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Trodelvy® (sacituzumab govitecan-hziy) Efficacy and Safety by Trop-2 Status in Patients With mTNBC

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and trophoblast cell surface antigen-2 (Trop-2) in patients with relapsed or refractory metastatic triple-negative breast cancer (mTNBC).

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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 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.

ASCENT: Trop-2 Analysis in Patients With mTNBC

The ASCENT study was conducted to investigate the efficacy and safety of SG in comparison with TPC in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease.[2] An exploratory, post hoc biomarker analysis of the association between Trop-2 expression and the efficacy of SG compared with that of TPC was conducted.[3] Among those in the SG and TPC groups, respectively, the outcomes, stratified by Trop-2 H-score, were as follows[3]:

Median progression-free survival (PFS)[3]:

- H-score 0–130: 2.7 months vs 1.5 months; hazard ratio (HR), 0.583 (95% CI: 0.339–1.003)
- H-score 130–220: 4.8 months vs 2.8 months; HR, 0.517 (95% CI: 0.291–0.92)
- H-score 220–275: 6.8 months vs 1.6 months; HR, 0.196 (95% CI: 0.105–0.364)
- H-score 275–300: 6.9 months vs 2.8 months; HR, 0.314 (95% CI: 0.166–0.592)

Median overall survival (OS)[3]:

- H-score 0–130: 8.7 months vs 7 months; HR, 0.739 (95% CI: 0.457–1.196)
- H-score 130–220: 13.4 months vs 8.8 months; HR, 0.69 (95% CI: 0.408–1.168)
- H-score 220–275: 15.2 months vs 6.5 months; HR, 0.344 (95% CI: 0.207–0.573)
- H-score 275–300: 14.5 months vs 7.1 months; HR, 0.358 (95% CI: 0.216–0.594)

Incidence of Grade ≥3 treatment-emergent adverse events (TEAEs)[3]:

- H-score 0–130: 77% vs 61%.
- H-score 130–220: 66% vs 72%.
- H-score 220–275: 84% vs 57%.
- H-score 275–300: 66% vs 63%.

Results should be interpreted with caution due to the small sample size.[3]

ASCENT Study

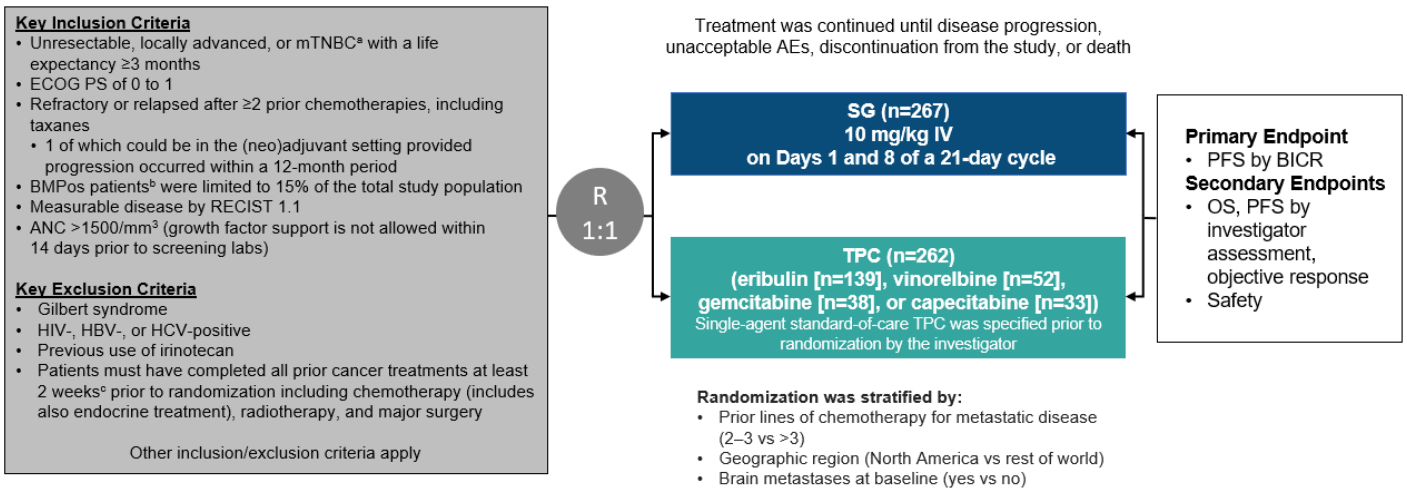
Overall Study Design[2]

ASCENT, a global, open-label, randomized, confirmatory, phase 3 study, was conducted to investigate the efficacy and safety of SG in comparison with TPC in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapies for unresectable, locally advanced, or metastatic disease.

A total of 529 patients were enrolled and randomly assigned to receive SG (n=267) or TPC (n=262; eribulin, vinorelbine, capecitabine, or gemcitabine; Figure 1).

The primary endpoint was PFS in patients negative for brain metastases at baseline, as measured by a blinded independent central review (BICR). See Figure 1 for key secondary endpoints.

Figure 1. ASCENT Design[2,4]



Abbreviations: AE=adverse events; ANC=absolute neutrophil count; BMPos=positive for brain metastases; ECOG PS=Eastern Cooperative Oncology Group Performance Status; R=randomized; RECIST=Response Evaluation Criteria in Solid Tumors.

[a]TNBC diagnosis determined per American Society of Clinical Oncology-College of American Pathologists guidelines. mTNBC was histologically or cytologically confirmed.
[b]Had stable central nervous system disease for ≥4 weeks and could use stable, low-dose corticosteroids (≤20 mg of prednisone/prednisolone or equivalent).
[c]Prior antibody treatment for cancer must have been completed ≥3 weeks prior to randomization.

ASCENT Trop-2 Subanalysis in mTNBC

An exploratory, post hoc biomarker analysis of the association between Trop-2 expression and the efficacy of SG compared with that of TPC was conducted.[3] At study entry, primary or metastatic biopsy or surgical specimens were requested, and Trop-2 expression was determined using a validated immunohistochemistry assay and histochemical scoring.[5] H-scores (0 to 300) and the percentage of membrane cells were used to categorize Trop-2 expression. Only patients with known Trop-2 expression were included in this analysis.[3]

Patient Disposition and Demographics[3]

Of the 529 patients in the overall ITT population, 60% had Trop-2 expression data available. Of the 267 patients who were randomly assigned to receive SG, 168 patients had Trop-2 expression data available and were included in this analysis; of the 262 patients who were assigned to the TPC group, 150 patients had Trop-2 expression data available and were included in this analysis. Key baseline demographics and characteristics are presented in Table 1.

Table 1. Demographics and Disease Characteristics in the ITT Population and Trop-2-Evaluable Population[3]

Variable		ITT Population		Trop-2-Evaluable Population	
		SG (n=267)	TPC (n=262)	SG (n=168)	TPC (n=150)
Age at study entry, median (range), y		54 (27–82)	53 (27–81)	53 (30–82)	53 (30–81)
Race, n (%)	White	215 (81)	203 (77)	135 (80)	115 (77)
	Black	28 (10)	34 (13)	18 (11)	23 (15)
	Asian	13 (5)	9 (3)	8 (5)	5 (3)
	Other	11 (4)	16 (6)	7 (4)	7 (5)
ECOG PS, n (%)	0	121 (45)	108 (41)	73 (43)	63 (42)
	1	146 (55)	154 (59)	95 (57)	87 (58)
Number of previous chemotherapies, 2–3/>3, n (%)		184 (69)/83 (31)	181 (69)/81 (31)	126 (75)/42 (25)	109 (73)/41 (27)

Efficacy[3]

SG demonstrated improved PFS and OS outcomes vs TPC, regardless of Trop-2 H-score (Table 2), and findings were comparable with those for the ITT population. Objective response rates (ORRs) were greater among those who received SG than among those who received TPC in all Trop-2 H-score subgroups, with greater improvement in those with higher Trop-2 levels. Additional efficacy outcomes stratified by Trop-2 H-score are presented in Table 2.

For PFS, there was no significant interaction between Trop-2 expression and treatment (range, *P*=0.244–0.726). For OS, the interaction between with continuous Trop-2 expression and treatment was significant (by Trop-2 H-score, *P*=0.039; by percentage of membrane cells, *P*=0.046).

Results should be interpreted with caution due to the small sample size.

Safety

Results for safety outcomes in the overall population and according to Trop-2 H-score are presented in Table 2.

Table 2. ASCENT: Efficacy and Safety According to Trop-2 H-Score[3]

Efficacy	ITT Population		H-Score 0-130		H-Score 130-220		H-Score 220-275		H-Score 275-300	
	SG (n=267)	TPC (n=262)	SG (n=35)	TPC (n=45)	SG (n=47)	TPC (n=33)	SG (n=39)	TPC (n=40)	SG (n=47)	TPC (n=32)
PFS, events, n	191	171	25	33	31	22	30	32	32	18
Median (95% CI), mo	4.8 (4.1–5.8)	1.7 (1.5–2.5)	2.7 (1.4–5.7)	1.5 (1.4–2.2)	4.8 (2.9–7.1)	2.8 (1.7–4.3)	6.8 (4.3–8.3)	1.6 (1.4–2.7)	6.9 (5.6–8.1)	2.8 (1.4–3.1)
HR (95% CI)	0.413 (0.33–0.517)		0.583 (0.339–1.003)		0.517 (0.291–0.92)		0.196 (0.105–0.364)		0.314 (0.166–0.592)	
OS, events, n	201	222	29	40	34	24	28	37	34	30
Median (95% CI), mo	11.8 (10.5–13.8)	6.9 (5.9–7.7)	8.7 (6.9–12.9)	7 (4.9–9.6)	13.4 (7.8–16.5)	8.8 (4.8–10.2)	15.2 (11.8–17.5)	6.5 (4.1–8.2)	14.5 (10.6–18.3)	7.1 (4.9–9.8)
HR (95% CI)	0.514 (0.422–0.625)		0.739 (0.457–1.196)		0.69 (0.408–1.168)		0.344 (0.207–0.573)		0.358 (0.216–0.594)	
ORR, n (%)	83 (31)	11 (4)	8 (23)	2 (4)	13 (28)	5 (15)	16 (41)	0	21 (45)	0
OR (95% CI)	11 (5.7–21.4)		6.4 (1.3–32.3)		2.1 (0.7–6.7)		NE		NE	
Best overall response, n (%)										
CR	10 (4)	2 (1)	3 (9)	0	2 (4)	2 (6)	3 (8)	0	2 (4)	0
PR	73 (27)	9 (3)	5 (14)	2 (4)	11 (23)	3 (9)	13 (33)	0	19 (40)	0
CBR, n (%)[a]	108 (40)	21(8)	8 (23)	4 (9)	20 (43)	6 (18)	22 (56)	2 (5)	26 (55)	2 (6)
OR (95% CI)	8.1 (4.8–13.5)		3 (0.8–11.1)		3.3 (1.2–9.6)		24.6 (5.2–116.6)		18.6 (4–86.8)	
DOR, median (95% CI), mo[b]	6.3 (5.5–7.9)	3.6 (2.8–NE)	11.3 (3.5–NE)	NE	6.9 (2.8–NE)	3.6 (2.9–NE)	9 (5.5–12.3)	NE	5.6 (4.2–9.8)	NE
TTR, median (95% CI), mo[b]	1.5 (0.7–10.6)	1.5 (1.3–4.2)	1.5 (1.2–1.5)	1.4 (1.3–NE)	2.8 (1.4–3.3)	1.4 (1.3–NE)	1.5 (1.4–4.2)	NE	1.6 (1.5–4.2)	NE
Safety, n (%)	**SG (n=258)**	**TPC (n=224)**	**SG (n=35)**	**TPC (n=44)**	**SG (n=47)**	**TPC (n=32)**	**SG (n=38)**	**TPC (n=37)**	**SG (n=47)**	**TPC (n=30)**
Any TEAE[c]	257 (100)	219 (98)	35 (100)	43 (98)	46 (98)	32 (100)	38 (100)	36 (97)	47 (100)	30 (100)
Grade ≥3	188 (73)	145 (65)	27 (77)	27 (61)	31 (66)	23 (72)	32 (84)	21 (57)	31 (66)	19 (63)
Leading to:										
Dose reduction	57 (22)	59 (26)	7 (20)	12 (27)	9 (19)	12 (38)	9 (24)	5 (14)	15 (32)	8 (27)
Dose delay	162 (63)	87 (39)	24 (69)	17 (39)	27 (57)	10 (31)	24 (63)	12 (32)	32 (68)	13 (43)
Treatment DC	12 (5)	12 (5)	2 (6)	2 (5)	3 (6)	3 (9)	2 (5)	2 (5)	1 (2)	0
Death	1 (<1)[d]	3 (1)	0	1 (2)	0	0	0	1 (3)	0	0

Abbreviations: CBR=clinical benefit rate; CR=complete response; DC=discontinuation; DOR=duration of response; NE=not evaluable; OR=odds ratio; PR=partial response; TTR=time to response.
[a]Defined as the percentage of patients with a confirmed best overall response of CR, PR, or SD with a duration of ≥6 months.
[b]Only patients achieving CR or PR were including in the DOR and TTR analyses.
[c]TEAE was defined as an adverse event with a start date on or after the date of the first study drug dose and up to 30 days after the date of the last dose of study treatment.
[d]Considered unlikely to be related to SG treatment.

References

1. TRODELVY® Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med*. Apr 22 2021;384(16):1529-1541.
3. Bardia A, Rugo HS, Tolaney SM, et al. Final results from the randomized phase III ASCENT clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *J Clin Oncol*. 2024;42(15):1738-1744.
4. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer [Protocol]. *N Engl J Med*. 2021;384(16):1529-1541.
5. Bardia A, Tolaney SM, Punie K, et al. Biomarker analyses in the phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. *Ann Oncol*. Sep 2021;32(9):1148-1156.

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

For any additional questions, please contact Trodelvy Medical Information at:

☎1-888-983-4668 or 🖱 www.askgileadmedical.com

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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

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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