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Trodelvy® (sacituzumab govitecan-hziy) Efficacy and Safety by HER2 Status in Patients with HR+/HER2- mBC

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 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.

Efficacy and Safety by HER2 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]

- In the first planned interim analysis, SG demonstrated a significant risk reduction of median PFS (5.5 vs 4 mo; HR, 0.66; *P*=0.0003)[2]; median OS was significantly improved vs TPC (14.4 vs 11.2 mo; HR, 0.79; *P*=0.02) in the second planned OS analysis.[3]

An exploratory post hoc subgroup analysis showed SG improved median PFS vs TPC in HER2 IHC0 and HER2-low groups, consistent with outcomes in the ITT population.[4]

- Median PFS in the HER2 IHC0 group was 5 mo vs 3.4 mo, HR 0.72 (95% CI: 0.51–1) and in the HER2-low group was 6.4 mo vs 4.2 mo, HR 0.58 (95% CI: 0.42–0.79).
- The safety profile of SG in these subgroups was generally consistent with that of the overall TROPiCS-02 safety population.

A final exploratory analysis, at a median follow-up of 12.8 mo, analyzed median OS and median PFS in the IT population and by HER2 status.[5]

- Median PFS (95% CI) in the HER2 IHC0 group was 5 mo (3.9–7.2) vs 3.4 mo (1.8–4.2), HR 0.7 (95% CI: 0.51–0.98), and in the HER2-low group was 5.8 mo (4.1–8.4) vs 4.2 mo (2.8–4.5), HR 0.6 (95% CI: 0.44–0.82).
- Median OS (95% CI) in the HER2 IHC0 group was 13.6 mo (12.1–16) vs 10.8 mo (9.2–14.2), HR 0.85 (95% CI: 0.63–1.14) and median OS in the HER2-low group was 15.4 mo (13.5–19.1) vs 11.5 mo (10.1–12.9), HR 0.75 (95% CI: 0.57–0.97).

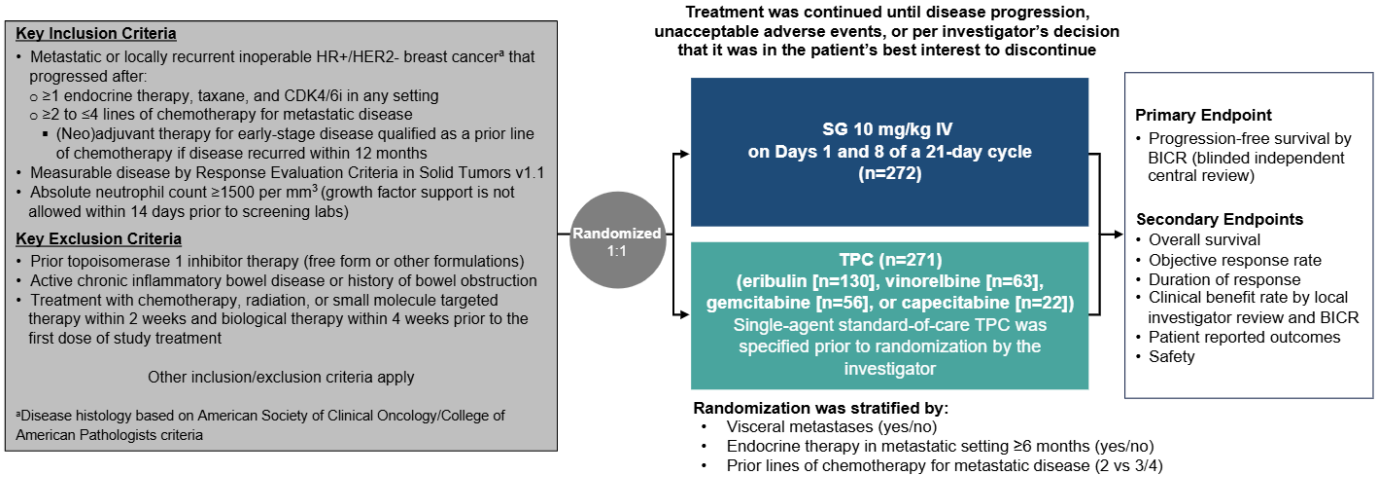
Efficacy and Safety by HER2 Status in Patients With HR+/HER2- mBC

TROPiCS-02 Study

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 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 (Figure 1).[2,3]

Figure 1. TROPiCS-02: Study Design[2,3,6]



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 (defined as 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 were generally similar between the three groups (Table 1).[4]

Table 1. TROPiCS-02: Baseline Demographics and Disease Characteristics According to HER2 Status[2,4]

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, n (%)[a]	≤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 are based on total number of patients in each group.

Efficacy

The median duration of follow-up, at the first planned interim analysis, was 10.2 mo (11.3 and 9.8 mo for SG and TPC respectively);[2] at that time, an exploratory post hoc sub group analysis showed that the median PFS for SG in the HER2 IHC0, HER2-low and ITT groups was 5, 6.4, and 5.5 mo, and for TPC was 3.4, 4, and 4.2 mo, respectively (Table 2). Within the HER2-low group, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7 vs 4.3 (HR, 0.57) and 5.6 vs 4 (HR, 0.58) mo, respectively. The HR for median PFS in a sensitivity analysis of the HER2-low subgroup (excluding ISH-unverified) was similar (HR, 0.53). See Table 2 for overall response by HER2 status.[4]

Table 2. TROPiCS-02: Efficacy According to HER2 Status[2,4]

Variable[a]	ITT		HER2 IHC0		HER2-Low	
	SG (n=272)	TPC (n=271)	SG (n=101)	TPC (n=116)	SG (n=149)	TPC (n=134)
PFS, median (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)	
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.
[a]PFS and OS are from analyses with median follow-ups of 12.8 mo and 12.5 mo, respectively, in the ITT population and from analyses with a median follow-up of 12.8 mo in the HER2 IHC0 and HER2-low populations. Response rates, CBR, and DOR are from analyses with a median follow-up of 12.5 mo.

A second planned interim analysis was conducted at a median follow-up of 12.5 mo, median OS [95% CI] was significantly improved with SG vs TPC (14·4 mo [13·0–15·7] vs 11·2 mo [10·1–12·7]; HR 0·79 [0·65–0·96], *P*=0·020).[3]

A final exploratory analysis, at a median follow-up of 12.8 mo, analyzed OS and PFS in the IT population and by HER2 status, see Table 3 for results.[5]

Table 3. TROPiCS-02: Final Exploratory OS Analysis[5]

Variable	ITT		HER2 IHC0		HER2-Low	
	SG (n=272)	TPC (n=271)	SG (n=101)	TPC (n=116)	SG (n=149)	TPC (n=134)
PFS, median (95% CI), mo	5.5 (4.2–6.9)	4.0 (3.0–4.4)	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)	
OS, median (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)	

Note: PFS and OS probability was estimated using an unstratified Cox model using treatment (SG vs TPC) as the only predictor.

Safety

The safety profile of SG in the HER2 IHC0 and HER2-low groups, at the first planned interim analysis, was generally consistent with that of the OSP (Table 4).[2,4]

Table 4. TROPiCS-02: Safety Summary According to HER2 Status[2,4]

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)
Led to treatment discontinuation	17 (6)	11 (4)	7 (7)	8 (7)	9 (6)	2 (2)
Led to dose delay	178 (66)	109 (44)	61 (62)	56 (52)	98 (67)	44 (35)
Led to dose reductions	89 (33)	82 (33)	26 (26)	37 (35)	54 (37)	37 (30)
Serious AEs	74 (28)	47 (19)	33 (33)	15 (14)	38 (26)	25 (20)
Led to death	6 (2)	0	3 (3)	0	3 (2)	0
Treatment-related	1 (<1)	0	0	0	1 (1)	0

Abbreviation: AE=adverse event.
Note: TEAEs are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date. Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than one event per preferred term.

Of the 6 TEAEs leading to death, 1 death from septic shock due to neutropenic colitis was considered by the investigator as treatment related. The other 5 TEAEs were COVID-19 pneumonia, pulmonary embolism, pulmonary sepsis, nervous system disorder, and arrythmia. No patterns were identified upon detailed review of the TEAEs leading to death.[2]

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 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.
4. 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.
5. 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.
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
HER2-=human epidermal growth factor receptor 2-negative
HR=hazard ratio
HR+=hormone receptor positive
IHC=immunohistochemistry
ISH=in situ hybridization
mBC=metastatic breast cancer
ORR=objective response rate
OS=overall survival
OSP=overall safety population
PFS=progression-free survival
SG=sacituzumab govitecan-hziy
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

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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
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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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