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Trodelvy® (sacituzumab govitecan-hziy) Efficacy and Safety by Trop-2 Status in Patients With 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) in patients with 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 Labeling[1]

SG is indicated for the treatment of adult patients with unresectable locally advanced or metastatic HR+/HER2- (IHC 0, IHC 1+ or IHC 2+/ISH–) 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. Sacituzumab 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 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-day 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 Trop-2 gene (*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 who progressed on or within 12 mo of adjuvant endocrine therapy, and 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/mm^2), 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 HR+/HER2- mBC

TROPiCS-02 Study in HR+/HER2- mBC

Study design and demographics

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-day 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 a significant risk reduction of PFS (HR, 0.66; *P*<0.001)[2] and significantly improved OS vs TPC (median, 14.4 vs 11.2 mo; HR, 0.79; *P*=0.02).[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), PFS and OS were numerically improved with SG vs TPC (Table 1). Numerical benefits were also observed with SG vs TPC for PFS and OS 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 Expression[3]

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 Expression[3]

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)

Abbreviation: NR=not reached

[a]The percentage of patients with a confirmed best overall response of complete response, partial response, and stable disease ≥6 mo.

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

Table 3. TROPiCS-02: mPFS and mOS Outcomes According to *TACSTD2* Expression[4]

TACSTD2	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).

Table 4. TROPiCS-02: Responses According to *TACSTD2* Expression[4]

	ITT		*TACSTD2* <10.5 TPM		*TACSTD2* ≥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)

Abbreviations: CR=complete response; OR=odds ratio; PR=partial response.

[a]The percentage of patients with a confirmed best overall response of CR, PR, and stable disease ≥6 mo.

Safety[2]

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

Table 5. TROPiCS-02: Safety Summary According to Trop-2 Expression[2]

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)
SAEs		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]	56 (58)	76 (54)	43 (46)	43 (35)
	Febrile neutropenia	7 (7)	9 (6)	4 (4)	6 (5)
	Diarrhea	10 (10)	13 (9)	1 (1)	1 (1)

Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event.
[a]Five 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.
[b]Included combined terms of neutropenia, neutrophil count decreased, and febrile neutropenia.

SACI-IO HR+ Study in HR+/HER2- mBC[5]

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 and 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 PFS or OS by treatment arm or PD-L1 status.

Table 6. Association of Trop-2 with mPFS and mOS[5]

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
Limit of linearity	≤ LOL (ref)	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 (ref)	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% (ref)	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

All (n=82)	Group	mPFS (95% CI)	HR (95% CI), Log-rank *P*-value	mOS (95% CI)	HR (95% CI), Log-rank *P*-value
	> 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. ≥ Grade 3 TEAEs by Trop-2 QIF Expression (Overall Cohort)[5]

All (n=82)	Group	n/N	Odds Ratio	Wald Test *P*-value
Continuous	1-unit increase in log of amol/mm^2	-	1 (0.74–1.31)	0.99
Median	< Median (ref)	30/41	0.89 (0.33–2.33)	0.81
	≥ Median	29/41		
Quartile	≤ 25% (ref)	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

Abbreviation: n/N=number of events/number of patients analyzed.

References

1. TRODELVY® Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022;40(29):3365-3376.
3. Rugo H, Bardia A, Marme F. Sacituzumab govitecan vs treatment of physician's choice by agent and Trop-2 expression in the TROPiCS-02 study of patients with HR+/HER2- metastatic breast cancer [Poster]. Presented at: SABCS; December 6-10, 2022; San Antonio, TX.
4. Bardia A, Rugo HS, Cortes J, et al. Trop-2 mRNA expression and association with clinical outcomes with sacituzumab govitecan in patients with HR+/HER2- metastatic breast cancer: Biomarker results from the phase 3 TROPiCS-02 study. [Abstract 1082]. Presented at: American Society of Clinical Oncology (ASCO); June 2-6, 2023; Chicago, Illinois.
5. Garrido-Castro AC, Kim SE, He M, et al. Correlation of TROP2 expression with outcomes of sacituzumab govitecan with or without pembrolizumab in patients with metastatic hormone receptor-positive/HER2-negative breast cancer: An exploratory analysis from the phase II SACI-IO HR+ trial [Poster P2-09-24]. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 10-14, 2024; San Antonio, TX.
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
DOR=duration of response
H-score=histochemical-score

HER2-=human epidermal growth factor receptor 2-negative
HR=hazard ratio
HR+=hormone receptor-positive
LOL=limit of linearity
mBC=metastatic breast cancer
mOS=median overall survival
mPFS=median progression-free survival
ORR=objective response rate
OS=overall survival
Pembro=pembrolizumab
PFS=progression-free survival
QIF=quantitative immunofluorescence
SG-hziy=sacituzumab govitecan
TACSTD2=Trop-2 gene
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.

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