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Trodelvy® (sacituzumab govitecan-hziy) Incidence of Treatment-Related Neutropenia and Growth Factor Support: mUC Studies

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan [SG]), incidence of treatment-related neutropenia, and the use of growth factors in metastatic urothelial cancer (mUC).

Gilead continually assesses safety data from all sources for unidentified drug reactions and updates the product label information accordingly to reflect the safety profile of SG. Because case reports of potential adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

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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.

Summary

Incidence of SG-Related Neutropenia and Growth Factor Use in mUC Clinical Studies

TROPiCS-04, a global, multicenter, open-label, randomized controlled, phase 3 study, evaluated the efficacy and safety of SG vs chemotherapy TPC in patients with locally advanced unresectable or mUC who progressed after prior PLT-based and checkpoint inhibitor CPI-based therapy in the advanced setting.[1,2]

- Grade ≥3 neutropenia occurred in 35% of patients in the SG group and in 10% in the TPC group; Grade ≥3 febrile neutropenia occurred in 12% and 4%, respectively. In the SG group, 16 patients died due to infections in the setting of neutropenia (7 of which were considered treatment related); 11 of these patients had also received G-CSF (primary prophylaxis, n=2; therapeutic, n=9).
- In the SG and TPC groups, G-CSF as primary prophylaxis was used in 21% and 22%, respectively; G-CSF as secondary prophylaxis was used in 15% and 4%; and G-CSF was used therapeutically in 30% and 10%.

TROPHY-U-01, a global, multicohort, open-label phase 2 study, is investigating the efficacy and safety of SG in patients with unresectable locally advanced or mUC.[3-6]

- In Cohorts 1 and 2 of this study, Grade ≥3 neutropenia occurred in 35% and 34% of patients treated with SG as monotherapy, respectively, and febrile neutropenia occurred in 10% and 8% of patients.[4,6,7] In Cohort 3, Grade ≥3 neutropenia and febrile neutropenia occurred in 37% and 10% of patients treated with SG + pembro.[5] One treatment-related death occurred due to febrile neutropenia-related sepsis in Cohort 1.[4]
- In Cohort 1, 22% of patients received G-CSF as primary prophylaxis and 23% as secondary prophylaxis. In Cohort 2, G-CSF was used as prophylaxis and treatment in 18% and 26% of SG-treated patients, respectively. In patients treated with SG + pembro in Cohort 3, G-CSF was used as prophylaxis and treatment in 22% and 20% of patients, respectively.[4-6]

In the phase 1/2 IMMU-132-01 basket study[8] in patients with metastatic epithelial cancers, including mUC (n=45), SG-related Grade ≥3 neutropenia/neutrophil count decrease was reported in 38% of patients.[9]

- Growth factor support (filgrastim, pegfilgrastim, or G-CSF) was permitted; however, incidence of its use was not reported within the mUC cohort.[8,9]

Incidence of SG-Related Neutropenia and Growth Factor Use in Real-World Studies

A US retrospective observational cohort study (January 2011 to October 2022) evaluated SG data in 86 patients with locally advanced/mUC in a mostly community-based setting. Grade 3 and 4 neutropenia occurred in 10% and 8% of patients, respectively. Febrile neutropenia occurred in 6% of patients.[10]

- Incidence of G-CSF use as primary and secondary prophylaxis was 26% and 19%, respectively, while incidence of therapeutic G-CSF use was 27%. One patient who had primary G-CSF prophylaxis developed Grade ≥3 neutropenia.

A US retrospective study (November 2020 to December 2022) evaluated SG after EV monotherapy use in 18 patients with advanced UC. Fourteen patients required a dose reduction in Cycle 1 and prophylactic growth factor support.[11]

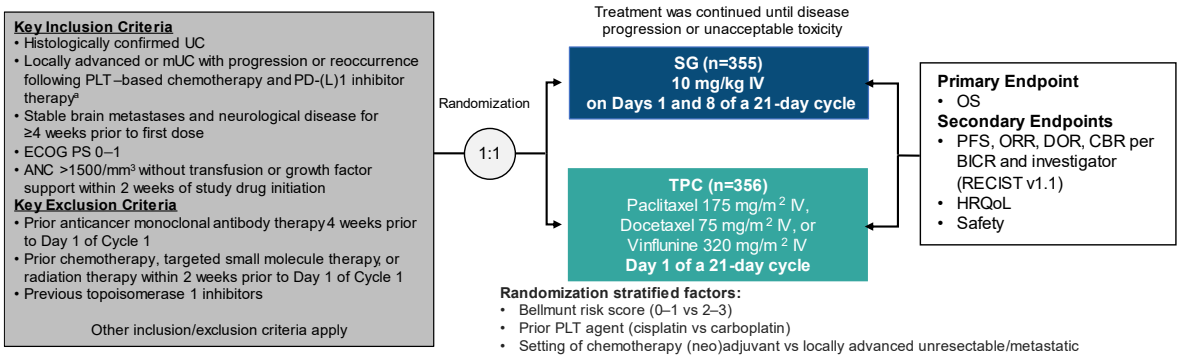
Incidence of SG-Related Neutropenia and Use of Growth Factors in mUC Clinical Studies

TROPiCS-04 Study in mUC

Study design

TROPiCS-04 was a global, multicenter, open-label, randomized, controlled phase 3 study that evaluated the efficacy and safety of SG vs TPC in patients with locally advanced unresectable or mUC who progressed after prior PLT-based and CPI-based therapy in the advanced setting (Figure 1).[1]

Figure 1. TROPiCS-04: Study Design[1,12]



Abbreviations: BICR=blinded independent central review; CBR=clinical benefit rate; DOR=duration of response; HRQoL=health-related quality of life; OS=overall survival; PD-(L)1=programmed death-ligand 1; PFS=progression-free survival; RECIST=responsive evaluation criteria in solid tumors.
[a]Patients who received prior EV were eligible for the study, as were patients who were ineligible for or unable to tolerate EV.

Neutropenia management with growth factor support[1]

Investigators were encouraged to consider the use of G-CSF as primary prophylaxis for neutropenia, but it was not required per study protocol. AEs of special interest included neutropenia and serious infections secondary to neutropenia.

Safety

Neutropenia was the most common TEAE and was reported in 194 patients (56%) in the SG group and 67 patients (20%) in the TPC group. Serious infections secondary to neutropenia were reported in 27 patients (8%) and 13 patients (4%) in the SG and TPC groups, respectively. Neutropenia and febrile neutropenia were two of the most common any-grade and Grade ≥3 TRAEs reported (Table 1). Overall, 37% of patients in the SG group and 26% in the TPC group received G-CSF as prophylaxis. The incidences of neutropenia and Grade ≥3 neutropenia were 43% and 32%, respectively, with primary G-CSF prophylaxis and 59% and 48% without it.[1,2]

Table 1. TROPiCS-04: Incidence of Treatment-Related Neutropenia and Febrile Neutropenia and G-CSF Use (Safety Population)[1,2]

n (%)		SG (n=349)	TPC (n=337)
Neutropenia[a]	Any grade	166 (48)	51 (15)
	Grade ≥3	122 (35)	35 (10)
Febrile neutropenia[a]	Any grade	41 (12)	15 (4)
	Grade ≥3	41 (12)	15 (4)
G-CSF use	Primary prophylaxis[b]	74 (21)	73 (22)
	Secondary prophylaxis[c]	54 (15)	14 (4)
	Therapeutic[d]	106 (30)	33 (10)

[a]AEs that occurred after the first dose of study drug through 30 days after the last dose of study drug are included.
[b]Defined as G-CSF use on or after Day 1 of Cycle 1 and before the onset of neutropenia.
[c]Defined as G-CSF use after resolution of Grade ≥2 to Grade ≤1 neutropenia or after occurrence of Grade 1 neutropenia and before any subsequent incidence of Grade ≥2 neutropenia.
[d]Defined as G-CSF use during Grade ≥2 neutropenia.
Note: The safety population included all patients who received ≥1 dose of study drug.

TEAEs led to death in 25 patients (7%) in the SG group and 7 (2%) in the TPC group. In the SG group, 16 patients died due to infections in the setting of neutropenia (7 of which were considered treatment related, and 7 more were possibly treatment related); 14 of those deaths occurred in the first month of treatment. Eleven of the patients in the SG group who died had also received G-CSF (primary prophylaxis, n=2; therapeutic, n=9). Patient who received SG and experienced fatal infections with neutropenia were generally older (81% were ≥65 years of age), 81% had a history of major urinary tract procedure, 56% had a prior cystectomy, 50% had prior radiotherapy, and 50% had received ≥3 prior anticancer regimens. In the TPC group, 4 patients died due to infections in the setting of neutropenia.[1,2]

TROPHY-U-01 Study in mUC

Study design

TROPHY-U-01 (NCT03547973), a global, multicohort, open-label phase 2 study, is investigating the efficacy and safety of SG in patients with unresectable locally advanced or mUC.[5-7,13] All patients will receive SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle (with and without other therapies) until loss of clinical benefit or unacceptable toxicity. Results are currently available for Cohorts 1 through 3.[4-6,14]

Cohort 1 (n=113) included patients whose disease had progressed after previous treatment with PLT-based chemotherapy + CPI therapy. Median (range) follow-up was 10.5 (0.3–40.9) mo.[4,14]

Cohort 2 (n=38) included patients in a 1L metastatic setting who were ineligible for PLT-based chemotherapy and who had progressed after prior CPI monotherapy. Median (range) follow-up was 9.3 (0.5–30.6) mo.[6]

Cohort 3 (n=41) included CPI-naive patients who had progressed after prior PLT-based chemotherapy. Patients were treated with SG + pembro 200 mg on Day 1 of 21-day cycle. Median follow-up was 14.8 mo (95% CI: 12.6–16.8).[5]

Neutropenia management with growth factor support[3]

Prior to each SG infusion, complete blood counts were obtained, and SG was administered only if ANC was ≥1500/mm^3 and ≥1000/mm^3 on Days 1 and 8, respectively. Use of growth factors was permitted in addition to treatment modifications (dose delay and/or reduction) for patients with febrile neutropenia, Grade ≥3 neutropenia following previous infusions, or for those at high risk of poor neutropenia-related clinical outcomes (ie, prolonged neutropenia, ANC <100/mm^3, febrile neutropenia, and serious infections). Growth factors could be administered prophylactically as clinically indicated.

Cohort 3: neutropenia management in patients treated with SG + pembro[3]

Neutropenia is one of the main AEs associated with both SG and pembro treatment.

Dose reduction was not permitted for pembro; however, suspension of pembro treatment was recommended for repeat episodes of Grade ≥3 neutropenia that occurred despite a 50% reduction of SG and prophylactic growth factor support. Pembro could also be suspended following prolonged (>3 weeks) neutropenia that failed to recover to Grade ≤1, despite growth factor support. If either agent was discontinued due to toxicity, the second agent could be continued until disease progression or toxicity.

Safety

Neutropenia was one of the most common all-grade and Grade ≥3 TRAEs across the three cohorts (Table 2).[4-7,14]

Table 2. TROPHY-U-01: Incidence of Neutropenia and Febrile Neutropenia and G-CSF Use[4-6,14]

n (%)		Cohort 1 SG (N=113)	Cohort 2 SG (N=38)	Cohort 3 SG + pembro (N=41)
Neutropenia	All Grade	53 (47)	17 (45)	21 (51)
	Grade 3	25 (22)	6 (16)	8 (20)
	Grade 4	14 (12)	7 (18)	7 (17)
Febrile neutropenia	All Grade	11 (10)	3 (8)	4 (10)[a]
	Grade 3	8 (7)	2 (5)	4 (10)[a]
	Grade 4	3 (3)	1 (3)	0
G-CSF use	Prophylaxis	Not reported (22)	17 (44)[b]	9 (22)
	Treatment	Not reported (23)	Not reported	8 (20)

[a]None of these patients received prophylactic G-CSF.
[b]Primary prophylaxis, n=7 (18%); secondary prophylaxis, n=10 (26%).

Cohort 1: safety analysis by UGT1A1

A total of 45, 47, and 14 patients were homozygous for the WT *UGT1A1* allele, heterozygous for the *UGT1A1*28* allele, and homozygous for the *UGT1A1*28* allele, respectively. A safety analysis by *UGT1A1* genotype status demonstrated that the rates of all-grade neutropenia were 44%, 47%, and 57% in patients homozygous for the WT allele, heterozygous, and homozygous for the *UGT1A1*28* allele, respectively.[4]

One treatment-related death occurred due to febrile neutropenia-related sepsis in a 65-year-old male homozygous for the WT *UGT1A1* allele and with mUC, Stage 3 chronic kidney disease, and a history of lung cancer.[4]

IMMU-132-01 Study in Metastatic Epithelial Cancer

Study design[8]

A phase 1/2, single-arm, open-label basket study investigated SG 8 to 18 mg/kg IV on Days 1 and 8 of a 21-day cycle in patients with metastatic epithelial cancers, including mUC (n=45), who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease. Patients who received SG 10 mg/kg for mUC were analyzed.

Neutropenia management with growth factor support[8]

Growth factor support (eg, filgrastim, pegfilgrastim, or G-CSF) was allowed as clinically necessary; however, prophylactic growth factor support was not permitted before Day 1 of Cycle 1.

Safety[9]

In the mUC cohort, Grade ≥3 neutropenia/neutrophil count decreased was reported in 38% of patients. Incidence of growth factor use was not reported in this cohort.

Incidence of SG-Related Neutropenia and Use of Growth Factors in Real-World Studies

US Real-World Safety Study of SG in mUC[10]

Study design and patient characteristics

A retrospective, observational cohort study evaluated SG data from a longitudinal database (Flatiron Health [from January 2011 to October 2022]) in a mostly community-based setting in the US in 86 patients with locally advanced/mUC. The median start and final dose of SG was 10 mg/kg, and there was no dose change in 53% of patients. Median (IQR) treatment duration was 61 (36–113) days.

The median (range) age of patients was 71 (25–85) years, 70% of patients were male, and 27% had an ECOG PS score of ≥2. Most patients (92%) had previously received PLT-based chemotherapy, and 71% had received EV in the line prior to SG. Most patients (94%) received SG as monotherapy, and 99% received SG as ≥2L.

Results

The most common any-grade AE of interest was neutropenia (Table 3). Febrile neutropenia resulted in treatment discontinuation for 1 patient and hospitalization for 4 patients (5%). Of note, 14 patients were hospitalized due to AEs, of which 7 patients had multiple reasons for hospitalization.

Table 3. Incidence of Neutropenia and Febrile Neutropenia (Parikh et al)[10]

AE,[a] n (%)	All (N=86)	1L and 2L (n=11)	3L (n=31)	4L (n=25)	≥5L (n=19)
Neutropenia	34 (40)	4 (36)	9 (29)	10 (40)	11 (58)
Grade 2	13 (15)	3 (27)	3 (10)	5 (20)	2 (11)
Grade 3	9 (10)	0	5 (16)	1 (4)	3 (16)
Grade 4	7 (8)	1 (9)	0	2 (8)	4 (21)
Febrile neutropenia	5 (6)	0	2 (6)	1 (4)	2 (11)

Abbreviations: 3L=third-line; 4L=fourth-line; ≥5L=fifth-line or later.
[a]Included all AEs that were not present at baseline.

During SG treatment, 52% of patients used G-CSF (Table 4). One patient who received primary G-CSF prophylaxis developed Grade ≥3 neutropenia.

Table 4. G-CSF Use (Parikh et al)[10]

	Any Use[a]	Any Use During SG Treatment	Primary Prophylaxis[b]	Secondary Prophylaxis[c]	Therapeutic Use[d]
G-CSF use, n (%)	66 (77)	45 (52)	22 (26)	16 (19)	23 (37)

[a]Included G-CSF use outside of treatment line (eg, prior to SG use).
[b]Use prior to neutropenia onset and within 7 days of index date.
[c]Use prior to end of index treatment and after neutropenia resolution date.
[d]Use on/after neutropenia onset and prior to date of resolution (if applicable) or end of index treatment.

US Real-World Study of SG Following EV in Advanced UC[15]

Study design and demographics

In a US retrospective study at the Johns Hopkins Greenberg Bladder Cancer Institute (November 2020 to December 2022), 18 patients with advanced UC were treated with SG after progression on EV monotherapy. The median (range) age was 71 (46–81) years, 10 patients (56%) were male, 15 (83%) were White or Caucasian, and 3 (17%) were African American. Eight patients (44%) had metastatic disease in the liver, 8 (44%) had metastatic disease in the lungs, 3 (17%) had metastatic disease in the lymph nodes only, and 2 (11%) had metastatic disease in bone.

Results

The median (range) number of SG cycles was 3.8 (1.5–6). Fourteen patients required a dose reduction in Cycle 1 and prophylactic growth factor support.

Clinical Guidelines for Neutropenia Management

For guidance on the management of neutropenia please refer to NCCN,[16] ASCO,[17] and ESMO[18] Guidelines.

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Abbreviations

1L=first line
2L=second line
AE=adverse event
ANC=absolute neutrophil count
ASCO=American Society of Clinical Oncology
CPI=checkpoint inhibitor
ECOG PS=Eastern Cooperative Oncology Group Performance Status
ESMO=European Society for Medical Oncology
EV=enfortumab vedotin
G-CSF=granulocyte colony-stimulating factor
mUC=metastatic urothelial cancer
NCCN=National Comprehensive Cancer Network
pembro=pembrolizumab
PLT=platinum
SG=sacituzumab govitecan
TEAE=treatment-emergent adverse event
TPC=treatment of physicians' choice
TRAE=treatment-related adverse event
UC=urothelial cancer
UGT1A1=uridine diphosphate glucuronosyltransferase 1A1
WT=wild-type

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.

Follow-Up

For any additional questions, please contact Trodelvy Medical Information at:

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