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Trodelvy® (sacituzumab govitecan-hziy) Neutropenia and Growth Factor Support: SG Clinical Studies in mBC

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]), neutropenia, and use of growth factors in the metastatic breast cancer (mBC) studies: triple-negative breast cancer (TNBC) and hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer.

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 causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

This document summarizes data for SG monotherapy (10 mg/kg IV on Days 1 and 8 of a 21-day treatment cycle) from phase 2 and 3 clinical studies, with a focus on patients with mBC.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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

Relevant Product Labeling[1]

SG can cause severe, life-threatening, or fatal neutropenia as early as the first cycle of treatment. Neutropenia occurred in 64% of patients treated with SG. Grade 3-4 neutropenia occurred in 49% of patients. FN occurred in 6% of patients. The median time to first onset of neutropenia (including FN) was 16 days (range: 1–435 days). Neutropenia occurred earlier in patients with reduced UGT1A1 activity. Neutropenic colitis occurred in 1.4% of patients.

Primary prophylaxis with G-CSF is recommended starting in the first cycle of treatment in all patients at increased risk of FN, including older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities.

Monitor ANC during treatment. Withhold SG for ANC below 1500/mm^3 on Day 1 of any cycle or below 1000/mm^3 on Day 8 of any cycle. Withhold SG for neutropenic fever. Dose modifications may be required due to neutropenia. Treat neutropenia with G-CSF and administer prophylaxis in subsequent cycles as clinically indicated or indicated in Table 2 of the US FDA-approved Prescribing Information.

Incidence of Neutropenia and Use of Growth Factors: Pooled Safety Analyses

A total of 1063 patients from four studies (ASCENT,[2] TROPiCS-02,[3] TROPHY-U-01,[4] and IMMU-132-01[5]) were included in this analysis.[6] These studies included patients with mTNBC treated in the 2L+ setting and pre-treated HR+/HER2- mBC. The median (range) treatment duration of SG was 4.1 (0–63) mo.[7]

- The most common Grade ≥3 TEAE was neutropenia at 46%; FN occurred in 6% of patients.[6]
- Grade ≥3 neutropenia and FN were more common in patients with *UGT1A1 *28/*28* GT (58% and 14%, respectively) vs those with other GTs (**1/*1*, 43 and 6%; and **1/*28*, 49% and 5%).[6] *UGT1A1* testing is not required as per the US FDA-approved Prescribing Information.[1]
- Neutropenia led to treatment discontinuation in 1% of patients.[6]
- Median onset of any-grade and Grade ≥3 neutropenia was 2.3 weeks, resolving in 1.1 weeks.[6]
- An exploratory analysis showed that G-CSF prophylaxis reduced neutropenia rates: incidence of any-grade neutropenia was 31% vs 65% in patients who did vs did not receive primary prophylaxis and was 41% vs 61% in patients who did vs did not receive secondary prophylaxis, respectively. Incidence of Grade ≥3 neutropenia was 26% vs 50% in patients who did vs did not receive primary prophylaxis, and was 25% vs 46% in patients who did vs did not receive secondary prophylaxis, respectively.[6]

A total of 969 patients, with either mTNBC treated in the 2L+ setting or pretreated HR+/HER2- mBC, were included in a pooled analysis of clinical studies in NA/EU (ASCENT,[2] TROPiCS-02,[3] IMMU-132-01[5]) and Asia (EVER-132-001,[8] EVER-132-002,[9] and ASCENT-J02[10]). The median (range) duration of treatment in the NA/EU and Asia groups were 4.6 (<0.1–62.6) mo and 5.2 (<0.1–24.9) mo, respectively.[11]

- Across NA/EU (n=688) and Asia (n=281), patients treated with primary G-CSF prophylaxis experienced less any-grade neutropenia (40% and 58%, respectively) and Grade ≥3 neutropenia (29% and 47%) than patients who did not receive G-CSF as primary prophylaxis (any-grade, 72% and 91%; Grade ≥3, 56% and 69%).[11]
- Patients in Asia, compared with those in NA/EU, had higher rates of any-grade neutropenia (87% vs 68%, respectively) and Grade ≥3 neutropenia (65% vs 51%). Across both groups, neutropenia most commonly occurred early in treatment (median onset, 16 d), with rates falling overtime. Neutropenia led to SG-discontinuation in both groups (Asia, 1%; NA/EU, <1%).[11]

Incidence of Neutropenia and Use of Growth Factors: SG Clinical Studies

In ASCENT, a study in 2L+ mTNBC, incidence of Grade ≥3 treatment-related neutropenia and FN was 51% and 6% (SG) vs 33% and 2% (TPC). Growth factor use was 49% (SG) and 23% (TPC).[2] A post-hoc analysis showed that neither OS nor PFS was adversely impacted by Grade ≥3 neutropenia.[12]

In ASCENT-03, a study in 1L mTNBC, incidence of Grade ≥3 treatment-emergent neutropenia was 43% with SG and 41% with TPC. Twelve patients treated with SG reported FN; none had received primary prophylactic G-CSF.[13]

- In patients treated with SG and TPC, primary prophylaxis with G-CSF was used in 54 and 28 patients, respectively; secondary prophylaxis was used in 81 and 51 patients.[14]
- Six deaths in the SG arm were deemed treatment-related (sepsis, n=4; neutropenic colitis, n=1; pneumonia, n=1); all were due to infections.[13,14]

In TROPiCS-02, a study in pretreated HR+/HER2- mBC, the incidence of Grade ≥3 treatment-related neutropenia and FN was 51% and 5%, respectively, with SG vs 38% and 4% with TPC. Incidence of G-CSF use was 54% with SG and 33% with TPC. Six TEAEs led to death in the SG arm; of those, 1 treatment-related death was due to septic shock following Grade 4 neutropenic colitis with large intestine perforation.[3,15]

In ASCENT-07, a study in 1L post-ET HR+/HER2- mBC, Grade ≥3 treatment-emergent neutropenia occurred in 56 and 21 patients treated with SG and TPC, respectively. Seven TEAEs led to death in the SG arm; 1 due to FN. Incidence of primary and secondary G-CSF prophylaxis was 20% and 43%, respectively, with SG and 5% and 10% with TPC.[16]

In IMMU-132-01, a study in metastatic epithelial cancer,[5,17,18] the incidence of Grade ≥3 neutropenia and FN in the mTNBC cohort was 42% and 8%, respectively; growth factor support was not reported.[17] Incidence of Grade ≥3 neutropenia and FN in the HR+/HER2- mBC cohort was 50% and 3.7%, respectively; 48.1% received growth factors.[18]

PRIMED (N=50) evaluated the impact of primary prophylactic G-CSF as management of neutropenia and primary prophylactic loperamide as management of diarrhea. The primary safety analysis (median follow-up, 4.3 mo), after 2 cycles of SG, reported incidences of any-grade, Grade 3, and 4 neutropenia as 28%, 12%, and 4%, respectively. The extended safety analysis (median follow-up 9 mo) reported incidences of any-grade, Grade 3, and 4 neutropenia as 42%, 18%, and 6%, respectively.[19]

NCCN Hematopoietic Growth Factors Clinical Practice Guidelines[20]

SG is included in the NCCN Guidelines as a regimen with an intermediate risk (10–20%) for FN. Patient risk factors should be assessed for FN to help guide prophylactic G-CSF use.

Pooled SG Safety Analyses

Safety Analysis in Patients With Multiple Epithelial Tumors

A pooled analysis examined exposure to SG in 1063 patients from four studies.[2-6] These studies included patients with mTNBC treated in the 2L+ setting and pre-treated HR+/HER2- mBC (Figure 1). The median (range) treatment duration of SG was 4.1 0–63) mo.[7]

Figure 1. Pooled Clinical Studies in Patients With Multiple Epithelial Tumors[6]

ASCENT, Phase 3 (SG, n=258) An open label, randomized, confirmatory study in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapy regiments, at least 1 for metastatic disease	**TROPiCS-02, Phase 3 (SG, n=268)** An open-label, randomized, multicenter study in patients with HR+/HER2- mBC who had received ≥1 taxane, ≥1 endocrine therapy, and ≥1 CDK4/6i in any setting and 2 –4 prior chemotherapy regimens for metastatic disease.
SG 10 mg/kg IV on Days 1 and 8 of a 21 -day cycle Continue treatment until loss of clinical benefit or unacceptable toxicity	
TROPHY-U-01, Phase 2 (SG, n=135) A multi -cohort, open -label study in patients with unresectable locally advanced, or mUC whose disease progressed: Cohort 1: After prior PLT-based and CPI-based therapies Cohort 2: After CPI-based therapies and who were ineligible for PLT-based therapy.	**IMMU-132-01, Phase 1/2 (SG, n=402)** A single-arm, open-label basket study in patients with metastatic epithelial cancers (including cervical, colorectal, endometrial, esophageal, gastric adenocarcinoma, glioblastoma multiforme, hepatocellular, non -small cell lung, non-TNBC, ovarian, pancreatic, prostate, renal cell, small -cell lung, squamous cell head and neck, TNBC, and urothelial) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease.

Abbreviations: CDK4/6i=cyclin-dependent 4/6 inhibitor; CPI=checkpoint inhibitor; PLT=platinum.

Table 1. Pooled Safety in Multiple Epithelial Tumors: Baseline Demographics and Disease Characteristics[6]

Key Demographics and Characteristics		All Patients (N=1063)
Age, median (range), y		59 (27–90)
Sex, n (%)	Female	840 (79)
Race, n (%)	White/Black/Asian	826 (78)/55 (5)/38 (4)
	Other or unknown	144 (14)
ECOG PS, %	0/1	36/64
Time since metastatic disease diagnosis, median (range), mo		28.7 (-0.1 to 412.6)
Number of prior lines of systemic therapy, median (range), n		5 (1–17)
Presence of visceral metastasis, n (%)		882 (83)
UGT1A1 status, n (%)	**1/*1*	416 (39)
	**1/*28*	420 (40)
	**28/*28*	112 (11)
	Other/unknown	13 (1)/102 (10)

Neutropenia incidence, onset, and duration

The most common Grade ≥3 TEAE was neutropenia (46%); FN occurred in 6% of patients. Grade ≥3 neutropenia and FN were more common in patients with *UGT1A1 *28/*28* GT vs other GTs (Table 2).[6] *UGT1A1* testing is not required as per the US FDA-approved Prescribing Information.[1]

Table 2. Pooled Safety in Multiple Epithelial Tumors: Neutropenia by *UGT1A1* GT[6]

TEAE, %	**1/*1* (n=416)	**1/*28* (n=420)	**28/*28* (n=112)
Grade ≥3 neutropenia	43	49	58
FN	6	5	14

See Table 3 for time to onset and resolution of neutropenia and FN.[6]

Table 3. Pooled Safety in Multiple Epithelial Tumors: Time to Onset and Resolution of Neutropenia and FN (N=1063)[6]

Time to Onset/Resolution, Median (Range), Wk	Time to Onset		Time to Resolution	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	2.3 (0.1–62.1)	2.3 (0.3–86.1)	1.1 (0.1–89.1)	1.1 (0.1–89.1)
FN	2.1 (1–67.3)	2.1 (1–67.3)	0.9 (0.1–3.3)	0.9 (1–2.3)

Neutropenia led to treatment discontinuation in 1% of patients.[6]

Neutropenia management[6]

An exploratory analysis of G-CSF use showed that fewer patients experienced any-grade or Grade ≥3 neutropenia after receiving prophylaxis vs those who did not receive prophylaxis. Prophylaxis was also associated with a longer time to onset of Grade ≥3 neutropenia (Table 4). A total of 9% of patients who received G-CSF for the first time required a dose reduction.

Table 4. Pooled Safety in Multiple Epithelial Tumors: Treatment of Neutropenia[6]

Patients, n (%)	Primary Prophylaxis[a]		Secondary Prophylaxis[b]	
	Received (n=54)	Did Not Receive (n=1009)	Received (n=116)	Did Not Receive (n=893)
Any-grade neutropenia[c]	17 (31)	658 (65)	48 (41)	542 (61)
Grade ≥3 neutropenia[c]	14 (26)	504 (50)	29 (25)	408 (46)

Patients, n (%)	Primary Prophylaxis[a]		Secondary Prophylaxis[b]	
	Received (n=54)	Did Not Receive (n=1009)	Received (n=116)	Did Not Receive (n=893)
Onset of first Grade ≥3 neutropenia, median, d	29	14	78	14

[a]G-CSF use on or after Cycle 1 Day 1 and prior to onset of first occurrence of any-grade neutropenia, or G-CSF use when there is no neutropenia event. For patients who received primary prophylaxis, neutropenia is subsequent to primary prophylaxis. For patients who did not receive primary prophylaxis, neutropenia is first occurrence since Cycle 1 Day 1.

[b]G-CSF use after resolution of Grade ≥2 neutropenia (to Grade ≤1) or occurrence of Grade ≥1 neutropenia, and prior to onset of any subsequent Grade ≥2 neutropenia or no occurrence of subsequent Grade ≥2 neutropenia. For patients who received secondary prophylaxis, neutropenia is subsequent to secondary prophylaxis. For patients who did not receive secondary prophylaxis, neutropenia is the first occurrence since Cycle 1 Day 1. Patients who received primary prophylactic G-CSF were excluded from the secondary prophylactic use analysis.

[c]Neutropenia includes preferred terms of neutropenia, neutrophil count decreased, and FN.

Safety Analysis in Patients With mBC

A pooled analysis of clinical studies in NA/EU (ASCENT,[2] TROPiCS-02,[3] IMMU-132-01[5]) and Asia (EVER-132-001,[8] EVER-132-002,[9] and ASCENT-J02[10]), evaluated SG in 969 patients with either mTNBC or HR+/HER2- mBC. TEAEs were analyzed by region: NA/EU and Asia.[11]

Baseline age, sex, and BMI were similar in both groups; race data are in Table 5. Asian vs NA/EU patients had a higher rate of ECOG PS 1 (67% vs 59%, respectively) and shorter time from metastatic diagnosis to randomization (25.2 mo vs 35.7 mo). *UGT1A1* GTs differed by region: NA/EU had more patients with**1/*28* and **28/*28* GTs, while Asia had more patients with **1/*1* and **1/*6* GTs.[11]

Table 5. Pooled Safety in mBC: Baseline Race by Region[11]

Race, n (%)	White	Black	Asian	Other/Unknown
NA/EU (n=688)	517 (75)	41 (6)	26 (4)	104 (15)
Asia (n=281)	0	0	281 (100)	0

Neutropenia incidence and management[11]

Patients in Asia had higher rates of neutropenia vs patients in the NA/EU region (Table 6). Across both regions, neutropenia occurred most commonly early in treatment (median onset, 16 d), with the rate falling over time. Neutropenia led to SG-discontinuation in both regions: NA/EU, <1%; Asia, 1%.

Table 6. Pooled Safety in mBC: Incidence of Treatment-Emergent Neutropenia[11]

Patients, n (%)	Total Patients (N=969)	
	NA/EU (n=688)	Asia (n=281)
Any-grade neutropenia	465 (68)	244 (87)
Grade ≥3 neutropenia	349 (51)	184 (65)

[a]Neutropenia includes preferred terms of neutropenia and neutrophil count decreased.

Neutropenia was treated according to label recommendations.[6] Patients treated with G-CSF as primary prophylaxis experienced less neutropenia across both regions (Table 7).[11]

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Table 7. Pooled Safety in mBC: Primary G-CSF Prophylaxis[11]

Patients, n (%)	Total Patients (N=969)			
	NA/EU (n=688)		Asia (n=281)	
	Received (n=65)	Did Not Receive (n=623)	Received (n=36)	Did Not Receive (n=245)
Any-grade neutropenia	26 (40)	450 (72)	21 (58)	223 (91)
Grade ≥3 neutropenia	19 (29)	347 (56)	17 (47)	170 (69)

SG Clinical Studies

ASCENT Study in 2L+ mTNBC

ASCENT (N=529) investigated the safety and efficacy of SG vs chemotherapy TPC (eribulin, vinorelbine, gemcitabine, or capecitabine) in patients with refractory or relapsed mTNBC. An absolute neutrophil count of >1500/mm^3 was required for inclusion.[2]

Patients received a median (range) of 7 (1–33) treatment cycles of SG, over a median (range) treatment duration of 4.4 (0.03–22.9) mo. In addition to treatment modifications (dose delay and/or reduction), patients were given growth factor support and/or blood transfusions for neutropenia.[2] Growth-factors could be initiated as clinically indicated, including prophylactically, as early as Cycle 1.[21]

Safety

In the OSP (n=482), Grade ≥3 neutropenia and FN were reported at a higher incidence with SG vs TPC (Table 8). Neutropenia was the most common TRAE in both study arms.[2]

Table 8. ASCENT: Incidence of Neutropenia[2]

TRAE, %	SG (n=258)			TPC (n=224)		
	All-Grade	Grade 3	Grade 4	All-Grade	Grade 3	Grade 4
Neutropenia,[a]	63	34	17	43	20	13
FN	6	5	1	2	2	<1

[a]Neutropenia and decreased neutrophil count were combined.

A post hoc analysis evaluated clinical outcomes according to the presence of Grade ≥3 neutropenia. Of the 258 SG-treated patients, 139 had Grade ≥3 neutropenia. Results showed that neither OS nor PFS were adversely impacted by Grade ≥3 neutropenia (Table 9).[12]

Table 9. ASCENT: Unstratified Analysis[a] of PFS and OS in Patients With and Without Grade ≥3 Neutropenia[12]

	Median (95% CI), Mo		HR (95% CI)	*P*-Value
	Grade ≥3 Neutropenia (n=138)	No Grade ≥3 Neutropenia (n=116)		
PFS	5.6 (4–6.5)	4.9 (4.1–5.9)	0.91 (0.68–1.21)	0.51
OS	13.5 (10.8–14.5)	11.2 (10.1–14.1)	0.99 (0.74–1.32)	0.95

[a]This analysis was unstratified and excluded 4 patients who died within 28 d of randomization.

Time to onset and duration of neutropenia (Table 10) were assessed.[22]

Table 10. ASCENT: Time to Onset and Duration of Neutropenia[22]

	Time to Onset of 1st Event, Median, Days				Duration of Event, Median, Days			
	All-Grade		Grade ≥3		All-Grade		Grade ≥3	
	SG	TPC	SG	TPC	SG	TPC	SG	TPC
Neutropenia	20	13	21	14	7	7	6	6.5

Myeloid growth factor was used as secondary prophylaxis (SG, 29%; TPC, 10%) and as treatment of neutropenia (SG, 30%; TPC, 17%).[22]

Dose reductions due to neutropenia or FN occurred in 11% and 19% of SG and TPC-treated patients, respectively. Neutropenia and FN-related dose interruptions occurred in 46% and 21% of patients who received SG and TPC, respectively. Patients homozygous for the *UGT1A1* *28 allele had a higher incidence of Grade ≥3 neutropenia than those who were heterozygous or had the wild-type allele (Table 11).[22]

Table 11. ASCENT: Neutropenia by *UGT1A1* GT[22]

TRAE, n (%)	SG (n=250)[a]					
	*1/*1 (n=113)		*1/*28 (n=96)		*28/*28 (n=34)	
	All-Grade	Grade ≥3	All-Grade	Grade ≥3	All-Grade	Grade ≥3
Neutropenia[b]	76 (67)	60 (53)	55 (57)	45 (47)	24 (71)	20 (59)
FN	3 (3)	3 (3)	5 (5)	5 (5)	6 (18)	6 (18)

[a]Patients with *UGT1A1* GTs in the OSP. Seven patients who had *UGT1A1* GTs are not listed in the table.
[b]Neutropenia and decreased neutrophil count were combined.

ASCENT-03 Study in 1L mTNBC

ASCENT-03, an ongoing, global, open-label, randomized, phase 3 study, is comparing the efficacy and safety of SG vs TPC (gem + carbo, paclitaxel, or nab-paclitaxel), as 1L treatment in patients (N=558) with previously untreated, locally advanced, inoperable or mTNBC who are not candidates for PD-(L)1 inhibitor therapy.[13] The median (range) duration of SG treatment at the final PFS analysis was 8.3 (<0.1–28.7) mo.[13,14]

Safety

The most common TEAE across both treatment arms was any-grade and Grade ≥3 neutropenia (Table 12). Of the 12 patients (4%) in the SG arm who experienced FN, none had received primary prophylaxis with G-CSF.[13]

Table 12. ASCENT-03: Any-Grade and Grade ≥3 Neutropenia[13a]

TEAE, n (%)	SG (n=275)		TPC (n=276)	
	Any-Grade	Grade ≥3	Any-Grade	Grade ≥3
Neutropenia[b]	183 (67)	118 (43)	157 (57)	112 (41)

[a]TEAEs began on or after the first dose date of study drug and ≤30 d after the last dose date of study drug (including crossover treatment if applicable) or the initiation of subsequent anticancer therapy, whichever occurred first.
[b]Included preferred terms of neutropenia and neutrophil count decreased.

Six deaths in the SG arm were deemed treatment-related (sepsis, n=4; neutropenic colitis, n=1; and pneumonia, n=1); all were due to infections. Of these, 5 deaths were due to infections secondary to neutropenia in patients who had risk factors for FN but did not receive prophylaxis with G-CSF; these events occurred early in treatment (2 patients on Day 26 [Cycle 2] and 1 patient each on Days 14, 15, and 21 [Cycle 1]). A death from pneumonia showed no evidence of preceding or concurrent neutropenia.[13,14]

Time to onset and duration of neutropenia[14]

Median time to onset of any-grade and Grade ≥3 neutropenia in the SG arm was 22 d; the median duration was 9 and 8 d, respectively (Table 13). Median duration of neutropenia was generally comparable between treatment arms.

Table 13. ASCENT-03: Time to Onset and Duration of Neutropenia[14]

	SG (n=275)				TPC (n=276)			
	Any-Grade		Grade ≥3		Any-Grade		Grade ≥3	
	n	Median (Range), d	n	Median (Range), d	n	Median (Range), d	n	Median (Range), d
Time to onset[a]	187	22 (6–274)	124	22 (7–720)	158	22 (6–406)	113	29 (7–295)
Duration[b]	183	9 (2–49)	122	8 (1–36)	155	14 (1–179)	112	8 (1–25)

[a]Defined as time from first dose date of study drug to onset date of first TEAE.
[b]Defined as the median duration among multiple preferred terms; within each preferred term, duration is median duration among multiple episodes (end date of TEAE – onset date of TEAE + 1 d for each episode).

Management of neutropenia[14]

G-CSF use as primary prophylaxis was associated with less frequent and less severe neutropenia in the SG arm (Table 14). Neutropenia led to dose reduction in 54 patients (20%) in both arms and treatment discontinuation in 1 patient (<1%) and 3 patients (1%) in the SG and TPC arms, respectively.

Table 14. ASCENT-03: Management of Neutropenia[14]

Neutropenia, n (%)	SG (n=275)		TPC (n=276)	
Primary G-CSF prophylaxis	Yes (n=54)	No (n=221)	Yes (n=28)	No (n=248)
Any-grade	28 (52)	159 (72)	21 (75)	137 (55)
Grade ≥3	15 (28)	109 (49)	14 (50)	99 (40)
Secondary G-CSF prophylaxis[a]	Yes (n=81)	No (n=75)	Yes (n=51)	No (n=85)
Any-grade	46 (57)	52 (69)	38 (75)	50 (59)
Grade ≥3	30 (37)	20 (27)	29 (57)	39 (46)

[a]Excluded patients that received primary G-CSF prophylaxis.

TROPiCS-02 Study in Pretreated HR+/HER2- mBC

TROPiCS-02 (N=543) investigated the safety and efficacy of SG vs TPC (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with pretreated HR+/HER2- mBC. In the OSP (n=517), patients received a mean (range) of 8.2 (1–35) SG cycles over a median (range) duration of 4.1 (0.03–24.2) mo.[3]

Safety

Growth factors could be used for FN and Grade 3 or 4 neutropenia following previous infusions, or for neutropenia in patients at high risk of poor clinical outcomes (Table 15). Routine prophylactic use was not recommended.[15]

Table 15. TROPiCS-02: Growth Factor Use in the OSP[15]

G-CSF Use, n (%)	SG (n=268)	TPC (n=249)
Total use	144 (54)	83 (33)
As prophylaxis	94 (35)	53 (21)
As treatment	75 (28)	47 (19)

Note: G-CSF use included patients with medications taken on/after first dose and ≤30 d after the last dose.

The absolute incidence of Grade ≥3 neutropenia was 51% (n=136) and 38% (n=94) in the SG and TPC arms, respectively. When treatment exposure was assessed in a post hoc exploratory analysis, the time-at-risk EAIR difference of Grade ≥3 neutropenia was similar between treatments (EAIR 0.03 95% CI -0.53 to 0.56). The absolute incidence of FN in the SG and TPC arms (5% vs 4%, respectively) remained similar with an EAIR difference of -0.02 (95% CI -0.16 to 0.09).[23]

Time to onset and duration of neutropenia (Table 16) were assessed.[24]

Table 16. TROPiCS-02: Time to Onset and Duration of Treatment-Related Neutropenia[24]

	Time to Onset of 1st Event, Median, d				Duration of Event, Median, d			
	All-Grade		Grade ≥3		All-Grade		Grade ≥3	
	SG	TPC	SG	TPC	SG	TPC	SG	TPC
Neutropenia	20	15	16	15	8	8	8	8

There was 1 treatment-related death in the SG arm. A 70+ year-old female, who was heterozygous for the *UGT1A1*28* allele, died on Day 14 of septic shock. The event was preceded by Grade 4 neutropenic colitis with large intestine perforation.[3,15]

ASCENT-07 Study in 1L Post-ET in HR+/HER2- mBC[16]

ASCENT-07, an ongoing, global, open-label, randomized, phase 3 study (N=690), is comparing the efficacy and safety of SG vs TPC (capecitabine, paclitaxel, or nab-paclitaxel) in patients with HR+/HER2- (IHC 0, IHC 1+, IHC2+/ISH-) locally advanced, inoperable, or mBC who have received prior ET. The median (range) duration of SG treatment at the PFS analysis was 8.3 (0–22.1) mo.

Safety

The most common Grade ≥3 TEAE for SG and TPC was neutropenia (Table 15). Any-grade FN was 8% with SG and 1% with TPC; 1 case of FN lead to death in the SG arm. The use of prophylactic G-CSF is presented in Table 17.

Table 17. ASCENT-07: Treatment-Emergent Neutropenia and G-CSF Use[16]

		SG (n=449)	TPC (n=232)
Neutropenia, %	Any-grade	76	39
	Grade ≥3	56	21
G-CSF use, n (%)	Primary prophylaxis	89 (20)	11 (5)
	Secondary prophylaxis	192 (43)	24 (10)

IMMU-132-01 Study in Metastatic Epithelial Cancer

IMMU-132-01 investigated the safety and efficacy of SG in patients with metastatic epithelial cancers, including mTNBC and HR+/HER2- mBC. Prophylactic growth factor support was not permitted before Day 1, Cycle 1.[5]

The mTNBC cohort received a mean (range) of 9.6 (1–51) SG cycles, with a median (range) duration of exposure of 5.1 (0.03–36.1) mo .[17] The median (range) duration of SG treatment was 4.6 (0–29.4) mo in the HR+/HER2- mBC cohort.[18]

Safety

In the mTNBC cohort, neutropenia was the second most common all-grade AE, the most common Grade ≥3 AE, and the most common cause of treatment interruption (Table 18). FN was the most common SAE.[17]

In the HR+/HER2- mBC cohort, neutropenia was the most common all-grade and Grade ≥3 TRAE. Of the 10 treatment-related SAEs, 2 were FN. One patient discontinued treatment due to Grade 3 neutropenia, which resolved with growth factor use following discontinuation. Growth factor support (filgrastim or peg-filgrastim) was received by 48.1% of patients.[18]

Table 18. IMMU-132-01: Incidence of Neutropenia[17,18]

mTNBC Cohort (n=108)				HR+/HER2- Cohort (n=54)			
Neutropenia,[a] n (%)		FN, n (%)		Neutropenia,[a] n (%)		FN, n (%)	
All-Grade	Grade ≥3	All-Grade	Grade ≥3	All-Grade	Grade ≥3	All-Grade	Grade ≥3
69 (64)	45 (42)	10 (9)	9 (8)	NR (72.2)	NR (50)	2 (3.7)	2 (3.7)

Abbreviation: NR=not reported.
[a]Included neutropenia and decreased neutrophil count.

PRIMED Study in mTNBC and HR+/HER2- mBC[19]

PRIMED, an open-label, single arm, phase 2 study in 50 patients with unresectable locally advanced mTNBC (n=32 [64%]) or HR+/HER2- mBC (n=18 [36%]), evaluated the impact of primary prophylactic G-CSF 0.5 MU/kg/d (Days 3, 4, 10, and 11) for neutropenia management. Primary endpoints included incidence of Grade ≥3 neutropenia per CTCAE version 5.0 during the first two treatment cycles.

The median (range) patient age was 52 (31–74) y, 60% (n=30) had ECOG PS 0, and 70% (n=35) had visceral disease. Prior to enrolment, patients had received a median (range) of 1 (0–2) prior line of chemotherapy for advanced disease. A total of 10 patients (20%) received SG as 1L therapy in the metastatic setting due to early relapse after completion of (neo)adjuvant treatment for early breast cancer.

Safety

Primary safety analysis and primary endpoint

Results were reported for 50 patients after the first two cycles of SG (Table 19), with a median (range) follow-up of 4.3 (0.2–8.6) mo. Any-grade neutropenia was reported with an incidence of 28%. Grade ≥3 neutropenia was reported in 8 patients, meeting the primary endpoint (*P*=0.00023). No patients experienced FN.

Table 19. PRIMED: Neutropenia After Two Treatment Cycles[19]

	Any-Grade	Grade 2	Grade 3	Grade 4	Grade ≥3
Neutropenia, n (%)	14 (28)	4 (8)	6 (12)	2 (4)	8 (16)
P-value	-	-	-	-	0.00023

There were no treatment discontinuations during the first two treatment cycles.

Extended safety analysis

The extended safety analysis had a median (range) follow-up of 9 (0.2–13.5) mo; see Table 20 for incidence of any-grade and Grade ≥3 neutropenia. No patients experienced FN.

Table 20. PRIMED: Neutropenia During Extended Follow-Up[19]

	Any-Grade	Grade 1	Grade 2	Grade ≥3
Neutropenia, n (%)	21 (42)	4 (8)	5 (10)	12 (24)

Continuation of G-CSF after the first two treatment cycles was at the discretion of the treating physician. There were 35 patients (70%) who received ≥1 dose of G-CSF after Cycle 2, with a median (range) duration of 6.1 (1.8–12.6) mo.

Clinical Guidelines for Neutropenia Management

SG is included in the NCCN Guidelines as a regimen with an intermediate risk (10–20%) for FN. Prior to the first treatment cycle, evaluation of overall FN risk should consider patient risk factors (Figure 2). For patients that have ≥1 risk factor, prophylactic G-CSF should be considered. Observation is recommended if no patient risk factors are identified.[20]

Figure 2. Assessment of Patient Risk Factors[20a,b]

- Prior chemotherapy or radiation therapy
- Persistent neutropenia
- Bone marrow involvement by tumor
- Poor performance status
- Recent surgery and/or open wounds
- Liver dysfunction (bilirubin >2 mg/dL)
- Renal dysfunction (CrCl <50 mL/min)
- Age >65 years and receiving full chemotherapy dose intensity

Abbreviation: CD4=cluster of differentiation 4.

[a]Other risk factors for FN include poor performance status or HIV infection (patients with low CD4 counts). Patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory patients with cancer receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoietic cell transplant.

[b]Other factors may warrant the use of G-CSF, including chronic immunosuppression in the post-transplant setting (including organ transplant).

For additional guidance on neutropenia management please refer to the American Society of Clinical Oncology (ASCO)[25] and European Society for Medical Oncology (ESMO) Guidelines.[26]

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Abbreviations

1L=first-line
2L+=second-line and later
AE=adverse event
ANC=absolute neutrophil count
EAIR=exposure-adjusted incidence rate
ECOG PS=Eastern Cooperative Oncology Group Performance Status
ET=endocrine therapy
EU=Europe
FN=febrile neutropenia
G-CSF=granulocyte colony-stimulating factor
GT=genotype
HR+/HER2-=hormone receptor-positive/human epidermal growth factor receptor 2-negative
IHC=immunohistochemistry
ISH=in situ hybridization
mBC=metastatic breast cancer
mTNBC=metastatic triple-negative breast cancer
NA=North America
NCCN=National Comprehensive Cancer Network
OS=overall survival
OSP=overall safety population
PD-(L)1=programmed death-(ligand) 1
PFS=progression-free survival
SAE=serious adverse event
SG=sacituzumab govitecan-hziy
TEAE=treatment emergent adverse event
TRAE=treatment-related adverse event
TPC=treatment of physician's choice
UGT1A1=uridine diphosphate-glucuronosyl transferase 1A1

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

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