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

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.

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. Febrile neutropenia occurred in 6% of patients. The median time to first onset of neutropenia (including febrile neutropenia) 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 febrile neutropenia, 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 Prescribing Information.

Incidence of Neutropenia and Use of Growth Factors in mBC Studies

A total of 969 patients, with either mTNBC or HR+/HER2- mBC, were included in a pooled analysis of six clinical studies (ASCENT,[2] TROPiCS-02,[3] IMMU-132-01,[4] EVER-132-001,[5] EVER-132-002,[6] and ASCENT-J02[7]).[8]

- Across both regions, NA/EU and Asia respectively, patients treated with G-CSF as primary prophylaxis experienced less any-grade neutropenia (40% and 58%) and Grade ≥3 neutropenia (29% and 47%) vs patients who did not receive G-CSF as primary prophylaxis (any-grade, 72% and 91%; Grade ≥3, 56% and 69%).[8]
- Patients in Asia (n=281) had higher rates of any-grade and Grade ≥3 neutropenia vs patients in the NA/EU (n=688) region (absolute numbers not reported). Across both regions, neutropenia most commonly occurred early in treatment (≤6 weeks), with rates falling over time. Neutropenia was one of the most common TEAEs leading to discontinuation across both regions (NA/EU, <1%; Asia 1%).[8]

In ASCENT, a mTNBC study, Grade ≥3 treatment-related neutropenia and FN occurred in 51% (n=132) and 6% (n=15) vs 33% (n=74) and 2% (n=5) of patients treated with SG and TPC, respectively. Growth factors were used in 49% and 23% of patients treated with SG and TPC, respectively.[2]

In ASCENT-03, a study in 1L mTNBC, Grade ≥3 treatment-emergent neutropenia occurred in 43% (n=118) and 41% (n=112) of patients treated with SG and TPC, respectively. Twelve patients (4%) treated with SG had FN during the study; none had received primary prophylaxis with G-CSF.[9]

- In patients treated with SG and TPC, respectively, primary prophylaxis with G-CSF was used in 54 and 28 patients; secondary prophylaxis was used in 81 and 51 patients.[10]
- Six deaths in the SG arm were deemed to be treatment-related (neutropenic colitis [n=1], pneumonia [n=1], and sepsis [n=4]). All of the treatment-related deaths were due to infections; five were due to infections secondary to neutropenia, in patients who had risk factors for febrile neutropenia but did not receive prophylaxis with G-CSF; these events occurred early in treatment (two patients on Day 26 [Cycle 2] and one patient each on days 14, 15, and 21 [Cycle 1]). A case of death from pneumonia showed no evidence of preceding or concurrent neutropenia.[9,10]

In TROPiCS-02, a HR+/HER2- mBC study, Grade ≥3 treatment-related neutropenia and FN occurred in 51% (n=136) and 5% (n=14) vs 38% (n=94) and 4% (n=11) of patients treated with SG and TPC, respectively. G-CSF was used in 54% and 33% of patients treated with SG and TPC, respectively. There was 1 SG-related death due to septic shock, preceded by Grade 4 neutropenic colitis with large intestine perforation.[3,11]

In IMMU-132-01, a metastatic epithelial cancer study,[4,12,13] the incidence of Grade ≥3 neutropenia and FN in the mTNBC cohort (n=108) was 42% and 8%, respectively. Growth factor support was permitted; however, usage was not reported.[12] The incidence of Grade ≥3 neutropenia and FN in the HR+/HER2- mBC cohort (n=54) was 50% and 3.7%, respectively. A total of 48.1% of patients received growth factor support (filgrastim or peg-filgrastim).[13]

PRIMED Study in mTNBC and HR+/HER2- mBC[14]

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% (n=14), 12% (n=6), and 4% (n=2), respectively.

The extended safety analysis (median follow-up 9 mo) reported incidences of any-grade, Grade 3, and 4 neutropenia as 42% (n=21), 18% (n=9) and 6% (n=3), respectively.

Real-World Data of SG and Neutropenia Management

RWE studies are described below.[15-19]

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.

Incidence of Neutropenia and Use of Growth Factors in mBC Studies

Pooled Safety Analysis in mBC

A pooled safety analysis of six clinical studies (ASCENT,[2] TROPiCS-02,[3] IMMU-132-01,[4] EVER-132-001,[5] EVER-132-002,[6] and ASCENT-J02[7]) examined exposure to SG 10 mg/kg IV as monotherapy in 969 patients with either mTNBC or HR+/HER2- mBC; TEAEs were analyzed by region, NA/EU and Asia.[8] Except for race (Table 1), baseline characteristics, including age, sex and body mass index, were comparable between the NA/EU and Asia regions.

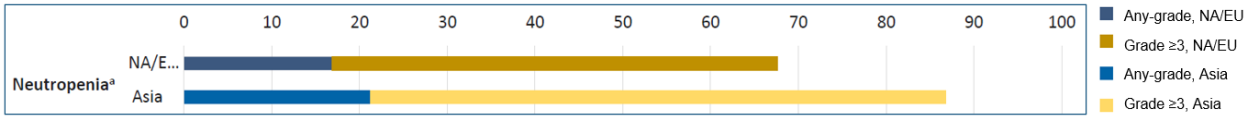
Table 1. Pooled Safety in mBC: Baseline Race by Region[8]

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[8]

Patients in Asia had higher rates of any-grade and Grade ≥3 neutropenia compared to patients in the NA/EU region (Figure 1). Across both regions, neutropenia occurred most commonly early in treatment (≤6 weeks), with the rate falling over time. Neutropenia was one of the most common TEAEs leading to discontinuation across both regions (NA/EU, <1%; Asia 1%).

Figure 1. Pooled Safety in mBC: Incidence of Any-Grade (≥20%) and Grade ≥3 (≥10%) Treatment-Emergent Neutropenia[8]



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

Neutropenia was treated according to label recommendations. Patients treated with G-CSF as primary prophylaxis experienced less any-grade and Grade ≥3 neutropenia across both regions (Table 2).

Table 2. Pooled Safety in mBC: Primary G-CSF Prophylaxis[8]

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)

ASCENT Study in mTNBC

ASCENT, an open-label, randomized, phase 3 study (N=529) investigated the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle vs TPC (eribulin, vinorelbine, gemcitabine, or capecitabine) in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease. An absolute neutrophil count of >1500/mm^3 was required.[2]

Patients received a median (range) of 7 (1–33) treatment cycles of SG, over a median (range) treatment duration of 4.4 mo (0.03–22.9).[2]

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

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

Table 3. 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.

Time to onset and duration of neutropenia (Table 4) were assessed.[22]

Table 4. ASCENT: Time to Onset and Duration of Neutropenia[22]

	Median Time to Onset of 1st Event, Days				Median Duration of Event, 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 WT allele (Table 5).[22]

Table 5. 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 had *UGT1A1* GTs 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, compares the efficacy and safety of SG vs chemotherapy 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.[9]

The median (range) duration of SG treatment at the time of the final PFS analysis was 8.3 mo (<0.1–28.7).[9,10]

Safety

The most common TEAE across both treatment arms was any-grade and Grade ≥3 neutropenia (Table 6). Of the 12 patients (4%) in the SG arm who experienced febrile neutropenia, none had received primary prophylaxis with G-CSF.[9]

Table 6. ASCENT-03: Any-Grade and Grade ≥3 Neutropenia[9a]

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 days after the last dose date of study drug (including crossover treatment if applicable) or the initiation of subsequent anticancer therapy, whichever occurred first.
[b]Includes preferred terms of neutropenia and neutrophil count decreased.

There were 6 deaths in the SG arm that were deemed to be treatment-related (neutropenic colitis [n=1], pneumonia [n=1], and sepsis [n=4]). All the treatment-related deaths were due to infections; five were due to infections secondary to neutropenia, in patients who had risk factors for febrile neutropenia but did not receive prophylaxis with G-CSF; these events occurred early in treatment (two patients on Day 26 [Cycle 2] and one patient each on days 14, 15, and 21 [Cycle 1]). A death from pneumonia showed no evidence of preceding or concurrent neutropenia.[9,10]

Time to onset and duration of neutropenia[10]

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 7). Median duration of neutropenia was generally comparable between treatment arms.

Table 7. ASCENT-03: Time to Onset and Duration of Neutropenia[10]

	SG (n=275)				TPC (n=276)			
	Any-Grade		Grade ≥3		Any-Grade		Grade ≥3	
	n	Days (range)	n	Days (range)	n	Days (range)	n	Days (range)
Median time to onset[a]	187	22 (6–274)	124	22 (7–720)	158	22 (6–406)	113	29 (7–295)
Median 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 day for each episode).

Management of neutropenia[10]

The use of G-CSF as primary prophylaxis was associated with less frequent and less severe neutropenia in the SG arm (Table 8). Neutropenia led to dose reduction in 54 (20%) patients in both arms and treatment discontinuation in 1 (<1%) and 3 (1%) patients in the SG and TPC arms, respectively.

Table 8. ASCENT-03: Management of Neutropenia[10]

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]Excludes patients that received primary G-CSF prophylaxis.

TROPiCS-02 Study in HR+/HER2- mBC

TROPiCS-02, a phase 3, open-label, randomized, multicenter study investigated the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle vs TPC (eribulin, vinorelbine, capecitabine, or gemcitabine) in 543 patients with HR+/HER2- mBC who received ≥2 and ≤4 prior chemotherapy regimens for metastatic disease, including ≥1 endocrine therapy, taxane, and cyclin-dependent kinase 4/6 inhibitor therapy in any setting. 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 mo (0.03–24.2).[3]

Safety

Growth factors could be used for FN, Grade 3 or 4 neutropenia following previous infusions, or for neutropenia in patients at high risk of poor clinical outcomes (Table 9). Routine prophylactic use was not recommended.[11]

Table 9. TROPiCS-02: Growth Factor Use in the OSP[11]

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. 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 (0.03 [95% CI: -0.53 to 0.56]). The absolute incidence of FN (5 vs 4%) in the SG and TPC arms 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 10) were assessed.[24]

Table 10. TROPiCS-02: Time to Onset and Duration of Treatment-Related Neutropenia[24]

	Median Time to Onset of 1st Event, Days				Median Duration of Event, Days			
	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 (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.[3,11]

IMMU-132-01 Study in Metastatic Epithelial Cancer

IMMU-132-01, a phase 1/2, single-arm, open-label basket study investigated the safety and efficacy of SG 8 to 18 mg/kg IV on Days 1 and 8 of a 21-day cycle in patients with metastatic epithelial cancers (including mTNBC and HR+/HER2- mBC) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease. Patients with mBC received SG 10 mg/kg. Prophylactic growth factor support was not permitted before Day 1, Cycle 1.[4]

The mTNBC cohort received a mean (range) of 9.6 (1–51) SG cycles, with a median (range) duration of exposure of 5.1 mo (0.03–36.1).[12] The median (range) DOT for SG was 4.6 mo (0–29.4) for the HR+/HER2- mBC cohort.[13]

Safety

In the mTNBC cohort, neutropenia was the second most common all-grade AE, and the most common Grade ≥3 AE and cause of treatment interruption (Table 11). FN was the most common SAE.[12]

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.[13]

Table 11. IMMU-132-01: Incidence of Neutropenia[12,13]

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 counts.

PRIMED Study in mTNBC and HR+/HER2- mBC[14]

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) as management of neutropenia and primary prophylactic loperamide as management of diarrhea. Primary

endpoints were incidence of ≥Grade 3 neutropenia or ≥Grade 2 diarrhea per CTCAE version 5.0, during the first two treatment cycles.

The median (range) patient age was 52 y (31–74), 60% (n=30) had ECOG PS 0, and 70% (n=35) had visceral disease. Prior to enrolment, patients had received a median (range) of one (0–2) prior lines 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 2 cycles of SG (Table 12); the median (range) follow-up was 4.3 mo (0.2–8.6). 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 patient experienced FN.

Table 12. PRIMED: Neutropenia After 2 Treatment Cycles[14]

	Any-Grade	Grade 2	Grade 3	Grade 4	Grade ≥3
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 mo (0.2–13.5). Incidence of any-grade and Grade ≥3 neutropenia was 42% and 24%, respectively (Table 13); no patient experienced FN.

Table 13. PRIMED: Neutropenia During Extended Follow-up[14]

	Any-Grade	Grade 1	Grade 2	Grade ≥3
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 (70.0%) who received ≥1 dose of G-CSF after cycle 2, with a median (range) duration of 6.1 mo (1.8–12.6).

Real World Studies of SG in mBC

Neutropenia Prevalence, G-CSF Use and Impact on DOT in the US[15]

An assessment of the IntegraConnect PrecisionQ database evaluated 447 patients who had received SG. Patients were on average (median) 58.5 y (60); 69% and 15% identified as White/Caucasian and as Black/African American, respectively. Cancer type was not reported. Of the patients who received SG, 438 (98%) developed neutropenia during therapy; of these, 61% received G-CSF. Median DOT was 119.5 d for patients with ≥12 mo follow-up (n=330). Median (range) DOT was 147 d (7–942) for patients who received G-CSF (n=204) vs 97 d (1–1013) for patients who did not receive G-CSF (n=126); *P*<0.001.

Incidence and Management of Neutropenia in the US[16]

A retrospective, observational cohort study used an electronic, nationwide, longitudinal, Flatiron Health database to evaluate 381 patients with mTNBC who had received SG in the 2L+ setting. The median (IQR) age of patients was 61 y (52–69); 61% and 18% identified as White and as Black/African American, respectively. Patients received a median (IQR) of 2 (1–3) prior lines of treatment in the metastatic setting. In the 2L setting, 31% (n=118) of patients received SG and 69% (n=263) of patients in the 3L+ setting.

Patients received a median (IQR) of 12 (5–21) SG doses. Of the patients with dosing data (n=308), 44% (n=137) had a dose reduction. Treatment duration is summarized in Table 14.

Table 14. SG Treatment Duration[16]

	All Patients (n=381)	SG in 2L (n=118)	SG in 3L+ (n=263)
Duration, median (IQR), mo	4 (1.9–7.6)	4.2 (1.6–8.1)	4 (2.1–7.4)

Safety

Incidence of Grade 2 and ≥3 neutropenia was 25% (n=94) and 27% (n=101), respectively. During SG treatment, 225 patients (59%) received G-CSF; 117 patients received G-CSF as prophylaxis (primary prophylaxis, defined as use on or after index date and before first neutropenia onset/end of treatment, [n=77]; secondary prophylaxis, defined as use after neutropenia resolution and before end of treatment, [n=36]; both [n=4]). Grade ≥3 neutropenia occurred in 12 patients (10%) after any G-CSF prophylaxis and in 3 patients (4%) receiving primary prophylaxis.

Median (IQR) time from start of SG treatment to first onset of Grade ≥3 neutropenia was 48 d (36–322) and 42 d (36–56) in patients who received primary and secondary G-CSF prophylaxis, respectively. Therapeutic use of G-CSF, defined as on or after neutropenia onset and before resolution or end of SG treatment, was observed in 24 patients (6%) with a median (IQR) time to Grade ≥3 neutropenia onset of 9 d (8–21).[25] Among 156 patients who did not receive G-CSF during SG treatment, 13% (n=21) experienced Grade ≥3 neutropenia with a median (IQR) time to Grade ≥3 neutropenia onset of 8 d (8–22).

SG Dose and Risk of Neutropenia in the US[17]

A retrospective, single-center cohort study, evaluated the relationship of neutropenia and different starting doses of SG (10 mg/kg [70%], 7.5 mg/kg [22%] or 5 mg/kg [8%]) in 366 patients with HER2- mBC. Patient demographics and disease characteristics, treatment patterns, safety outcomes, and G-CSF use were evaluated. To control for confounding variables, inverse probability weighting, based on propensity scores was applied.

Results showed that dose reductions were more common when patients initiated SG at 10 mg/kg (42%) vs 7.5 mg/kg (16%); 66% of the reductions were due to neutropenia. Three patients discontinued treatment due to toxicity. After adjusting for age, prior LoT and prophylactic G-CSF use, patients initiating SG at 10 mg/kg had a 2.8-fold higher OR of Grade 3-4 neutropenia vs those initiating SG at 5 mg/kg (OR 2.77, 95% CI: 1.29–6.27, P=0.011); DOT was shorter with the 5 mg/kg dose. Age was not associated with neutropenia risk after adjusting for starting dose, prophylactic G-CSF use, and prior LoT.

There was significantly less Grade 3-4 neutropenia with prophylactic G-CSF use (OR 0.12, 95% CI: 0.07–0.18, P<0.001) when controlling for age, prior LoT, and starting dose. Prophylactic G-CSF was most frequently used in patients who started treatment at reduced doses, but utilization rates did not differ by age.

Impact on OS With Prophylactic G-CSF in the US[18]

The IntegraConnect PrecisionQ database was used to evaluate the impact of prophylactic G-CSF use (defined as G-CSF use within 8 d following SG initiation) on TTD and rwOS among patients with mTNBC who had received SG (N=685). Patients were excluded if there was documentation of neutropenia (neutrophil count <1500/µL), discontinuation of SG, death, or censoring within 8 d of SG initiation.

Most patients were White (67%), 41% had ECOG PS 1, and 88% did not receive prophylactic G-CSF. Median (IQR) age at SG initiation was 60 y (53–69). Age, race, and ECOG status did not significantly differ by prophylactic G-CSF use.

At 4 mo, the cumulative incidence of neutropenia was significantly higher among those who did not receive prophylactic G-CSF (42% vs 30%, Gray's test *P*=0.002). Median TTD and rwOS did not significantly differ by prophylactic G-CSF use. From 0–4 mo, patients who did not receive prophylactic G-CSF vs those who received prophylactic G-CSF within 8 days of SG initiation were >2 times more likely to die, HR 2.37 (95% CI: 1.22–4.59, *P*=0.011); after 4 mo, the impact of not receiving prophylactic G-CSF on rwOS was less (HR 1.02, 95% CI: 0.79–1.50, *P*=0.4). There was no significant difference observed in TTD in either time-interval.

Impact on PFS and OS With Prophylactic G-CSF in a Multinational Cohort[19]

The impact of G-CSF as primary prophylaxis on real-world clinical outcomes and treatment-related adverse events was evaluated in a multinational cohort of patients with mTNBC who had received SG (N=303).

Baseline characteristics were balanced for prior systemic treatment for early-stage disease, the number of prior LoT in the metastatic setting, comorbidities, metastatic sites, and prior episodes of febrile neutropenia. However, ECOG PS 0 was more frequent in the prophylaxis group (50% vs 37.1%, *P*=0.034).

The use of G-CSF as primary prophylaxis was not associated with improved PFS or OS. Median PFS in the primary prophylaxis group was 4.2 mo vs 5.1 mo in the no-primary prophylaxis group (*P*=0.2); PFS rates at 6 mo were 38.5% vs 42.1%, respectively. Median OS in the primary prophylaxis group was 10.9 vs 11.6 mo in the no-primary prophylaxis group (*P*=0.95); OS rates at 12 mo were 44.9% vs 47.1%, respectively.

There were no statistically significant differences in the rates of all-grade adverse events between groups. There was less Grade ≥3 neutropenia in patients receiving G-CSF primary prophylaxis vs patients in the no-primary prophylaxis group (33% vs 50.7%, *P*=0.005); this was not accompanied by a reduction in FN rates (4% vs 4.4%, *P*=1).

Of those patients who did not receive G-CSF primary prophylaxis, 74.4% eventually required secondary G-CSF support. Only 17.2% of patients received SG without any G-CSF support.

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 >2.0)
Renal dysfunction (creatinine clearance <50)
Age >65 years receiving full chemotherapy dose intensity

[a]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)[26] and European Society for Medical Oncology (ESMO) Guidelines[27].

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Abbreviations

1L=first-line
2L=second-line
2L+=second-line and later
3L=third-line
AE=adverse event
DOT=Duration of Therapy
EAIR=exposure-adjusted incidence rate
ECOG PS=Eastern Cooperative Oncology Group performance status
FN=febrile neutropenia
G-CSF=granulocyte colony-stimulating factor
GT=genotype
HR+/HER2-=hormone receptor-positive/human epidermal growth factor receptor 2-negative
LoT=lines of treatment
mBC=metastatic breast

cancer
mTNBC=metastatic triple-negative breast cancer
NCCN=National Comprehensive Cancer Network
OR=odds ratio
OSP=overall safety population
PD-(L)1=programmed death-(ligand) 1
rwOS=real-world overall 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
TTD= time to treatment discontinuation
UGT1A1=uridine diphosphate-glucuronosyl transferase 1A1
WT=wild-type

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