Health-related quality of life (HRQoL) in the ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC)

Poster 257P

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Background

- Sacituzumab govitecan (SG) is an antibody-drug conjugate composed of an anti-Trop-2 antibody coupled to SN-38 via a proprietary hydrolyzable linker.
- In the phase 3 ASCENT trial, SG was compared with single-agent chemotherapy treatment of physician's choice (TPC) in patients with refractory or relapsed metastatic triple-negative breast cancer (mTNBC) [1].
- In the intent-to-treat (ITT) analysis, SG significantly prolonged progression-free survival (PFS; median 4.8 vs. 1.7 months; hazard ratio [HR]=0.41, 95% confidence interval [CI]: 0.32, 0.52; p<0.0001) and overall survival (OS; median 11.8 vs. 6.9 months; HR=0.51, 95% CI: 0.41, 0.62; p<0.0001) vs. TPC.
- In this analysis, we assessed the impact of SG on health-related quality of life (HRQoL) in the ASCENT trial.
- The main objective was to determine whether HRQoL was similar in patients receiving SG compared to those receiving TPC over the course of treatment.

Methods

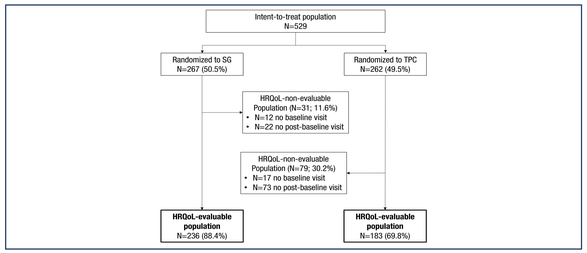
- In ASCENT (NCT02574455), patients with refractory or relapsed mTNBC after ≥2 prior lines of therapy (at least one in the metastatic setting) and with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 were randomized 1:1 to open-label treatment with SG or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine).
  - SG was administered on days 1 and 8 of a 21-day treatment cycle.
  - Treatment schedules for TPC varied between treatments.
  - SG treatment and TPC continued until disease progression or unacceptable adverse events.
- HRQoL was assessed at baseline (≤28 days before cycle 1 day 1), on day 1 of each cycle, and at the final study visit (4 weeks after the last dose of study drug or at premature study termination) and using the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30).
  - Global health status/QoL, physical functioning, role functioning, pain, and fatigue were selected a priori as the primary HRQoL domains in this analysis because they are clinically relevant to the target population and have been used as the primary HRQoL domains in other published studies [2-4].
  - The remaining EORTC QLQ-C30 domains were assessed as secondary HRQoL domains.
  - An increased score for the global health status/quality of life (QoL) and functioning domains reflects improvement, whereas an increased score for the symptom domains indicates worsening.
- The analyses were based on the HRQoL-evaluable population: all patients in the ITT population who had an evaluable assessment of the EORTC QLQ-C30 at baseline and at least one post-baseline assessment (an evaluable assessment was defined as at least one of the 15 EORTC QLQ-C30 domains being completed).
- Linear mixed-effect models for repeated measures (MMRM) were used to assess between-group differences in data collected up to cycle 6 (when n was ≥25 in both treatment arms), adjusting for baseline scores, treatment, visit, and the stratification factors.
- Least-square (LS) mean changes from baseline in HRQoL scores were estimated for SG and TPC and were compared between treatment arms.
- To assess non-inferiority and superiority of SG vs. TPC, minimal important difference (MID) values based on previously published thresholds were applied [5].
- Time to first clinically meaningful improvement or deterioration of HRQoL (improvement or worsening above a pre-specified threshold of 10 points [6]) was analyzed by the Kaplan-Meier product limit method.
- Cox proportional hazards regression models were used to estimate HRs for first clinically meaningful improvement or deterioration of HRQoL for SG vs. TPC. The models were adjusted for baseline score and were stratified by number of prior treatments for advanced disease (2 or 3 vs. >3), geographic region (North America vs. rest of the world), and known brain metastases at study entry (yes vs. no).

Results

Disposition

- The HRQoL-evaluable population comprised 236 patients randomized to SG and 183 randomized to TPC (**Figure 1**).

Figure 1. Patient Disposition



HRQoL, health-related quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Results (cont.)

Patients

- For the HRQoL-evaluable population, the two treatment arms were well balanced on demographics and baseline clinical characteristics (**Table 1**).

Table 1. Demographics and Baseline Clinical Characteristics

	SG (N=236)	TPC (N=183)
Age (years)		
Mean (standard deviation)	53.8 (11.8)	55.5 (11.8)
Median	54	54
Race, n (%)		
Asian	10 (4.2)	8 (4.4)
Black or African American	22 (9.3)	27 (14.8)
White	195 (82.6)	139 (76.0)
Other	9 (3.8)	9 (4.9)
Number of prior lines of chemotherapy, n (%)		
2 or 3	168 (71.2)	132 (72.1)
>3	68 (28.8)	51 (27.9)
Number or prior systemic therapies		
Mean (standard deviation)	4.4 (1.9)	4.4 (2.1)
Median	4	4
Known brain metastases at study entry, n (%)		
Yes	27 (11.4)	18 (9.8)
No	209 (88.6)	165 (90.2)
Geographic region, n (%)		
North America	153 (64.8)	119 (65.0)
Rest of the world	83 (35.2)	64 (35.0)
BRCA 1/BRCA 2 mutation status, n (%)		
Negative	136 (57.6)	101 (55.2)
Postive	15 (6.4)	14 (7.7)
Missing	85 (36.0)	68 (37.2)
Time from diagnosis to study entry (months)		
Mean (standard deviation)	61.2 (62.0)	65.1 (64.2)

SG, sacituzumab govitecan; TPC, treatment of physician's choice.

HRQoL Assessments

- The completion rate (number of valid HRQoL assessments divided by number of ITT patients expected to provide an HRQoL assessment at that timepoint) was generally ≥90% up to cycle 6 and was comparable between SG and TPC across visits.
- The available data rate (number of valid HRQoL assessments divided by the number of ITT patients randomized at the start of the study) declined in both treatment arms, but was consistently higher in the SG arm than in the TPC arm.
- Mean baseline scores (out of range 0 to 100) for the primary HRQoL domains were generally comparable between treatment arms (**Table 2**). Baseline functioning and symptoms were worse compared to a general population with similar age and gender distributions. TPC arm had worse global health status/QoL compared to the SG arm.

Table 2. Mean Scores for the Primary HRQoL Domains of the HRQoL-evaluable Population at Baseline

	SG (N=236)	TPC (N=183)	General population norm [7]	Between-group MID [5]
Global health status/QoL*	63.2 (20.6)	58.1 (21.9)	63.6	4
Physical functioning†	74.9 (20.5)	73.0 (20.3)	83.4	5
Role functioning†	69.6 (29.5)	67.9 (29.3)	83.0	6
Fatigue§	38.3 (25.2)	40.1 (25.2)	31.3	5
Pain§	36.4 (30.1)	40.3 (29.4)	26.7	6

Red: difference compared to the general population norm greater than the pre-specified MID. Underlined: TPC worse than SG by greater than MID.
*A higher score represents higher QoL
†A higher score represents a higher level of functioning
§A higher score represents a higher level of symptomatology
MID, minimal important difference; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

- SG was non-inferior to TPC on all primary HRQoL domains, and was superior to TPC on global health status/QoL, physical functioning, fatigue, and pain (**Table 3**).
- SG was inferior to TPC on nausea/vomiting and diarrhea, but was non-inferior to TPC on all other secondary HRQoL domains.
- SG was superior to TPC on emotional functioning, dyspnea, and insomnia.

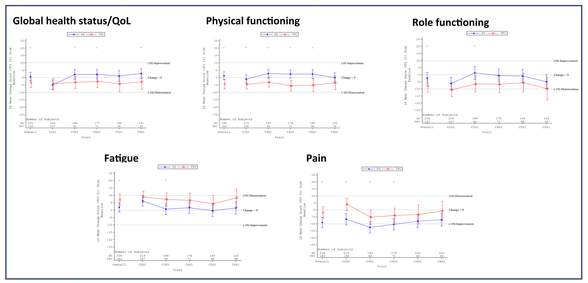
Table 3. Linear MMRM Analysis of Overall LS Mean Change from Baseline in Scores for the Primary and Secondary HRQoL Domains

	LS mean change from baseline (95% CI)			Non-inferiority margin (MID) [5]
	SG (N=236)	TPC (N=183)	SG minus TPC	
Primary HRQoL domains				
Global health status/QoL^	0.66 (-2.21, 3.53)	-3.42 (-6.77, -0.08)	4.08 (0.82, 7.35)*	-4
Physical functioning†	1.31 (-1.38, 3.99)	-4.39 (-7.52, -1.26)	5.69 (2.63, 8.76)**	-5
Role functioning†	-2.24 (-6.13, 1.65)	-7.83 (-12.41, -3.25)	5.59 (1.13, 10.05)*	-6
Fatigue§	1.97 (-1.20, 5.13)	7.13 (3.40, 10.87)	-5.17 (-8.81, -1.52)*	+5
Pain§	-8.93 (-12.57, -5.30)	-1.89 (-6.18, 2.40)	-7.04 (-11.24, -2.85)**	+6
Secondary HRQoL domains				
Emotional functioning†	3.34 (0.46, 6.22)	-0.55 (-3.94, 2.84)	3.89 (0.56, 7.22)*	-3
Cognitive functioning†	-1.22 (-4.00, 1.56)	-1.98 (-5.21, 1.24)	0.76 (-2.36, 3.89)	-3
Social functioning†	-1.51 (-5.47, 2.45)	-5.41 (-10.04, -0.78)	3.90 (-0.61, 8.40)	-5
Nausea/vomiting§	4.30 (1.92, 6.68)	2.50 (-0.23, 5.22)	1.81 (-0.83, 4.44)	+3
Dyspnea§	-3.79 (-7.52, -0.06)	3.95 (-0.51, 8.40)	-7.74 (-12.13, -3.35)**	+4
Insomnia§	-4.69 (-8.92, -0.46)	0.34 (-4.64, 5.32)	-5.03 (-9.89, -0.16)*	+4
Appetite loss§	3.52 (-0.47, 7.51)	7.00 (2.31, 11.68)	-3.47 (-8.05, 1.11)	+5
Constipation§	2.16 (-1.76, 6.08)	2.69 (-1.89, 7.27)	-0.53 (-4.97, 3.91)	+5
Diarrhea§	14.07 (9.94, 18.20)	-1.27 (-6.08, 3.54)	15.34 (10.65, 20.03)**	+3
Financial difficulties§	-2.87 (-6.39, 0.65)	0.68 (-3.50, 4.86)	-3.55 (-7.69, 0.59)	+3

Red: SG superior to TPC (based on the MID and significance testing). Underlined: upper or lower bound (as applicable) of the 95% CI did not exceed the non-inferiority margin.
* p<0.05; ** p<0.01
^A higher score represents higher QoL
†A higher score represents a higher level of functioning
§A higher score represents a higher level of symptomatology
CI, confidence interval; HRQoL, health-related quality of life; LS, least-square; MMRM, mixed-effect model for repeated measures; QoL, quality of life.

- For each of the primary HRQoL domains, the SG arm had statistically significantly better overall mean change and changes at one or more assessments (**Figure 2**).

Figure 2. LS Mean Changes from Baseline in Scores for the Primary HRQoL Domains



Data are from an MMRM analysis.
*Statistically significant (p<0.05) difference between SG and TPC.
CI, confidence interval; LS, least-square; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

- Time to first clinically meaningful deterioration (within individual worsening ≥ responder definition [RD] of 10) was significantly longer for SG vs. TPC for physical functioning, role functioning, fatigue, and pain, but not for global health status/QoL (**Table 4**).
- Time to first clinically meaningful improvement (within individual improvement ≥ RD of 10) in physical functioning (HR=1.66, p=0.01) and pain (HR=1.41, p=0.01) was significantly shorter in the SG arm than the TPC arm.

Table 4. Time to First Clinically Meaningful Deterioration of HRQoL for the Primary HRQoL domains

	Median time to first clinically meaningful deterioration (weeks)		HR	95% CI
	SG (N=236)	TPC (N=183)		
Global health status/QoL*	14.1	15.1	0.87	0.70, 1.07
Physical functioning†	22.1	12.1	0.61	0.49, 0.75**
Role functioning†	11.4	7.1	0.70	0.56, 0.86**
Fatigue§	7.7	6.0	0.82	0.66, 1.00*
Pain§	21.6	9.9	0.60	0.48, 0.74**

Death was treated as an event.
* p<0.05; ** p<0.01
CI, confidence interval; HR, hazard ratio; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Conclusions

- For the primary HRQoL domains, the SG arm showed statistically significant and/or clinically meaningful greater improvements than for the TPC arm.
- Although the SG arm had greater symptomatology than the TPC arm for nausea/vomiting and diarrhea, this did not seem to translate to an adverse impact on functioning or global health status/QoL domains at the cohort level.
- SG significantly prolonged time to first deterioration in all HRQoL domains except for global health status/QoL and significantly shortened time to improvement in physical functioning and pain.
- In patients with refractory or relapsed mTNBC after ≥2 prior lines of therapy (at least one in the metastatic setting), SG not only significantly extended PFS and OS compared to TPC but also maintained or improved HRQoL.

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