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Trodelvy® (sacituzumab govitecan-hziy) Patient-Reported Outcomes 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 patient-reported outcomes (PROs) in first-line (1L) treatment of 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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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, as a single agent, is indicated for the 1L treatment of adult patients with unresectable locally advanced or mTNBC who are not candidates for PD-(L)1 inhibitor based therapy.

PROs With SG Use in 1L PD-(L)1 Inhibitor-Ineligible mTNBC

ASCENT-03, an ongoing, global, open-label, randomized, phase 3 study, is comparing the efficacy and safety of SG vs chemotherapy TPC as 1L treatment in patients (N=558) with previously untreated, locally advanced, unresectable or mTNBC who were not candidates for PD-(L)1 inhibitor therapy.[2]

PROs, assessed using the EORTC QLQ-C30 questionnaire, were compared between the SG and TPC arms.[3]

- At BL, PRO scores for EORTC QLQ-C30 domains were generally comparable between treatment arms and general population norms.
- Key secondary endpoints from the EORTC QLQ-C30 were as follows:
  - Mean change from BL in the physical functioning domain at Week 25 (key secondary endpoint) was 1.1 in the SG arm and -6.2 in the TPC arm (LSM difference, 6.89; 95% CI: 3.5–10.28).
  - Median (95% CI) TTDs for the fatigue domain (key secondary endpoint) were similar between treatment arms: SG, 1.4 (1.1–1.7); TPC, 1.6 (1.2–1.9); stratified HR, 0.98 (95% CI: 0.8–1.19).
- Exploratory endpoints from the EORTC QLQ-C30 were as follows:
  - The LSM change from BL to Week 25 favored SG vs TPC in scores for several domains, including role functioning (-1.8 vs -10.12, respectively), GHS/QoL (-0.27 vs -4.67), pain (-5.93 vs 0.25), fatigue (4.29 vs 10.18), and dyspnea (2.32 vs 7.43),

and the change from BL to Week 25 for the diarrhea domain favored TPC vs SG (4.75 vs 10.27, respectively).
  - The median TTD for the dyspnea domain favored SG vs TPC (HR, 0.69; 95% CI: 0.54–0.87) and the TTDs for nausea/vomiting (HR, 1.44; 95% CI: 1.16–1.78) and diarrhea (HR, 1.98; 95% CI: 1.58–2.48) domains favored TPC vs SG.
  - Median (95% CI) TTCDs for the fatigue domain were similar between treatment arms: SG, 1.5 (1.1–2.1); TPC, 1.9 (1.2–2.7); stratified HR, 0.96 (95% CI: 0.78–1.18).
  - Among domains where >50% of patients were eligible for improvement, TTIs (HR; 95% CI) were shorter with SG than with TPC for the following domains, including physical functioning (1.7; 1.23–2.34); role functioning (1.47; 1.1–1.97); social functioning (1.3; 0.99–1.71); fatigue (1.43; 1.11–1.84); and insomnia (1.44; 1.12–1.85). These findings suggested that patients who had poor QoL at BL could experience a faster benefit with SG than with TPC.

In a post hoc analysis using pooled data from both treatment arms (N=558), associations between disease control and LSM change from BL through Week 25 in five EORTC QLQ-C30 domains were evaluated; *P*-values were nominal and results are descriptive only.[4]

- PD was associated with worsening from BL in GHS/QoL (-4.33), physical functioning (-2.24), role functioning (-4.53), and pain (6.06).
- OR (complete or partial response) was associated with improvements from BL in GHS/QoL (2.37), physical functioning (1.4), role functioning (2.14), and pain (-3.61).
- Compared with PD, OR (complete or partial response) was associated with more favorable changes from BL in all five domains assessed (GHS/QoL, physical functioning, role functioning, pain, and fatigue; each, nominal $P \leq 0.003$).
- Longer DOR was associated with modestly better GHS/QoL (0.03/day) and less fatigue (-0.034/day).

PROs With SG Use in 1L PD-(L)1 Inhibitor-Ineligible mTNBC

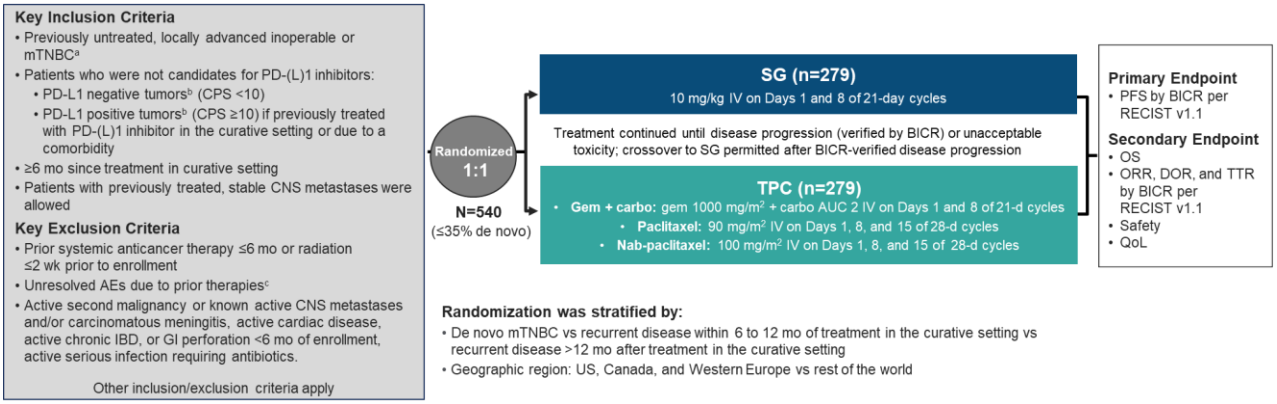
ASCENT-03 Study

Study design and demographics

ASCENT-03, an ongoing, global, open-label, randomized, phase 3 study, is comparing the efficacy and safety of SG vs TPC as 1L treatment in patients (N=558) with previously untreated, locally advanced, unresectable or mTNBC who were not candidates for PD-(L)1 inhibitor therapy (Figure 1).[2]

The study enrolled patients whose tumors did not express PD-L1 (PD-L1 negative tumors [CPS <10]) and patients whose tumors 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 BL 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.[2]

Figure 1. ASCENT-03: Study Design[2,5,6]



Abbreviations: AE=adverse event; AUC=area under the concentration-time curve; carbo=carboplatin; CNS=central nervous system; gem=gemcitabine; GI=gastrointestinal; IBD=inflammatory bowel disease; IHC=immunohistochemistry; ORR=objective response rate; OS=overall survival; TNBC=triple-negative breast cancer; TTR=time to response.
[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.

PRO endpoints and results

In the statistical testing hierarchy, OS will be formally tested for significance once PFS is statistically significant, followed by ORR, and QoL endpoints (once the prior endpoint in the hierarchy was significant).[5]

Specifically, key secondary PRO endpoints using the EORTC QLQ-C30 included the change from BL to Week 25 in the physical functioning domain and TTD in the fatigue domain. TTD was defined as the duration of time between treatment randomization and the study assessment at which the patient noted the first worsening that was exceeding prespecified MWPC from BL or death.[3]

Exploratory endpoints included the following[3]:

- Change from BL to Week 25 in EORTC QLQ-C30 domains other than physical functioning;
- TTD in domains except for fatigue;
- TTCD, which was defined as a meaningful deterioration from BL that was confirmed at the next study visit or was followed by a missing visit that assessed PROs or death that occurred <56 days after the last PRO assessment (or death that occurred <56 days post-randomization if the BL/post-BL assessments were missing);
- TTI, which was defined as the duration of time between treatment randomization and the first assessment at which the patient had an improvement that was exceeding prespecified MWPC from BL.

The assessment schedule for PROs was BL and Day 1 of all cycles until the end of treatment. At BL, PRO scores for EORTC QLQ-C30 domains were generally comparable between treatment arms and with general population norms; however, the physical functioning, role functioning, and pain domains generally had worse scores.[3]

Results[3]

EORTC QLQ-C30: physical functioning and fatigue domains

For the key secondary endpoint of change from BL to Week 25 in the physical functioning domain, scores were relatively stable through Week 25 for the SG arm (n=158; mean [SD] change from BL, 1.1 [18.32]) and tended to worsen in the TPC arm (n=135; mean [SD] change from BL, -6.2 [16.77]). The LSM changes from BL to Week 25 by treatment arm were as follows: SG, 0.32; TPC, -6.58; LSM difference [SE], 6.89 [1.72] (95% CI: 3.5–10.28; Table 1). The MID for this domain was 6.47, with positive values indicating an improvement and negative values indicating a deterioration. The LSM changes from BL were nominally different between groups beginning at Week 16 and continued through Week 25 (each, $P<0.05$).

For the key secondary endpoint of TTD in the fatigue domain, median (95% CI) TTDs were similar between treatment arms: SG, 1.4 (1.1–1.7); TPC, 1.6 (1.2–1.9); stratified HR, 0.98 (95% CI: 0.8–1.19). The MWPC prespecified threshold was a worsening from BL by ≥10-points or death.

EORTC QLQ-C30: change from BL to Week 25 in all domains

Results for change from BL to Week 25 favored SG vs TPC for physical functioning (key secondary endpoint) and for the exploratory endpoints, including role functioning, GHS/QoL, pain, fatigue, and dyspnea; the change for the diarrhea domain favored TPC vs SG (Table 1).

Table 1. ASCENT-03: Mean Change From BL in EORTC QLQ-C30 Scores at Week 25[3]

EORTC QLQ-C30 Domain	LSM Change From BL to Week 25		Difference (95% CI)	MID
	SG	TPC		
Functioning domains				
Physical functioning	0.32	-6.58	**6.89 (3.5–10.28)**[a,b]	6.47
Role functioning	-1.8	-10.12	**8.33 (3.6–13.05)**[a,b]	8.24
Social functioning	-4.39	-8.33	3.94 (-0.7 to 8.58)	7.69
Emotional functioning	3.94	1.06	2.89 (-1.13 to 6.9)	7.01
Cognitive functioning	-3.08	-4.83	1.74 (-1.64 to 5.13)	5.83
GHS/QoL	-0.27	-4.67	4.41 (0.58–8.24)[a]	6.44
Symptom domains				
Pain	-5.93	0.25	-6.18 (-11.2 to -1.16)[a]	8.52
Fatigue	4.29	10.18	-5.89 (-10.43 to -1.35)[a]	7.12
Dyspnea	2.32	7.43	-5.11 (-9.83 to -0.39)[a]	7.24
Appetite loss	-0.29	3.73	-4.03 (-9.2 to 1.14)	7.83
Insomnia	-4.04	-0.79	-3.24 (-8.53 to 2.04)	9.03
Constipation	1.84	2.74	-0.9 (-5.72 to 3.92)	7.45
Financial difficulties	1.55	1.08	0.47 (-4.02 to 4.96)	8.85
Nausea/vomiting	4.52	2.15	2.38 (-1.36 to 6.11)	4.29
Diarrhea	10.27	4.75	5.52 (0.84–10.2)[c]	4.24

[a]Cells shaded in light blue denote those where SG treatment was favored vs TPC: if difference (95% CI) was >0 for GHS/QoL and functioning domains or if difference (95% CI) was <0 for symptom domains.
[b]Bolded cells indicate those whose LSM difference was >MID of 0.3 × SD.
[c]Cells shaded in light teal denote those where TPC treatment was favored vs SG: if difference (95% CI) was <0 for GHS/QoL and functioning domains or if difference (95% CI) was >0 for symptom domains.

EORTC QLQ-C30: TTD in all domains

TTDs for most domains were generally similar between treatment arms, including for the fatigue domain (key secondary endpoint). Among the exploratory TTD endpoints (domains

other than fatigue), the TTD for the dyspnea domain favored SG vs TPC, and the TTDs for the nausea/vomiting and diarrhea domains favored TPC vs SG (Table 2).

Table 2. ASCENT-03: TTD in EORTC QLQ-C30 Domains[3]

EORTC QLQ-C30 Domain	TTD,[a] Median (95% CI), Months		HR (95% CI)[b]
	SG (n=279)	TPC (n=279)	
Functioning domains			
GHS/QoL	3.9 (2.2–5.4)	3.7 (2.8–4.5)	0.95 (0.76–1.18)
Physical functioning	5.3 (3.9–7.2)	3.8 (3.2–4.9)	0.88 (0.7–1.1)
Role functioning	1.6 (1.4–2.2)	2.6 (1.9–3.1)	1.05 (0.85–1.29)
Emotional functioning	7.3 (4.9–9.7)	7.3 (5.6–9)	1.01 (0.79–1.28)
Cognitive functioning	3.5 (2.8–4.6)	3.5 (2.8–3.8)	0.94 (0.76–1.16)
Social functioning	2.2 (1.6–3.1)	3.1 (2–4.1)	1.05 (0.85–1.3)
Fatigue	1.4 (1.1–1.7)	1.6 (1.2–1.9)	0.98 (0.8–1.19)
Symptom domains			
Nausea/vomiting	2 (1.6–2.8)	4 (2.8–5.8)	1.44 (1.16–1.78)[c]
Pain	5.2 (3.2–6.5)	3 (2.6–4.4)	0.85 (0.68–1.07)
Dyspnea	10 (6.3–12.2)	4.8 (3.4–5.7)	0.69 (0.54–0.87)[d]
Insomnia	5.3 (4–7.6)	4.2 (3.4–5.6)	0.89 (0.7–1.12)
Appetite loss	4 (2.4–5.2)	4.6 (3.1–5.6)	1.08 (0.86–1.35)
Constipation	2.8 (2.1–3.7)	3.8 (2.9–5.3)	1.14 (0.91–1.44)
Diarrhea	1.7 (1.4–2.2)	5.7 (4.7–8.4)	1.98 (1.58–2.48)[c]
Financial difficulties	8.5 (6.9–NR)	7.7 (5–11.5)	0.96 (0.74–1.26)

[a]TTD was defined as the duration of time between treatment randomization and the study assessment at which the patient first had a worsening in the assessment that exceeded the prespecified MWPC of ≥10-points (13.33 for the physical functioning domain, as this domain's scores increased in 6.67-point increments) from BL or death.
[b]The HR for the time to first meaningful deterioration for a domain or death, or without premature discontinuation due to a reason other than death, if it occurred <56 d from the last attended study visit.
[c]Cells shaded in light teal denote domains that favored TPC (HR >1 and log-rank nominal *P*<0.05).
[d]Cells shaded in light blue denote domains that favored SG (HR <1 and log-rank nominal *P*<0.05).

EORTC QLQ-C30: TTCD

The median (95% CI) TTCDs for the fatigue domain were similar between treatment arms: SG, 1.5 (1.1–2.1); TPC, 1.9 (1.2–2.7); stratified HR, 0.96 (95% CI: 0.78–1.18).

EORTC QLQ-C30: TTI

Several domains had TTIs that were shorter with SG than with TPC among domains where >50% of patients were eligible for improvement (defined as patients with BL scores ≤90 for functional domains and ≥10 for symptom domains), which suggested that patients who had poor QoL at BL could experience a faster benefit with SG than with TPC (Table 3).

Table 3. ASCENT-03: TTI in EORTC QLQ-C30 Domains With >50% of Patients Eligible for Improvement[3]

EORTC QLQ-C30 Domain	TTI,[a] Median (95% CI), Months		HR (95% CI)[b,c]
	SG (n=279)	TPC (n=279)	
GHS/QoL	5.7 (3–NR)	NR (6.3–NR)	1.25 (0.97–1.62)
Physical functioning	3.9 (2.5–9.9)	NR (19.6–NR)	1.7 (1.23–2.34)
Role functioning	1.7 (1.4–2.3)	2.1 (1.6–NR)	1.47 (1.1–1.97)
Emotional functioning	1.5 (1.2–1.9)	2.1 (1.6–2.8)	1.24 (0.99–1.56)
Social functioning	1.5 (1.4–2.1)	2 (1.5–3.7)	1.3 (0.99–1.71)
Fatigue	3 (1.8–5.3)	6.6 (3.1–NR)	1.43 (1.11–1.84)
Pain	1.4 (1–1.5)	1.1 (1–1.8)	1.21 (0.96–1.52)

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Insomnia	1.4 (1.1–1.8)	1.9 (1.5–2.7)	1.44 (1.12–1.85)

[a]Defined as the duration of time between treatment randomization and the time that a patient first had an improvement from BL that exceeded the prespecified MWPC by ≥10-points or death.
[b]HR >1 and Gray's test nominal *P*<0.05 favored SG vs TPC. Rows shaded in light blue denote domains favored SG vs TPC.
[c]Referred to the HR for the TTI in a domain prior to a premature discontinuation of treatment due to any cause.
Note: Eligible patients had BL scores ≤90 for functional domains and ≥10 for symptom domains.

Association between disease control and patient-reported functioning and QoL[4]

A post hoc analysis of pooled data from both treatment arms evaluated associations between disease control and LSM change from BL in five EORTC QLQ-C30 domains in the ITT population (N=558). PD and OR were modeled as binary time-varying covariates, and DOR as a continuous time-varying covariate, using mixed models for repeated measures, with data limited to assessments through Week 25 to minimize the risk of selection bias. *P*-values were nominal and not adjusted for multiplicity.

Results

PD was associated with worsening from BL in GHS/QoL, physical functioning, role functioning, and pain, and OR was associated with improvements from BL in the same domains. Compared with PD, OR (complete or partial response) was associated with more favorable changes from BL in all five domains. Longer DOR was associated with modestly better GHS/QoL and less fatigue (Table 4).

Table 4. ASCENT-03: Association Between Disease Control and LSM Change From BL in EORTC QLQ-C30 Scores Through Week 25 (Pooled ITT Population)[4]

EORTC QLQ-C30 Domain	PD vs No PD		OR vs No Response		OR vs PD		DOR per Day[a]	
	Difference in LSM Change	*P*-value	Difference in LSM Change	*P*-value	Difference in LSM Change	*P*-value	Difference in LSM Change	*P*-value
Functioning domains								
GHS/QoL	-4.33	<0.001	2.37	0.002	3.92	<0.001	0.03	0.026
Physical functioning	-2.24	0.018	1.4	0.028	1.89	0.003	0.019	0.139
Role functioning	-4.53	0.001	2.14	0.025	3.01	0.001	0.026	0.13
Symptom domains								
Pain	6.06	<0.001	-3.61	<0.001	-6.26	<0.001	-0.019	0.313
Fatigue	1.64	0.211	-1.16	0.201	-2.44	0.003	-0.034	0.04

[a]DOR represented cumulative days from first documented complete or partial response to PRO assessment; nonresponders were assigned a DOR of 0.

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Abbreviations

BICR=blinded independent central review
BL=baseline
CPS=combined positive score
DOR=duration of response
EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
GHS=global health status
HR=hazard ratio
LSM=least squares mean
MID=minimum important difference
MWPC=meaningful within patient change
NR=not reached
OR=objective response
ORR=objective response rate
OS=overall survival
PD=progressive disease
PFS=progression-free survival
QoL=quality of life
RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1
SG=sacituzumab govitecan-hziy
TPC=treatment of physicians' choice
TTCD=time to confirmed deterioration
TTD=time to first deterioration
TTI=time to first improvement

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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