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Trodelvy® (sacituzumab govitecan-hziy) Use in 1L PD-(L)1 Inhibitor-Ineligible mTNBC

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and its use as first-line (1L) treatment in patients with locally advanced unresectable or metastatic triple-negative breast cancer (mTNBC) who are ineligible for programmed death-(ligand) 1 (PD-[L]1) inhibitors.

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Trodelvy is not indicated for use as 1L treatment in patients with PD-(L)1 inhibitor ineligible mTNBC. 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

Clinical Data on SG in 1L PD-(L)1 Inhibitor-Ineligible mTNBC

ASCENT-03, an ongoing, global, open-label, randomized, phase 3 study, compares the efficacy and safety of SG vs chemotherapy TPC (eg, gem + carbo, paclitaxel, or nab-paclitaxel), as 1L treatment in patients (N=558) with previously untreated, locally advanced, inoperable or mTNBC who are not candidates for PD-(L)1 inhibitor therapy.[1]

- SG prolonged PFS by BICR per RECIST v1.1 (primary endpoint) vs TPC (9.7 vs 6.9 mo; HR 0.62 [95% CI 0.5–0.77] *P*<0.001).[1]
  - A higher proportion of patients treated with SG vs TPC, respectively, were alive and progression-free at 6 mo, 65% (95% CI 59–71) vs 53% (95% CI 47–59), and at 12 mo, 41% (95% CI 34–47) vs 24% (95% CI 19–30).
  - Median follow-up at the data cutoff was 13.2 mo (range, <0.1–29.2).
- Results for OS were immature at the time of the primary analysis and are descriptive only; a numerical trend in favor of SG vs PFS was observed (21.5 mo [95% CI 17.7–NR] vs 20.2 mo [18.2–NR], respectively). Further follow-up for OS is ongoing.[1] An ORR of 48% was observed in patients receiving SG vs 46% for TPC (OR 1.12; 95% CI 0.8–1.57). DOR (95% CI) with SG vs TPC was 12.2 (9.7–13.8) mo vs 7.2 (5.7–8.4) mo, respectively. Formal statistical analyses of these results were not conducted at this time.[1]
- The most common Grade ≥3 TEAEs for SG and TPC, respectively, were neutropenia (43 vs 41%), anemia (4 vs 16%), leukopenia (7 vs 13%), thrombocytopenia (1 vs 12%), and diarrhea, (9 vs 1%).[1]
- In the SG vs TPC arm, treatment-emergent SAEs were 26 vs 24%, of these, treatment-related SAEs were 17 vs 13%, respectively.[1,2]

- Incidence of TEAEs that led to treatment discontinuation was 4% with SG and 12% with TPC.[1] Neutropenia led to treatment discontinuation in 1 and 3 patients in the SG and TPC arms, respectively; diarrhea led to treatment discontinuation in 1 patient treated with SG. No case of diarrhea led to treatment discontinuation in the TPC arm.
- Primary prophylaxis of G-CSF was associated with less frequent and severe neutropenia in the SG arm.[3]
- A total of 137 and 35 patients received antidiarrheal treatment in the SG and TPC arms, respectively; loperamide was the most common treatment in both arms (SG: 90% vs TPC: 77%). For both treatments, multi-antidiarrheal regimens were used in 20% of patients that received any antidiarrheal treatment.[3]
- There were six treatment-related deaths due to infection in the SG arm; five were secondary infections due to neutropenia in patients who had risk factors for febrile neutropenia but did not receive prophylaxis with G-CSF; these events occurred early in treatment. A case of pneumonia showed no evidence of preceding or concurrent neutropenia. In the TPC arm, there was one treatment-related death due to pleural effusion.[1,3]
- Results from an exploratory safety analysis of EAIRs, which adjusted rates of TEAEs by treatment exposure, are described below.[3]

Clinical Data on SG in 1L PD-(L)1 Inhibitor-Ineligible mTNBC

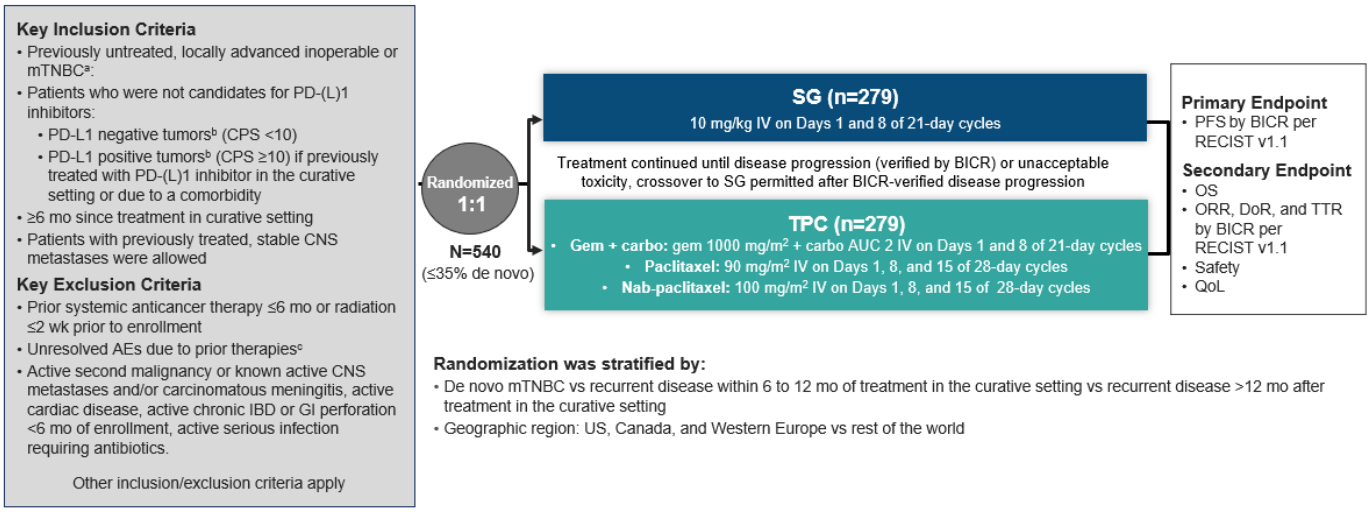
ASCENT-03 Study

Study design and demographics

ASCENT-03, an ongoing, global, open-label, randomized, phase 3 study compares the efficacy and safety of SG vs TPC as 1L treatment in patients (N=558) with previously untreated, locally advanced inoperable or mTNBC who were ineligible for PD-(L)1 inhibitor therapy (Figure 1).[1]

The study enrolled patients whose tumors did not express PD-L1 (PD-L1 negative tumors [CPS <10]) and patients who did express PD-L1 (PD-L1 positive tumors [CPS ≥10]) if they received prior PD-(L)1 inhibitor therapy in the (neo)adjuvant setting or had a comorbidity preventing treatment with a PD-(L)1 inhibitor (see Table 1 for further baseline demographics and disease characteristics). Patients must have had ≥6 mo between the completion of curative intent systemic treatment in the (neo)adjuvant setting and first documented local or distant disease recurrence. The primary endpoint is PFS by BICR per RECIST v1.1.[1]

Figure 1. ASCENT-03 Study Design[1,2,4]



Abbreviations: AEs=adverse events; DoR=duration of response; GI=gastrointestinal; IBD=inflammatory bowel disease; IHC=immunohistochemistry; OS=overall survival; ORR=objective response rate; TNBC=triple-negative breast cancer; TTR=time to onset of response; TTD=time to deterioration.
[a]Centrally confirmed and determined according to American Society of Clinical Oncology-College of American Pathologists criteria.
[b]PD-L1 (IHC 22C3 assay) and TNBC status centrally confirmed.
[c]Any-grade neuropathy and alopecia were allowed.

In the statistical testing hierarchy, OS will be formally tested for significance once PFS is statistically significant, followed by ORR, and quality of life endpoints (once the prior endpoint in the hierarchy was significant).[2]

Table 1. ASCENT-03: Baseline Demographics and Disease Characteristics[1]

Select Demographics and Characteristics		SG (n=279)	TPC (n=279)
Age, median (range), y		56 (28-84)	54 (23-86)
Age ≥65, n (%)		65 (23)	78 (28)
Sex, n (%)	Female	274 (>99)	274 (99)
Race or ethnic group, n (%)[a]	White/Asian/Black	178 (64)/66 (24)/10 (4)	178 (64)/65 (23)/7 (3)
	Other or not specified	25 (9)	29 (10)
Geographic region, n (%)[b]	US/Canada/Western Europe	89 (32)	89 (32)
	Rest of the world	190 (68)	190 (68)
ECOG PS, n (%)[c]	0/1	183 (66)/96 (34)	187 (67)/92 (33)
PD-L1 negative status, n (%)[d]		277 (99)	278 (>99)
Disease status, n (%)[e]	Metastatic at initial diagnosis	87 (31)	88 (32)
	Recurrent within 6–12 mo[f]	58 (21)	57 (20)
	Recurrent >12 mo[f]	134 (48)	134 (48)
Metastatic sites, n (%)	Lymph node	179 (64)	180 (65)
	Lung	166 (59)	170 (61)
	Bone	95 (34)	87 (31)
	Liver	81 (29)	72 (26)
	Brain	15 (5)	14 (5)
	Other	98 (35)	84 (30)
Prior (neo) adjuvant therapies, n (%)	Taxane	162 (58)	162 (58)
	Capecitabine	50 (18)	57 (20)
	Platinum agents	51 (18)	49 (18)
	PD-(L)1 inhibitors	13 (5)	11 (4)

Select Demographics and Characteristics	SG (n=279)	TPC (n=279)
Time since diagnosis of metastatic or locally advanced unresectable disease to randomization, median (range), mo	1.9 (0.4-26.7)	1.9 (0.1-18.9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Patient reported.
[b]Western Europe: Austria, Belgium, France, Germany, Italy, Netherlands, Spain, Switzerland, and United Kingdom. Rest of the world: Argentina, Australia, Brazil, Chile, China, Czech Republic, Hong Kong, Hungary, Israel, Japan, Malaysia, Mexico, Poland, South Korea, Romania, Slovakia, South Africa, Taiwan, and Turkey.
[c]Scores range from 0 to 5; higher scores indicate greater disability.
[d]PD-L1 status assessed using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies) at the time of enrollment; one patient in each treatment arm was considered PD-L1 positive. One patient in the SG arm had PD-L1 CPS missing.
[e]From completion of treatment in the curative setting.
[f]Corresponding numbers: SG: 86 de novo, 59 recurrent disease within 6 to 12 mo, 134 recurrent disease >12 mo; TPC: 83 de novo, 62 recurrent disease within 6 to 12 mo, 134 recurrent disease >12 mo.

Efficacy

Primary endpoint

A total of 349 PFS events were observed at the at the time of the primary analysis. SG significantly improved median PFS vs TPC with a 38% reduction in the risk of disease progression or death, and a higher proportion of patients alive and progression-free at the 6- and 12-mo timepoints (Table 2).[1]

Table 2. ASCENT-03: Primary Endpoint[1]

			SG (n=279)	TPC (n=279)
BICR	PFS, median (95% CI), mo		9.7 (8.1–11.1)	6.9 (5.6–8.2)
	Stratified HR (95% CI); *P*-value		0.62 (0.5–0.77); <0.001	
	PFS rate, % (95% CI)	6-mo	65 (59–71)	53 (47–59)
		12-mo	41 (34–47)	24 (19–30)

Secondary endpoints

At the data cut-off for the final PFS analysis, results for OS were immature and are descriptive only; a numerical trend in favor of SG vs TPC was observed (21.5 mo [17.7–NR] vs 20.2 mo [18.2–NR], respectively).[1]

Statistical testing was not conducted for subsequent endpoints in the statistical hierarchy as the statistical boundary for OS was not crossed, results of these endpoints can, therefore, only be described descriptively. ORR (95% CI) was 48% (42–54) with SG vs 46% (40–52) with TPC (OR 1.12; 95% CI 0.8–1.57). DOR (95% CI) was 12.2 (9.7–13.8) mo vs 7.2 (5.7 8.4) mo with SG vs TPC, respectively.[1]

Safety

The median duration (range) of treatment at the time of the final PFS analysis with SG, taxane, and gem + carbo was 8.3 (<0.1–28.7) mo, 6.3 (<0.1–24.2) mo, and 5.8 (<0.1–23.1) mo, respectively.[1]

The number of patients with TEAEs (any-grade, Grade ≥3, and SAEs) was similar across treatment arms (Table 3). In the SG and TPC arms, TEAEs which resulted in dose interruption, dose reduction, and those which lead to treatment discontinuation occurred in 66% vs 62%, 37% vs 45%, and 4% vs 12% of patients, respectively.[1]

In the SG arm, there were seven deaths due to TEAEs (Table 3); 6 deaths were deemed to be treatment-related (neutropenic colitis [n=1], pneumonia [n=1], and sepsis [n=4]). A single case of acute respiratory failure was not deemed to be treatment-related. All treatment-related deaths in the SG arm were due to infections; five were due to infections secondary to neutropenia, in patients who had risk factors for febrile neutropenia but did not receive prophylaxis with G-CSF; these events occurred early in treatment (two patients on Day 26 [Cycle 2] and one patient each on days 14, 15, and 21 [Cycle 1]). A case of pneumonia showed no evidence of preceding or concurrent neutropenia. In the TPC arm, there was one death due to pleural effusion, this was deemed to be treatment-related.[1,3]

Table 3. ASCENT-03: Safety Summary[1,2]

Safety Outcomes, n (%)	SG (n=275)	TPC (n=276)
Any TEAE	273 (99)	269 (97)
Grade ≥3	181 (66)	171 (62)
Treatment-emergent SAE	71 (26)	67 (24)
Treatment-related	46 (17)	37 (13)
TEAEs that led to treatment discontinuation	10 (4)	33 (12)
TEAEs that led lead to dose interruption	181 (66)	171 (62)
TEAEs that led to dose reduction	101 (37)	124 (45)
TEAEs that led to death	7 (3)	1 (<1)
Treatment-related	6 (2)	1 (<1)

The most common any-grade and Grade ≥3 adverse events are presented in Table 4.

Table 4. ASCENT-03: Any-Grade TEAEs (≥15%) and Grade ≥3 TEAEs (≥5%)[a1]

TEAEs, n (%)	SG (n=275)		TPC (n=276)	
	Any-Grade	Grade ≥3	Any-Grade	Grade ≥3
Neutropenia[b]	183 (67)	118 (43)	157 (57)	112 (41)
Nausea	167 (61)	5 (2)	95 (34)	1 (<1)
Alopecia[c]	151 (55)	-	75 (27)	-
Diarrhea	148 (54)	25 (9)	55 (20)	2 (1)
Fatigue[d]	130 (47)	9 (3)	129 (47)	11 (4)
Anemia[e]	107 (39)	12 (4)	138 (50)	45 (16)
Constipation	104 (38)	0	68 (25)	0
Leukopenia[f]	70 (25)	20 (7)	70 (25)	35 (13)
Vomiting	69 (25)	5 (2)	35 (13)	4 (1)
ALT increased	56 (20)	9 (3)	81 (29)	17 (6)
Cough	49 (18)	0	35 (13)	1 (<1)
Decreased appetite	48 (17)	2 (1)	27 (10)	1 (<1)
AST increased	47 (17)	3 (1)	69 (25)	7 (3)
Headache	47 (17)	1 (<1)	33 (12)	0
Stomatitis	42 (15)	3 (1)	18 (7)	0
Abdominal pain	41 (15)	2 (1)	16 (6)	0
Thrombocytopenia[g]	12 (4)	2 (1)	78 (28)	33 (12)

[a]TEAEs began on or after the first dose date of study drug and ≤30 days after the last dose date of study drug (including crossover treatment if applicable) or the initiation of subsequent anticancer therapy, whichever occurred first. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities, version 27.1, and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
[b]Includes preferred terms of neutropenia and neutrophil count decreased.
[c]Is Grade 1 or 2 per National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0.
[d]Includes preferred terms of fatigue and asthenia.

[e]Includes preferred terms of anemia, hemoglobin decreased, and RBC decreased.
[f]Includes preferred terms of leukopenia and WBC count decreased.
[g]Includes preferred terms of thrombocytopenia and platelet count decreased.

Time to onset and duration of neutropenia and diarrhea[3]

Median time to onset of any-grade and Grade ≥3 diarrhea was shorter for patients treated with SG vs TPC (Table 5). Median duration of diarrhea and neutropenia was generally comparable between treatment arms. These results should be interpreted with caution due to small sample sizes in the TPC arm for time to onset and duration of any-grade and Grade ≥3 diarrhea, and due to the small sample size in the SG arm for time to onset and duration of ≥3 diarrhea.

Table 5. ASCENT-03: Time to Onset and Duration of Neutropenia and Diarrhea[3]

		SG (n=275)				TPC (n=276)			
		Any-Grade		Grade ≥3		Any-Grade		Grade ≥3	
		n	Days (range)	n	Days (range)	n	Days (range)	n	Days (range)
Median time to onset[a]	Neutropenia	187	22 (6–274)	124	22 (7–720)	158	22 (6–406)	113	29 (7–295)
	Diarrhea	148	13 (1–427)	25	67 (6–356)	55	26 (1–296)	2	210 (110–310)
Median duration[b]	Neutropenia	183	9 (2–49)	122	8 (1–36)	155	14 (1–179)	112	8 (1–25)
	Diarrhea	130	6 (1–273)	24	6 (1–18)	48	6 (1–370)	2	1 (1–1)

[a]Defined as time from first dose date of study drug to onset date of first TEAE.
[b]Defined as the median duration among multiple preferred terms; within each preferred term, duration is median duration among multiple episodes (end date of TEAE – onset date of TEAE + 1 day for each episode).

Management of neutropenia[3]

The use of G-CSF as primary prophylaxis was associated with less frequent and less severe neutropenia in the SG arm (Table 6). Neutropenia led to dose reduction in 54 (20%) patients in both arms and treatment discontinuation in 1 (<1%) and 3 (1%) patients in the SG and TPC arms, respectively.

Table 6. ASCENT-03: Management of Neutropenia[3]

Neutropenia, n (%)	SG (n=275)		TPC (n=276)	
Primary G-CSF prophylaxis	Yes (n=54)	No (n=221)	Yes (n=28)	No (n=248)
Any-Grade	28 (52)	159 (72)	21 (75)	137 (55)
Grade ≥3	15 (28)	109 (49)	14 (50)	99 (40)
Secondary G-CSF prophylaxis[a]	Yes (n=81)	No (n=75)	Yes (n=51)	No (n=85)
Any-Grade	46 (57)	52 (69)	38 (75)	50 (59)
Grade ≥3	30 (37)	20 (27)	29 (57)	39 (46)

[a]Excludes patients that received primary G-CSF prophylaxis.

Management of diarrhea[3]

Across treatment arms, most cases of diarrhea were Grade 1–2 (SG: 45% vs TPC: 19%, respectively).

A total of 137 (50%) and 35 (13%) patients received antidiarrheal treatment in the SG and TPC arms, respectively; loperamide was the most common treatment in both arms (SG: 90% vs TPC: 77%). In both treatment arms, multi-antidiarrheal regimens were used in 20% of patients that received any antidiarrheal treatment. Diarrhea led to dose reduction in 15 (5%) patients and to treatment discontinuation in 1 (<1%) patient treated with SG; 3 (1%) cases led to dose reduction. No case of diarrhea led to treatment discontinuation with TPC.

Exploratory analysis: EAIRs[3]

EAIRs, defined as the number of patients with ≥1 specified TEAE per PYE, were calculated as the number of patients with a specific TEAE divided by the total PYE in each group; PYE was defined as the sum of each patient's time at risk (exposure duration) within the study. Due to the exploratory nature of this post hoc analysis, all results presented in Table 7 should be considered nominal.

Any-grade EAIR (95% CI) for SG vs TPC was 40.21 (35.58–45.27) vs 21.66 (19.14– 24.40), respectively. Compared with TPC, the incidence of diarrhea remained higher for SG when adjusted for treatment exposure; compared with SG, the incidence of anemia, thrombocytopenia, and peripheral neuropathy remained higher for TPC when adjusted for treatment exposure.

Table 7. ASCENT-03: Exploratory analysis: EAIRs[3]

TEAEs	SG (n=275)		TPC (n=276)		EAIR Difference (95% CI)
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	
Grade ≥3	181 (66)	1.85 (1.59, 2.14)	171 (62)	2.02 (1.73, 2.35)	-0.18 (-0.59, 0.23)
SAE	71 (26)	0.4 (0.31, 0.51)	67 (24)	0.49 (0.38, 0.63)	-0.09 (-0.25, 0.06)
Led to dose interruption	181 (66)	2.05 (1.76, 2.37)	171 (62)	2.14 (1.83, 2.48)	-0.09 (-0.54, 0.36)
Led to dose reduction	101 (37)	0.68 (0.55, 0.82)	124 (45)	1.15 (0.96, 1.37)	-0.48 (-0.73, -0.23)
Led to treatment discontinuation	10 (4)	0.05 (0.02, 0.09)	33 (12)	0.22 (0.15, 0.3)	-0.17 (-0.26, -0.09)
Led to death	7 (3)	0.03 (0.01, 0.07)	1 (<1)	0.01 (0, 0.04)	0.03 (-0.01, 0.07)
Neutropenia	183 (67)	2.48 (2.13, 2.87)	157 (57)	2.01 (1.71, 2.35)	0.47 (-0.02, 0.96)
Febrile neutropenia	12 (4)	0.06 (0.03, 0.11)	3 (1)	0.02 (0, 0.06)	0.04 (0, 0.09)
Anemia	107 (39)	0.77 (0.63, 0.93)	138 (50)	1.51 (1.27, 1.78)	-0.74 (-1.05, -0.45)
Thrombocytopenia	12 (4)	0.06 (0.03, 0.11)	78 (28)	0.63 (0.5, 0.78)	-0.57 (-0.73, -0.43)
Diarrhea	148 (54)	1.42 (1.2, 1.67)	55 (20)	0.41 (0.31, 0.54)	1.01 (0.76, 1.28)
Fatigue	130 (47)	1.15 (0.96, 1.37)	129 (47)	1.24 (1.03, 1.47)	0.08 (-0.38, 0.21)
Peripheral neuropathy	12 (4)	0.06 (0.03, 0.11)	35 (13)	0.25 (0.17, 0.34)	0.18 (-0.28, -0.1)

References

1. Cortés J, Punie K, Barrios C, et al. Sacituzumab govitecan in untreated, advanced triple-negative breast cancer. *N Engl J Med.* 2025;393(19):1912-1925.
2. Cortés J, Punie K, Barrios C, et al. Sacituzumab govitecan in untreated, advanced triple-negative breast cancer [Supplementary Appendix]. *N Engl J Med.* 2025;393(19):1912-1925.
3. Hurvitz S, Bardia A, Tolaney SM, et al. Safety analysis of ASCENT-03, a Phase 3 study of sacituzumab govitecan vs chemotherapy for previously untreated advanced triple-negative breast cancer in patients who are not candidates for PD-(L)1 inhibitors [Poster PS1-13-24]. Presented at: San Antonio Breast Cancer Symposium (SABCS); 09-12 December 2025; San Antonio, TX.
4. Cortés J, Bardia A, Punie K, et al. Primary results from ASCENT-03: A randomized Phase 3 study of sacituzumab govitecan vs chemotherapy in patients with previously untreated metastatic triple-negative breast cancer who are unable to receive PD-(L)1 inhibitors [Oral LBA20]. Presented at: European Society For Medical Oncology (ESMO) Congress; 17-21 October, 2025; Berlin, Germany.

Abbreviations

1L=first-line
BICR=blinded independent central review
carbo=carboplatin
CPS=combined positive score
EAIRs=exposure-adjusted incidence rates
ECOG PS=Eastern Cooperative Oncology Group Performance Status
G-CSF=granulocyte-colony stimulating factor
gem=gemcitabine
mTNBC=metastatic triple-negative breast cancer
NR=not reached
PD-(L)1=programmed death (ligand) 1
PFS=progression-free survival
PYE=patient-year of exposure
RECIST=Response Evaluation Criteria in Solid Tumors
TEAE=treatment-emergent adverse event
TPC=treatment of physicians' 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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