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Trodelvy® (sacituzumab govitecan-hziy) Dose Modifications in mBC Studies

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) monotherapy and the rate and impact of dose modifications in metastatic breast cancer (mBC) clinical studies.

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]

Warning—Neutropenia and Diarrhea: SG can cause severe, life-threatening, or fatal neutropenia. Withhold SG for absolute neutrophil count <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.

Dosage and Administration: The recommended dosage of SG is 10 mg/kg administered as an IV infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer SG at doses >10 mg/kg.

Monitor patients during the infusion and for at least 30 minutes after completion of infusion. Treatment interruption and/or dose reduction may be needed to manage adverse reactions.

Premedication: Prior to each dose of SG, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended. Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions. Premedicate with a two or three drug

combination regimen (eg, dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist, as well as other drugs as indicated).

Prophylaxis for Neutropenia: Primary prophylaxis with G-CSF is recommended starting in the first cycle for all patients at increased risk of febrile neutropenia.

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of SG as described in Tables 1 and 2 of the US FDA-approved Prescribing Information. Do not re-escalate the SG dose after a dose reduction for adverse reactions has been made.

Dose Modifications During SG mBC Clinical Studies

A total of 1063 patients from four studies of multiple epithelial tumors (ASCENT,[2] TROPiCS-02,[3] TROPHY-U-01,[4-6] and IMMU-132-01[7]) were included in this pooled safety analysis.[8] These studies included patients with mTNBC, HR+/HER2- mBC, and mUC. The median treatment duration with SG was 4.1 (range: 0–63) mo.[1]

- Overall, dose reductions and interruptions due to any-grade TEAEs occurred in 31% and 58% of patients, respectively. Data related to dose reduction were not collected within IMMU-132-01, thus, they were excluded from the overall data [8]

Another pooled safety analysis of SG 10 mg/kg IV as monotherapy examined safety outcomes in 969 patients from six studies of multiple epithelial tumors, including mBC, in North America/EU (ASCENT,[2] TROPiCS-02,[3] and IMMU-132-01[7]) and Asia (EVER-132-001,[9] EVER-132-002,[10] and ASCENT-J02[11]).[12]

- Dose reductions due to any-grade TEAEs occurred in 28% and 24% of patients in North America/EU and Asia, respectively; 61% and 63% of patients had TEAEs that led to dose interruptions. Data related to dose reduction were not collected in IMMU-132-01; thus, they were excluded from the overall data.[12]

In ASCENT, 61% and 33% of patients with mTNBC in the SG and TPC groups, respectively, had a dose interruption. Dose reductions occurred in 26% and 22% of patients in the SG and TPC groups, respectively.[13]

- Patients in the SG group had improved ORR, CBR, and PFS vs patients in the TPC group, regardless of these dose modifications.[13]

In TROPiCS-02, in patients with HR+/HER2- mBC, AEs that led to dose delays and dose reductions occurred in 66% and 33% of patients in the SG group vs 44% and 33% of patients in the TPC group, respectively.[3,14]

- In the SG group, rates of PFS, OS, CR, and CBR declined with decreases in RDI.[15]

In IMMU-132-01, AEs led to SG treatment interruption and dose reductions in 51.7% and 32.3% of patients with metastatic epithelial cancer, respectively.[7]

In an exposure-response analysis of patients with mTNBC in IMMU-132-01 and ASCENT (N=277), the risk of dose reductions, dose delays, any-grade AEs of vomiting, diarrhea, nausea, or neutropenia, and Grade ≥3 neutropenia increased as the $CAVG_{SG}$ increased. The likelihood of continuing SG without requiring a dose reduction or delay was lower with an SG 10 mg/kg starting dose than with SG 8 mg/kg.[16]

Dose Modifications During SG mBC Real-World Studies

A database study (N=433) found that patients who received the recommended SG starting dose of 10 mg/kg had a median DoT of 136 d compared with 77 d for patients with a starting

dose of 7.5 mg/kg or less (*P*=0.012). Additionally, dose reductions resulted in a DoT of 172 d compared with 89 d for those without dose reductions (*P*<0.001).[17]

A retrospective cohort study analyzed data from medical records of 83 patients with mTNBC in four oncology centers in Poland. Median OS was 8.43 mo for the 74 patients who received >80% of the initial SG dose vs 2.8 mo for the 9 patients who received ≤80% of the initial SG dose (HR: 4.826, 95% CI: 2.06–11.3; *P*<0.001). There was no significant impact on PFS between those who received >80% vs ≤80% of the initial SG dose. Initial dose reduction did not significantly affect the toxicity profile (further dose reductions, Grade ≥2 or ≥3 AEs) or the need for G-CSF administration.[18]

Dose Modifications of SG in mBC Clinical Studies

Adverse reactions were managed with established supportive care measures and included dose modifications.[3,7,19]

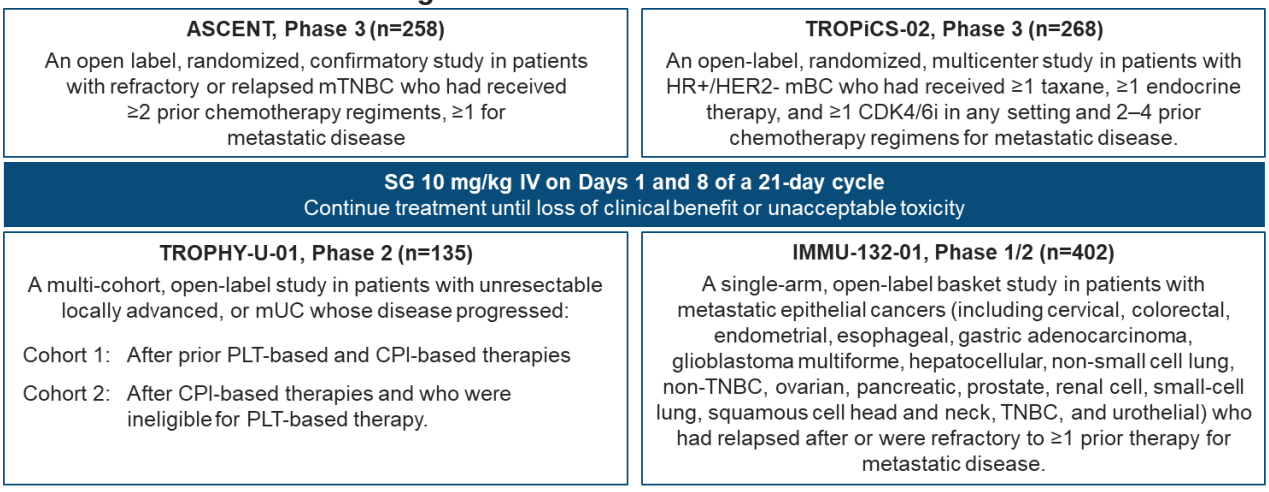
Information summarized below from pooled safety analyses include data for SG monotherapy (10 mg/kg IV on Days 1 and 8 of a 21-d treatment cycle) from phase 2 and 3 clinical studies that constitute the largest pooled safety population of SG.

Pooled Safety Analysis

A pooled safety analysis (Figure 1) examined exposure to SG 10 mg/kg IV as monotherapy in 1063 patients from four studies of multiple epithelial tumors (ASCENT,[2] TROPiCS-02,[3] TROPHY-U-01,[4-6] and IMMU-132-01,[7]). These studies included patients with mTNBC, HR+/HER2- mBC, and mUC.[8]

The median treatment duration with SG in this population was 4.1 (range: 0–63) mo.[1]

Figure 1. Pooled Clinical Studies[8]



Abbreviations: CDK4/6i=cyclin-dependent 4/6 inhibitor; PLT=platinum; TNBC=triple-negative breast cancer.

Dose reductions and interruptions[8]

SG dose reductions and interruptions due to any-grade TEAEs occurred in 31% and 58% of patients, respectively (Table 1); data related to dose reduction were not collected within IMMU-132-01, thus, they were excluded from the overall data. Of patients with available

UGT1A1 GTs, those with the **28/*28* GT had a numerically higher rate of dose reductions and interruptions than those with **1/*1* or **1/*28* GTs (Table 1).

Table 1. Pooled Safety in Multiple Epithelial Tumors: Dose Reductions and Interruptions[8]

TEAEs, n (%) or n/N (%)	All Patients (N=1063)	*UGT1A1* GT[a]		
		**1/*1* (n=416)	**1/*28* (n=420)	**28/*28* (n=112)
Led to dose reduction[b]	205/661 (31)	69/268 (26)	89/270 (33)	30/76 (39)
Led to dose interruption	615 (58)	243 (58)	230 (55)	78 (70)

[a]Other GTs, n=13; missing GTs/not done, n=102.
[b]These data were not collected in IMMU-132-01; those patients were not included in the total.

In an exploratory analysis of G-CSF use that evaluated its use from Day 1 of SG through 30 d after the last SG dose, 9% of those who received a first dose of G-CSF for neutropenia also necessitated a dose reduction.

Pooled Safety Analysis: North America/EU vs Asia

Another pooled safety analysis examined exposure to SG 10 mg/kg IV as monotherapy in 969 patients from six studies of multiple epithelial tumors[12]: ASCENT (n=258), TROPiCS-02 (n=268), and IMMU-132-01 (n=162) in North America/EU; EVER-132-001 (n=80; mTNBC that was relapsed or refractory to ≥2 prior chemotherapy regimens),[9] EVER-132-002 (n=165; locally recurrent inoperable or metastatic HR+/HER2- BC that progressed after 2–4 prior systemic therapies),[10] and ASCENT-J02 (mTNBC cohort, n=36; mTNBC that was relapsed or refractory to ≥2 prior chemotherapy regimens, ≥1 for metastatic disease)[11] in Asia. Safety data were analyzed by region as follows, North America/EU (n=688) and Asia (n=281).[12]

Dose reductions and interruptions[12]

Rates of TEAEs that led to dose reductions and interruptions are presented in Table 2.

Table 2. Pooled Safety in Multiple Epithelial Tumors: Dose Reductions and Interruptions by Study Region[12]

TEAEs, n (%) or n/N (%)	North America/EU (n=688)	Asia (n=281)
Led to dose reduction[a]	147/526 (28)	68 (24)
Led to dose interruption	417 (61)	177 (63)

[a]These data were not collected in IMMU-132-01; those patients were not included in the total.

The analysis also evaluated whether certain AEs led to dose reduction. Nausea led to dose reduction in 2% of patients (7/318) in the North America/EU region and 1% (2/159) in the Asian region. Vomiting led to dose reduction in 3% (5/151) and 2% (2/116) of patients in the North America/EU and Asian regions, respectively.

ASCENT Study in mTNBC

In ASCENT, patients in the SG group received a median (range) of 7 (1–33) treatment cycles, with a median (range) treatment duration of 4.4 (0.03–22.9) mo.[19]

Efficacy[13]

The primary analysis assessed efficacy in patients who were BMNeg and who received ≥1 dose of SG or TPC. A post hoc analysis evaluated efficacy in patients who were BMNeg

and who required dose interruption or dose reduction, compared with the overall BMNeg population. SG improved ORR, CBR, and PFS vs TPC, regardless of dose modifications. Additionally, patients in the SG group who had dose interruption(s) or reduction(s) experienced similar efficacy outcomes vs patients without dose modifications (Table 3).

Table 3. ASCENT: Efficacy Outcomes by Dose Reduction and Interruption (BMNeg Population)[13]

		ORR,[a] n (%)	CBR,[a] n (%)	Best Overall Response, n (%)		PFS,[a] Median (95% CI), Mo
				CR	Partial Response	
Overall BMNeg population	SG (n=235)	82 (35)	105 (45)	10 (4)	72 (31)	5.6 (4.3–6.3)
	TPC (n=233)	11 (5)	20 (9)	2 (1)	9 (4)	1.7 (1.5–2.6)
Dose reductions	SG (n=62)	29 (47)	37 (60)	5 (8)	24 (39)	8.3 (5.4–10.3)
	TPC (n=52)	7 (13)	11 (21)	1 (2)	6 (12)	2.9 (2.7–4.3)
No dose reductions	SG (n=173)	53 (31)	68 (39)	5 (3)	48 (28)	4.6 (3.5–5.7)
	TPC (n=181)	4 (2)	9 (5)	1 (1)	3 (2)	1.5 (1.4–1.7)
Dose interruptions	SG (n=144)	56 (39)	71 (49)	7 (5)	49 (34)	5.7 (4.3–7)
	TPC (n=78)	5 (6)	12 (15)	0	5 (6)	2.7 (1.7–3)
No dose interruptions	SG (n=91)	26 (29)	34 (37)	3 (3)	23 (25)	4.2 (2.9–6.8)
	TPC (n=155)	6 (4)	8 (5)	2 (1)	4 (3)	1.6 (1.5–2.2)

[a]Assessed via BICR.

Safety

The safety population included all patients who received ≥1 dose of study treatment.[2,13]

Dose reductions occurred in 26% and 22% of patients in the SG and TPC groups, respectively. Dose reductions due to treatment-related neutropenia or febrile neutropenia were observed in 11% and 19% of patients in the SG and TPC groups, respectively. Dose reductions due to treatment-related diarrhea occurred in 5% and <1% of patients in the SG and TPC groups, respectively.[13]

Dose interruptions occurred in 61% and 33% of patients in the SG and TPC groups, respectively. Dose interruptions due to treatment-related neutropenia or febrile neutropenia were observed in 46% and 21% of patients in the SG and TPC groups, respectively. No patients in the TPC group and 5% of patients in the SG group required dose interruption(s) due to treatment-related diarrhea.[13]

TROPiCS-02 Study in HR+/HER2- mBC

In the OSP (n=517), patients received a mean (range) of 8.2 (1–35) treatment cycles of SG over a median (range) duration of 4.1 (0.03–24.2) mo.[3] Efficacy specific to patients who required dose interruption(s) or reduction(s), was not reported.[3,20]

A post hoc subgroup analysis found that ORR, CBR, PFS, and OS results in the SG group decreased numerically as RDI decreased (Table 4).[15]

Table 4. TROPiCS-02: Efficacy Outcomes According to RDI in SG Group[15]

Subgroup		ORR,[a] n (%)	CBR,[a] n (%)	PFS,[a] Median (95% CI), Mo	OS,[a] Median (95% CI), Mo
ITT population (n=272)		57 (21)	92 (34)	5.5 (4.2–7)	14.4 (13–15.7)
RDI[b]	>90% (n=88)	25 (28)	37 (42)	7.3 (4.4–8.9)	16.5 (13.9–19.1)
	>74–90% (n=89)	17 (19)	29 (33)	5.3 (4.1–7)	15.2 (11.9–18.7)
	≤74% (n=88)	13 (15)	24 (27)	4.2 (2.8–5.7)	13.1 (11.6–15.3)

[a]Assessed via BICR.
[b]RDI accounted for dose reductions and delays; calculated as actual cumulative dose/total planned dose.

In the SG group, AEs that led to dose delays and dose reductions occurred in 178 and 89 patients, respectively. In the TPC group, AEs that led to dose delays and dose reductions occurred in 109 and 82 patients, respectively.[20]

The absolute incidence rate for TEAEs that led to dose reduction(s) and dose delay(s), EAIRs, and EAIR difference with SG and TPC are presented in Table 5.[14]

Table 5. TROPiCS-02: Absolute Incidence, EAIRs,[a] and EAIR Differences[14]

		SG (n=268)	TPC (n=249)
TEAEs that led to dose reduction[b]	n (%)	89 (33)	82 (33)
	Patient-years of exposure	85.8	50.1
	EAIR (95% CI)	1.04 (0.83–1.28)	1.64 (1.3–2.03)
	EAIR difference vs TPC (95% CI)	-0.6 (-1.05 to -0.19)	
TEAEs that led to dose delay[c]	n (%)	178 (66)	109 (44)
	Patient-years of exposure	57.1	44.6
	EAIR (95% CI)	3.12 (2.67–3.61)	2.44 (2.01–2.95)
	EAIR difference vs TPC (95% CI)	0.67 (0.002–1.33)	

[a]Reported as patients with >1 event per 1 patient-year of exposure.
[b]Upper bound of 95% CI <0 indicates statistically significant (nominally) lower EAIR in SG than TPC.
[c]Lower bound of 95% CI >0 indicates statistically significant (nominally) higher EAIR in SG than TPC.

A post hoc analysis of outcomes according to age (<65 y vs ≥65 y) was conducted among the SG and TPC groups (Table 6). The incidence of TEAEs that led to treatment interruptions was higher with SG than TPC and did not differ between age groups.[15]

Table 6. TROPiCS-02: TEAEs That Led to Dose Modifications According to Age Group[15]

Outcome, n (%)	SG		TPC	
	<65 Y (n=196)	≥65 Y (n=72)	<65 Y (n=188)	≥65 Y (n=61)
TEAEs that led to dose reduction	63 (32)	27 (38)	65 (35)	17 (28)
TEAEs that led to treatment interruption	129 (66)	49 (68)	82 (44)	27 (44)

IMMU-132-01 Study in Metastatic Epithelial Cancer

In IMMU-132-01, the median (range) treatment duration was 3.7 (0–55.2) mo,[7] and *UGT1A1* testing was performed in all patients.[7]

Efficacy specific to patients who required dose interruption(s) or reduction(s) was not reported.[7]

All patients who received ≥1 dose of SG were included in the OSP (N=495). AEs that led to treatment interruption occurred in 51.7% of patients (n=256) and included neutropenia (21%), decreased neutrophil count (9.5%), and anemia (5.3%). Overall, ≥1 dose reductions were required in 160 patients (32.3%); 130 patients (26.3%) required a single dose

reduction. The median (range) time to first dose reduction was 33 (7–609) d after the first dose of SG.[7]

Dose interruption(s) due to TEAEs were assessed in the safety subpopulation of patients with *UGT1A1* GT (n=403), excluding 92 patients with a status of "not done" and missing records. The dose interruptions were observed in 82 (46.3%), 87 (48.3%), and 33 (71.7%) patients with the **1/*1* (n=177), **1/*28* (n=180), and **28/*28* (n=46) GTs, respectively.[21]

Exposure-Response Analyses of Efficacy and Safety in the IMMU-132-01 and ASCENT Studies[16]

The relationship between exposure to SG and outcomes was assessed in 277 patients with mTNBC from ASCENT and IMMU-132-01 who received SG starting doses 8 or 10 mg/kg. Of the 277 patients, 24 patients were from IMMU-132-01 (8 mg/kg, n=16; 10 mg/kg, n=5; 12 mg/kg, n=3) and 253 patients were from ASCENT (8 mg/kg, n=4; 10 mg/kg, n=249). Measures of exposure, such as CAVG (defined as the CAVG [eg, for SG, free SN-38, and total antibody] between the first SG dose and the time of event, and accounted for dose reductions and delays), were assessed. Models were used to predict response outcomes for SG 8 mg/kg and 10 mg/kg starting doses which included the following covariates: body weight, age, race, region, study (safety only), prior treatment, prior lines of treatment, ECOG PS status, *UGT1A1* GT, and use of UGT1A1 inhibitors/inducers; lactate dehydrogenase and baseline trophoblast cell-surface antigen 2 (efficacy assessments only); and granulocyte colony stimulating factor (neutropenia assessment only).

In this dataset, the median (range) age and body weight were 54 (27–82) y and 66.7 (37.2–132) kg, respectively; 99.3% were female, 80.5% were White, and 67.9% were from North America.

Exposure-safety analysis

As $CAVG_{SG}$ increased, the probability of any-grade AEs of vomiting, diarrhea, nausea, or neutropenia, and Grade ≥3 neutropenia were increased. Within the SG 10 mg/kg starting dose group, the model-predicted proportions of patients with any-grade AE vomiting, diarrhea, nausea, and neutropenia were 35.9%, 67.4%, 64.7%, and 67.1%, respectively; the model-predicted rate of Grade ≥3 neutropenia in this group was 54.3%.

$CAVG_{SG}$ was the most statistically significant exposure metric that correlated with the time to first dose reduction and time to first dose delay (P<0.001); as $CAVG_{SG}$ increased, the risk of dose reductions and delays increased (Table 7).

None of the evaluated covariates had a significant effect on the time to first dose reduction, after adjusting for the effect of $CAVG_{SG}$. Patient body weight had a significant effect on the probability of dose delays (P<0.001); patients with a higher body weight were estimated to have a lower risk of dose delays than those with a lower body weight. The likelihood of continuing SG without requiring a dose reduction or delay was lower with an SG 10 mg/kg dose than with SG 8 mg/kg.

Table 7. Exposure-Response Analysis for IMMU-132-01 and ASCENT: Model-Predicted Probability of Dose Modifications Over 12 Mo According to CAVG by Starting Dose[16]

Endpoint	Probability at Mean 8 mg/kg $CAVG_{SG}$ (95% CI)	Probability at Mean 10 mg/kg $CAVG_{SG}$ (95% CI)
Dose reduction	0.0674 (0.0356–0.0993)	0.212 (0.148–0.276)
Dose delay[a]	0.512 (0.43–0.594)	0.886 (0.831–0.941)

[a]Based on a median body weight of 66.7 kg.

Dose Modifications During SG mBC Real-World Studies

Impact of Starting Dose and Dose Reductions on DoT[17]

A real-world study utilizing the Integra Connect PrecisionQ database was conducted to evaluate how SG starting dose and rate of dose reduction impacted DoT in patients with ≥12 mo of follow-up (N=433). Patient average age was 59.6 y (median: 61 y). Patient diagnosis was not specified in the study.

Results

Three starting doses were evaluated: the recommended starting dose of 10 mg/kg (358/433 [83%]), 7.5 mg/kg (57/433 [13%]), and ≤5 mg/kg (18/433 [4%]).

The overall dose reduction rate was 37% (159/433). The rate of dose reduction for patients who started on 10 mg/kg SG was 35% and was not significantly different compared to those who started SG at 7.5 mg/kg or less (43%; *P*>0.05). The dose reduction rate was also not significantly different for patients who started on 7.5 mg/kg SG (39%) compared to those who started SG at doses of ≤5 mg/kg (56%; *P*>0.05).

The median DoT overall was 116 d (n=336). Patients who started on 10 mg/kg SG (n=254) had a longer DoT compared to those who started on doses of ≤7.5 mg/kg (n=61): 136 d vs 77 d, respectively (*P*=0.012). Additionally, patients who had a dose reduction (n=125) had a longer DoT compared to those (n=190) who did not have a dose reduction: 172 d vs 89 d, respectively (*P*<0.001).

Efficacy and safety were not reported in this study.

Impact of Initial SG Dose Reduction on Efficacy and Safety in Patients With mTNBC[18]

A retrospective cohort study analyzed data from medical records of 83 patients with mTNBC in four oncology centers in Poland. The impact of initial SG dose reduction on clinical outcomes and tolerability was assessed. Median (IQR) age was 55 (30–86) y and median (IQR) follow-up was 7.5 (3.22–11.29) mo.

Results

In the full cohort of 83 patients (initial SG dose; >80% [n=74], ≤80% [n=9]), median (95% CI) PFS and OS were 3.9 (2.77–4.55) mo, and 8 (6.38–9.83) mo, respectively. Grade ≥2 and ≥3 AEs were observed in 69 (83.1%) and 47 (56.6%) of the 83 patients, respectively. G-CSF was administered in 70 cases (84.3%).

Median OS was 8.43 mo for the 74 patients who received >80% of the initial SG dose vs 2.8 mo for the 9 patients who received ≤80% of the initial SG dose (HR: 4.826, 95% CI: 2.06–11.3; *P*<0.001). There was no significant impact on PFS between those who received >80% vs ≤80% of the initial SG dose. Initial dose reduction did not significantly affect the toxicity profile (further dose reductions, Grade ≥2 or ≥3 AEs) or the need for G-CSF administration.

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Abbreviations

5-HT3=5-hydroxytryptamine type 3
AE=adverse event
BICR=blinded independent central review
BMNeg=negative for brain metastasis
CAVG=average concentration
CBR=clinical benefit rate
CPI=checkpoint inhibitor
CR=complete response
DoT=duration of therapy
EAIR=exposure-adjusted incidence rate
ECOG PS=Eastern Cooperative Oncology Group Performance Status
G-CSF=granulocyte colony-stimulating factor
GT=genotype
H1/H2=histamine 1/2 receptor
HER2-=human epidermal growth factor
receptor 2-negative
HR=hazard ratio
HR+=hormone receptor-positive
mBC=metastatic breast cancer
mTNBC=metastatic triple-negative breast cancer
mUC=metastatic urothelial cancer
NK_1=neurokinin-1
OR=odds ratio
ORR=objective response rate
OS=overall survival
OSP=overall safety population
PFS=progression-free survival
RDI=relative dose intensity
SG=sacituzumab govitecan-hziy
SN-38=active metabolite of irinotecan
TEAE=treatment-emergent adverse event
TPC=treatment of physician's choice
UGT1A1=uridine diphosphate-glucuronosyl transferase 1A1

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