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Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.10.003.

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Abstract

Background: The antibody–drug conjugate sacituzumab govitecan (SG) prolongs progression-free survival and overall survival in patients with refractory/relapsed metastatic triple-negative breast cancer (mTNBC). Here, we investigated its effect on health-related quality of life (HRQoL).

Methods: This analysis was based on the open-label phase III ASCENT trial (NCT02574455). Adults with refractory/relapsed mTNBC who had received ≥2 prior systemic therapies (≥1 in

the metastatic setting) were randomised 1:1 to SG or treatment of physician's choice (TPC; capecitabine, eribulin, vinorelbine, or gemcitabine). HRQoL was assessed on day 1 of each treatment cycle using the EORTC QLQ-C30. Score changes from baseline were analysed using linear mixed-effect models for repeated measures. Stratified Cox regressions evaluated time to first clinically meaningful change of HRQoL.

Results: The analysis population comprised 236 patients randomised to SG and 183 to TPC. For global health status (GHS)/QoL, physical functioning, fatigue, and pain, changes from baseline were superior for SG versus TPC. Compared with TPC, SG was inferior regarding changes from baseline for nausea/vomiting and diarrhoea but non-inferior for other QLQ-C30 domains. Median time to first clinically meaningful worsening was longer for SG than for TPC for physical functioning (22.1 versus 12.1 weeks, $P < 0.001$), role functioning (11.4 versus 7.1 weeks, $P < 0.001$), fatigue (7.7 versus 6.0 weeks, $P < 0.05$), and pain (21.6 versus 9.9 weeks, $P < 0.001$).

Conclusions: SG was generally associated with greater improvements and delayed worsening of HRQoL scores compared with TPC. This supports the favourable profile of SG as an mTNBC treatment.

Keywords

Antibody–drug conjugate; Clinical trial; Phase III; EORTC QLQ-C30; Quality of life; Sacituzumab govitecan; Triple-negative breast neoplasms

1. Introduction

Metastatic triple-negative breast cancer (mTNBC) is an aggressive form of cancer associated with poor prognosis. Available single-agent and combination chemotherapies have exhibited limited effectiveness, unfavourable toxicity, and negative effects on quality of life [1–3].

Antibody–drug conjugates target chemotherapeutic agents to cancer cells, thereby reducing toxicities seen with non-targeted therapies. Sacituzumab govitecan (SG) is an antibody–drug conjugate that directs SN-38 (the active metabolite of irinotecan) to cells expressing Trop-2, a transmembrane glycoprotein that is highly expressed in TNBC [4,5]. In the open-label phase III ASCENT trial (NCT02574455), SG significantly prolonged progression-free survival (PFS) and overall survival (OS) compared with single-agent chemotherapy treatment of physician's choice (TPC) in patients with refractory or relapsed mTNBC [6]. SG is now FDA-approved for patients with unresectable locally advanced TNBC or mTNBC who have received ≥2 prior systemic therapies, including ≥1 for metastatic disease [7].

Adverse event (AE) data from ASCENT indicate that SG has a generally manageable safety profile [6]. However, proportions of patients with certain AEs, including grade 3/4 neutropenia and diarrhoea, were higher for SGthan for TPC [6]. Because AEs can negatively affect quality of life (QoL), it is important to capture QoL data in clinical trials to support treatment decisions. In the present analysis using data from ASCENT—the first detailed health-related QoL (HRQoL) analysis of an SN-38 antibody–drug conjugate—we compared the effect of SG versus TPC on HRQoL.

2. Material and methods

2.1. Patients and overall study design

Full details of the ASCENT trial are provided elsewhere [6]. Briefly, patients were adults with histologically or cytologically confirmed refractory or relapsed advanced (unresectable, locally advanced, or metastatic) TNBC. They had received ≥2 prior systemic therapies (≥1 in the metastatic setting) and had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. All patients provided written informed consent.

Patients were randomised 1:1 to treatment with SG or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine). SG was administered as a 10 mg/kg intravenous infusion on days 1 and 8 of a 21-day treatment cycle. SG treatment and TPC continued until disease progression, unacceptable AEs, or death. Patients who discontinued study treatment underwent a safety follow-up within 4 weeks after discontinuation and were followed up for survival every 4 weeks thereafter.

2.2. HRQoL assessments

HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients (EORTC QLQ-C30) questionnaire. The QLQ-C30 consists of 30 items arranged into 15 domains: a two-item global health status (GHS)/QoL domain, five multi-item functioning domains, three multi-item symptom domains, and six single-item symptom domains.

Patients completed the QLQ-C30 at baseline (within 28 days of cycle 1 day 1 [C1D1]), on day 1 of each treatment cycle, and at their final study visit (4 weeks after the last dose of study drug or at premature discontinuation). The QLQ-C30 was scored according to the Scoring Manual [8]. For the GHS/QoL and functioning domains, higher scores indicate better HRQoL; for the symptom domains, higher scores indicate worse symptomatology.

A QLQ-C30 summary score was calculated as the mean of the scores for 13 of the 15 domains (excluding GHS/QoL and financial difficulties domains) if all 13 included domains had available scores [9]. The symptom domains were reverse scored prior to calculation of the summary score.

2.3. Statistical analyses

Analyses were conducted using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA) for the HRQoL-evaluable population: patients with an evaluable QLQ-C30 assessment (defined as at least one of the 15 QLQ-C30 domains being completed) at both baseline and at least one post-baseline assessment. GHS/QoL, physical functioning, role functioning, pain, and fatigue were selected as the primary-focused HRQoL domains *a priori* because of clinical relevance to the target population and use as primary HRQoL domains in other studies [10–12]. The other QLQ-C30 domains were assessed as secondary-focused HRQoL domains.

Baseline HRQoL scores were compared with QLQ-C30 norm scores derived from a general population from 11 EU countries (N = 11 343) [13], which were reweighted based on the HRQoL-evaluable population's age and gender distributions.

HRQoL score changes from baseline and between-group differences in changes from baseline were analysed using linear mixed-effect models for repeated measures (MMRM). The analysis used data collected up to and including the last cycle when n was ≥25 in both treatment arms. Missing data were imputed assuming that they were missing at random. The MMRM included the intercept and time point (treatment cycle) as random effects and the following covariates as fixed effects: treatment arm (SG or TPC), time point (modelled as a discrete variable), baseline score, baseline score × time point and treatment arm × time point interaction terms, and the factors used to stratify the randomization. Least-square (LS) mean HRQoL score changes from baseline at each post-baseline assessment and overall were estimated. A 10-point threshold [14] was used to define the within-group minimal important difference (MID) for LS mean change from baseline. Non-inferiority and superiority of SG versus TPC were assessed using MID values from published thresholds [15–17]. Non-inferiority was inferred when the lower bound (GHS/QoL, functioning domains, and QLQ-C30 summary score) or upper bound (symptom domains) of the 95% confidence interval (CI) for the between-group difference in overall LS mean change from baseline did not exceed the MID. Superiority was inferred when the between-group LS mean difference exceeded the MID and was statistically significant.

Clinically meaningful worsening and improvement at the patient level were defined using a ≥10-point score change as the responder definition (RD). Percentages of patients with clinically meaningful worsening or improvement were compared between treatment arms using logistic regression models that included treatment, baseline score, and the randomization stratification factors as covariates.

Time to first clinically meaningful worsening (TTW) and improvement (TTI) were defined as the time between randomization and the first worsening/improvement meeting the ≥10-point RD threshold. Patients who never experienced clinically meaningful worsening/improvement were censored at the time of their last non-missing assessment. Death was treated as an event in TTW analysis.

The Kaplan–Meier product-limit method estimated survival distribution functions for each treatment arm for TTW and TTI. Hazard ratios (HRs) were estimated using Cox proportional hazards regression models that included treatment arm and baseline score as covariates and were stratified by the randomization stratification factors.

For the primary-focused HRQoL domains, MMRM were additionally used to compare SG and TPC on overall LS mean score changes from baseline in different subgroups of patients. The same subgroups were used in a Cox proportional hazards regression analysis of TTW. Forest plots were generated to illustrate the results of these subgroup analyses.

3. Results

3.1. Patients and data availability

The HRQoL-evaluable population comprised 419 patients: 236 randomised to SG and 183 to TPC (Supplementary Fig. S1). The two treatment arms were well balanced regarding demographics and baseline clinical characteristics (Table 1). Over two-thirds of patients had received 2 or 3 prior systemic therapies in any setting.

Mean time since diagnosis was 61 months in the SG arm and 65 months in the TPC arm. QLQ-C30 completion rate and available data rate are shown in Supplementary Fig. S2. The available data rate declined over time in both treatment arms but was consistently higher in the SG arm than in the TPC arm.

3.2. Baseline HRQoL

Mean baseline scores for the primary-focused HRQoL domains were generally worse in both treatment arms than in an age- and gender-matched general population (Table 2). When comparing treatment arms, mean baseline scores were worse for TPC versus SG for GHS/QoL (58.1 versus 63.2) and insomnia (36.1 versus 31.6). However, the two treatment arms had the same median baseline GHS/QoL score (66.7). The mean baseline financial difficulties score was also worse in the SG arm than in the TPC arm (27.2 versus 23.0), although the median score was 0 in both treatment arms. Otherwise, the two treatment arms had similar mean baseline QLQ-C30 scores for each domain and for the summary score.

3.3. Effect of treatment on HRQoL

3.3.1. Change from baseline—The analysis of change from baseline used data collected up to C6D1. At the group level, scores for the primary-focused HRQoL domains (Fig. 1) tended to be maintained during treatment. For each of the primary-focused HRQoL domains, the SG arm had a significantly better LS mean change from baseline at one or more assessments during the first six treatment cycles. In the TPC arm, clinically meaningful worsening of role functioning was observed at C2D1. Clinically meaningful improvements in pain were observed in the SG arm at C3D1 and C4D1.

Data for the secondary-focused HRQoL domains are shown in Supplementary Fig. S3.

In an MMRM analysis comparing treatment arms, SG was non-inferior to TPC on all primary-focused HRQoL domains (Table 3). Importantly, for four of the primary-focused HRQoL domains (GHS/QoL, physical functioning, fatigue, and pain), SG was superior to TPC (difference both statistically significant and clinically meaningful).

Results for the corresponding subgroup analysis are shown in Supplementary Fig. S4. For the secondary-focused HRQoL domains, SG was superior to TPC on emotional functioning, dyspnoea, and insomnia; inferior on nausea/vomiting (difference not statistically significant) and diarrhoea; and non-inferior on all other domains (Table 3). Finally, the SG arm had a significantly better QLQ-C30 summary score LS mean change from baseline than the TPC arm.

3.3.2. Clinically meaningful worsening and improvement—For the primary-focused HRQoL domains, the percentage of patients with clinically meaningful improvement was generally higher for SG than for TPC at most assessments during the first six cycles of treatment, and the percentage of patients with clinically meaningful worsening was generally lower for SG than for TPC (Supplementary Fig. S5). Compared to the TPC arm, the SG arm had higher proportions of patients with clinically meaningful worsening of diarrhoea (differences significant at each cycle) and nausea/vomiting (differences not significant) (Supplementary Fig. S5). For the QLQ-C30 summary score, the SG arm had consistently higher proportions of patients with clinically meaningful improvement than the TPC arm (differences significant at C4D1 and C5D1).

Median TTW of GHS/QoL was similar in both treatment arms (14.1 weeks for SG and 15.1 weeks for TPC; HR = 0.87, 95% CI 0.70 to 1.07; $P = 0.18$) (Fig. 2). For the other primary-focused HRQoL domains, median TTW was significantly longer for SG than for TPC: 22.1 versus 12.1 weeks for physical functioning (HR = 0.61, 95% CI 0.49 to 0.75; $P < 0.001$), 11.4 versus 7.1 weeks for role functioning (HR = 0.70, 95% CI 0.56 to 0.86; $P < 0.001$), 7.7 versus 6.0 weeks for fatigue (HR = 0.82, 95% CI 0.66 to 1.00; $P < 0.05$), and 21.6 versus 9.9 weeks for pain (HR = 0.60, 95% CI 0.48 to 0.74; $P < 0.001$).

Results for the corresponding subgroup analysis are shown in Supplementary Fig. S6.

Compared with TPC, SG showed significantly longer TTW of emotional functioning, social functioning, dyspnoea, insomnia, financial difficulties, and QLQ-C30 summary score, and significantly shorter TTW of diarrhoea (Supplementary Fig. S7). Compared with TPC, SG showed significantly shorter TTI of physical functioning, pain, dyspnoea, and QLQ C30 summary score (Supplementary Fig. S8).

4. Discussion

Patients with mTNBC have a high unmet need. A key treatment goal in this setting is improving or maintaining HRQoL, particularly in later treatment lines, where HRQoL is worsened as a result of the disease and residual toxicities from prior therapies [19,20]. In this analysis, the SG arm showed significantly greater improvements than did the TPC arm in scores for all five primary-focused HRQoL domains at the group level. For four of the primary-focused HRQoL domains, SG was superior to TPC to a clinically meaningful extent. SG was inferior to TPC for nausea/vomiting (difference not statistically significant) and diarrhoea but was non-inferior or superior to TPC on all other secondary-focused HRQoL domains and the QLQ-C30 summary score. Moreover, compared with TPC, SG delayed clinically meaningful worsening for four of the primary-focused HRQoL domains.

The worsening of nausea/vomiting and diarrhoea with SG did not apparently translate to a negative effect on GHS/QoL, QLQ-C30 summary score, or functioning. These results are consistent with published safety findings from ASCENT [6,21], where the higher incidence of certain AEs, such as nausea, diarrhoea, vomiting, and neutropenia, with SG compared with TPC was not associated with a higher proportion of patients discontinuing study treatment due to AEs [6]. In ASCENT, nausea, vomiting, and diarrhoea were managed with

antiemetics, antidiarrheal agents, and supportive measures, as needed. Grade 3/4 AEs that could not be controlled in this way were managed with 25% and 50% SG dose reductions [6]. Collectively, the available clinical data indicate that SG has a manageable AE profile [22] that may be improved further with additional supportive measures for nausea, vomiting, and diarrhoea. These AEs are typically easier to treat than others like dyspnoea and fatigue, which were substantially better with SG than with TPC.

This was the first detailed analysis of the effect of an SN-38 antibody–drug conjugate on HRQoL in patients with mTNBC. The present results are of interest because they contrast strongly with previous studies in the mTNBC setting, which either have reported increased toxicity and a consequent decline in QoL relative to single-agent chemotherapy or have failed to demonstrate improvements in HRQoL [3,23]. It is worth noting that baseline HRQoL scores were worse in both treatment arms than in a reference European general population, indicating that patients entered this trial with their HRQoL already negatively impacted.

Limitations of the present study include assessment of HRQoL in less than 50% of patients in the TPC arm from C3D1. However, the available data rate was consistently higher in the SG arm than in the TPC arm, generally reflecting the pattern of PFS [6]. Patients discontinuing treatment because of AEs could have worse HRQoL than those remaining on study. However, the percentage of patients who discontinued treatment because of AEs was approximately 5% in both treatment arms [6]. Thus, AE-related discontinuations are unlikely to account for the better HRQoL seen with SG. The open-label design could also have influenced patient responses by biasing patient responses in favour of one intervention [24]. However, studies assessing the influence of level of blinding on HRQoL outcomes in oncology trials have yielded mixed findings [25]. A final limitation is that the analyses were not adjusted for multiple comparisons.

5. Conclusion

Overall, SG was associated with greater improvements in HRQoL than TPC was, mainly on physical and emotional functioning and global health status/QoL, and delayed worsening of HRQoL. The greater worsening of nausea/vomiting (statistically non-significant) and diarrhoea scores in the SG arm compared with the TPC arm did not translate to an adverse impact on functioning or overall HRQoL. Moreover, SG generally delayed worsening of HRQoL. Viewed together with efficacy data from ASCENT showing that SG extended PFS and OS in patients with refractory or relapsed mTNBC, our findings indicate that SG also maintained or improved HRQoL. This further supports the favourable profile of SG for treating patients with mTNBC who have previously received two or more systemic therapies, at least one of them in the metastatic setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

[1]. O'Reilly D, Sendi MA, Kelly CM. Overview of recent advances in metastatic triple negative breast cancer. World J Clin Oncol 2021;12:164–82. [PubMed: 33767972]

[2]. Li CH, Karantza V, Aktan G, Lala M. Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. Breast Cancer Res 2019;21:143. [PubMed: 31842957]

[3]. Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J,et al. Global analysis of advanced/metastatic breast cancer: decade report (2005–2015). Breast 2018;39:131–8. [PubMed: 29679849]

[4]. Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. Oncotarget 2018;9:28989–9006. [PubMed: 29989029]

[5]. Nagayama A, Vidula N, Ellisen L, Bardia A. Novel antibody-drug conjugates for triple negative breast cancer. Ther Adv Med Oncol 2020;12:1758835920915980. [PubMed: 32426047]

[6]. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med 2021;384:1529–41. [PubMed: 33882206]

[7]. U.S. Food & Drug Administration. FDA grants regular approval to sacituzumab govitecan for triple-negative breast cancer. 2021.

[8]. EORTC QLQ-C30 scoring manual. Brussels, Belgium: EORTC Data Center; 2001.

[9]. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol 2016;69:79–88. [PubMed: 26327487]

[10]. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Inst 2002;94:39–49. [PubMed: 11773281]

[11]. Bordeleau L, Szalai JP, Ennis M, Leszcz M, Speca M, Sela R, et al. Quality of life in a randomized trial of group psychosocial support in metastatic breast cancer: overall effects of the intervention and an exploration of missing data. J Clin Oncol 2003;21:1944–51. [PubMed: 12743147]

[12]. Brandberg Y, Johansson H, Hellstrom M, Gnant M, Mobus V, Greil R, et al. Long-term (up to 16 months) health-related quality of life after adjuvant tailored dose-dense chemotherapy vs. standard three-weekly chemotherapy in women with high-risk early breast cancer. Breast Cancer Res Treat 2020;181:87–96. [PubMed: 32232698]

[13]. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer 2019;107:153–63. [PubMed: 30576971]

[14]. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44. [PubMed: 9440735]

[15]. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011;29:89–96. [PubMed: 21098316]

[16]. Gerlinger C, Schmelter T. Determining the non-inferiority margin for patient reported outcomes. Pharm Stat 2011;10:410–3. [PubMed: 21932298]

[17]. Cocks K, King MT, Velikova G, de Castro G Jr, Martyn St-James M, Fayers PM, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012;48:1713e21. [PubMed: 22418017]

[18]. Mouelhi Y, Jouve E, Castelli C, Gentile S. How is the minimal clinically important difference established in health-related quality of life instruments? Review of anchors and methods. Health Qual Life Outcomes 2020;18:136. [PubMed: 32398083]

[19]. McClelland SI, Holland KJ, Griggs JJ. Quality of life and metastatic breast cancer: the role of body image, disease site, and time since diagnosis. Qual Life Res 2015;24:2939–43. [PubMed: 26038224]

[20]. Gegechkori N, Haines L, Lin JJ. Long-term and latent side effects of specific cancer types. Med Clin N Am 2017;101:1053–73. [PubMed: 28992854]

[21]. Rugo HS, Tolaney SM, Loirat D, Punie K, Bardia A, Hurvitz SA, et al. Impact of UGT1A1 status on the safety profile of sacituzumab govitecan in the phase 3 ASCENT study in patients with metastatic triple-negative breast cancer [poster]. In: 43rd Annual San Antonio Breast Cancer Symposium (SABCS); virtual meeting, 8–11 December, 2020. San Antonio, TX2020.

[22]. Spring LM, Nakajima E, Hutchinson J, Viscosi E, Blouin G, Weekes C, et al. Sacituzumab govitecan for metastatic triple-negative breast cancer: clinical overview and management of potential toxicities. Oncologist 2021;26:827–34. [PubMed: 34176192]

[23]. Adams S, Dieras V, Barrios CH, Winer EP, Schneeweiss A, Iwata H, et al. Patient-reported outcomes from the phase III IMpassion130 trial of atezolizumab plus nab-paclitaxel in metastatic triple-negative breast cancer. Ann Oncol 2020;31:582–9. [PubMed: 32178964]

[24]. Page MJ, Higgins JP, Clayton G, Sterne JA, Hrobjartsson A, Savovic J. Empirical evidence of study design biases in randomized trials: systematic review of meta-epidemiological studies. PLoS One 2016;11:e0159267. [PubMed: 27398997]

[25]. Roydhouse JK, Mishra-Kalyani PS, Bhatnagar V, Gutman R, King-Kallimanis BL, Sridhara R, et al. Does knowledge of treatment assignment affect patient report of symptoms, function, and health status? An evaluation using multiple myeloma trials. Value Health 2021;24:822–9. [PubMed: 34119080]

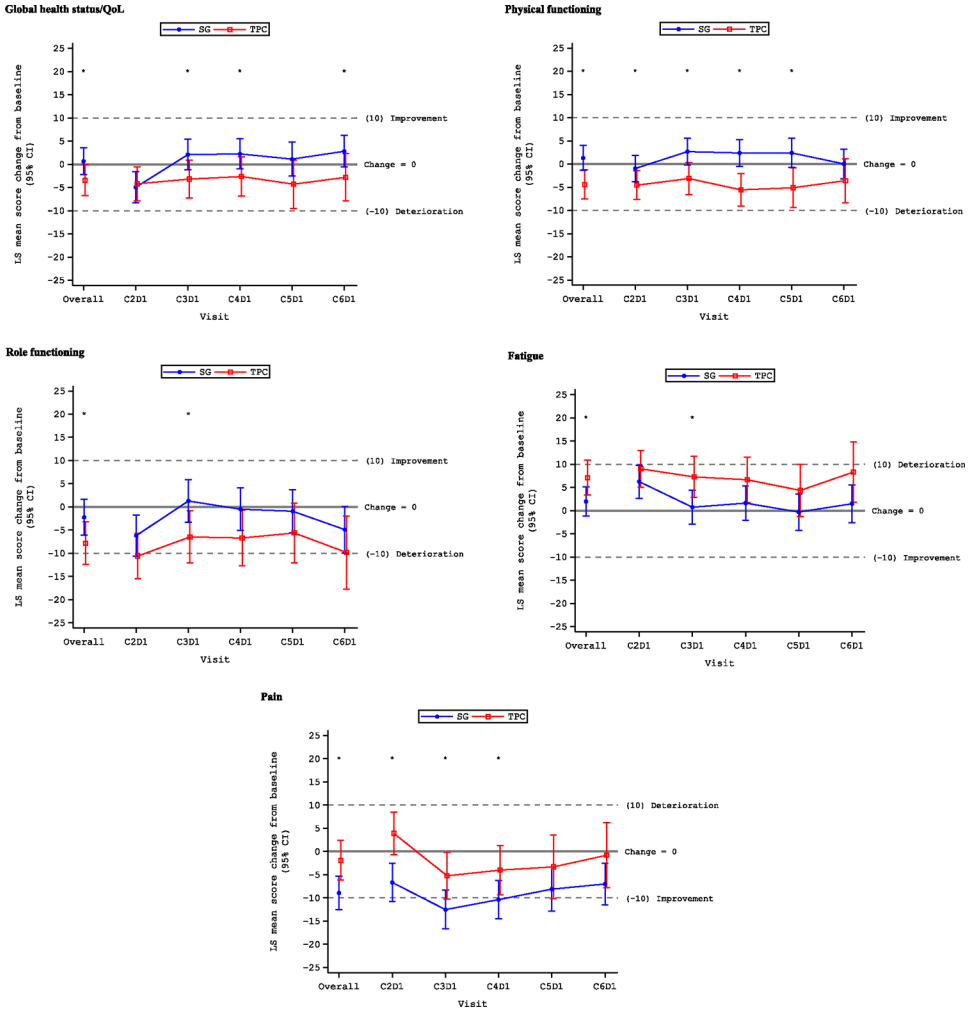

Fig. 1. Least-square mean change from baseline for the primary-focused HRQoL domains.

Data are from a mixed-effect model for repeated measures analysis. *$P < 0.05$ (SG versus TPC). C, cycle; D, day; HRQoL, health-related quality of life; LS, least-square; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

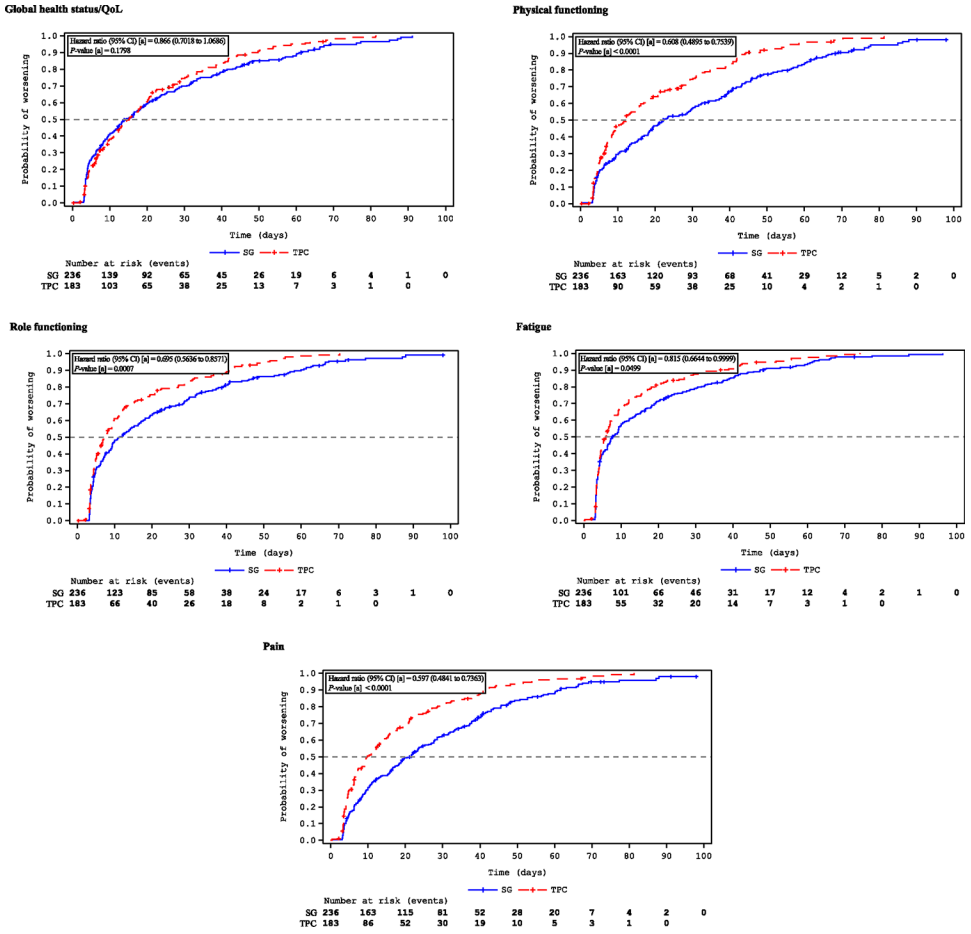

Fig. 2. Time to first clinically meaningful worsening for the primary-focused HRQoL domains.

[a] Estimated using a stratified Cox proportional hazards regression model with treatment arm (SG or TPC) and baseline score as covariates, and with number of prior systemic therapies for breast cancer, geographic region, and known brain metastases at study entry as stratification factors. Death was treated as an event. CI, confidence interval; HRQoL, health-related quality of life; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Table 1

Demographics and baseline clinical characteristics.

	HRQoL-evaluable population		Intent-to-treat population	
	SG *n* = 236	**TPC *n* = 183**	**SG *n* = 267**	**TPC *n* = 262**
Age (years)				
Mean (standard deviation)	53.8 (11.8)	55.5 (11.8)	54.0 (11.3)	54.0 (11.7)
Median	54	54	54	53
Race, *n* (%)				
Asian	10 (4)	8 (4)	13 (5)	9 (3)
Black or African American	22 (9)	27 (15)	28 (10)	34 (13)
White	195 (83)	139 (76)	215 (81)	203 (77)
Other	9 (4)	9 (5)	11 (4)	16 (6)
Ethnicity, *n* (%)				
Hispanic or Latina	17 (7)	23 (13)	20 (7)	25 (10)
Not Hispanic or Latina	210 (89)	155 (85)	234 (88)	226 (86)
Not reported/unknown	9 (4)	5 (3)	13 (5)	11 (4)
Geographic region, *n* (%) [a]				
North America	153 (65)	119 (65)	175 (66)	172 (66)
Rest of the world	83 (35)	64 (35)	92 (34)	90 (34)
ECOG performance status, *n* (%)				
0	113 (48)	74 (40)	121 (45)	108 (41)
1	123 (52)	109 (60)	146 (55)	154 (59)
Number of prior systemic therapies for breast cancer, *n* (%) [a]				
2 or 3	168 (71)	132 (72)	184 (69)	181 (69)
>3	68 (29)	51 (28)	83 (31)	81 (31)
Known brain metastases at study entry, *n* (%) [a]				
Yes	27 (11)	18 (10)	32 (12)	29 (11)
No	209 (89)	165 (90)	235 (88)	233 (89)
***BRCA1/BRCA2* mutation status, *n* (%)**				
Negative	136 (58)	101 (55)	150 (56)	146 (56)

	HRQoL-evaluable population		Intent-to-treat population	
	SG *n* = 236	**TPC *n* = 183**	**SG *n* = 267**	**TPC *n* = 262**
Positive	15 (6)	14 (8)	20 (7)	23 (9)
Missing	85 (36)	68 (37)	97 (36)	93 (35)
Diagnosis of *HER2* negativity, *n* (%)				
Immunohistochemistry: 0	124 (53)	91 (50)	145 (54)	141 (54)
Immunohistochemistry: 1	42 (18)	31 (17)	45 (17)	47 (18)
Fluorescence in situ hybridization[b]	70 (30)	61 (33)	77 (29)	74 (28)
Serum bilirubin (total), *n* (%)				
Normal	233 (99)	180 (98)	253 (95)	218 (83)
>1–1.5 ULN	2 (1)	1 (1)	5 (2)	4 (2)
>1.5 ULN	0	0	0	1 (0)
Missing	1 (0)	2 (1)	9 (3)	39 (15)
Time from diagnosis to study entry (months)				
Mean (standard deviation)	61 (62)	65 (64)	62 (62)	63 (60)

ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice; ULN, upper limit of normal.

[a]Randomization stratification factors.

[b]Fluorescent in situ hybridization was used to identify *HER2* negativity without immunohistochemistry or to distinguish *HER2* status if HER2 immunohistochemistry was scored as 2+.

Table 2

Baseline EORTC QLQ-C30 scores.

	SG *n* = 236	TPC *n* = 183	General population norm [13]	Between-group MID [15]
	Mean (SD)	Mean (SD)	Mean	
Primary-focused domains				
Global health status/QoL[a]	63.2 (20.6)	**58.1** (21.9)	63.6	4
Physical functioning[b]	**74.9** (20.5)	**73.0** (20.3)	83.4	5
Role functioning[b]	**69.6** (29.5)	**67.9** (29.3)	83.0	6
Fatigue[c]	**38.3** (25.2)	**40.1** (25.2)	31.3	5
Pain[c]	**36.4** (30.1)	**40.3** (29.4)	26.7	6
Secondary-focused domains				
Emotional functioning[b]	72.1 (22.2)	69.9 (23.4)	72.6	3[d]
Cognitive functioning[b]	82.5 (20.3)	**80.0** (23.6)	84.3	3
Social functioning[b]	**70.6** (29.3)	**71.2** (26.1)	85.1	5
Nausea/vomiting[c]	7.6 (15.4)	**9.9** (18.3)	5.2	3
Dyspnoea[c]	**24.7** (29.4)	**25.1** (28.6)	16.9	4
Insomnia[c]	31.6 (30.7)	**36.1** (31.2)	31.3	4
Appetite loss[c]	**19.2** (25.9)	**24.0** (28.9)	9.9	5
Constipation[c]	16.6 (26.6)	17.5 (25.2)	14.0	5
Diarrhoea[c]	7.4 (18.0)	6.4 (15.7)	8.9	3
Financial difficulties[c]	***27.2*** (34.5)	**23.0** (30.6)	11.6	3
EORTC QLQ-C30 summary score [a]	76.0 (15.9)	74.2 (16.0)	–	5[e]

MID, minimal important difference; QoL, quality of life; SD, standard deviation; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bold: difference compared with the general population norm greater than the MID.

Underlined: TPC worse than SG by more than the MID.

Italics: SG worse than TPC by more than the MID.

[a] A higher score represents better QoL.

[b] A higher score represents better functioning.

[c] A higher score represents worse symptomatology.

[d] The between-group MID could not be estimated, so a within-group MID based on a previously published threshold [17] was used instead.

[e] For the EORTC QLQ-C30 summary score, the MID was derived as 0.3 × SD for the overall sample (16.8) [18].

Table 3

Overall least-square mean change from baseline during the first six cycles of treatment.

	Least-square mean change from baseline (95% CI)			Non-inferiority margin (MID) [15]
	SG (*n* = 236)	**TPC (*n* = 183)**	**SG minus TPC**	
Primary-focused domains				
				Lower bound of 95% CI
Global health status/QoL[a]	0.66 (−2.21 to 3.53)	−3.42 (−6.77 to −0.08)	**4.08** (0.82–7.35) *	−4
Physical functioning[b]	1.31 (−1.38 to 3.99)	−4.39 (−7.52 to −1.26)	**5.69** (2.63–8.76) **	−5
Role functioning[b]	−2.24 (−6.13 to 1.65)	−7.83 (−12.41 to −3.25)	5.59 (1.13–10.05) *	−6
				Upper bound of 95% CI
Fatigue[c]	1.97 (−1.20 to 5.13)	7.13 (3.40–10.87)	**−5.17** (−8.81 to −1.52) **	þ5
Pain[c]	−8.93 (−12.57 to −5.30)	−1.89 (−6.18 to 2.40)	**−7.04** (−11.24 to −2.85) **	+6
Secondary-focused domains				
				Lower bound of 95% CI
Emotional functioning[b]	3.34 (0.46–6.22)	−0.55 (−3.94 to 2.84)	**3.89** (0.56–7.22) *	−3[d]
Cognitive functioning[b]	−1.22 (−4.00 to 1.56)	−1.98 (−5.21 to 1.24)	0.76 (−2.36 to 3.89)	−3
Social functioning[b]	−1.51 (−5.47 to 2.45)	−5.41 (−10.04 to −0.78)	3.90 (−0.61 to 8.40)	−5
				Upper bound of 95% CI
Nausea/vomiting[c]	4.30 (1.92–6.68)	2.50 (−0.23 to 5.22)	1.81 (−0.83 to 4.44)	+3
Dyspnoea[c]	−3.79 (−7.52 to −0.06)	3.95 (−0.51 to 8.40)	**−7.74** (−12.13 to −3.35) **	+4
Insomnia[c]	−4.69 (−8.92 to −0.46)	0.34 (−4.64 to 5.32)	**−5.03** (−9.89 to −0.16) *	+4
Appetite loss[c]	3.52 (−0.47 to 7.51)	7.00 (2.31–11.68)	−3.47 (−8.05 to 1.11)	+5
Constipation[c]	2.16 (−1.76 to 6.08)	2.69 (−1.89 to 7.27)	−0.53 (−4.97 to 3.91)	+5
Diarrhoea[c]	14.07 (9.94–18.20)	−1.27 (−6.08 to 3.54)	15.34 (10.65 to 20.03) **	+3
Financial difficulties[c]	−2.87 (−6.39 to 0.65)	0.68 (−3.50 to 4.86)	−3.55 (−7.69 to 0.59)	+3
				Lower bound of 95% CI
EORTC QLQ-C30 summary score [a]	−0.67 (−2.73 to 1.39)	−3.15 (−5.54 to −0.75)	2.48 (0.14–4.81) *	−5[e]

CI, confidence interval; MID, minimal important difference; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.