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Trodelvy® (sacituzumab govitecan-hziy) Relationship of Diarrhea and Neutropenia Events With Patient Outcomes

This document is in response to your request for information about Trodelvy® (sacituzumab govitecan-hziy [SG]) and the relationship of diarrhea and neutropenia events with patient outcomes in metastatic breast cancer (mBC).

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 Trodelvy®. 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. Withhold SG for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Primary prophylaxis with G-CSF is recommended for all patients at increased risk of febrile neutropenia. Initiate anti-infective treatment in patients with febrile neutropenia without delay.

SG can cause severe diarrhea. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold SG until resolved to ≤Grade 1 and reduce subsequent doses.

ASCENT Post Hoc Analysis: Diarrhea and Neutropenia Events and Patient Outcomes

The ASCENT study investigated the efficacy and safety of SG compared with TPC in patients with refractory or relapsed mTNBC who relapsed after ≥2 prior chemotherapies.[2] A post hoc analysis evaluated clinical outcomes according to the presence of Grade ≥3 neutropenia or Grade ≥2 diarrhea.[3]

- Of the 258 SG -treated patients, 139 patients (54%) had Grade ≥3 neutropenia, and 81 (32%) had Grade ≥2 diarrhea.[3]
- PFS and OS were similar between patients with and without Grade ≥3 neutropenia.[3]

- Both PFS and OS were longer among patients with Grade ≥2 diarrhea than among those without Grade ≥2 diarrhea. In a time-varying Cox regression model that adjusted for age, race, and BMI, no difference in either PFS or OS was observed between those with and without Grade ≥2 diarrhea.[3]

PRIMED[4,5]

PRIMED is a phase 2 study evaluating the impact of 1) primary prophylactic G-CSF as management of neutropenia and 2) primary prophylactic loperamide as management of diarrhea in 50 patients with unresectable locally advanced mTNBC or HR+/HER2- mBC.

Efficacy[5]

- mPFS in patients with mTNBC was 6.4 months (95%CI; 6.1-10.3) and 5.8 months (95%CI; 4.2-NA) in patients with HR+/HER2- mBC.
- ORR and CBR of 34.4% and 71.9% in patients with mTNBC, and 16.7% and 44.4% in patients with HR+/HER2- mBC, respectively.

Primary safety analysis (median follow-up 4.3 months)[4]

- Incidence of any grade diarrhea and neutropenia after 2 cycles of SG was 34% (n=17) and 28% (n=14), respectively.
- Grade ≥2 diarrhea was 16% (n=8), and Grade 3 diarrhea was 4% (n=2) after 2 cycles of SG.
- Grade ≥3 neutropenia was 16% (n=8) after 2 cycles of SG.

Extended safety analysis (median follow-up 9 months)[5]

- Incidence of any grade diarrhea and neutropenia were 44% and 42%, respectively.
- Nine patients (18%) had Grade ≥2 diarrhea and no Grade 4.
- Nine patients (18%) had Grade 3 neutropenia and 3 patients (6%) had Grade 4 neutropenia.
- Four patients discontinued due to AEs, 2 of which were SG-related.

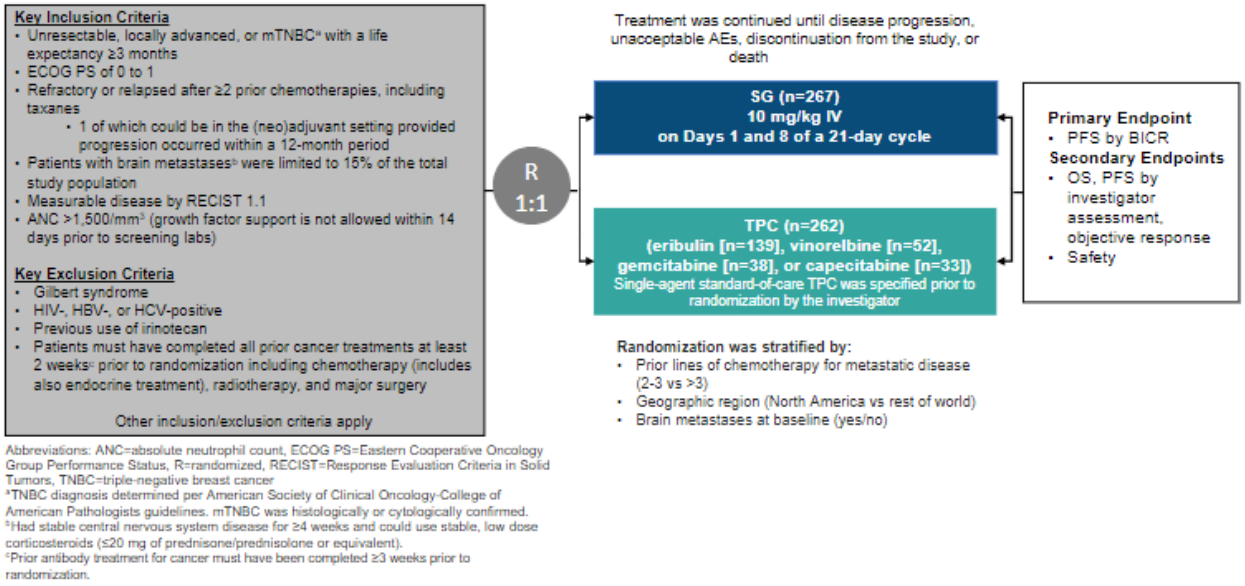
SG Clinical Data: Diarrhea and Neutropenia Events and Patient Outcomes

ASCENT Study in mTNBC

Study design and demographics[2]

ASCENT, a global, open-label, randomized, confirmatory, phase 3 study, was conducted to investigate the efficacy and safety of SG in comparison with TPC in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease (Figure 1).[2]

Figure 1. ASCENT Study Design[2,6]



Abbreviations: ANC=absolute neutrophil count, ECOG PS=Eastern Cooperative Oncology Group Performance Status, R=randomized, RECIST=Response Evaluation Criteria in Solid Tumors, TNBC=triple-negative breast cancer
[a]TNBC diagnosis determined per American Society of Clinical Oncology-College of American Pathologists guidelines. mTNBC was histologically or cytologically confirmed.
[b]Had stable central nervous system disease for ≥4 weeks and could use stable, low dose corticosteroids (≤20 mg of prednisone/prednisolone or equivalent).
[c]Prior antibody treatment for cancer must have been completed ≥3 weeks prior to randomization.

A post hoc subgroup analysis evaluated the clinical outcomes (PFS and OS) according to the presence of Grade ≥3 neutropenia or Grade ≥2 diarrhea (data cutoff date: February 25, 2021).[3]

Patient Disposition and Demographics[3]

Of the 258 SG-treated patients, 139 patients had Grade ≥3 neutropenia, and 81 had Grade ≥2 diarrhea. No Grade 5 events of neutropenia or diarrhea occurred. One patient discontinued the study due to diarrhea (Grade 2), which was considered unrelated to study drug. Baseline characteristics, duration of treatment, and relative dose intensity are shown in Table 1.

Table 1. ASCENT Post Hoc Analysis: Baseline Demographics, Duration of Treatment, and Relative Dose Intensity[3]

Variable	All SG-Treated Patients[a] (N=258)	Neutropenia[b]		Diarrhea	
		Grade ≥3 Neutropenia (n=139)	No Grade ≥3 Neutropenia (n=119)	Grade ≥2 Diarrhea (n=81)	No Grade ≥2 Diarrhea (n=177)
Age, <65/≥65 y, n (%)	209 (81)/ 49 (19)	115 (83)/ 24 (17)	94 (79)/ 25 (21)	65 (80)/ 16 (20)	144 (81)/ 33 (19)
Race, White/Black/Asian/Other, %	82/10/4/4	81/9/6/5	83/11/3/3	84/8/3/6	81/11/5/3
Visceral metastases at baseline, n (%)	213 (83)	115 (83)	98 (82)	68 (84)	145 (82)
Time from metastases to first dose, median (min, max), mo	17.9 (-0.1, 191.4)	18.2 (0.6, 191.4)	16.3 (-0.1, 88.2)	19.5 (3.3, 98.8)	16.4 (-0.1, 191.4)
Prior systemic anticancer regimens, median (min, max), n	4 (2, 17)	4 (2, 17)	4 (2, 9)	4 (2, 17)	4 (2, 11)

BMI at baseline, median (min, max), kg/m^2	25.3 (15, 49.3)	26 (16, 49.3)	24.7 (15, 44.5)	27.7 (15.7, 49.3)	24.4 (15, 43.4)
Duration of treatment, median (min, max), wk	19.1 (0.1, 128.6)	21.9 (0.1, 123.1)	18 (0.1, 128.6)	27.1 (0.9, 128.6)	17.4 (0.1, 106.4)
Relative dose intensity, median (min, max), %	99.7 (53.7, 107.1)	99.1 (53.7, 107.1)	99.8 (59.8, 106.9)	97.7 (53.7, 105.5)	99.8 (56.8, 107.1)

Abbreviations: max=maximum, min=minimum, mo=month, wk=week.
[a]N=258 in this analysis. [b]Preferred term: neutropenia, neutrophil count decreased, and febrile neutropenia.

Results[3]

Neither OS nor PFS was adversely impacted by either Grade ≥3 neutropenia or Grade ≥2 diarrhea (Table 2).

Table 2. ASCENT Post Hoc Analysis: Unstratified Analysis[a] of PFS and OS in Patients With and Without Grade ≥3 Neutropenia or Grade ≥2 Diarrhea[3]

	Median (95% CI), Months		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
	Grade ≥2 Diarrhea (n=81)	No Grade ≥2 Diarrhea (n=173)	HR (95% CI)	*P*-Value
PFS	6.9 (4.2–8.3)	4.9 (3.7–5.7)	0.72 (0.52–0.98)	0.04
OS	14.3 (11.8–16.7)	10.9 (9.5–13.8)	0.69 (0.5–0.94)	0.02

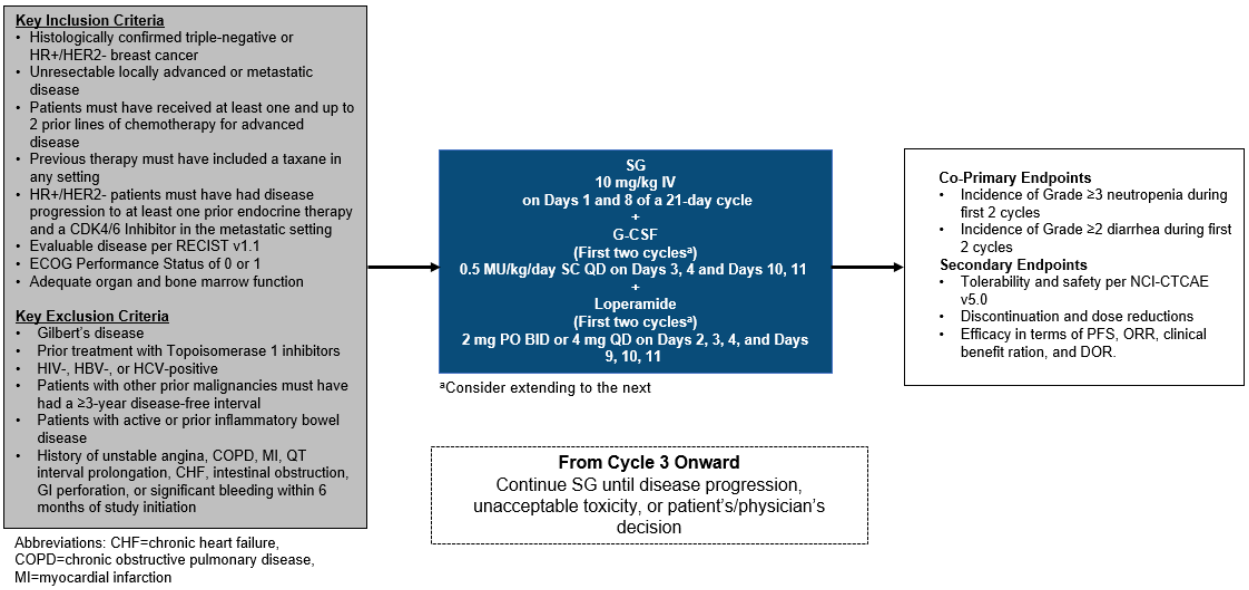
[a]This analysis was unstratified and excluded 4 patients who died within 28 days of randomization.

PRIMED Study in mTNBC and HR+/HER2- mBC

Study design and demographics

PRIMED is an open-label, single-arm, phase 2 study (NCT05520723) evaluating the impactof 1) primary prophylactic G-CSF as management of neutropenia and 2) primary prophylactic loperamide as management of diarrhea in 50 patients with unresectable locally advanced mTNBC (n=32) or HR+/HER2- mBC (n=18) (Figure 2).[4]

Figure 2. PRIMED Study Design[4,5]



The baseline characteristics and prior therapy of patients included in the study are shown in Table 3.

Table 3. PRIMED Baseline Characteristics and Prior Treatments[4,5]

Variable	mTNBC (n=32)	HR+/HER2- mBC (n=18)	Overall (n=50)
Age, median (range), years	51 (31-74)	53.5 (37-72)	52 (31-74)
ECOG PS, n (%)			
0	18 (56.3)	12 (66.7)	30 (60)
1	14 (43.8)	6 (33.3)	20 (40)
Visceral disease, n (%)			
Yes	20 (62.5)	15 (83.3)	35 (70)
No	12 (37.5)	3 (16.7)	15 (30)
Prior chemotherapy in (neo)adjuvant setting, n (%)			
Yes	19 (59.4)	5 (27.8)	24 (48)
No	13 (40.6)	13 (72.2)	26 (52)
Prior chemotherapy regimens for advanced disease, n (%)			
0[a]	8.2 (25)	2 (11.1)	10 (20)
1	18 (56.3)	11 (61.1)	29 (58)
2	6 (18.8)	5 (27.8)	11 (22)

[a]Earlier systemic treatment in the curative setting was considered as one line of therapy if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period after completion of chemotherapy or immunotherapy.

Efficacy[5]

At the data cut-off (May 5, 2024), the median follow-up was 9 months (range; 0.2-13.5) and 9 patients remained on treatment. Median PFS for patients with mTNBC was 6.4 months (95% CI: 6.1-10.3), and for patients with HR+/HER2- mBC, it was 5.8 months (95% CI: 4.2-NA). 6-month PFS for patients with mTNBC and HR+/HER2- mBC was 66% (95% CI: 51.1-85.9) and

44% (95% CI: 25.4-76.6), respectively. The ORR and CBR were 34.4% and 71.9% for patients with mTNBC, and 16.7% and 44.4% for patients with HR+/HER2 mBC, respectively. OS data was immature at the time of analysis.[7]

Safety

Primary Safety Analysis[4]

The primary safety analysis had a median follow-up time was 4.3 months (0.2-8.6). At data cut-off, October 18, 2023, 31 patients (62%) remained on treatment. Disease progression was the primary reason for treatment discontinuation in 16 patients (32%). Results were reported for 50 patients after the first 2 cycles of SG with the incidence of any Grade diarrhea (34%) and any Grade neutropenia (28%) (Table 4). Grade ≥3 neutropenia was reported in 8 patients (16%), meeting the primary endpoint (*P*<0.001). No patients experienced febrile neutropenia. Grade ≥2 diarrhea was reported in 8 patients (16%) (*P*=0.084).

Extended Safety Analysis[5]

The extended safety analysis had a median follow-up of 9 months (range; 0.2-13.5). At data cut-off, May 5, 2024, the incidence of any Grade neutropenia and diarrhea were 42.0% and 44.0%, respectively (Table 4). A total of 12 patients (24.0%) had Grade ≥3 neutropenia (no febrile neutropenia) and 9 patients (18.0%) had Grade ≥2 diarrhea (no Grade 4). The overall rate of AEs associated with dose reductions and treatment interruptions was 22% and 50%, respectively. Four patients discontinued due to AEs, two of which were SG-related (Grade 2 enteritis and Grade 3 diarrhea) (Table 5). Other TEAEs can be found in Table 6.

Table 4. PRIMED: Neutropenia and Diarrhea During First 2 Cycles and Until Data Cut-Off[4,5]

	Neutropenia					Diarrhea			
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade
After 2 cycles	2 (4)	4 (8)	6 (12)	2 (4)	14 (28)	9 (18)	6 (12)	2 (4)	17 (34)
Data cut-off	4 (8)	5 (10)	9 (18)	3 (6)	21 (42)	13 (26)	7 (14)	2 (4)	22 (44)

Table 5. PRIMED: Dose Reductions, Treatment Interruptions, and Discontinuations due to AEs[5]

n (%)	Dose Reductions	Treatment Interruptions	Permanent Discontinuations
After 2 cycles	7(14)	15(30)	0(0)
Data cut-off	11(22)	25(50)	4(8)

Table 6. PRIMED: Any Grade and Grade ≥3 TEAEs Occurring in Patients Until Data Cut-Off[5]

TEAEs, n (%)	Any Grade	Grade ≥ 3
All TEAEs	**50 (100)**	**26 (52)**
Gastrointestinal Disorders	47 (94)	6 (12)
Constipation	28 (56)	0 (0)
Diarrhea	22 (44)	2 (4)

TEAEs, n (%)	Any Grade	Grade ≥ 3
Nausea	27 (54)	0 (0)
Intestinal Obstruction	1 (2)	1 (2)
Abdominal Upper Pain	9 (18)	2 (4)
Neutropenic Colitis	1 (2)	1 (2)
Blood and Lymphatic System Disorders	**32 (64)**	**13 (26)**
Neutropenia	21 (42)	12 (24)
Anemia	24 (48)	2 (4)
General Disorders and Administration Site Conditions	**38 (76)**	**8 (16)**
Pain	1 (2)	1 (2)
Asthenia	35 (70)	7 (14)
Infections and Infestations	**23 (46)**	**1 (2)**
Acute Pyelonephritis	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders	**30 (60)**	**5 (10)**
Alopecia	20 (40)	4 (8)
Urticaria	2 (4)	1 (2)
Investigations	**14 (28)**	**2 (4)**
Increased Gamma-Glutamyltransferase	6 (12)	2 (4)
Hepatobiliary Disorders	**5 (10)**	**1 (2)**
Hepatic Failure	1 (2)	1 (2)

References

1. TRODELVY® Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med*. Apr 22 2021;384(16):1529-1541.
3. de Azambuja E, Jacobs F, Lambertini M, et al. Relationship of diarrhea and neutropenia events with outcomes in patients (pts) with metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG): post hoc analysis from the phase 3 ASCENT study [Poster 198P]. Presented at: European Society for Medical Oncology (ESMO); May 11-13, 2023; Berlin, Germany.
4. Perez-Garcia JM, Gion M, Ruiz-Borrego M, et al. Prevention of sacituzumab govitecan-related neutropenia and diarrhea in patients with triple-negative or HR+/HER2- advanced breast cancer (PRIMED): a phase 2 trial [Poster 1101]. Presented at: American Society of Clinical Oncology (ASCO); May 31-June 4 2024; Chicago, IL.
5. Perez-Garcia JM, Gion M, Ruiz-Borrego M, et al. Efficacy analysis and updated safety from the phase 2 PRIMED study of prophylactic granulocyte-colony stimulating factor (G-CSF) and loperamide for patients with HER2-negative advanced breast cancer treated with sacituzumab govitecan [Poster P1-02-06]. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 10-13 2024; San Antonio, TX.
6. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer [Protocol]. *N Engl J Med*. Apr 22 2021;384(16):1529-1541.
7. Perez-Garcia JM, Gion M, Ruiz-Borrego M, et al. Efficacy analysis and updated safety from the phase 2 PRIMED study of prophylactic granulocyte-colony stimulating factor (G-CSF) and loperamide for patients (pts) with HER2-negative advanced breast cancer (ABC) treated with sacituzumab govitecan (SG) [Abstract]. San Antonio Breast Cancer Symposium (SABCS); December 10-13 2024; San Antonio, TX.

Abbreviations

AE=adverse event
ANC=absolute neutrophil count
BID=twice daily
DOR=duration of response
ECOG PS=Eastern Cooperative Oncology Group performance status
G-CSF=granulocyte colony stimulating factor
HR=hazard ratio
IV=intravenous
HR+/HER2- mBC=hormone receptor-positive/human
mTNBC=metastatic triple-negative breast cancer
NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events
OS=overall survival
PFS=progression-free survival
PO=orally
QD=daily
RECIST=Response Evaluation Criteria in Solid Tumors
SC=subcutaneous
SG=sacituzumab govitecan
TEAE=treatment emergent adverse event
TPC=treatment of physician's choice

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:

☎1-888-983-4668 or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 https://www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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