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Trodelvy® (sacituzumab govitecan-hziy) Use in Early Breast Cancer

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and its use in early breast cancer (BC).

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Trodelvy is not indicated for use in patients with localized BC. 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 Studies: SG Use in Early BC

SASCIA, an ongoing phase 3 study, is evaluating patients with early HER2- BC and RD after NACT.[1,2]

- A prespecified SIA, conducted after 50 patients had completed 4 treatment cycles (SG or TPC, including cape), demonstrated higher rates of any-grade AEs, any-grade hematological AEs, and Grade 3 to 4 hematological AEs with SG vs TPC. Rates of ≥1 dose delay and delays for hematological toxicity were higher with SG than with cape; rates of ≥1 dose reduction were numerically similar.[1]

NeoSTAR, an ongoing, multicohort, phase 2 study, is evaluating neoadjuvant SG ± pembro in patients with early BC.[3,4]

- In the completed Cohort A1, 50 treatment-naive patients with early TNBC received SG. After 4 cycles of SG, 29 patients went directly to surgery without additional NACT, and 21 patients received additional NACT prior to surgery. Fifteen patients (30%) had pCR, and 32 patients (64%) had ORR after SG monotherapy. Grade 3/4 TEAEs included neutropenia (14%), diarrhea (10%), leukopenia (6%). Six percent of patients required reductions in their SG dose. No patients discontinued SG due to AEs or PD.[3,5]
- In the completed Cohort A2, 50 treatment-naive patients with early TNBC received SG + pembro. The primary end point of per-protocol pCR rate (direct to surgery after 4 cycles of SG + pembro without additional NACT) was achieved by 16 patients (32%, 95% CI 19.5–46.7). An additional 9 patients achieved non-protocol pCR after receiving additional NACT prior to surgery due to suspected residual disease on imaging. Overall, 25 (50%, 95% CI 35.5–64.5) patients had pCR at surgery.[6] The most common Grade ≥2 AEs for SG were alopecia (48%), neutropenia (38%) and nausea (32%); and for pembro were hypothyroidism (16%) and colitis (8%). Dose reduction and dose hold occurred in 8% and 24% of patients, respectively. Treatment discontinuations occurred in 5 patients due to toxicity and in 1 patient for PD.[4]

Clinical Studies: SG Use in Early BC

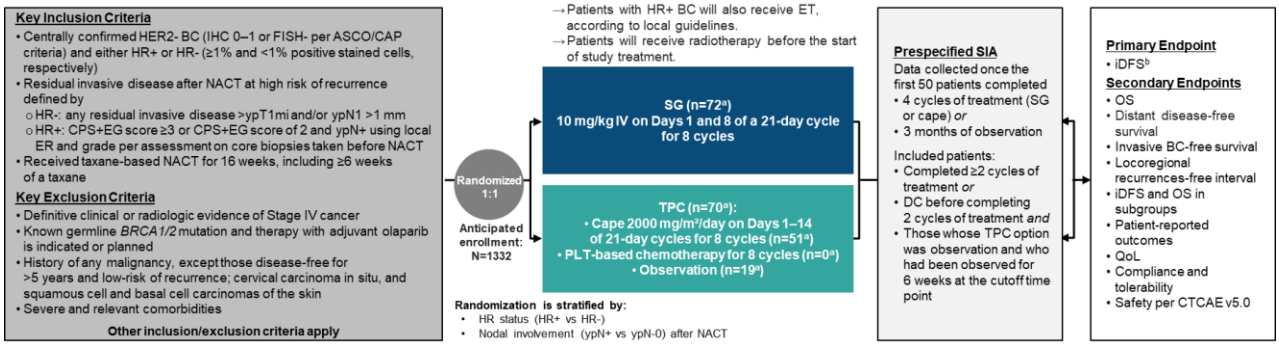
SASCIA Study in Primary HER2- BC

Study design and prespecified SIA population and demographics

SASCIA is an ongoing, phase 3, prospective, multicenter, randomized, open-label, parallel-group study in patients with early HER2- BC with RD after NACT (Figure 1). iDFS is defined as the time from randomization until the first iDFS event (primary endpoint). OS and iDFS are also being assessed according to stratified and predefined exploratory subgroups.[1,2,7]

At the time of the SIA, 88 patients were included in the dataset: SG, n=45; TPC, n=43 (cape, n=32; observation, n=11; Table 1). At the time of presentation, the following proportions of patients were still receiving treatment: SG, 75% (n=33); cape, 65.6% (n=21). Five patients (11.4%) in the SG arm and 8 (25%) in the cape arm had completed treatment.[1]

Figure 1. SASCIA Study Design[1,2,7]



Abbreviations: ASCO/CAP=American Society of Clinical Oncology/College of American Pathologists; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; PLT=platinum; ypT1mi=very small tumor after neoadjuvant therapy.
[a]Number of patients included in the prespecified SIA.
[b]Included local invasive recurrence following mastectomy, local invasive recurrence in the ipsilateral breast after lumpectomy, regional or distant recurrence, contralateral invasive BC, second non-breast primary cancer (excluding squamous or basal cell carcinoma of the skin), or death from any cause.

Table 1. SASCIA SIA: Select Baseline Demographics and Disease Characteristics[1]

Key Demographics and Characteristics		SG (n=45)	TPC (n=43)
Age, median (range), y		46 (24–71)	51 (32–74)
ECOG PS, 0/1, n (%)		41 (91.1)/4 (8.9)	33 (76.7)/10 (23.3)
ypN classification, ypN0/ypN+, n (%)		22 (48.9)/23 (51.1)	24 (55.8)/19 (44.2)
Grading, G2/G3, n (%)		7 (15.6)/38 (84.4)	8 (18.6)/35 (81.4)
ER/progesterone receptor status (central),[a] n (%)	Both negative (TNBC)	30 (66.7)	29 (67.4)
	≥1 positive	15 (33.3)	14 (32.6)
CPS+EG score (HR+ patients only), n (%)	CPS+EG score ≥3	10 (66.6)	9 (64.3)
	CPS+EG score 2, ypN+	5 (33.3)	5 (35.7)
Prior NACT, n (%)	EC/AC, taxane, carbo	23 (51.1)	29 (67.4)
	EC/AC, taxane	20 (44.4)	9 (20.9)
	iddETC	1 (2.2)	3 (7)
	TAC	1 (2.2)	0
	Pembro	1 (2.2)	0

Key Demographics and Characteristics		SG (n=45)	TPC (n=43)
	Taxane + cyclophosphamide	0	2 (4.6)
Background ET (ER+ patients only: SG, n=15; TPC, n=14), n (%)	ET	10 (66.7)	8 (57.1)
	Tamoxifen	6 (40)	6 (42.9)
	Letrozole	4 (26.7)	2 (14.3)
	Ovarian ablation	3 (20)	2 (14.3)

Abbreviations: EC/AC=epirubicin + cyclophosphamide/doxorubicin + cyclophosphamide; iddETC=intense dose-dense epirubicin, paclitaxel, and cyclophosphamide; TAC=docetaxel + doxorubicin + cyclophosphamide.
[a]Cutoff: ≥1% positive stained cells from residual cancer, lymph nodes, or core biopsy.

SIA results[1]

A higher rate of any-grade AEs was observed with SG vs TPC (Table 2). Six SAEs occurred with SG (blood and lymphatic system disorders, n=2; infections and infestations, cardiac disorders, gastrointestinal disorders, and investigations, n=1 each), and 1 SAE occurred with TPC (infection and infestation).

Table 2. SASCIA SIA: Incidence of Any-Grade (≥30%) and High-Grade AEs in Overall Treatment Arms and Among Those Treated With Cape[1]

AEs, %	SG (n=45)		TPC (n=43)		Cape (n=32)	
	Any Grade	High Grade	Any Grade	High Grade	Any Grade	High Grade
Any	100[a]	66.7[b]	86[a]	20.9[b]	100	28.1
Any hematological	97.8[a]	55.6[b]	72.5[a]	0[b]	87.5	0
Leukopenia	97.8[a]	28.9[b]	63.2[a]	0[b]	75	0
Neutropenia[c]	82.2[a]	42.2[b]	31.6[a]	0[b]	37.5	0
Anemia	80[a]	2.2	39.5[a]	0	43.8	0
Any non-hematological	100[a]	33.3	83.7[a]	20.9	96.9	28.1
Alopecia	68.9[a]	0	12.5[a]	0	15.6	0
Nausea	60[a]	4.4	27.5[a]	0	34.4	0
Diarrhea	46.7[a]	4.4	22.5[a]	2.5	28.1	0
Constipation	33.3[a]	0	10[a]	0	12.5	0
Palmar plantar erythrodysesthesia	4.4[a]	0	32.5[a]	7.5	40.6	9.4

[a]*P*<0.05, for SG vs TPC arms for any-grade AEs. [b]*P*<0.05, for SG vs TPC for high-grade AEs.
[c]Febrile neutropenia was observed in 3 patients in the SG arm and in no patients in the TPC arm.

The dose modification rate was generally similar between arms (Table 3), and no unanticipated AEs/toxicities were observed with SG; as a result, the independent data monitoring committee recommended continuation of the study with no modifications.

Table 3. SASCIA SIA: Dose Delays, Reductions, and Treatment Discontinuation[1]

n or n (%)	Dose Delays		Dose Reductions		Discontinued Treatment[a]	
	SG	Cape	SG	Cape	SG	Cape
Number of events	44	16	14	13	6 (13.6)	3 (9.4)
≥1 dose delay/reduction	30 (66.7)	13 (43.3)	12 (26.7)	9 (28.1)	N/A	N/A
Hematological toxicity	21 (46.7)	3 (10)	6 (13.3)	1 (3.1)	N/A	N/A
Organizational reason	10 (22.2)	2 (6.7)	N/A	N/A	N/A	N/A
Unknown reason	4 (8.9)	1 (3.3)	2 (4.4)	5 (15.6)	N/A	N/A
Non-hematological toxicity	3 (6.7)	7 (23.3)	5 (11.1)	6 (18.8)	N/A	N/A
AE not related to study medication	3 (6.7)	1 (3.3)	1 (2.2)	0	N/A	N/A
Other reason	3 (6.7)	1 (3.3)	0	1 (3.1)	N/A	N/A
Patient mistake	N/A	1 (3.3)	N/A	N/A	N/A	N/A

[a]Patient decision (SG, n=3; cape, n=1); investigator decision (SG, n=2; cape, n=1); relapse (SG, n=1; cape, n=1).

Efficacy data for the SASCIA study have not yet been presented.

NeoSTAR Study in Early BC

Study design and demographics

NeoSTAR is an ongoing, multicohort, single-arm, phase 2 Gilead-supported study evaluating the safety and efficacy of neoadjuvant SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle ± pembro on Day 1 of each cycle in treatment-naive patients with early BC across different subtypes. The primary objective is to assess the pCR rate with SG ± pembro.[3]

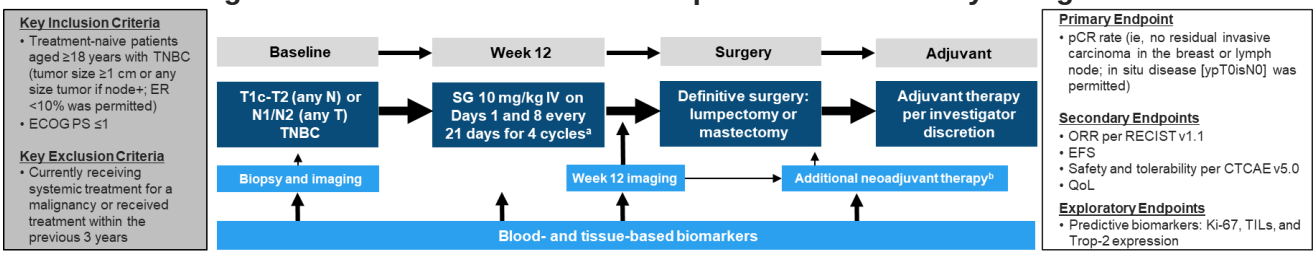
Several cohorts are enrolling patients: Cohort B1/2, SG ± pembro in HR+/HER2- BC (defined as Stage II–III BC with a primary tumor >1.5 cm and high genomic risk); and Cohort C, SG + pembro in HER2- IBC (defined as T4d and any N).[3,8] Results of Cohorts A1/2 are summarized below.

Cohort A1

Adult patients with TNBC (T≥1 cm or any size tumor if node+) who were treatment-naïve were eligible for inclusion.[3]

The median (range) age of patients at diagnosis was 48.5 (31–77) y, 39 patients (78%) had lymph node-negative disease, and 9 (18%) were *BRCA*+ (unknown status, n=1). Most patients (52%; n=26) had Stage II disease; 13 (26%) had Stage I and 11 (22%) had Stage III disease. Most patients (98%) received 4 cycles of SG as monotherapy.[3]

Figure 2. NeoSTAR: Cohort A1 Response-Guided Study Design[3,5]

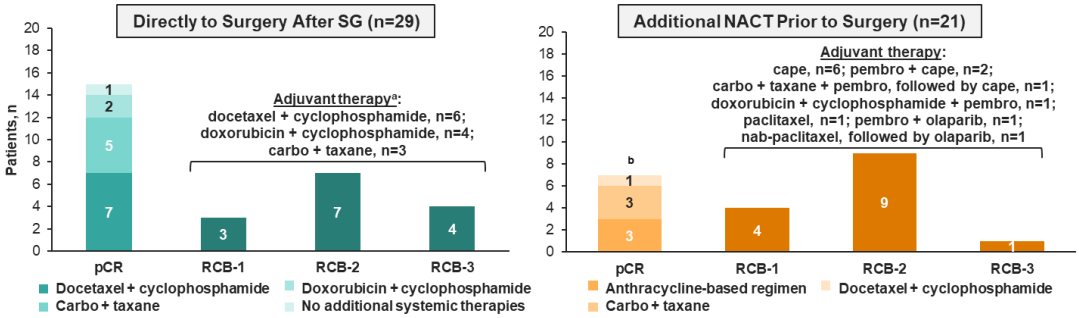


Abbreviations: RECIST=Response Evaluation Criteria in Solid Tumors; T=tumor status (size and extent).
[a]If progression occurred during SG treatment, patients could discontinue SG and undergo surgery or receive NACT (taxane/carbo or dose-dense doxorubicin + cyclophosphamide) per investigator discretion.
[b]If biopsy-confirmed RD was found on Week 12 imaging (after 4 cycles of SG), additional neoadjuvant therapy could be administered per investigator discretion.

Efficacy results: Cohort A1[3]

After 4 cycles of neoadjuvant SG, 29 patients went directly to surgery and 21 patients received additional NACT prior to surgery. Fifteen patients (30%) had a pCR with SG alone (Figure 3), and 32 patients (64%) had an ORR with SG alone (Table 4).

Figure 3. NeoSTAR Cohort A1: Disposition After 4 Cycles of SG Overall and by RCB[3]



Abbreviation: RCB=residual cancer burden.
[a]One patient with RCB-3 at surgery had a metastatic recurrence during radiation therapy. [b]None received adjuvant chemotherapy.

Table 4. NeoSTAR Cohort A1: pCR and ORR Overall, by Disease Stage, and by *BRCA* Status[3]

	Overall (N=50)	Stage I (n=13)	Stage II (n=26)	Stage III (n=11)	*BRCA*+ (n=9)	*BRCA*- (n=40)
pCR, % (95% CI)	30 (18–45)	50 (21–79)[a]	27 (12–48)	18 (2–52)	66.7 (30–93)	Not reported
ORR, % (95% CI)	64 (77–98)	54 (25–81)	69 (48–86)	64 (31–89)	55.6 (21–86)[b]	67.5 (51–81)[c]

[a]Evaluated for pCR, n=12. [b]Five patients achieved a CR or partial response, and 4 patients had stable disease. [c]Twenty-seven patients achieved a CR or partial response, 12 had stable disease, and 1 had PD.

After a median follow-up duration of 18.9 mo (95% CI: 16.3–21.9), the Year 2 EFS was 95% (95% CI: 88–100%). Of the 15 patients who had a pCR after 4 cycles of SG, the Year 2 EFS was 100% (95% CI: inestimable), and the Year 2 EFS was 92% (95% CI: 82–100%; *P*=0.29) among the 35 patients who had RD after SG. The 2 events (death due to BC) occurred in patients with RD who had Stage III disease, high Trop-2 expression, and low TILs.

Safety results: Cohort A1[3,5]

The most common (>50%) all-grade TEAEs included nausea (84%), fatigue (80%), hair loss (76%), neutropenia (58%), and diarrhea (56%). Grade 3 TRAEs included neutropenia (10%), diarrhea (10%), leukopenia (4%), fatigue (4%), and nausea (2%); Grade 4 TRAEs included neutropenia (4%) and leukopenia (2%). Six percent of patients required a reduction in their SG dose. No patients discontinued SG due to an AE or PD. One patient discontinued SG at the discretion of the investigator due to minimal response to therapy.

Biomarker results: Cohort A1[3]

Ninety percent of patients had baseline samples for Ki-67, Trop-2, and %TILs available for analysis. The median (range) Ki-67 and %TIL values were 67 (17.3–90.8) and 40 (1–90), respectively. Twenty-eight patients had H-scores >100; 14 patients had H-scores ≥100, and 3 had H-scores <100.

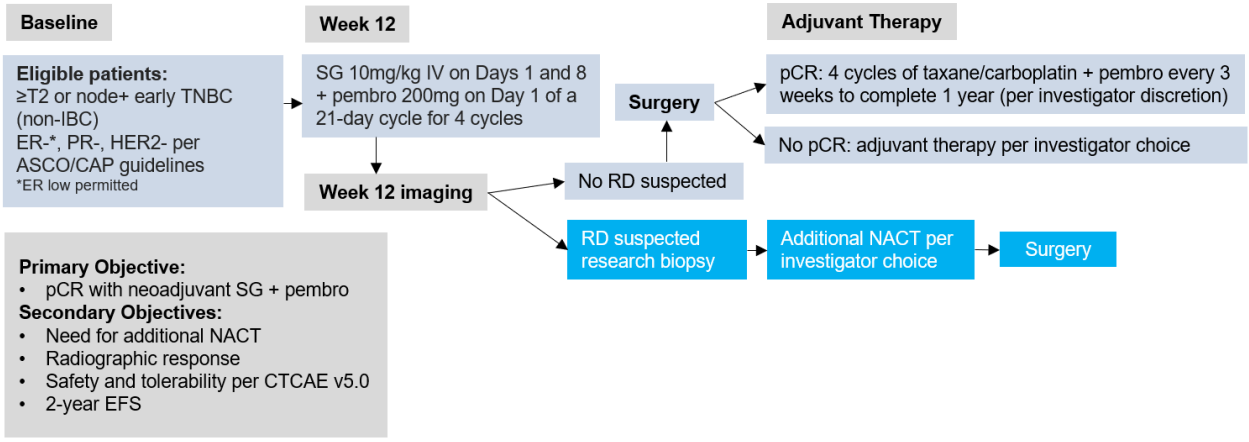
Ki-67 values at baseline were significantly higher among patients with pCR after SG monotherapy than among those who had RD (71.5 vs 55.3; *P*=0.007). Similarly, TIL values at baseline were significantly higher among those with pCR than among those with RD (55% vs 31%; *P*=0.002). Trop-2 expression (*P*=0.44) and H-score (*P*=0.626) were not significantly associated with achievement of pCR.

Cohort A2

Adult patients with early TNBC (T≥2 cm or node+) who were treatment-naïve were eligible for inclusion (Figure 4).[4]

The median (range) age of patients at diagnosis was 57 (23–77) y, 32 patients (64%) had lymph node- disease, and 5 (10%) were *BRCA*+ (unknown status, n=3). Most patients (96%; n=48) had Stage II disease; 2 (4%) had Stage III disease and 90% of patients (n=45) were T≥2 cm.[4]

Figure 4. NeoSTAR: Cohort A2 Response-Guided Study Design[4]



Efficacy results: Cohort A2

After 4 cycles of neoadjuvant SG + pembro, 16 patients (32%) achieved per protocol pCR and went directly to surgery without additional NACT (Table 5). The radiographic response rate (complete or partial response) was 66% (95% CI 50–78): 30% and 36% of patients achieved complete and partial response, respectively. EFS at 18 months was achieved by 90.6% (95% CI 89.2–100) of patients. [4] A total of 9 patients achieved non-protocol pCR after receiving additional NACT as per physician discretion (none with anthracycline-containing regimens): 2 patients had RD confirmed on biopsy, 6 patients had a negative or non-diagnostic RD biopsy, and 1 patient had no biopsy. Overall, 25 (50%, 95% CI 35.5–64.5) patients had pCR at surgery.[6]

Table 5. NeoSTAR Cohort A2: pCR Overall and by Subgroup[4]

	Overall (n=50)	Stage II (n=48)	Stage III (n=2)	BRCA+ (n=5)
pCR, % (95% CI)	32 (19.5–46.7)	33.3 (20.4–48.4)	0 (0–84.2)	60 (14.7–94.7)
	ER low (n=8)	ER- (n=42)	Node+ (n=18)	Node- (n=32)
	37.5 (8.5–75.5)	31 (17.6–47.1)	11.1 (1.4–34.7)	43.8 (26.4–62.3)

Safety results: Cohort A2[4]

The most common Grade ≥2 AEs for SG and pembro are shown in Table 6. A total of 44 patients (88%) completed the study regimen; 5 patients (10%) stopped due to toxicity and 1 patient (2%) progressed on treatment. Dose reduction and dose hold occurred in 4 (8%) and 12 patients (24%), respectively. Growth-factors were used in 13 patients (26%).

Table 6. SG and Pembro Grade ≥2 AEs[4]

AE, n (%)	Grade 2	Grade 3	Grade 4	Total (Grade ≥2)
SG				
Alopecia	24	0	0	24 (48)
Neutropenia	13	5	1	19 (38)
Nausea	14	2	0	16 (32)
Diarrhea	8	2	0	10 (20)
Fatigue	7	1	0	8 (16)
Anemia	5	1	0	6 (12)
Leukopenia	4	0	0	4 (8)
Pembro				
Hypothyroid	8	0	0	8 (16)
Colitis	1	2	1	4 (8)
ALT elevation	0	1	0	1 (2)
Dermatitis	0	1	0	1 (2)
Hyperglycemia	0	1	0	1 (2)
Psoriasis	1	0	0	1 (2)

ASCENT-05: SG in Early BC[9]

The ongoing phase 3 ASCENT-05 study (NCT05633654) will compare the efficacy and safety of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle + pembro 200 mg IV on Day 1 of a 21-day cycle for 8 cycles with that of TPC (pembro [dosed as above] ± cape 1000 mg/m^2 orally twice daily on Days 1 to 14 of a 21-day cycle for 8 cycles) in patients with TNBC and residual disease after surgery and neoadjuvant therapy.

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Abbreviations

AE=adverse event
BC=breast cancer
BRCA=breast cancer gene
cape=capecitabine
carbo=carboplatin
CPS+EG=clinical stage and post-treatment pathologic score and estrogen receptor status and tumor grade
CTCAE=Common Terminology Criteria for Adverse Events
ECOG PS=Eastern Cooperative Oncology Group performance status
EFS=event-free survival
ER=estrogen receptor
ET=endocrine therapy
H-score=histochemical score
HER2=human epidermal growth factor receptor 2
HR=hormone receptor
IBC=inflammatory breast cancer
iDFS=invasive disease-free survival
Ki-67=antigen Kiel 67
Node+=node positive
Node-=node negative
N=node status
Nab-paclitaxel=nanoparticle albumin-bound paclitaxel
NACT=neoadjuvant chemotherapy
ORR=overall response rate
OS=overall survival
pCR=pathological complete response
PD=progressive disease
pembro=pembrolizumab
QoL=quality of life
RD=residual disease
SAE=serious adverse event
SG=sacituzumab govitecan-hziy
SIA=safety interim analysis
T≥1=tumor size ≥1 cm
T≥2=tumor size ≥2 cm
TIL=tumor infiltrating lymphocyte
TNBC=triple-negative breast cancer
TPC=treatment of physician's choice
TRAE=treatment-related adverse event
Trop-2=trophoblast cell surface antigen 2
ypN=lymph node status after neoadjuvant therapy

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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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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