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Trodelvy® (sacituzumab govitecan-hziy) Use in Pretreated HR+/HER2- mBC: Efficacy and Safety by HER2 Status

This document is in response to your request for information about Trodelvy® (sacituzumab govitecan-hziy [SG]) and its efficacy and safety by human epidermal growth factor receptor 2 (HER2) status in patients with pretreated hormone receptor-positive (HR+)/HER2-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.

Use in Pretreated HR+/HER2- mBC: Efficacy and Safety by HER2 Status

TROPiCS-02, a phase 3 study, compared the efficacy and safety 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 ET, 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 evaluated mPFS in patients stratified by HER2 status: HER2 IHC0 (SG, n=101; TPC, n=116); and HER2-low (HER2 IHC1+ or IHC2+ and ISH-negative/unverified; SG, n=149; TPC, n=134). mPFS results in the HER2 subgroups were consistent with those in the ITT population. mPFS in patients treated with SG vs TPC, respectively, was[3]:

- 5.5 vs 4 mo (HR 0.66; 95% CI: 0.53–0.83; *P*=0.0003) in the ITT population.
- 5 vs 3.4 mo (HR 0.72; 95% CI: 0.51–1; *P*=0.05) in the HER2 IHC0 subgroup.
- 6.4 vs 4.2 mo (HR 0.58; 95% CI: 0.42–0.79; *P*<0.001) in the HER2-low subgroup.
  - 7 vs 4.3 mo (HR 0.57) in patients with IHC1+ tumors.
  - 5.6 vs 4 mo (HR 0.58) in patients with IHC2+ tumors.
- The safety profile of SG in the HER2 subgroups was generally consistent with that of the OSP. Within the OSP, Grade ≥3 TEAEs with SG vs TPC occurred in 74% vs 60% of patients, respectively; in the HER2 IHC0 subgroup, they occurred in 71% vs 62% of patients, and by 74% vs 59% in the HER2-low subgroup.

The final exploratory analysis, at a median follow-up of 12.8 mo, evaluated mPFS and mOS by HER2 status. In patients treated with SG vs TPC[4]:

- mPFS (95% CI) in the HER2 IHC0 subgroup was 5 (3.9–7.2) vs 3.4 (1.8–4.2) mo, respectively (HR 0.7; 95% CI: 0.51–0.98), and 5.8 (4.1–8.4) vs 4.2 (2.8–4.5) mo (HR 0.6; 95% CI: 0.44–0.82) in the HER2-low subgroup.
- mOS (95% CI) in the HER2 IHC0 subgroup was 13.6 (12.1–16) vs 10.8 (9.2–14.2) mo (HR 0.85; 95% CI: 0.63–1.14), and 15.4 (13.5–19.1) vs 11.5 (10.1–12.9) mo (HR 0.75; 95% CI: 0.57–0.97) in the HER2-low subgroup.
- Safety outcomes in patients stratified by HER2 status were not reported.

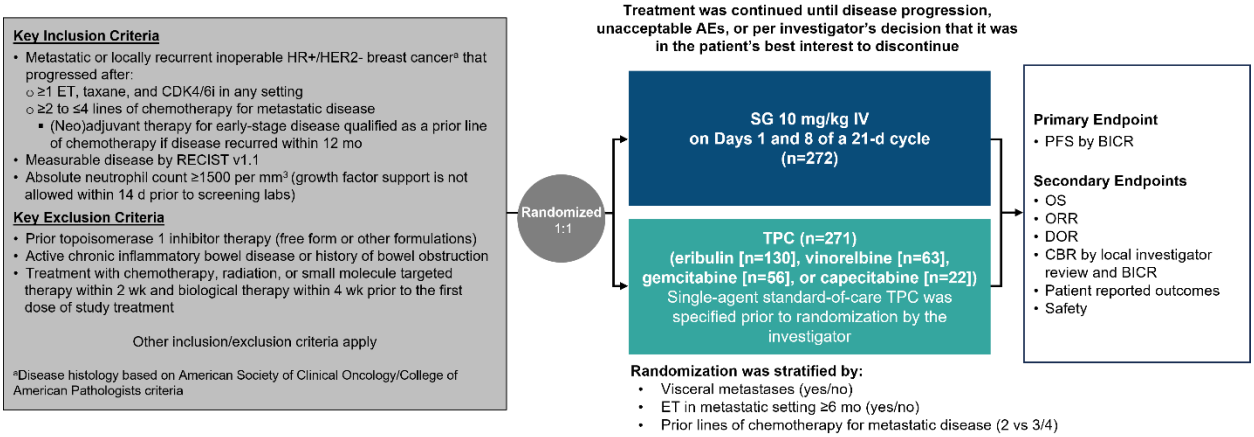
Use in Pretreated HR+/HER2- mBC: Efficacy and Safety by HER2 Status

TROPiCS-02 Study

Study design

TROPiCS-02, a phase 3 study, compared the efficacy and safety of SG vs TPC in 543 patients with HR+/HER2- mBC who were previously treated with ≥1 taxane, ≥1 ET, and ≥1 CDK4/6i in any setting and who had received 2 to 4 prior chemotherapy regimens for metastatic disease (Figure 1).[2,5]

Figure 1. TROPiCS-02: Study Design[2,5,6]



Abbreviations: BICR=blinded independent central review; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Exploratory post hoc analysis by HER2 status

An exploratory post hoc subgroup analysis evaluated the efficacy and safety of SG vs TPC according to HER2 status by retrospectively analyzing local IHC and ISH results for the ITT population. Of the 543 patients in the ITT population, 92% were HER2 evaluable by IHC and were included in this analysis. Forty percent of patients were HER2 IHC0, and 52% of patients were HER2-low (HER2 IHC1+ or IHC2+ and ISH-negative/unverified). Thirty-nine patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with trial eligibility criteria to enroll HER2-

negative patients. Key demographics and baseline characteristics in the ITT population and HER2 subgroups were generally similar (Table 1).[3]

Table 1. TROPiCS-02: Baseline Demographics and Disease Characteristics in the ITT Population and According to HER2 Status[2,3]

Key Demographics and Characteristics		ITT		HER2 IHC0		HER2-Low	
		SG (n=272)	TPC (n=271)	SG (n=101)	TPC (n=116)	SG (n=149)	TPC (n=134)
Female, n (%)		270 (99)	268 (99)	100 (99)	114 (98)	148 (99)	133 (99)
Age, median (range), y		57 (29–86)	55 (27–78)	58 (29–84)	55 (32–78)	58 (29–86)	57 (27–77)
Race, n (%)	White	184 (68)	178 (66)	68 (67)	78 (67)	98 (66)	80 (60)
	Non-White	19 (7)	23 (8)	3 (3)	12 (10)	14 (9)	11 (8)
	Not reported	69 (25)	70 (26)	30 (30)	26 (22)	37 (25)	43 (32)
ECOG PS, n (%)	0	116 (43)	126 (46)	43 (43)	62 (53)	61 (41)	52 (39)
	1	156 (57)	145 (54)	58 (57)	54 (47)	88 (59)	82 (61)
Number of prior chemotherapies, n (%)	2	113 (42)	113 (42)	42 (42)	49 (42)	65 (44)	53 (40)
	3-4	159 (58)	158 (58)	59 (58)	67 (58)	84 (56)	81 (60)
Prior CDK4/6i use,[a] n (%)	≤12 mo	161 (60)	166 (62)	65 (65)	74 (64)	84 (58)	81 (62)
	>12 mo	106 (40)	102 (38)	35 (35)	42 (36)	61 (42)	50 (38)
	Missing	5 (2)	3 (1)	1 (1)	0	4 (3)	3 (2)

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status.
[a]Percentage calculations for prior CDK4/6i use ≤12 or >12 mo were based on the total number of patients with available data; percentage calculations for patients missing CDK4/6i use data were based on total number of patients in each group.

Efficacy

Longer mPFS was observed with SG vs TPC across the HER2 subgroups and was consistent with the ITT population (Table 2). Within the HER2-low subgroup, mPFS with SG vs TPC among patients with IHC1+ tumors was 7 vs 4.3 mo, respectively (HR 0.57), and 5.6 vs 4 mo (HR 0.58) among patients with IHC2+ tumors. The HR for mPFS in a sensitivity analysis of the HER2-low subgroup (excluding ISH-unverified) was similar (HR 0.53).[3]

Table 2. TROPiCS-02: Efficacy Outcomes in the ITT Population and According to HER2 Status[2,3]

Variable	ITT		HER2 IHC0		HER2-Low	
	SG (n=272)	TPC (n=271)	SG (n=101)	TPC (n=116)	SG (n=149)	TPC (n=134)
mPFS (95% CI), mo	5.5 (4.2–7)	4 (3.1–4.4)	5	3.4	6.4	4.2
HR (95% CI)	0.66 (0.53–0.83); *P*=0.0003		0.72 (0.51–1); *P*=0.05		0.58 (0.42–0.79); *P*<0.001	
ORR, n (%)	57 (21)	38 (14)	16 (16)	17 (15)	38 (26)	16 (12)
OR (95% CI)	1.63 (1.04–2.55)		1.1 (0.52–2.3)		2.52 (1.33–4.78)	
Best overall response, n (%)						
CR	2 (1)	0	0	0	2 (1)	0
PR	55 (20)	38 (14)	16 (16)	17 (15)	36 (24)	16 (12)
SD	142 (52)	106 (39)	56 (55)	39 (34)	73 (49)	61 (46)
SD ≥6 mo	35 (13)	21 (8)	15 (15)	8 (7)	18 (12)	10 (7)
PD	58 (21)	76 (28)	23 (23)	38 (33)	29 (19)	36 (27)
NE	15 (6)	51 (19)	6 (6)	22 (19)	9 (6)	21 (16)
CBR, n (%)	92 (34)	59 (22)	31 (31)	25 (22)	56 (38)	26 (19)
OR (95% CI)	1.84 (1.25–2.69)		1.61 (0.87–2.97)		2.5 (1.46–4.3)	

Variable	ITT		HER2 IHC0		HER2-Low	
	SG (n=272)	TPC (n=271)	SG (n=101)	TPC (n=116)	SG (n=149)	TPC (n=134)
DOR, median (95% CI), mo	7.4 (6.5–8.6)	5.6 (3.8–7.9)	8.1 (4.1–NE)	6.1 (2.8–8.3)	7.4 (5.8–8.9)	4.1 (2.8–6.1)

Abbreviations: CR=complete response; NE=not evaluable; OR=odds ratio; PD=progressive disease; PR=partial response; SD=stable disease.

Safety

The safety profile of SG in the HER2 subgroups were generally consistent with that of the OSP (Table 3).[3]

Table 3. TROPiCS-02: Safety Summary in the OSP and According to HER2 Status[2,3]

TEAEs, n (%)	OSP		HER2 IHC0		HER2-Low	
	SG (n=268)	TPC (n=249)	SG (n=99)	TPC (n=107)	SG (n=147)	TPC (n=124)
Grade ≥3	198 (74)	149 (60)	70 (71)	66 (62)	109 (74)	73 (59)
That led to dose delay	178 (66)	109 (44)	61 (62)	56 (52)	98 (67)	44 (35)
That led to dose reductions	89 (33)	82 (33)	26 (26)	37 (35)	54 (37)	37 (30)
That led to treatment discontinuation	17 (6)	11 (4)	7 (7)	8 (7)	9 (6)	2 (2)
Serious TEAEs	74 (28)	47 (19)	33 (33)	15 (14)	38 (26)	25 (20)
That led to death[a]	6 (2)	0	3 (3)	0	3 (2)	0
Treatment-related	1 (<1)	0	0	0	1 (1)	0

Abbreviation: TEAE=treatment emergent adverse event.
[a]TEAEs that led to death were due to COVID-19 pneumonia, pulmonary embolism, pulmonary sepsis, nervous system disorder, arrhythmia, and 1 treatment-related event of septic shock due to neutropenic colitis.
Note: TEAEs were defined as adverse events that occurred on or after the first dose of study treatment and up to 30 d after the last dose. TEAEs were assessed in the OSP, which included all patients who received ≥1 dose of study treatment. Patients could report >1 event per preferred term.

Final exploratory OS analysis[4]

mPFS and mOS in the ITT population and in the HER2 subgroups were evaluated in a final exploratory analysis after a median follow-up of 12.8 mo (Table 4).

Table 4. TROPiCS-02 Final Exploratory OS Analysis: Efficacy Outcomes in the ITT Population and According to HER2 Status[4]

Variable	ITT		HER2 IHC0		HER2-Low[a]	
	SG (n=272)	TPC (n=271)	SG (n=101)	TPC (n=116)	SG (n=149)	TPC (n=134)
mPFS (95% CI), mo	5.5 (4.2–6.9)	4 (3–4.4)	5 (3.9–7.2)	3.4 (1.8–4.2)	5.8 (4.1–8.4)	4.2 (2.8–4.5)
HR (95% CI); nominal *P*-value	0.65 (0.53–0.81); 0.0001		0.7 (0.51–0.98)		0.6 (0.44–0.82)	
mOS (95% CI), mo	14.5 (13–16)	11.2 (10.2–12.6)	13.6 (12.1–16)	10.8 (9.2–14.2)	15.4 (13.5–19.1)	11.5 (10.1–12.9)
HR (95% CI); nominal *P*-value	0.79 (0.65–0.95); 0.0133		0.85 (0.63–1.14)		0.75 (0.57–0.97)	

[a]Defined as HER2 IHC1+ or IHC2+ and ISH-negative/unverified.
Note: mPFS and mOS probability were estimated using an unstratified Cox model using treatment (SG vs TPC) as the only predictor.

This analysis did not report safety outcomes in patients stratified by HER2 status.

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. Schmid P, Cortes J, Marme F, et al. Sacituzumab govitecan efficacy in HR+/HER2- metastatic breast cancer by HER2 immunohistochemistry status in the phase 3 TROPiCS-02 study [Oral Presentation 214MO]. Presented at: European Society for Medical Oncology (ESMO) Congress; 9-13 September, 2022; Paris, France.
4. Tolaney SM, Bardia A, Marmé F, et al. Final overall survival analysis from the phase 3 TROPiCS-02 study of sacituzumab govitecan in patients with hormone receptor positive/HER2-negative metastatic breast cancer [Oral Presentation 1003]. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, IL.
5. 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.
6. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer [Protocol]. *J Clin Oncol.* 2022;40(29):3365-3376.

Abbreviations

CBR=clinical benefit rate
CDK4/6i=cyclin-dependent kinase 4/6 inhibitor
DOR=duration of response
ET=endocrine therapy
HER2=human epidermal growth factor receptor 2
HR=hazard ratio
HR+=hormone receptor positive
IHC=immunohistochemistry
ISH=in situ hybridization
mBC=metastatic breast cancer
mOS=median overall survival
mPFS=median progression-free survival
ORR=objective response rate
OSP=overall safety population
SG=sacituzumab govitecan-hziy
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.

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