Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC)

Poster P5-16-01

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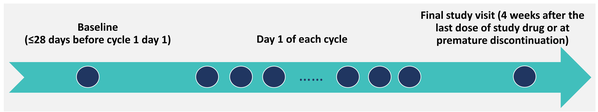
Background

- Overall survival (OS) among patients with metastatic triple-negative breast cancer (mTNBC) remains low, with a five-year OS rate of 12%[1]
- Sacituzumab govitecan (SG) is an antibody-drug conjugate that targets Trop-2 receptors on cancer cells.[2] Extracellular hydrolysis of its linker releases SN-38 (the active metabolite of irinotecan) into the tumor microenvironment[3]
- SG is approved to treat patients with mTNBC who have received ≥2 prior treatments, including ≥1 for metastatic disease[2] and has been granted accelerated approval for metastatic urothelial cancer[4]
- The confirmatory ASCENT phase 3 randomized trial compared single-agent chemotherapy treatment of physician's choice (TPC) with SG in patients with mTNBC[5]
  - SG significantly prolonged median progression-free survival (primary endpoint) and median OS compared to TPC among patients without brain metastases
  - SG also showed a manageable safety profile
  - More patients with brain metastases achieved stable disease in the SG arm vs the TPC arm and SG numerically improved progression-free survival for this patient population[6]
- In a previous analysis, SG demonstrated improvements in health-related quality of life (HRQoL) compared to TPC, including a longer time to deterioration and a shorter time to improvement[7]
- The purpose of the present analysis was to compare HRQoL according to clinical response in patients with mTNBC who received SG or TPC in the ASCENT trial

Methods

- In the ASCENT trial,[5] patients with refractory or relapsed mTNBC after ≥2 prior lines of therapy (including ≥1 for metastatic disease) and with an Eastern Cooperative Oncology Group 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
  - TPC was administered per the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[6]
  - SG treatment and TPC continued until disease progression, unacceptable adverse events, withdrawal from the trial, or death[5]
- ASCENT received ethics committee approval and all patients provided written informed consent
- HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30; version 3)
  - Five domains of the EORTC QLQ-C30—global health status/quality of life (QoL), physical functioning, role functioning, pain, and fatigue—were the primary focus of the analysis because of their clinical relevance to patients with mTNBC[8-10]
- HRQoL was assessed per the schedule shown in **Figure 1**

Figure 1. Timeline of HRQoL Assessments



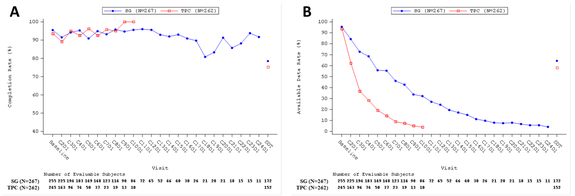
- The HRQoL-evaluable population comprised all randomized patients with an evaluable EORTC QLQ-C30 assessment at baseline and at least one post-baseline visit
  - A patient was considered to have an evaluable assessment of EORTC QLQ-C30 if at least one of the 15 domains/subscales was completed at a given assessment
  - Completion rates (calculated using the number of patients who were expected to provide an HRQoL assessment as the denominator) and available data rates (calculated using the number of intention-to-treat [ITT] patients as the denominator) were calculated
  - Missing data were not imputed
- Patients were classified into two subgroups based on best overall response (per Response Evaluation Criteria in Solid Tumors)
  - Clinical responders: best overall clinical response of partial response (PR) or complete response (CR)
  - Non-responders: best overall clinical response of stable disease, progressive disease, or not evaluable
- Mixed-effect regression models for repeated measures (MMRM) were used to determine least-square (LS) mean changes from baseline for clinical responders and non-responders within each treatment arm
- The MMRM analysis used HRQoL data for baseline through cycle 6 day 1 (C6D1, where n was ≥25 in both treatment arms)
- **Due to the small number of TPC responders, inferential statistical testing to compare between-group difference was not performed**
- Time to first deterioration (TTD) in HRQoL by clinical response status was assessed using Cox proportional hazards regression models with baseline HRQoL score, treatment arm, best overall response (PR or CR vs not PR or CR), and a treatment arm*best overall response interaction term as covariates
- TTD was calculated as the time between randomization and the time a patient experienced worsening from baseline of ≥10 points.[10] Patients with no worsening were censored at the time of the last non-missing assessment visit
- Cumulative probability of subjects who experienced a deterioration was presented using the Kaplan-Meier product-limit failure curve by treatment arm and clinical response status. Death was considered an event

Results

Data Availability

- Completion rates were high (generally ≥90%) for both SG and TPC and were similar between treatment arms across visits up to C10D1 (when n was ≥10 for both treatment arms) (**Figure 2A**)
- Available data rates decreased over time in both treatment arms, but were consistently higher in the SG arm than in the TPC arm (**Figure 2B**)

Figure 2. Completion and Available Data Rates for the EORTC QLQ-C30 by Visit and Treatment Arm



Patients

- Of the HRQoL-evaluable patients, 82/236 (35%) patients in the SG arm and 11/183 (6%) patients in the TPC arm had a clinical response to treatment (**Table 1**)
- Generally, responders and non-responders were comparable in demographics and disease characteristics

Table 1. Demographics and Baseline Clinical Characteristics

	SG Responders (N=82)	SG non-responders (N=154)	TPC responders (N=11)	TPC non-responders (N=172)
Age (years)				
Mean (standard deviation)	56.4 (11.5)	52.4 (11.7)	52.8 (7.6)	55.6 (12.0)
Median	57.0	52.5	57.0	54.0
Race, n (%)				
Asian	3 (3.7)	7 (4.5)	0	8 (4.7)
Black or African American	8 (9.8)	14 (9.1)	2 (18.2)	25 (14.5)
White	69 (84.1)	126 (81.8)	8 (72.7)	131 (76.2)
Other	2 (2.4)	7 (4.5)	1 (9.1)	8 (4.7)
Geographic region, n (%)				
North America	47 (57.3)	106 (68.8)	6 (54.5)	113 (65.7)
Rest of the world	35 (42.7)	48 (31.2)	5 (45.5)	59 (34.3)
Number of prior chemotherapies, n (%)				
2 to 3	66 (80.5)	102 (66.2)	7 (63.6)	125 (72.7)
>3	16 (19.5)	52 (33.8)	4 (36.4)	47 (27.3)
Number of prior systemic therapies				
Mean (standard deviation)	4.0 (1.6)	4.7 (2.1)	4.9 (2.5)	4.4 (2.1)
Median	4	4	5	4
Known brain metastases at study entry, n (%)				
Yes	1 (1.2)	26 (16.9)	0	18 (10.5)
No	81 (98.8)	128 (83.1)	11 (100)	154 (89.5)
***BRCA* 1/*BRCA* 2 mutational status, n (%)**				
Negative	45 (54.9)	91 (59.1)	7 (63.6)	94 (54.7)
Postive	3 (3.7)	12 (7.8)	1 (9.1)	13 (7.6)
Missing	34 (41.5)	51 (33.1)	3 (27.3)	65 (37.8)
Time from diagnosis to study entry (months)				
Mean (standard deviation)	62.4 (62.0)	60.5 (62.2)	66.7 (92.9)	65.0 (62.3)

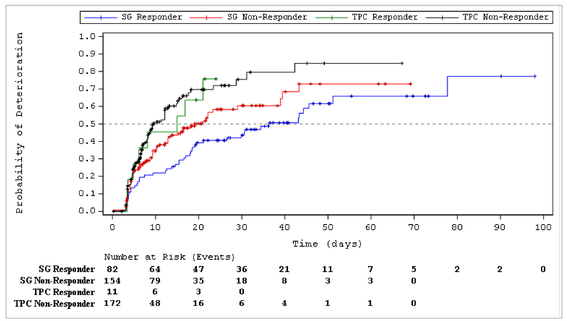
SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Time to First Deterioration

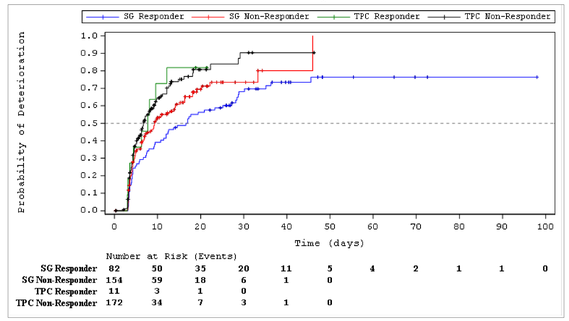
- For all primary focused domains in the analyses, SG responders had longer TTD than SG non-responders (**Figure 3**)
- Compared to TPC responders, SG responders had more prolonged TTD for all primary focused domains in the analyses, except fatigue in which SG responders and TPC responders had similar TTD (hazard ratio = 1.03, 95% CI: 0.61-1.72)

Figure 3. Kaplan-Meier Plots of Time to First HRQoL Deterioration in EORTC QLQ-C30 by Clinical Response Status and Treatment Arm (death as an event): (HRQoL-evaluable population)

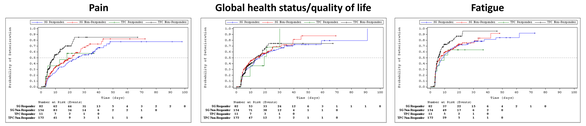
Physical functioning



Role functioning



Pain | **Global health status/quality of life** | **Fatigue**



LS Mean Changes in HRQoL Scores

- Irrespective of their clinical response status, patients treated with SG showed more favorable LS mean changes than patients who received TPC for most EORTC QLQ-C30 domains (**Table 2**)
- The exceptions were nausea/vomiting and diarrhea, for which LS mean score changes were less favorable for SG than for TPC
- Additionally, emotional functioning was less favorable in SG non-responders vs TPC responders, cognitive functioning was less favorable in SG non-responders vs TPC non-responders, and appetite loss was less favorable in SG non-responders vs TPC non-responders

Table 2. Overall LS Mean Changes in HRQoL Scores in SG and TPC Responders and Non-responders

	Least-square Mean Change from Baseline (95% confidence interval)			
	SG Responders (N=82)	SG Non-responders (N=154)	TPC Responders (N=11)	TPC Non-responders (N=172)
Global health status/QoL*	2.46 (-1.52 - 6.43)	-0.57 (-3.68 - 2.54)	-1.64 (-10.22 - 6.95)	-2.29 (-5.63 - 1.05)
Functioning†				
Physical	2.93 (-0.92 - 6.79)	0.22 (-2.71 - 3.15)	-3.47 (-11.93 - 4.99)	-3.75 (-6.87 - -0.63)
Role	-0.35 (-5.74 - 5.04)	-3.23 (-7.45 - 0.99)	-8.40 (-19.93 - 3.13)	-7.33 (-11.88 - -2.78)
Emotional	6.20 (2.23 - 10.18)	1.97 (-1.12 - 5.06)	4.87 (-3.70 - 13.44)	0.08 (-3.24 - 3.40)
Cognitive	0.90 (-2.99 - 4.79)	-2.25 (-5.26 - 0.76)	-4.46 (-12.87 - 3.95)	-1.26 (-4.49 - 1.98)
Social	2.06 (-3.50 - 7.61)	-3.35 (-7.65 - 0.95)	-5.79 (-18.29 - 6.72)	-4.36 (-8.99 - 0.27)
Symptoms§				
Fatigue	0.90 (-3.49 - 5.28)	2.84 (-0.60 - 6.29)	4.15 (-5.34 - 13.65)	6.65 (2.93 - 10.38)
Nausea/vomiting	4.68 (1.42 - 7.95)	4.03 (1.42 - 6.64)	1.38 (-5.53 - 8.29)	2.62 (-0.21 - 5.45)
Pain	-11.40 (-16.43 - -6.36)	-8.57 (-12.48 - -4.66)	-11.99 (-22.85 - -1.13)	-0.24 (-4.47 - 3.99)
Dyspnea	-7.88 (-13.09 - -2.67)	-1.90 (-5.93 - 2.13)	1.97 (-9.33 - 13.27)	3.86 (-0.47 - 8.18)
Insomnia	-6.12 (-11.99 - -0.26)	-3.51 (-8.04 - 1.02)	4.83 (-7.85 - 17.51)	-0.98 (-5.86 - 3.90)
Appetite loss	0.22 (-5.25 - 5.70)	5.45 (1.15 - 9.75)	8.67 (-3.05 - 20.40)	4.60 (-0.05 - 9.26)
Constipation	0.93 (-4.57 - 6.43)	2.20 (-2.09 - 6.49)	3.87 (-7.96 - 15.70)	3.52 (-1.12 - 8.16)
Diarrhea	16.03 (10.32 - 21.74)	13.65 (9.19 - 18.11)	2.46 (-9.88 - 14.80)	-1.53 (-6.34 - 3.29)
Financial difficulties	-3.57 (-8.54 - 1.39)	-2.44 (-6.21 - 1.34)	-4.41 (-15.27 - 6.46)	0.61 (-3.42 - 4.64)

Blue: primary focused domains
The analysis used data collected up to C6D1.
*A higher score represents higher QoL; †A higher score represents a higher level of functioning; §A higher score represents a higher level of symptomatology.
QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Conclusions

- For the primary focused domains, patients treated with SG generally showed more favorable score changes and longer TTD than patients who received TPC, regardless of clinical response status
- For SG, clinical responders showed greater improvements in HRQoL than clinical non-responders, indicating that patients with mTNBC whose cancer responds well to SG also benefit the most from improved HRQoL
- 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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Acknowledgements

- The authors thank the patients and their caregivers for participating in this study
- The authors also thank the clinical trial investigators and team members, as well as medical writers Holly Richendrfer and Stephen Gilliver of Evidera; editorial support was provided by Colleen Dumont of Evidera
- This study was sponsored by Gilead Services, Inc. Medical writing support was provided in accordance with Good Publication Practice guidelines (GPP3; http://www.ismpp.org/gpp3)

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