

Trodelvy[®] (sacituzumab govitecan-hziy)

Efficacy and Safety by Trop-2 Status in Patients With Pretreated HR+/HER2- mBC

This document is in response to your request for information about Trodelvy[®] (sacituzumab govitecan-hziy [SG]) and trophoblast cell-surface antigen 2 (Trop-2) status in patients with pretreated hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC).

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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 Labeling¹

SG is indicated for the treatment of adult patients with unresectable locally advanced or metastatic HR+/HER2- (IHC 0, IHC 1+ or IHC 2+/in situ hybridization negative) breast cancer who have received endocrine-based therapy and ≥2 additional systemic therapies in the metastatic setting.

SG is a Trop-2-directed antibody-drug conjugate. SG is a humanized antibody that recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that SG binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

Efficacy and Safety by Trop-2 Status in Patients With Pretreated HR+/HER2- mBC

TROPiCS-02, a phase 3 study, compared the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-d cycle to chemotherapy TPC in 543 patients with HR+/HER2- mBC who were previously treated with ≥1 taxane, ≥1 endocrine therapy, and ≥1 CDK4/6i in any setting and who had received 2 to 4 prior chemotherapy regimens for metastatic disease.²

- An exploratory post hoc subgroup analysis (n=462) evaluated outcomes according to Trop-2 status. Across both H-score groups (<100 or ≥100), mPFS and mOS were numerically improved with SG vs TPC. The safety profile of SG was generally consistent regardless of Trop-2 expression.³
- A separate exploratory post hoc analysis (n=197) evaluated efficacy outcomes according to *TACSTD2* mRNA expression. Regardless of *TACSTD2* expression, SG demonstrated

a numerically higher mPFS and mOS compared to TPC; benefit was also seen with ORR, CBR, and DOR vs TPC.⁴

SACI-IO HR+, an ongoing, open-label, randomized, phase 2 study, is investigating SG + pembro vs SG monotherapy in patients (N=104) with HR+/HER2- mBC who have progressed on ≥ 1 line of endocrine therapy for metastatic disease, or who have progressed on or within 12 mo of adjuvant endocrine therapy, and who have received 0 to 1 prior chemotherapy regimen.⁵

- An exploratory analysis (n=82) evaluated outcomes according to Trop-2 expression by QIF. Trop-2 expression was not significantly associated with mPFS as a continuous variable (1 unit increase in log of amol/mm²), by quartiles, or dichotomized by LOL or median. mOS was significantly decreased in Quartile 2 vs Quartile 1 (mOS 12.5 [95% CI 10–NA]; HR 3.46 [95% CI 1.19–10.1]; $P=0.02$); however, no trend was observed across quartiles. No significant association between Trop-2 expression by QIF and Grade ≥ 3 TEAEs was observed.

Efficacy and Safety by Trop-2 Status in Patients With Pretreated HR+/HER2- mBC

TROPiCS-02 Study in HR+/HER2- mBC

Study design

TROPiCS-02, a phase 3 study, compared the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-d cycle to chemotherapy TPC in 543 patients who were previously treated with ≥ 1 taxane, ≥ 1 endocrine therapy, and ≥ 1 CDK4/6i in any setting and who had received 2 to 4 prior chemotherapy regimens for metastatic disease.²

In the primary analysis, SG demonstrated significantly improved mPFS (5.5 vs 4 mo; HR, 0.66; $P=0.0003$)² and mOS (14.4 vs 11.2 mo; HR, 0.79; $P=0.02$) vs TPC.⁶

An exploratory post hoc subgroup analysis evaluated efficacy outcomes according to Trop-2 expression. Membrane Trop-2 expression on archival tumor tissue was assessed by immunohistochemistry and expressed as a H-score of 0 to 300. Outcomes were assessed in H-score groups of <100 and ≥ 100 . Very low Trop-2 expression was further subdivided as H-scores ≤ 10 and >10 to <100 .³

A separate post hoc subgroup analysis evaluated efficacy outcomes according to *TACSTD2* mRNA expression. RNA was isolated from archival tumor tissue samples. High and low *TACSTD2* expression were defined as expression above 10.5 TPM and expression below the median (10.5 TPM), respectively.⁴

Patient disposition and demographics

Of the 543 randomized patients, 238 (88%) in the SG arm vs 224 (83%) in the TPC arm were evaluable for Trop-2. Approximately 95% of patients had tumors with a Trop-2 H-score >0 (H-score <100 , n=192 [42%] and H-score ≥ 100 , n=270 [58%]).³ Of the 543 randomized patients, 100 (37%) in the SG arm and 97 (36%) in the TPC arm were evaluable for *TACSTD2* expression.⁴ Baseline demographics and disease characteristics were generally consistent regardless of Trop-2 and *TACSTD2* expression.^{3,4}

Efficacy

Across both H-score groups (<100 and ≥100), mPFS and mOS were numerically improved with SG vs TPC (Table 1). Numerical benefits were also observed with SG vs TPC for mPFS and mOS in patients with very low Trop-2 expression (H-score ≤10); however, due to the small sample size, caution is recommended in the interpretation of this data.³

Table 1. TROPiCS-02: mPFS and mOS Outcomes According to Trop-2 Expression³

Trop-2 Expression, H-Score	n/n (SG/TPC)	SG vs TPC			
		mPFS, mo	HR (95% CI)	mOS, mo	HR (95% CI)
≥100	142/128	6.4 vs 4.1	0.6 (0.44–0.81)	14.4 vs 11.2	0.83 (0.62–1.11)
<100	96/96	5.3 vs 4	0.77 (0.54–1.09)	14.6 vs 11.3	0.75 (0.54–1.04)
>10 to <100	62/51	5 vs 3.5	0.67 (0.42–1.07)	13.7 vs 11	0.81 (0.54–1.23)
≤10	34/45	5.5 vs 4.3	0.89 (0.51–1.57)	17.6 vs 12.3	0.61 (0.34–1.08)

In patients receiving SG, a disease response was observed in those with an H-score of ≤10 (n=34). A response was also observed in a Trop-2 negative subgroup (n=10), see Table 2.³

Table 2. TROPiCS-02: Response Rates According to Trop-2 Expression³

H-Score	ORR, n (%)	CBR, ^a n (%)	DOR, Median (95% CI), mo
≤10 (n=34)	8 (24)	11 (32)	7.5 (2.5–NR)
>10 to <100 (n=62)	11 (18)	17 (27)	7.4 (4.1–NR)
≥100 (n=142)	33 (23)	55 (39)	8.5 (5.9–16.9)

^aThe percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 mo.

Table 3 shows a numerical benefit for mPFS and mOS regardless of *TACSTD2* expression.⁴

Table 3. TROPiCS-02: mPFS and mOS Outcomes According to *TACSTD2* Expression⁴

<i>TACSTD2</i>	n/n (SG/TPC)	SG vs TPC			
		mPFS, mo	HR (95% CI)	mOS, mo	HR (95% CI)
<10.5 TPM	47/51	5.6 vs 2.9	0.82 (0.5–1.35)	14.2 vs 10.6	0.69 (0.44–1.1)
≥10.5 TPM	53/46	7.3 vs 5.6	0.62 (0.35–1.12)	14.4 vs 11.8	1 (0.63–1.59)

A numerical benefit was seen for SG vs TPC for ORR, CBR, and DOR by *TACSTD2* expression (Table 4).⁴

Table 4. TROPiCS-02: Responses According to *TACSTD2* Expression⁴

	ITT		<i>TACSTD2</i> <10.5 TPM		<i>TACSTD2</i> ≥10.5 TPM	
	SG (n=272)	TPC (n=271)	SG (n=47)	TPC (n=51)	SG (n=53)	TPC (n=46)
CR, n (%)	2 (1)	0	1 (2)	0	0	0
PR, n (%)	55 (20)	38 (14)	8 (17)	8 (16)	11 (21)	4 (9)
CBR, ^a n (%)	92 (34)	60 (22)	16 (34)	10 (20)	20 (38)	11 (24)
OR (95% CI)	1.8 (1.23–2.63)		2.12 (0.85–5.3)		1.93 (0.8–4.63)	
DOR, median (95% CI), mo	8.1 (6.7–9.1)	5.6 (3.8–7.9)	7.4 (2.8–NR)	6.8 (4.1–NR)	18.6 (5.8–NR)	4.3 (4.3–NR)

^aThe percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 mo.

Safety²

Regardless of Trop-2 expression, the safety profile of SG was generally consistent.

Table 5. TROPiCS-02: Safety Summary According to Trop-2 Expression²

TEAEs, n (%)	SG (n=236)		TPC (n=219)	
	H-Score <100 (n=96)	H-Score ≥100 (n=140)	H-Score <100 (n=94)	H-Score ≥100 (n=123)
Grade ≥3	76 (79)	103 (74)	58 (62)	78 (63)
Led to treatment discontinuation	2 (2)	11 (8)	5 (5)	5 (4)
Led to dose delay	68 (71)	93 (66)	43 (46)	52 (42)
Led to dose reduction	32 (33)	51 (36)	37 (39)	35 (28)
Serious adverse events	25 (26)	42 (30)	18 (19)	27 (22)
Led to death ^a	1 (1)	4 (3)	0	0
Treatment-related	1 (1)	0	0	0
Select Grade ≥3 TEAEs	Neutropenia ^b	76 (54)	43 (46)	43 (35)
	Febrile neutropenia	9 (6)	4 (4)	6 (5)
	Diarrhea	13 (9)	1 (1)	1 (1)

^aFive of 6 patients who experienced a TEAE leading to death had a known H-score. One TEAE, septic shock due to neutropenic colitis, was considered to be treatment-related. The others were COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. No patterns were identified.

^bIncluded combined terms of neutropenia, neutrophil count decreased, and febrile neutropenia.

SACI-IO HR+ Study in HR+/HER2- mBC⁵

SACI-IO HR+, an ongoing, open-label, randomized, phase 2 study, is investigating SG + pembro vs SG monotherapy in patients who have progressed on ≥1 line of endocrine therapy for metastatic disease who progressed on or within 12 mo of adjuvant endocrine therapy, and have received 0 to 1 prior chemotherapy regimen.

A prespecified exploratory analysis evaluated outcomes according to Trop-2 expression by QIF. Median follow-up was 11.2 mo. Of the 104 patients in the ITT population, 82 patients (SG + pembro, n=38; SG, n=44) had baseline tissues available for Trop-2 QIF.

Efficacy

Trop-2 expression was not significantly associated with mPFS as a continuous variable, by quartiles, or dichotomized by LOL or median. mOS was significantly decreased in Quartile 2 vs Quartile 1; however, no trend was observed across quartiles (Table 6). Trop-2 expression was not significantly associated with mPFS or mOS by treatment arm or PD-L1 status.

Table 6. SACI-IO HR+ Study: Association of Trop-2 With mPFS and mOS⁵

All (n=82)	Group	mPFS (95% CI)	HR (95% CI); Log-Rank P-Value	mOS (95% CI)	HR (95% CI); Log-Rank P-Value
Continuous	1-unit increase in log of amol/mm ²	-	0.96 (0.83–1.1); 0.55	-	1.05 (0.85–1.3); 0.66
LOL	≤ LOL (reference)	6.7 (4–8.7)	0.63 (0.3–1.34); 0.23	18 (16.9–NA)	0.99 (0.29–3.38); 0.98
	> LOL	8.7 (5.6–NA)		NA (11.5–NA)	
Median	< Median (reference)	5.9 (3–10)	0.77 (0.46–1.28); 0.31	18 (16.9–NA)	0.93 (0.43–2.01); 0.86
	≥ Median	6.7 (4.2–11.6)		17.3 (15.8–NA)	
Quartile	≤25% (reference)	8.7 (2–NA)	-	20 (18.5–NA)	-
	>25–50%	4.5 (2.5–NA)	1.86 (0.91–3.8); 0.09	12.5 (10–NA)	3.46 (1.19–10.1); 0.02
	>50–75%	6.7 (2.6–NA)	1.14 (0.54–2.39); 0.74	16.6 (15.8–NA)	1.73 (0.6–5.03); 0.31
	>75%	6.2 (4.2–NA)	0.91 (0.44–1.9); 0.81	17.3 (12.4–NA)	1.51 (0.4–5.66); 0.54

Safety

Trop-2 expression by QIF was not associated with Grade ≥ 3 TEAEs among all patients (Table 7), by treatment arm (SG + pembro: OR 0.81, $P=0.42$; SG: OR 1.16, $P=0.41$) or by PD-L1 status (PD-L1+: OR 1.09, $P=0.67$; PD-L1-: OR 0.93, $P=0.73$). See Table 7 for results by quartiles or dichotomized by median.

Table 7. SACI-IO HR+: Grade ≥ 3 TEAEs by Trop-2 QIF Expression (Overall Cohort)⁵

All (n=82)	Group	n/N	OR (95% CI)	Wald Test P-Value
Continuous	1-unit increase in log of amol/mm ²	-	1 (0.74–1.31)	0.99
Median	< Median (reference)	30/41	0.89 (0.33–2.33)	0.81
	$\geq$ Median	29/41		
Quartile	$\leq 25\%$ (reference)	14/21	-	-
	>25–50%	16/20	2 (0.5–9.02)	0.34
	>50–75%	13/20	0.93 (0.25–3.42)	0.91
	>75%	16/21	1.6 (0.42–6.51)	0.5

Note: n/N refers to the number of events/number of patients analyzed.

References

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6. Rugo HS, Bardia A, Marmé F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. *The Lancet*. 2023;402(10411):1423-1433.

Abbreviations

CBR=clinical benefit rate
CDK4/6i=cyclin-dependent kinase 4/6 inhibitor
CR=complete response
DOR=duration of response
H-score=histochemical-score

HER2=human epidermal growth factor receptor
2-negative
HR=hazard ratio
HR+=hormone receptor-positive
IHC=immunohistochemistry
LOL=limit of linearity

mBC=metastatic breast cancer
mOS=median overall survival
mPFS=median progression-free survival
NR=not reached
OR=odds ratio

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ORR=objective response rate
pembro=pembrolizumab
PD-L1=programmed death-ligand 1
PR=partial response

QIF=quantitative immunofluorescence
SD=stable disease
SG=sacituzumab govitecan-hziy
TEAE=treatment-emergent adverse event

TPC=treatment of physician's choice
TPM=transcripts per million
Trop-2=trophoblast cell surface antigen-2

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

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