committee review, as well as safety.

Results: Overall, 711 patients were randomized. After a median follow-up of 9.2 months, the primary endpoint was not met [median OS for SG versus TPC: 10.3 months versus 9.0 months, hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.73-1.02, $P = 0.087$]. Median PFS with SG and TPC was 4.2 months and 3.6 months, respectively (HR 0.86, 95% CI 0.72-1.03); ORR (95% CI) was 23% (18% to 27%) and 14% (10% to 18%). The most common grade $\geq$3 treatment-related adverse event (TRAE) with SG was neutropenia (35%, including 12% with febrile neutropenia). Incidence of grade $\geq$3 TRAEs (67% versus 35%) and grade 5 treatment-emergent adverse events (TEAEs; 7% versus 2%) was higher with SG versus TPC. In the SG group, 16/25 grade 5 TEAEs were infections with neutropenia mostly occurring early in the treatment course of patients with multiple risk factors for febrile neutropenia. Primary prophylactic granulocyte colony-stimulating factor (G-CSF) usage with SG and TPC was 21% and 22%, respectively.

Conclusions: SG did not result in a significant improvement in OS or PFS compared with TPC in pretreated aUC, although SG activity was demonstrated by a higher ORR. Early toxicity-related complications with SG may have impacted efficacy outcomes.

Key words: antibody–drug conjugate, bladder cancer, metastatic urothelial carcinoma, sacituzumab govitecan, SN-38, topoisomerase I inhibitor

INTRODUCTION

Until recently, patients with advanced urothelial carcinoma (aUC) whose cancer progresses on or after platinum-based chemotherapy and programmed cell death-(ligand) 1 [PD-(L)1] inhibitors have had relatively limited approved

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treatment options and poor prognosis.[1-6] Historically, second-line single-agent chemotherapy with vinflunine (approved in the European Union only), paclitaxel, or docetaxel has provided a median overall survival (OS) of 7-9 months,[7-9] emphasizing a need for new safe and effective treatment options. An OS of 10-13 months has been observed with immune checkpoint inhibitors, erdafitinib, and the antibody–drug conjugate (ADC) enfortumab vedotin (EV) in the second-line and later setting.[8,10,11] There has been a rapid evolution in the first-line treatment landscape, with approvals of pembrolizumab plus EV, combinations of gemcitabine/cisplatin with nivolumab, and platinum-based chemotherapy followed by avelumab switch maintenance therapy.[3,5,12-18] Despite the significant improvements in OS and progression-free survival (PFS) observed with these regimens, there remains a major need for more therapies, especially in patients with progression on prior treatments.

Sacituzumab govitecan (SG), an antibody directed to Trophoblast cell surface antigen 2 (Trop-2), has shown notable antitumor activity in various solid tumors.[19-22] SG is approved for the treatment of unresectable, locally advanced or metastatic triple-negative breast cancer and hormone receptor (HR)-positive, human epidermal growth factor (HER)-2-negative breast cancer in pretreated patients.[23,24]

In cohort 1 of the phase II TROPHY-U-01 study, which included 113 patients with aUC whose cancer had progressed on or after prior platinum-based and PD-(L)1 inhibitor therapies, SG treatment led to an objective response rate (ORR) of 28% and median duration of response (DOR) of 8.2 months.[25] Clinical activity was also observed with SG monotherapy in 38 platinum-ineligible patients with aUC whose cancer had progressed after checkpoint inhibitor therapy (cohort 2) and with SG plus pembrolizumab in 41 checkpoint inhibitor-naive patients whose cancer had progressed after platinum-based chemotherapy (cohort 3).[26,27]

We hypothesized that SG would be superior to standard chemotherapy in patients with previously treated aUC. Here, we report efficacy and safety results from the final analysis of TROPiCS-04 (NCT04527991), a phase III study of SG in this patient population.

METHODS

Trial oversight

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The study protocol and amendments were approved by an institutional review board or independent ethics committee at each participating center. All patients provided written informed consent. An independent data monitoring committee (IDMC) met regularly to assess safety data, review efficacy results, and oversee study conduct.

Patients

Eligible patients were aged ≥18 years and had histologically confirmed, locally advanced unresectable or metastatic UC with predominantly conventional urothelial histology, including tumors of upper and lower urinary tract origin. Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 and may have had stable/asymptomatic brain metastases. Prior treatment must have included platinum-based chemotherapy [cisplatin or carboplatin in the advanced setting, and (neo)adjuvant cisplatin with progression within 12 months were counted toward eligibility] and anti-PD-(L)1 therapy in the advanced setting; prior treatment with erdafitinib, EV, and investigational agents was allowed. Patients were ineligible if they had received prior chemotherapy for UC with topoisomerase 1 inhibitor, paclitaxel, docetaxel, or vinflunine, had an active second malignancy, serious infection requiring treatment, or history of active interstitial lung disease or noninfectious pneumonitis. In addition, patients had to have adequate hematological parameter values at enrollment (including absolute neutrophil count ≥1500/mm^3) without blood transfusion or growth factor support within 2 weeks of initiation of SG or treatment of physician's choice (TPC). Full eligibility criteria are listed in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2025.01.011.

Study design and treatment

In this global, multicenter, open-label randomized controlled phase III study, eligible patients were randomly assigned (1 : 1 ratio) to receive intravenous infusions of SG (10 mg/kg) on days 1 and 8 of 21-day cycles, or protocol-specified TPC (paclitaxel 175 mg/m^2, docetaxel 75 mg/m^2, or vinflunine 320 mg/m^2), each administered intravenously on day 1 of 21-day cycles (suppliers for the individual TPC varied by country and site). The percentage of patients who received each TPC agent was not capped. Randomization was carried out centrally by an interactive voice or web response system and was stratified by the number of Bellmunt risk factors (0-1, 2-3),[28] type of most recent prior platinum-based chemotherapy (cisplatin or carboplatin), and setting in which the most recent prior platinum-based chemotherapy was administered [neo(adjuvant), locally advanced unresectable/metastatic]. Treatment continued until cancer progression, unacceptable toxicity, death, withdrawal of consent, or until another treatment discontinuation criterion was met per protocol. Study drug treatment beyond radiological progression was permitted for patients who derived clinical benefit as per investigator's assessment. Dose modifications or delays were permitted according to the protocol. After study drug discontinuation, patients were followed up for survival every 8 weeks until death, withdrawal of consent, loss to follow-up, or completion of study by the sponsor, whichever occurred first. Granulocyte colony-stimulating factor (G-CSF) primary prophylactic use for neutropenia was not required per study protocol, but investigators were encouraged to consider prophylaxis per American Society of Clinical Oncology (ASCO) guidelines for use of growth factors.[29] These recommendations were strengthened in a memorandum submitted to the participating sites in September 2022, in conjunction with the

IDMC, which strongly recommended the use of primary prophylaxis with G-CSF starting at cycle 1 in patients at high risk for developing febrile neutropenia, based on ASCO guidelines.

Primary prophylaxis was defined as G-CSF use on or after cycle 1 day 1 and before 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 $\geq$2 neutropenia (to grade $\leq$1) or after occurrence of grade 1 neutropenia; and before any subsequent grade $\geq$2 neutropenia or no occurrence of subsequent grade $\geq$2. G-CSF use was considered therapeutic if administered during grade $\geq$2 neutropenia.[29]

Endpoints and assessments

The primary endpoint was OS, defined as the time from date of randomization to date of death from any cause. Secondary endpoints included PFS (defined as the time from date of randomization to date of the first objectively documented progressive disease or death from any cause, whichever occurs first), ORR (defined as the proportion of patients with complete or partial response as their best overall response), clinical benefit rate (CBR; defined as the proportion of patients with complete response, partial response, or stable disease for $\geq$6 months), and DOR [defined as the time from first response (complete or partial response) to disease progression or death, whichever occurs first], each evaluated by investigator assessment and blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1),[30] as well as safety. Prespecified subgroup analyses of OS by demographics, disease characteristics, prognostic factors, and prior treatments at baseline were carried out on the intent-to-treat population. Tumor response (using RECIST v1.1) was assessed by contrast imaging of the chest, abdomen, pelvis, and other disease sites every 6 weeks for 12 months, then every 9 weeks until radiographic disease progression or initiation of new therapy. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; relationship to study drug was assessed by the investigators. AEs of special interest as defined in the statistical analysis plan (serious infections secondary to neutropenia, severe diarrhea, neutropenia, and hypersensitivity) were also summarized.

For the prespecified exploratory analyses of biomarkers, the formalin-fixed paraffin-embedded archival tumor tissue blocks or slides were collected (sample collection was optional). Trop-2 expression was assessed by immunohistochemistry (IHC) using the EPR20043 assay (Abcam, clone EPR20043; Roche Tissue Diagnostics, Tucson, AZ). Samples were scored by pathologists and tumor membrane H-scores (scale 0-300) were reported as measure of Trop-2 expression.

Statistical analyses

A sample size of approximately 696 patients was estimated to permit the study to have at least 90% power to detect a significant difference in the primary endpoint of OS between treatment groups at an overall two-sided type I error rate of 0.05, assuming a hazard ratio (HR) of 0.755 for death, a median OS of 8.3 months with TPC and 11 months with SG, and 10% annual dropout rate. An interim analysis of OS was planned after at least 75% of targeted 536 OS events (at least 402 deaths) were observed (which occurred in June 2023). Final analysis of the primary endpoint was planned to occur after the accrual of 536 deaths (which occurred in March 2024). 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.

The intent-to-treat (ITT) population consisted of all randomized patients and was the primary analysis set for efficacy analyses. The safety analysis set included all patients who received at least one dose of SG or TPC. A stratified log-rank test was used to compare the two treatment groups for the time-to-event endpoints. Estimates of HR and 95% confidence intervals (CIs) were based on the stratified Cox proportional hazard regression model. The randomization stratification factors were used in all stratified efficacy analyses. To ensure the overall type I error rate was strictly controlled at a two-sided alpha of 0.05, if the result of the primary endpoint of OS was significant, the key secondary endpoint of PFS based on BICR was to be tested with the use of a hierarchical testing strategy. Median follow-up was defined as the median time from randomization to death or last known alive date. All analyses were carried out with the use of SAS® software, version 9.4 or higher (SAS Institute, Cary, NC).

The biomarker analysis set included all patients in the ITT analysis set with at least one evaluable biomarker measurement available. Combined data from both the SG and TPC treatment groups were used to determine medians, as well as tertiles of Trop-2 expression (H-score). Associations of Trop-2 expression median and tertile subgroups with OS and PFS were evaluated in the biomarker analysis set using the Cox proportional hazards regression model. HR and 95% CIs were reported (ties were handled using Efron's method).

RESULTS

Patients

Between 13 January 2021 and 13 December 2022, 711 patients were enrolled at 169 sites in 25 countries. Patients were randomly assigned to receive SG ($n = 355$) or single-agent TPC ($n = 356$). Of these, 349 patients in the SG group and 337 patients in the TPC group received at least one dose of study treatment (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.01.011).

Patient characteristics at baseline were balanced between treatment groups (Table 1). Briefly, patients had a median age of 67 years in the SG group and 68 years in the TPC group. Most patients in both groups were male, had a Bellmunt risk of 0 or 1, and had metastatic disease at the time of enrollment. Approximately 10% to 14% of the patients presented

Table 1. Patient demographics and baseline clinical characteristics (intent-to-treat population)

Characteristic	Sacituzumab govitecan (n = 355)	Treatment of physician's choice (n = 356)[a]
Median age, years (range)	67 (41-89)	68 (30-85)
Age ≥65 years, *n* (%)	222 (63)	225 (63)
Sex, *n* (%)		
Female	71 (20)	77 (22)
Male	284 (80)	279 (78)
Geographic region, *n* (%)		
North America	20 (6)	9 (3)
Europe	230 (65)	260 (73)
Rest of the world[b]	105 (30)	87 (24)
ECOG PS 0-1, *n* (%)[c]	355 (100)	352 (99)
Bellmunt risk score[d]		
0-1	262 (74)	267 (75)
2-3	93 (26)	89 (25)
Stage of cancer at enrollment, *n* (%)		
Locally advanced/unresectable	25 (7)	36 (10)
Metastatic	330 (93)	320 (90)
Site of primary tumor, *n* (%)[e]		
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)
Prior anticancer regimens, median (range)	2 (1-7)	2 (1-6)
1-2, *n* (%)	243 (68)	252 (71)
≥3, *n* (%)	112 (32)	104 (29)
Most recent prior platinum 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)
Prior use of enfortumab vedotin, *n* (%)	24 (7)	15 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]164 patients were randomized to paclitaxel (157 treated), 143 to docetaxel (137 treated), and 48 to vinflunine (43 treated).
[b]Includes China, Korea, Australia, Taiwan, Singapore, Hong Kong.
[c]In the treatment of physician's choice group, three patients had an ECOG PS of 2 and one patient an ECOG PS of 3.
[d]Bellmunt risk scores range from 0 to 3 according to the presence of the following risk factors: a hemoglobin level of <10 g/dl, an ECOG PS >0, and liver metastases.
[e]One patient in the sacituzumab govitecan group and four patients in the treatment of physician's choice group had missing data.

with lymph-node-only disease, and ∼30% had liver metastasis at baseline. At the data cutoff of 8 March 2024, median follow-up was 9.2 months (range 0-33.7 months). A total of 674 (95%) patients discontinued treatment due to cancer progression (67%), AEs (15%), withdrawal of consent (6%), or other reasons (7%). Overall, 179 (50%) patients randomized to SG and 174 (49%) to TPC received any subsequent anticancer therapy. The most frequent subsequent anticancer therapy after study treatment discontinuation was EV in the SG (19%) and TPC (21%) groups; paclitaxel (15%) and carboplatin (5%) were the next most common subsequent anticancer therapies in the SG group, and paclitaxel (6%) and gemcitabine (6%) in the TPC group.

Efficacy

The primary endpoint of improved OS with SG versus TPC was not met. Median OS was 10.3 months (95% CI 9.1-11.8 months) in the SG group and 9.0 months (95% CI 7.5-9.7 months) in the TPC group (HR 0.86, 95% CI 0.73-1.02, P = 0.087; Figure 1A). The OS analysis results in prespecified subgroups is shown in Figure 1B.

Median PFS by BICR was 4.2 months (95% CI 3.8-4.5 months) with SG and 3.6 months (95% CI 2.9-4.2 months) with TPC (HR 0.86; 95% CI 0.72-1.03; Figure 2). Investigator-assessed PFS showed a similar trend (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.01.011).

ORR by BICR was 23% (95% CI 18% to 27%) for SG versus 14% (95% CI 10% to 18%) for TPC. A confirmed complete response was observed in 19/355 patients (5%) in the SG group and in 9/356 (3%) in the TPC group. Investigator-assessed ORR showed a similar trend (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.01.011). CBR by BICR was 30% (95% CI 25% to 35%) and 21% (95% CI 16% to 25%), respectively. Median DOR by BICR was 7.2 months with SG and 6.5 months with TPC (Table 2).

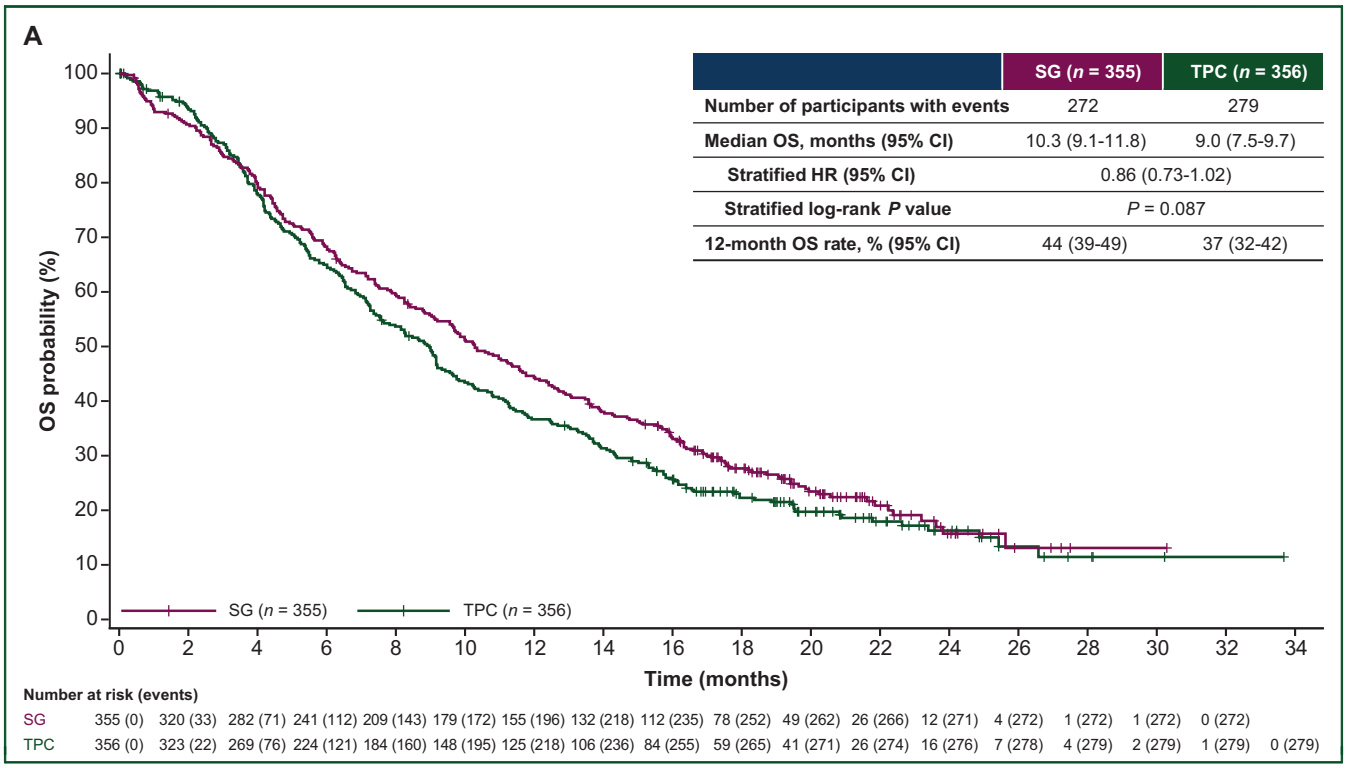
Safety

Median treatment duration was 3.0 months with SG and 2.1 months with TPC. Treatment-emergent AEs (TEAEs) of any grade occurred in 347/349 (99%) patients with SG and 320/337 (95%) with TPC, with grade ≥3 TEAEs occurring in 269 (77%) and 171 (51%) patients, respectively. The most common TEAEs (occurring in ≥15% of patients in either group) are shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.01.011.

Among TEAEs of special interest, neutropenia was most frequently observed, reported in 194 (56%) patients in the SG group and 67 (20%) patients in the TPC group. Serious infections secondary to neutropenia were observed in 27 (8%) patients treated with SG and 13 (4%) patients with TPC, and severe diarrhea was reported in 54 (15%) patients treated with SG and 12 (4%) patients with TPC.

The incidence of grade ≥3 treatment-related AEs (TRAEs) was 67% in the SG group and 35% in the TPC group. The most common grade ≥3 TRAE with SG was neutropenia, reported in 122 (35%) patients, with 41 (12%) patients experiencing febrile neutropenia (Table 3). TRAEs resulting in dose reduction, interruption, or treatment discontinuation, respectively, occurred in 37%, 52%, and 11% of patients in the SG group and in 26%, 18%, and 12% in the TPC group (Table 3).

A total of 32 TEAEs leading to death [SG: n = 25 (7%); TPC: n = 7 (2%)] were observed in the study (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.01.011). Of the 25 grade 5 TEAEs in the SG group, 16 were infections in the setting of neutropenia, with 14 occurring within the first month of treatment (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.01.011).



	SG (*n* = 355)	TPC (*n* = 356)
Number of participants 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)

Figure 1. Overall survival. (A) Kaplan–Meier plot of overall survival intent-to-treat analysis set. (B) Forest plot of overall survival across prespecified subgroups. CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

In general, patients with SG who experienced fatal infections with neutropenia had a higher burden of risk factors associated with medical complications compared with the overall SG group: 81% of patients were aged ≥65 years; 56% of patients had a prior cystectomy and 81% had a prior major urinary tract procedure, 50% had prior radiotherapy and 50% had received three or more prior anticancer regimens (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.01.011). No trends in types of events were identified in the nine grade 5 TEAEs not related to neutropenia, eight of which were considered not related to SG (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.01.011). In the TPC group, four TEAEs leading to death were infections with neutropenia (1%) and three were not related to an infection.

Despite the high burden of risk factors for neutropenic complications in the study population, the use of G-CSF as primary prophylaxis was only 21% and 22% with SG and TPC, respectively. Overall, 37% of those treated with SG received any prophylactic G-CSF during the study, and 30% received G-CSF as treatment (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.01.011). The incidence of grade ≥3 neutropenia with and without primary G-CSF prophylaxis was 32% and 48%, respectively (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.01.011).

Of the 16 patients in the SG group who experienced grade 5 TEAEs of infections with neutropenia, two patients had received primary prophylaxis with G-CSF and nine received G-CSF as treatment.

Biomarker analyses

Trop-2 data were available for only 30% of the ITT population ($n = 211$) as tumor collection was optional in the study. Trop-2 was highly expressed in these samples, with a median membrane H-score of 243 (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.01.011). Subgroup analyses of OS and PFS in the biomarker analysis set showed consistent results across Trop-2 median and tertile subgroups (Supplementary Tables S8 and S9, and Figure S3, available at https://doi.org/10.1016/j.annonc.2025.01.011). Overall, Trop-2 expression in archival tissue specimens as a biomarker did not identify a subgroup of patients who derived greater benefit from SG versus TPC in the biomarker analysis set.

DISCUSSION

In patients with unresectable locally advanced or metastatic UC, treatment with SG monotherapy after platinum-based chemotherapy and anti-PD-(L)1 therapy did not result in a statistically significant improvement in OS or PFS versus standard chemotherapy. The median OS of 9.0 months in the TPC group was similar to that reported previously in clinical trials of aUC refractory to platinum-based chemotherapy.[8,9,31] Despite lack of significant survival benefit, a higher ORR was observed with SG versus TPC, and SG response rates were consistent with previous results from the phase II TROPHY-U-01 study, thus confirming that SG has activity in aUC.

In TROPiCS-04, the overall safety results were generally consistent with the known toxicity profile of SG across other

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Category (all randomized)	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)
Race	White (SG, *n* = 194, TPC, *n* = 188)	10.3 (8.1-11.8)	7.2 (5.8-9.0)	0.81 (0.64-1.01)
	Asian (SG, *n* = 92; TPC, *n* = 82)	9.7 (7.2-12.7)	9.8 (8.1-12.5)	1.10 (0.78-1.56)
	Other (SG, *n* = 69; TPC, *n* = 86)	12.6 (9.0-14.7)	9.8 (7.6-13.5)	0.87 (0.61-1.23)
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	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	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	(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)

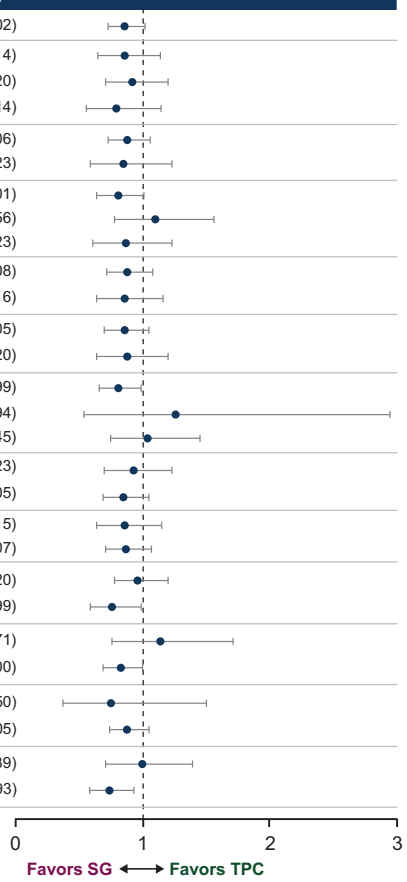

Figure 1. Continued.

tumor types; higher incidences of grade ≥3 neutropenic events, grade ≥3 infections secondary to neutropenia, and grade 5 TEAEs were, however, observed. Reflecting the general population with aUC, the patients in this study presented with multiple known risk factors for febrile neutropenia and for subsequent complications, according to ASCO guidelines, including age ≥65 years, extensive visceral disease, and poor renal function.[29]

The use of growth factors in the primary prophylactic setting was low despite the high risk for neutropenic complications in this patient population. All 16 patients in the SG group with grade 5 TEAEs of infections in the setting of neutropenia had multiple risk factors for which primary prophylaxis with G-CSF is recommended, including age ≥65 years, previous anticancer therapy, and multiple comorbid conditions. Among these, none of the 14 patients who experienced fatal infections within the first month of SG treatment received prophylactic G-CSF. The remaining two patients died after the first month of treatment and represent atypical cases; both were deemed unlikely related or unrelated to the study drug by the investigator. Stronger protocol recommendation regarding the use of G-CSF as primary prophylaxis might have mitigated the risk of early fatal events in the SG group that are likely to have impacted the efficacy outcomes.

An increased occurrence of grade 5 events from neutropenic complications was not observed in the phase II TROPHY-U-01 cohort 1, in which four of the 113 patients treated with SG (3%) experienced an AE leading to death; there was one death (1%) due to infectious complications secondary to neutropenia that was deemed related to SG.[25] No fatalities due to SG were reported in the phase II TROPHY-U-01 study cohorts 2 and 3, phase III ASCENT study (SG versus chemotherapy, pretreated mTNBC), phase II TROPiCS-03 study (SG, endometrial cancer), or phase I DAD study (SG + EV, pretreated aUC).[26,27,32-34] One instance of death related to SG and due to sepsis was reported in the phase II SURE-01 study (neoadjuvant SG, MIBC); the protocol was amended after the interim safety analysis to reduce SG dose to 7.5 mg/kg, mandate the use of primary prophylaxis with G-CSF, and exclude patients with more than three risk factors for febrile neutropenia based on ASCO guidelines.[29,35] Similarly, in the phase III TROPiCS-02 study (HR-positive/HER2-negative mBC), one death (<1%) related to SG was due to septic shock secondary to neutropenic colitis.[36] Substantial comorbid disease and worse prognostic factors in patients enrolled in TROPiCS-04

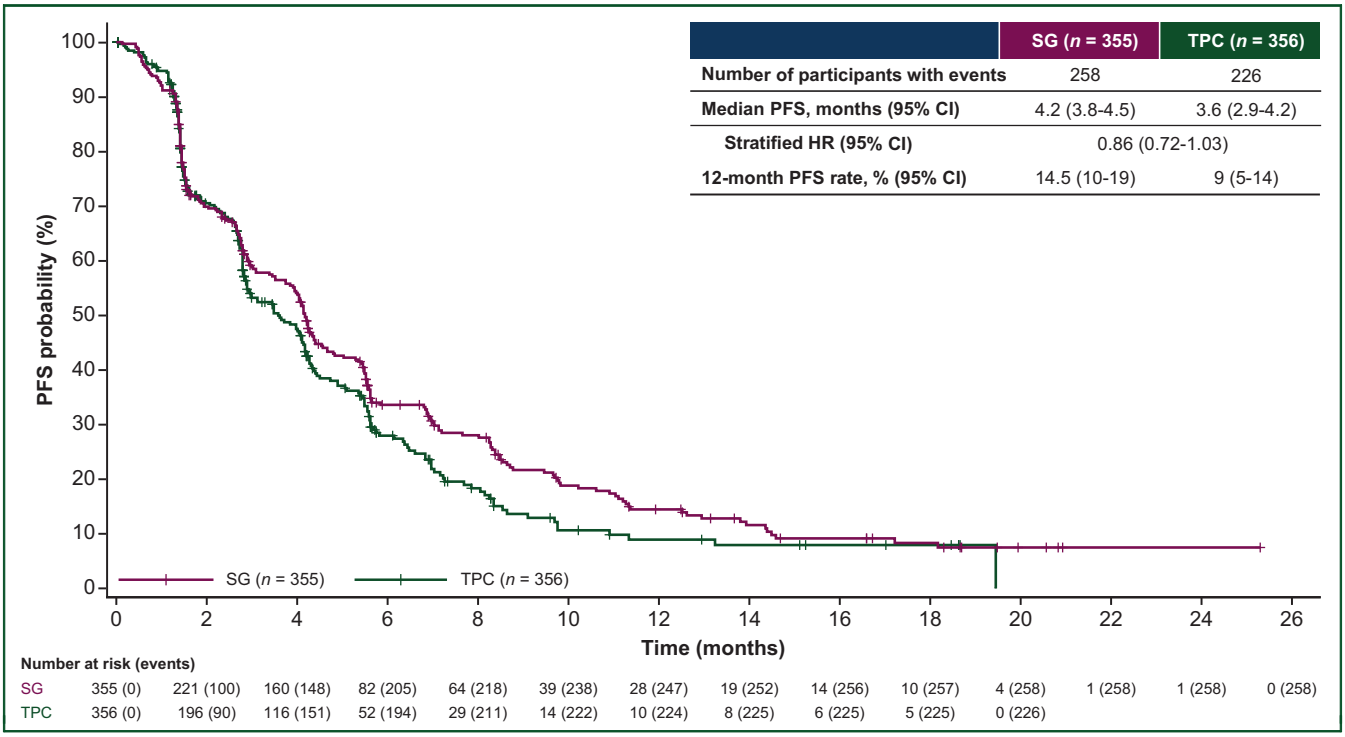

Figure 2. Kaplan–Meier plot of progression-free survival by blinded independent central review.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

compared with other studies,[23,24] coupled with low use of prophylactic G-CSF, may have contributed to the unexpectedly high rate of neutropenic complications observed. Patients with germline *UGT1A1* variants have altered SN-38 (the payload in SG) metabolism that may impact safety outcomes following SG treatment.[20,21,37] In previous studies of SG in aUC or other indications, patients with certain *UGT1A1* genotypes experienced an increased incidence of hematologic toxicities, including neutropenia, and diarrhea.[25,38,39] In TROPiCS-04, *UGT1A1* testing was not mandatory, and therefore the data available on the impact of the variants on outcomes are limited and inconclusive. There is no current consensus on testing for *UGT1A1* genotypes in routine practice,[40-43] although this information could be useful to inform dose modifications and increased monitoring of patients with mutations conferring high risk for toxicity.

Table 2. Response by blinded independent central review

Variable	Sacituzumab govitecan (n = 355)	Treatment of physician's choice (n = 356)
ORR,[a] n [% (95% CI)]	80 [23 (18-27)]	49 [14 (10-18)]
Stratified odds ratio (95% CI)	1.84 (1.24-2.73)	
BOR, 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)
DOR, median (95% CI), months	7.2 (6.3-8.4)	6.5 (5.2-8.3)
CBR,[b] n [% (95% CI)]	106 [30 (25-35)]	73 [21 (16-25)]
Stratified odds ratio (95% CI)	1.68 (1.19-2.37)	

BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]ORR is defined as the proportion of patients who achieved a CR or PR as BOR. CR and PR are confirmed with a subsequent assessment at least 4 weeks later.
[b]CBR is defined as the percentage of patients with advanced or metastatic cancer who have achieved CR, PR, and SD for ≥6 months to therapeutic intervention in a clinical study.

The high levels of Trop-2 expression observed in tumor tissue samples in the biomarker analysis set were consistent with those reported in the TROPHY-U-01 study (cohorts 1-3) and in other large datasets from independent advanced bladder cancer cohorts.[44,45] Subgroup analyses of OS and PFS showed a consistent benefit for SG versus TPC across both median and tertile Trop-2 subgroups; higher baseline Trop-2 expression was not associated with improved SG efficacy versus TPC. Results from this analysis should be interpreted with caution as archival tissue was used and only 30% of the ITT population was included in the biomarker analysis set.

TROPiCS-04 was an open-label study in which both investigators and patients were aware of the treatment assignment. This design may have contributed to the relatively larger proportion of patients in the control group who dropped out following randomization and before receiving study treatment; however, this may have likely affected PFS more than OS. Changes in the therapeutic landscape during the study, including approval of new treatment options for aUC, resulted in a limited patient population enrolled in North America. More patients (about half) in this study had access to subsequent systemic therapies than in other previous studies, which may have influenced the results.[11,16]

Table 3. Summary of TRAEs (safety population)

Event, *n* (%)	Sacituzumab govitecan (*n* = 349)		Treatment of physician's choice (*n* = 337)	
Any TRAEs	339 (97)		296 (88)	
Grade ≥3 TRAEs	233 (67)		119 (35)	
Serious TRAEs	120 (34)		60 (18)	
TRAEs leading to dose reduction	129 (37)		86 (26)	
TRAEs leading to dose interruption	183 (52)		61 (18)	
TRAEs leading to discontinuation	39 (11)		42 (12)	
TRAEs leading to death	15 (4)		5 (1)	
Most common TRAEs, *n* (%)	**Any grade[a]**	**Grade ≥3[b]**	**Any grade[a]**	**Grade ≥3[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.
TRAE, treatment-related adverse event.
[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 preferred terms of fatigue and asthenia.
[d]Includes preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased.
[e]Includes preferred terms of neutropenia and neutrophil count decreased.
[f]Includes preferred terms of leukopenia and white blood cell count decreased.

TROPiCS-04 did not demonstrate a significant OS benefit versus TPC in patients with aUC whose cancer progressed on platinum-based chemotherapy and PD-(L)1 inhibitor therapy. Further validation of SG activity is needed in prospective randomized trials that utilize consistent primary prophylaxis with G-CSF starting at cycle 1 to mitigate the risk of complications arising from SG-related high-grade neutropenia. The efficacy and safety of SG as a first-line therapy either as monotherapy or in combination with other agents are also being assessed in the TROPHY-U-01 (NCT03547973) cohorts 4, 6, and 7.[46-48]

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DATA SHARING

Gilead Sciences Inc. shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting no conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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SUPPLEMENTARY APPENDIX

Supplement to: Powles T, Tagawa S, Vulsteke C, et al. Sacituzumab govitecan in advanced urothelial carcinoma: TROPiCS-04, a phase III randomized trial

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Full Inclusion and Exclusion Criteria

Inclusion criteria

1) Female or male patients, ≥18 years of age, able to understand and give written informed consent.
2) Patients with histologically documented UC that is metastatic or locally advanced unresectable defined as tumor (T) 4b, any node (N) or any T, N 2-3
   a) Tumors of upper and lower urinary tract are permitted. Mixed histologic types are allowed if urothelial is the predominant histology.
3) ECOG PS score of 0 or 1.
4) Patients with progression or recurrence following receipt of platinum-containing regimen and anti-PD-1/PD-L1 therapy for metastatic or locally advanced unresectable disease will be enrolled.
   a) Patients with recurrence or progression ≤12 months following completion of cisplatin-containing chemotherapy given in the neo-adjuvant/adjuvant setting may utilize that line of therapy to be eligible for the study. The 12-month period is counted from completion of surgical intervention or cisplatin therapy, respectively. These patients must receive anti-PD-1/PD-L1 therapy in the metastatic or locally advanced unresectable setting to be eligible.
   b) Patients who received either carboplatin or anti-PD-1/PD-L1 therapy in the neo-adjuvant/adjuvant setting will not be able to count that line of therapy towards eligibility for the study.
   c) Cisplatin-ineligible patients who meet one of the below criteria and who were treated with carboplatin in the metastatic or locally advanced unresectable settings may count that line of therapy towards eligibility. They must then have received anti-PD-1/PD-L1 therapy in metastatic or locally advanced unresectable setting to be eligible for the study. Cisplatin ineligibility is defined as meeting one of the following criteria:
      i. Creatinine Clearance <60 mL/min
      ii. Grade ≥2 Audiometric Hearing Loss
      iii. Grade ≥2 Peripheral Neuropathy
      iv. New York Heart Association (NYHA) Class III heart failure
      v. ECOG PS ≥2
   d) Anti PD-1/PD-L1 therapy administered as part of maintenance therapy may be counted towards eligibility for the study.
   e) Patients who have progressed after receiving enfortumab vedotin in prior lines of therapy, and patients who are either ineligible or unable to tolerate enfortumab vedotin therapy, are eligible to enroll in the study.
   f) Patients who received only concurrent chemoradiation for bladder preservation without further systemic therapy are not eligible to enroll in the study. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen and no progression was noted prior to the change in platinum.
5) Patients with previously treated brain metastases may participate in the study provided they have stable CNS disease for at least 4 weeks prior to the first dose of study drug and stabilization of all neurologic symptoms, have no evidence of new or enlarging brain metastases, and are not using steroids >20 mg of prednisone (or equivalent) daily for brain metastases for at least 7 days prior to first dose of the study drug.
6) Adequate hematologic counts without transfusion or growth factor support within 2 weeks of study drug initiation (hemoglobin ≥9 g/dL, absolute neutrophil count [ANC] ≥1,500/mm3, and platelets ≥100,000/μL).

7) Adequate hepatic function (bilirubin ≤1.5x institutional upper limit of normal [IULN], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 x IULN or ≤5 x IULN if known liver metastases and serum albumin ≥3 g/dL).
   a) Docetaxel will only be an option in TPC group for patients with a total bilirubin ≤1 x IULN, and an AST and/or ALT ≤1.5 x IULN if alkaline phosphatase is also >2.5 x IULN.
8) Creatinine clearance ≥30 mL/min as assessed by the Cockcroft-Gault equation or other validated instruments (e.g., Modification of Diet in Renal Disease [MDRD] equation.
9) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.

Exclusion criteria

1) Women who are pregnant or lactating.
2) Have had a prior anti-cancer mAb/ADC within 4 weeks prior to C1D1 or have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to C1D1. Patients participating in observational studies are eligible.
3) Have received prior chemotherapy for UC with any available SOC therapies in the control group (ie, either prior paclitaxel and docetaxel in countries where vinflunine is not an approved therapy, or either prior paclitaxel, docetaxel and vinflunine in countries where vinflunine is approved and is commercially available).
4) Have not recovered (ie, ≤Grade 1) from AEs due to previously administered chemotherapeutic agent.
   - Note: Patients with ≤Grade 2 neuropathy or any grade of alopecia are an exception to this criterion and will qualify for the study.
   - Note: If patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study therapy.
5) Have previously received topoisomerase 1 inhibitors.
6) Have an active second malignancy.
   - Note: Patients with a history of malignancy that have been completely treated and with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically cured tumors with low risk of recurrence are allowed to enroll in the study after discussion with the medical monitor.
7) Have active cardiac disease, defined as:
   a) Myocardial infarction or unstable angina pectoris within 6 months of C1D1
   b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication); history of QT interval prolongation.
   c) NYHA Class III or greater congestive heart failure or left ventricular ejection fraction of <40%.
8) Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or GI perforation within 6 months of enrollment.
9) Have an active serious infection requiring anti-infective therapy (Contact medical monitor for clarification).
10) Have uncontrolled HIV-1/2 viral load (ie, ≥ 200 copies/mL and/or CD4+ count < 350 cells/mm3) and/or on medications that may interfere with SN-38 metabolism.
11) Have active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV). In patients with a history of HBV or HCV, patients with a detectable viral load will be excluded.

12) Have other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.
13) Have inability to tolerate or are allergic to any potential TPC agent or sacituzumab govitecan or unable or unwilling to receive the doses specified in the protocol.
14) Have inability to complete all specified study procedures for any reason.
15) History of active interstitial lung disease or noninfectious pneumonitis.

Supplementary tables

Table S1. Response by investigator assessment

Variable	Sacituzumab govitecan (*n* = 355)	Treatment of physician's choice (*n* = 356)
ORR,[a] *n* (% [95% CI])	70 (20 [16-24])	56 (16 [12-20])
Stratified odds ratio (95% CI)	1.32 (0.90-1.95)	
BOR, *n* (%)		
CR	8 (2)	7 (2)
PR	62 (17)	49 (14)
SD	152 (43)	147 (41)
SD ≥ 6 months	42 (12)	22 (6)
PD	89 (25)	99 (28)
Not evaluable	44 (12)	54 (15)
DOR, median (95% CI), months	7.1 (5.8-9.0)	5.8 (3.7-7.0)
CBR,[b] *n* (% [95% CI])	112 (32 [27-37])	78 (22 [18-27])
Stratified odds ratio (95% CI)	1.67 (1.19-2.34)	

BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]ORR is defined as the proportion of patients who achieved a CR or PR as BOR. CR and PR are confirmed with a subsequent assessment at least 4 weeks later.

[b]CBR is defined as the percentage of patients with advanced or metastatic cancer who have achieved CR, PR, and SD for ≥6 months to therapeutic intervention in a clinical study.

Table S2. Summary of TEAEs (safety population)

Event, *n* (%)	**Sacituzumab govitecan (*n* = 349)**		**Treatment of physician's choice (*n* = 337)**	
Any TEAEs	347 (99)		320 (95)	
Grade ≥3 TEAEs	269 (77)		171 (51)	
Serious TEAEs	183 (52)		110 (33)	
TEAEs leading to dose reduction	132 (38)		94 (28)	
TEAEs leading to dose interruption	232 (66)		105 (31)	
TEAEs leading to discontinuation	54 (15)		50 (15)	
TEAEs leading to death	25 (7)		7 (2)	
Most common TEAEs, *n* (%)	**Any grade[a]**	**Grade ≥3[b]**	**Any grade[a]**	**Grade ≥3[b]**
Fatigue[c]	201 (58)	45 (13)	146 (43)	23 (7)
Anemia[d]	188 (54)	55 (16)	117 (35)	29 (9)
Diarrhea	199 (57)	54 (15)	66 (20)	12 (4)
Alopecia	138 (40)	0	113 (34)	2 (1)
Neutropenia[e]	167 (48)	124 (36)	55 (16)	38 (11)
Nausea	157 (45)	11 (3)	61 (18)	3 (1)
Constipation	104 (30)	1 (<1)	66 (20)	3 (1)
Decreased appetite	95 (27)	9 (3)	60 (18)	2 (1)
Vomiting	84 (24)	11 (3)	24 (7)	4 (1)
Pyrexia	64 (18)	6 (2)	28 (8)	2 (1)
Leukopenia[f]	68 (19)	36 (10)	22 (7)	9 (3)
Febrile neutropenia	41 (12)	41 (12)	16 (5)	16 (5)
Neuropathy peripheral	12 (3)	0	59 (18)	9 (3)

TEAE, treatment-emergent adverse event.
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 preferred terms of fatigue and asthenia.
[d]Includes preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased.
[e]Includes preferred terms of neutropenia and neutrophil count decreased.
[f]Includes preferred terms of leukopenia and white blood cell count decreased.

Table S3. Summary of grade 5 TEAEs in patients who received sacituzumab govitecan

Type of TEAEs	Patient	Age (years)	Sex	Relation to treatment[a]	TEAEs leading to death (preferred term)	Time from first dose to death (days)
Infection in the setting of neutropenia	**1**	67	F	Related	Leukopenia	12
	2	81	F	Related	Sepsis	13
	3	65	F	Possibly related	Sepsis	22
	4	71	M	Possibly related	Sepsis	13
	5	68	M	Unlikely related	Sepsis	72
	6	72	M	Related	Neutropenic sepsis	17
	7	69	M	Related	Neutropenic sepsis	14
	8	72	M	Possibly related	Neutropenic sepsis	17
	9	79	M	Related	Neutropenic sepsis	14
	10	84	M	Possibly related	Pseudomonal sepsis	28
	11	65	M	Possibly related	Pulmonary sepsis	22
	12	64	M	Related	Septic shock	15
	13	74	M	Related	Septic shock	16
	14	62	M	Not related	Septic shock	48
	15	60	M	Possibly related	Acute respiratory distress syndrome	16
	16	66	M	Possibly related	Acute kidney injury	21
Not neutropenia-related	**17**	57	M	Not related	COVID-19	66
	18	61	M	Possibly related	Respiratory failure	3

	19	66	M	Not related	Respiratory failure	27
	20	63	F	Unlikely related	Apnea	29
	21	52	F	Unlikely related	Hepatobiliary disease	18
	22	74	F	Unlikely related	Hypoglycemia	26
	23	67	M	Not related	Cardiac arrest	195
	24	58	M	Not related	Cerebral infarction	115
	25	70	M	Not related	Death of unknown cause	344

F, female; M, male; TEAE, treatment-emergent adverse event.
[a]Per investigator's assessment.

Table S4. Demographics and baseline characteristics of patients who received sacituzumab govitecan and had fatal infections secondary to neutropenia

Characteristic	Patients receiving sacituzumab govitecan (*n* = 349)	Patients with grade 5 TEAEs receiving sacituzumab govitecan (*n* = 16)[a]
Age group, *n* (%)		
<65 years	132 (38)	3 (19)
65-74 years	150 (43)	10 (63)
≥75 years	67 (19)	3 (19)
Male	279 (80)	13 (81)
Eastern Cooperative Oncology Group performance status, *n* (%)		
0	131 (38)	4 (25)
1	218 (62)	12 (75)
Bellmunt risk factors, *n* (%)		
0-1	257 (74)	9 (56)
2-3	92 (26)	7 (44)
Patients with prior radical cystectomy, *n* (%)	133 (38)	9 (56)
Patients with major urinary tract procedure, *n* (%)[b]	231 (66)	13 (81)
Patients with prior radiotherapy, *n* (%)	129 (37)	8 (50)
Number of prior anticancer regimens		
1	81 (23)	1 (6)
2	160 (46)	7 (44)
3	81 (23)	8 (50)
>3	27 (8)	0

TEAE, treatment-emergent adverse event.
Total may add up to more than 100% due to rounding.
[a]All patients with fatal infections secondary to neutropenia were treated with sacituzumab govitecan.
[b]Major urinary tract procedures include partial and/or total nephrectomies, ureterectomies, and cystectomies; it excludes transurethral resection of bladder.

Table S5. Overall G-CSF use

	Sacituzumab govitecan (*n* = 349)	**Treatment of physician's choice (*n* = 337)**
Any prophylaxis, *n* (%)	128 (37)	87 (26)
Primary prophylaxis	74 (21)	73 (22)
Secondary prophylaxis	54 (15)	14 (4)
Therapeutic, *n* (%)	106 (30)	33 (10)

G-CSF, granulocyte colony-stimulating factor.

Table S6. Incidence of neutropenia and neutropenic complications by primary G-CSF prophylaxis in patients treated with sacituzumab govitecan

Event, *n* (%)	With primary prophylaxis (*n* = 74)	Without primary prophylaxis (*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)

AESI, adverse event of special interest; G-CSF, granulocyte colony-stimulating factor.
[a]AESI neutropenia includes preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia.
[b]AESI serious infections secondary to neutropenia includes an adverse event 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]One patient had a preexisting open wound/ulceration, underwent an invasive procedure without adequate (per protocol) healing before next sacituzumab govitecan dose, and did not receive prophylactic G-CSF with their last sacituzumab govitecan 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 sacituzumab govitecan dose (per protocol); the patient died of septic shock.
[d]Includes one patient with serious infection occurring on 15 days after neutropenia, therefore outside the window of AESIs of serious infection secondary to neutropenia.

Table S7. Summary of Trop-2 expression levels (biomarker analysis set)

	Overall (*N* = 211)	**Sacituzumab govitecan (*n* = 95)**	**Treatment of physician's choice (*n* = 116)**
Trop-2 membrane H-score			
Median	243	225	250
T1, T2	216, 265	205, 265	225, 265
Q1, Q3	201, 280	194, 280	209, 281
Min, max	0, 300	0, 300	0, 299

Q1, first quartile; Q3, third quartile; T1, 33.33 percentile; T2, 66.67 percentile; Trop-2, Trophoblast cell surface antigen 2.

Table S8. Summary of overall survival by Trop-2 expression levels (biomarker analysis set)

	Sacituzumab govitecan (*n* = 95)		**Treatment of physician's choice (*n* = 116)**		
	***n* (events)**	**OS Median (95% CI), months**	***n* (events)**	**OS Median (95% CI), months**	**HR (95% CI)**
Median subgroups					
H-score <243	51 (39)	10.7 (7.9-13.9)	51 (44)	9.0 (6.6-10.8)	0.71 (0.46-1.09)
H-score ≥243	44 (34)	11.0 (5.5-15.7)	65 (51)	7.3 (5.1-9.2)	0.85 (0.55-1.32)
Tertile subgroups					
Tertile 1: H-score <216	38 (30)	11.6 (8.0-13.9)	32 (27)	9.1 (4.2-11.3)	0.75 (0.45-1.27)
Tertile 2: H-score ≥216 to ≤265	26 (18)	11.9 (4.2-21.8)	46 (41)	7.5 (4.9-10.8)	0.54 (0.30-0.96)
Tertile 3: H-score >265	31 (25)	11.0 (4.7-15.7)	38 (27)	7.2 (5.0-12.5)	1.14 (0.66-1.975)

CI, confidence interval; HR, hazard ratio; OS, overall survival; Trop-2, Trophoblast cell surface antigen 2.

Table S9. Summary of progression-free survival by Trop-2 expression level (biomarker analysis set)

	Sacituzumab govitecan (*n* = 95)		**Treatment of physician's choice (*n* = 116)**		
	***n* (events)**	**PFS Median (95% CI), months**	***n* (events)**	**PFS Median (95% CI), months**	**HR (95% CI)**
Median subgroups					
H-score <243	51 (37)	3.9 (1.7-8.6)	51 (39)	2.9 (2.6-4.1)	0.62 (0.38-1.00)
H-score ≥243	44 (34)	5.3 (3.4-6.8)	65 (48)	2.8 (2.4-3.8)	0.62 (0.40-0.98)
Tertile subgroups					
Tertile 1: H-score <216	38 (29)	4.3 (2.3-8.6)	32 (24)	2.9 (2.6-5.1)	0.62 (0.34-1.11)
Tertile 2: H-score ≥216 to ≤265	26 (18)	4.2 (1.5-9.8)	46 (38)	2.8 (1.4-3.1)	0.50 (0.28-0.90)
Tertile 3: H-score >265	31 (24)	4.2 (2.8-6.8)	38 (25)	2.9 (2.4-5.5)	0.75 (0.42-1.34)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; Trop-2, Trophoblast cell surface antigen 2.

Supplementary figures

Figure S1. CONSORT diagram of patient disposition.

The most frequent reasons for screen failure (observed in 2.8% of patients screened for each reason) were: Eastern Cooperative Oncology group performance status ≥2, not meeting protocol-specified requirements for prior systemic anticancer treatment, and not being able to complete study procedures. [a]164 patients were randomized to paclitaxel, 143 to docetaxel, and 48 to vinflunine. [b]157 patients received paclitaxel, 137 docetaxel, and 43 vinflunine. COVID-19, coronavirus disease 2019; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

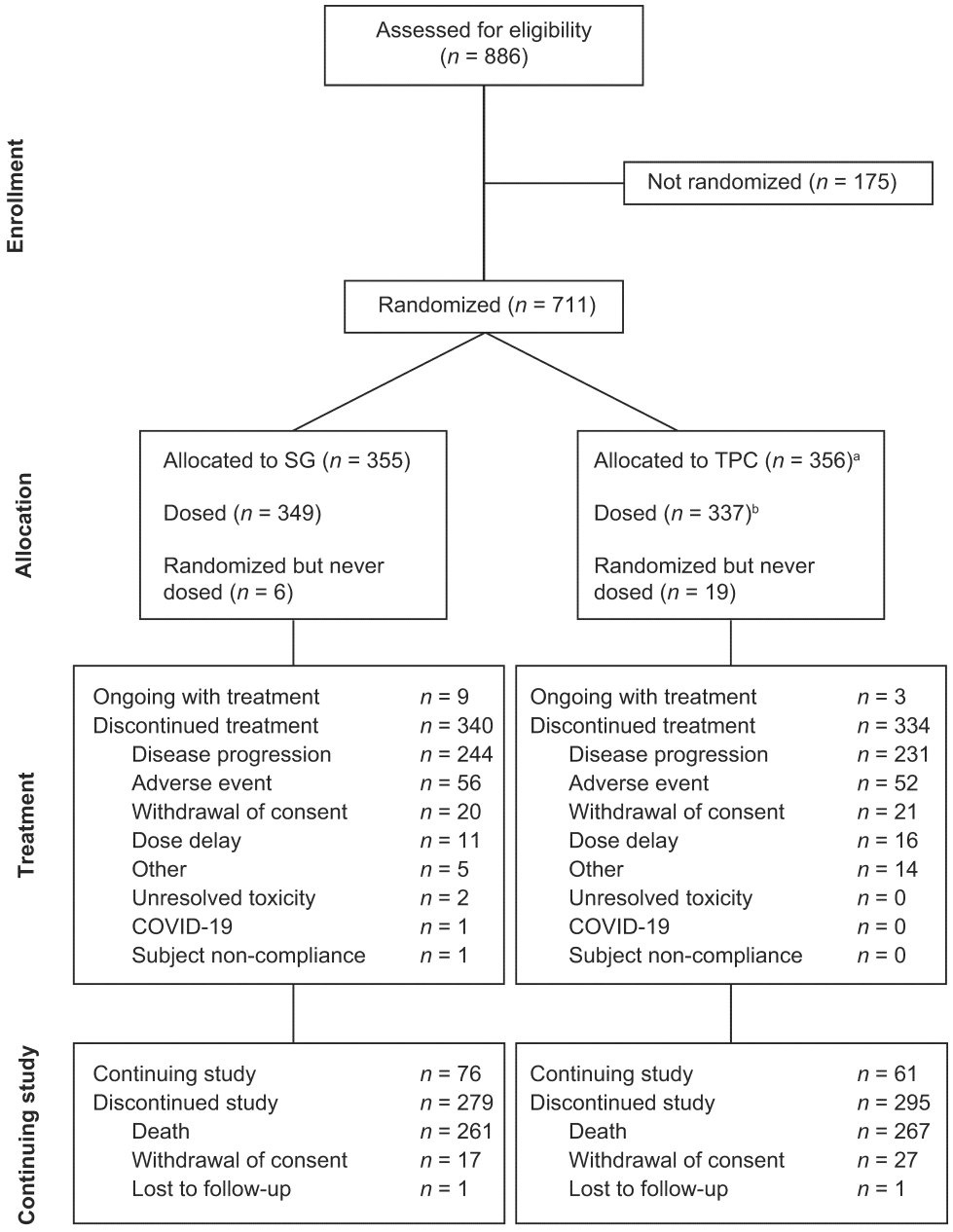
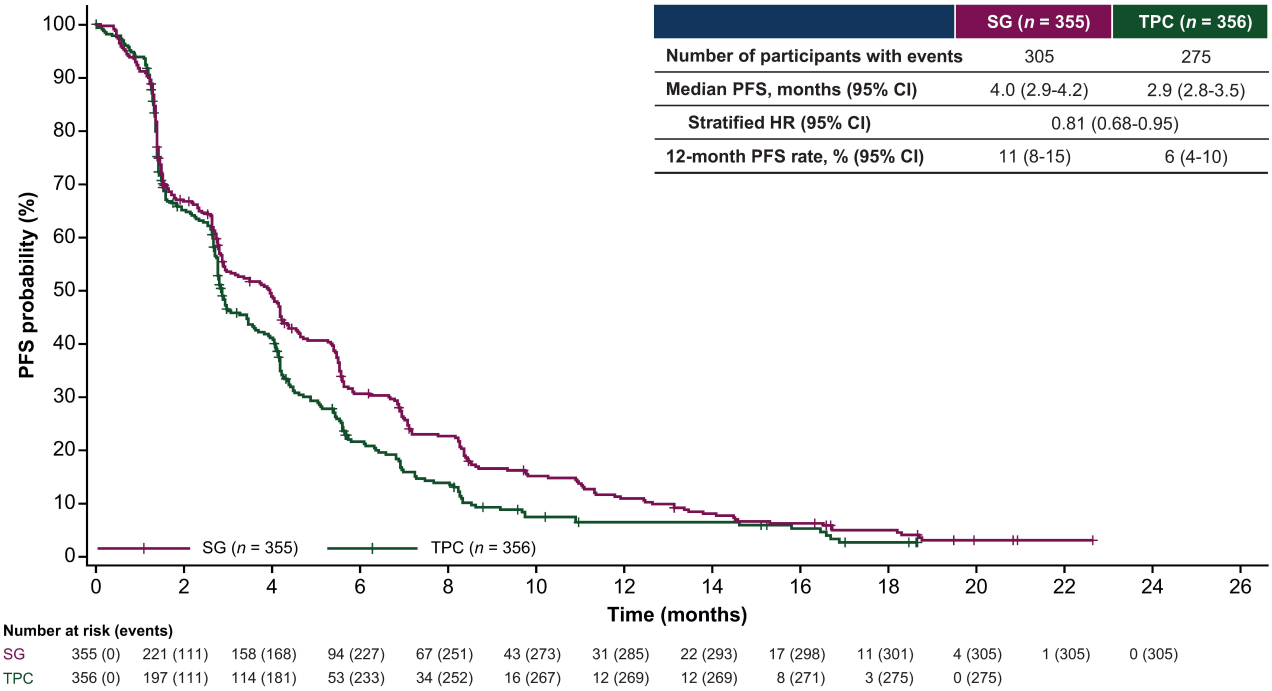
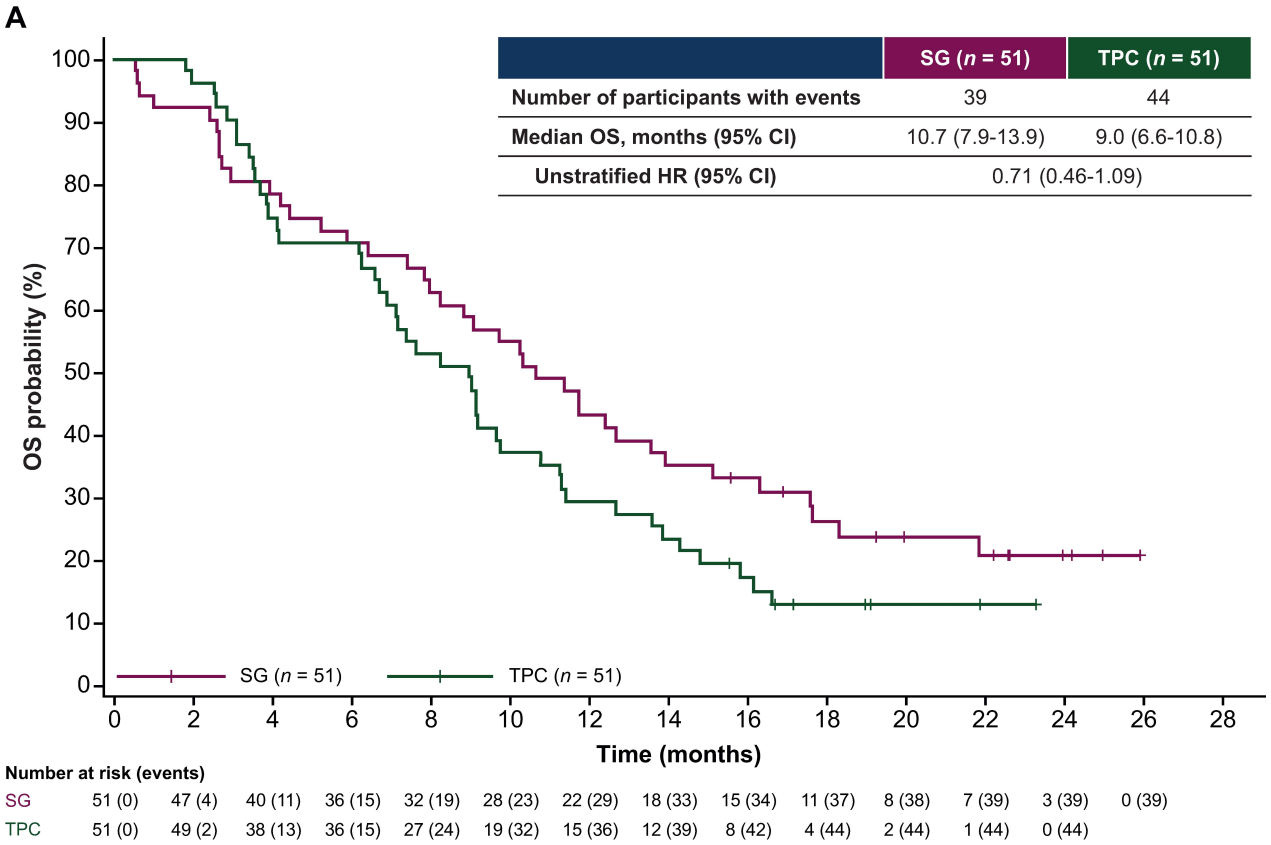


Figure S2. Kaplan–Meier plot of progression-free survival by investigator assessment.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

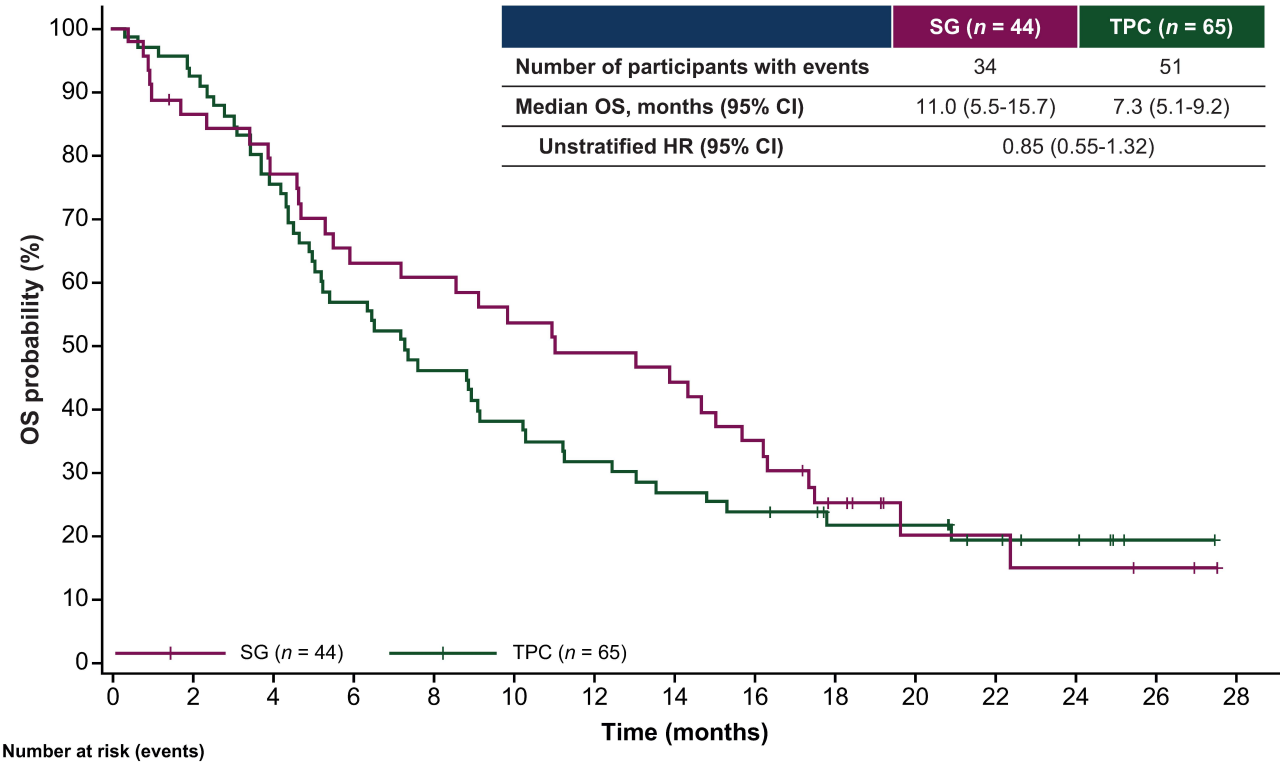


	SG (*n* = 355)	TPC (*n* = 356)
Number of participants with events	305	275
Median PFS, months (95% CI)	4.0 (2.9-4.2)	2.9 (2.8-3.5)
Stratified HR (95% CI)	0.81 (0.68-0.95)	
12-month PFS rate, % (95% CI)	11 (8-15)	6 (4-10)

Figure S3. Overall survival in Trop-2 median subgroups A. Kaplan–Meier plot of overall survival with SG versus TPC for the subgroup of patients with Trop-2 expression levels below median. B. Kaplan–Meier plot of overall survival with SG versus TPC for the subgroup of patients with Trop-2 expression levels above median. CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.



B



	SG (*n* = 44)	TPC (*n* = 65)
Number of participants with events	34	51
Median OS, months (95% CI)	11.0 (5.5-15.7)	7.3 (5.1-9.2)
Unstratified HR (95% CI)	0.85 (0.55-1.32)	

Number at risk (events)

SG	44 (0)	37 (6)	33 (10)	27 (16)	26 (17)	23 (20)	21 (22)	19 (24)	15 (28)	9 (32)	4 (33)	4 (33)	3 (34)	2 (34)	0 (34)
TPC	65 (0)	60 (5)	49 (16)	37 (28)	29 (35)	24 (40)	20 (44)	17 (47)	15 (49)	11 (50)	11 (50)	7 (51)	5 (51)	1 (51)	0 (51)