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Original Article

Health-related quality of life with sacituzumab govitecan in HR+/HER2– metastatic breast cancer in the phase III TROPiCS-02 trial

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Abstract

Background: The TROPiCS-02 study (NCT03901339) demonstrated that sacituzumab govitecan (SG) has superior clinical outcomes over treatment of physician's choice (TPC) chemotherapy in patients with hormone receptor-positive, human epidermal growth factor 2 receptor-negative (HR+/HER2–) metastatic breast cancer (mBC). Here, we present health-related quality of life (HRQoL) patient-reported outcome (PRO) findings from this study.

Patients and Methods: Eligible adults with HR+/HER2– mBC who previously received a taxane, endocrine-based therapy, a CDK4/6 inhibitor, and 2-4 lines of chemotherapy were randomized 1:1 to receive SG or TPC until progression or unacceptable toxicity. PROs were assessed at baseline and on day 1 of each cycle, using the European Organization for Research and Treatment of Cancer Quality-of-Life Core 30 (EORTC QLQ-C30), EQ-5D-5L, and PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Results: Compared to TPC, overall least square mean change from baseline was significantly better for SG for physical functioning and dyspnea, but worse for diarrhea. Time to first clinically meaningful worsening or death was significantly longer for SG in global health status/quality of life, physical functioning, fatigue, emotional functioning, dyspnea, insomnia, and financial difficulties of the EORTC QLQ-C30 and the EQ-VAS, but longer for TPC in diarrhea. Few patients in both arms reported experiencing any worsening to level 3 or 4 treatment-related symptomatic events during treatment, as assessed by 16 PRO-CTCAE items, except for diarrhea frequency and amount of hair loss, which favored TPC.

Conclusions: SG was associated with an HRQoL benefit in most symptoms and functioning, compared with TPC. This supports the favorable profile of SG as a treatment option for patients with pretreated HR+/HER2– mBC.

Key words: antibody–drug conjugate; HR+/HER2–, phase III; EORTC QLQ-C30; quality of life; Sacituzumab govitecan; metastatic breast cancer.

Implications for practice

Treatment of HR+/HER2– metastatic breast cancer with sacituzumab govitecan (SG) resulted in health-related quality-of-life (QoL) benefits compared with treatment of physician's choice (TPC). Improvement was greater with SG than TPC in physical functioning and reduction in breathlessness, and SG prolonged the time to worsening of physical functioning, tiredness, and global health status/QoL more than TPC. Diarrhea and hair loss were worse with SG than TPC, but these are known aspects of SG's safety profile and diarrhea is manageable according to established guidelines. For other symptomatic treatment-related adverse events, few patients experienced worsening severity with SG or TPC.

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Introduction

Breast cancer (BC) is the most common cancer and leading cause of cancer mortality in women.[1] Hormone receptor positive, human epidermal growth factor 2 receptor negative (HR+/HER2–) is the most common subtype of BC and comprises approximately 65%-70% of all BC cases.[2,3] For patients with locally advanced HR+/HER2– metastatic BC (mBC), the preferred first- and second-line treatments include endocrine therapy with a targeted agent when appropriate.[4,5]

Sequential single-agent chemotherapy has been the next treatment option for patients after resistance to endocrine therapies.[6] However, chemotherapy in later lines has reduced efficacy and cumulative toxicity, and it is associated with poor quality of life (QoL).[7]

Sacituzumab govitecan (SG) is a novel antibody-drug conjugate (ADC) designed to deliver its potent payload specifically to cancer cells, improving efficacy and potentially reducing toxicities seen with non-targeted therapies.[8]

SG is approved in Europe and the US for the treatment of patients with unresectable locally advanced or metastatic triple-negative BC (mTNBC), who have received 2 or more prior systemic therapies (at least one for metastatic disease), based on the findings from the ASCENT study (NCT02574455), and also for patients with HR+/HER2– mBC following endocrine-based therapy and at least 2 additional systemic therapies based on the TROPiCS-02 study (NCT03901339).[9-12]

TROPiCS-02 was a study of SG vs chemotherapy in patients with metastatic or locally recurrent inoperable HR+/HER2– mBC who had previously received a taxane, endocrine-based therapy, a CDK4/6 inhibitor, and 2 to 4 lines of chemotherapy. In patients treated with SG, median progression-free survival (PFS) was 5.5 months and median overall survival (OS) was 14.4 months.[13-15] In addition to clinical efficacy and safety, health-related quality of life (HRQoL) is also important when evaluating treatment benefit, and SG has been shown to improve HRQoL in mTNBC.[16] HRQoL was formally tested as part of the testing hierarchy in TROPiCS-02. SG significantly extended time-to-deterioration of global health status (GHS)/QoL (HR, 0.75; $P = .006$) and fatigue (HR, 0.73; $P = .002$) vs TPC.[14] Here we report the results of the detailed HRQoL PRO analysis of patients with HR+/HER2– mBC from the TROPiCS-02 study.

METHODS

Patients and overall study design

The TROPiCS-02 study was described previously.[15] Briefly, adults with metastatic or locally recurrent inoperable HR+/HER2– BC who had previously received a taxane, endocrine-based therapy, a CDK4/6 inhibitor, and 2-4 lines of chemotherapy were considered for inclusion. Eligible patients were randomized 1:1 to treatment with SG or TPC (eribulin, capecitabine, gemcitabine, or vinorelbine). Randomization was stratified by number of prior chemotherapy regimens for treatment of metastasis (2 vs 3/4 lines), visceral metastasis (yes or no), and endocrine therapy in the metastatic setting for at least 6 months (yes or no).

SG was administered by intravenous infusion on days 1 and 8 of a 21-day treatment cycle, while treatment schedules for TPC varied according to the treatment selected. Patients continued to receive treatment until a criterion for discontinuation was met. Criteria included disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, investigator decision, pregnancy, or study termination by the sponsor. The study received ethical approval and all patients provided written informed consent.

PRO assessments

Assessments are based on the data from the second interim analysis (cutoff date: July 01, 2022).

PROs were assessed using the European Organization for Research and Treatment of Cancer Quality-of-Life Core 30 (EORTC QLQ-C30) questionnaire, EQ-5D-5L questionnaire, and the PRO-Common Terminology Criteria for Adverse Events (PRO-CTCAE).

The EORTC QLQ-C30 is a PRO questionnaire designed to assess symptoms, functions, and overall QoL from the patient's perspective.[17] It consists of 30 items that address 15 domains: 5 multi-item functional domains, 3 multi-item symptom domains, one 2-item GHS/QoL domain, and 6 single-item symptom domains.[18] For this analysis, an EORTC QLQ-C30 summary score was also calculated as the mean score for 13 of the 15 domains (GHS/QoL and financial difficulties were excluded[19,20]). Each domain, including the summary score, had a score range of 0 to 100.[19,20]

The EQ-5D is a generic measure of health status, consisting of a descriptive system (ie, EQ-5D-5L) scale and a visual analog scale (VAS).[21] The EQ-5D-5L descriptive system is a 5-item, self-reported measure of functioning and well-being, which assesses 5 dimensions of health. Each of these—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—has 5 response options (no, slight, moderate, severe, and extreme) to evaluate problem severity.

PRO-CTCAE is a PRO measurement system developed by the United States National Cancer Institute to evaluate symptoms possibly related to cancer treatments.[22-24] The study assessed 9 relevant symptoms for a total of 16 items: decreased appetite (2 items for S and I), nausea (2 items for F and S), vomiting (2 items for F and S), constipation (1 item for S), diarrhea (1 item for F), abdominal pain (3 items for F, S, and I), shortness of breath (2 items for S and I), hair loss (1 item for A), and fatigue (2 items for S and I). These symptoms were chosen based on the common symptomatic adverse event (AE) profiles of the study treatments.

The GHS/QoL, physical functioning, role functioning, pain, and fatigue domains of the EORTC QLQ-C30 were the primary PRO focused domains of interest in the analyses. These domains were selected a priori because they are clinically relevant to the target population and have been used as primary PRO domains in other published BC studies.[25-27] The other EORTC QLQ-C30 domains, EQ-5D-5L health utility index, EQ-VAS, and PRO-CTCAE items were secondary PRO focused domains.

Additional information on PRO assessments is available as Supplementary material.

Statistical analyses

The proportion of patients eligible for PRO assessment and the extent of missing PRO data across assessment visits were evaluated in the intent-to-treat (ITT) population. The effects of treatment on PRO endpoints, assessed by the EORTC QLQ-C30 and EQ-5D-5L, were performed on each of the corresponding PRO-evaluable populations. PRO-evaluable population was defined as the ITT population patients who had an evaluable assessment of the target PRO measures (defined

respectively for the EORTC QLQ-C30 and EQ-5D-5L) at baseline and ≥ 1 evaluable assessment at a post-baseline visit.

Clinically meaningful change (responder definition [RD]) thresholds were pre-specified and used to identify meaningful worsening or improvement from baseline in each of the PRO domains. Likewise, clinically important differences (CIDs) were pre-specified, based on data obtained from literature, to interpret whether a within-group score change versus baseline or between-group difference in mean score change was clinically meaningful. For the EORTC QLQ-C30 domains, the RD threshold and within-group CID were set to a 10-point change,[28] while the between-group CID was set to a difference of 3-6 points, depending on the domain of interest.[29] The RD and CIDs for the EQ-5D-5L health utility index were set to 0.08, while those for the EQ-VAS were set to 7.[30]

The proportion of ITT patients remaining eligible for PRO assessment at each visit and specific reasons for becoming ineligible was descriptively summarized by treatment arm.

For each domain and summary score of the EORTC QLQ-C30 and the EQ-5D-5L (health utility index and EQ-VAS), descriptive statistics of observed changes from baseline at each postbaseline visit were summarized by treatment arm. The percentage of patients experiencing any worsening to level 3 or 4 during treatment (ie, from cycle 2, day 1 to the last non-missing postbaseline assessment visit, including the end of treatment visit) was summarized descriptively for each of the 16 symptom items of the PRO-CTCAE by treatment arm.

Patients experiencing a score change from baseline in a given PRO domain equaling or exceeding the corresponding RD threshold for worsening or improvement were considered to have clinically meaningful worsening or improvement for that domain. Logistic regression was used to compare the proportions of subjects with a clinically meaningful worsening or improvement in PRO domains at each post-baseline visit in each treatment arm, while controlling for the baseline score and randomization stratification factors.

The time to first clinically meaningful worsening or death was calculated as time between randomization and first worsening (ie, change from baseline ≥ RD threshold for worsening) in a given PRO domain or death, whichever came first.

The analyses were considered exploratory, and *P*-values were not adjusted for multiplicity. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient disposition

The ITT population included 543 patients: 272 (50.1%) in the SG arm and 271 patients (49.9%) in the TPC arm (Supplementary Figure S1A). Of 272 patients in the SG arm, 236 (86.8%) were included in the EORTC QLQ-C30-evaluable population (Supplementary Figure S1B) and 238 (87.5%) in the EQ-5D-5L-evaluable population. Of the 271 patients in the TPC arm, 210 (77.5%) were included in the EORTC QLQ-C30-evaluable population (Supplementary Figure S1B) and 207 (76.4%) in the EQ-5D-5L-evaluable population. The safety population consisted of 517 patients (95.2%) from the ITT population, 268 from the SG arm and 249 from the TPC arm, who received ≥ 1 dose of study treatment (Supplementary Figure S1A).

Extent of missing PRO data over time

The proportion of patients in the ITT population expected to provide PRO assessment at a given visit declined over time in both arms up to day 1 of cycle 11 (C11D1) (Supplementary Figure S2A). The decline occurred more rapidly in the TPC arm, mostly because treatment discontinuation due to disease progression, withdrawal of consent, protocol deviation, loss to follow up, etc. occurred more often than in the SG arm. Discontinuation due to AEs was similar between treatment arms and accounted for a small proportion (< 7%) of patients who did not provide PRO assessments over time.

Among ITT patients expected to provide a PRO assessment at a given visit, the completion rates for the EORTC QLQ-C30 (Supplementary Figure S2B) and EQ-5D-5L (not shown) were generally > 85% on most visits and comparable between the SG and TPC arms up to visit C11D1 ($n < 25$ in the TPC arm thereafter).

Demographics and baseline disease characteristics

The demographic and disease characteristics of ITT patients are summarized in Table 1. Overall, characteristics of the EORTC QLQ-C30-evaluable population were well balanced between treatment arms.

Demographic characteristics of the EORTC QLQ-C30-evaluable and non-evaluable populations were similar (**Table 1**). The baseline disease characteristics of these populations were also comparable, except that in the SG arm, the time from mBC diagnosis to randomization was shorter in the non-evaluable population, whereas in the TPC arm, the time from neoadjuvant/adjuvant chemotherapy to mBC diagnosis was shorter, and the proportion of patients receiving chemotherapy in a neoadjuvant/adjuvant setting was higher, in the non-evaluable population. Demographic characteristics of the EQ-5D evaluable and non-evaluable populations were similar between treatment arms, and demographic characteristics were similar between treatment arms in the safety population (data not shown).

Baseline PRO scores

Overall, baseline EORTC QLQ-C30 scores of study participants for most EORTC QLQ-C30 domains were numerically worse than those of the general population[31] with a similar age-by-gender distribution, regardless of study arm, particularly for role functioning, social functioning, nausea/vomiting, appetite loss, and financial difficulties. Mean EORTC QLQ-C30 symptom domain scores for pain, insomnia, appetite loss, and financial difficulties were higher in the TPC arm than in the SG arm. All other mean EORTC QLQ-C30 domain scores were generally similar between treatment arms at baseline (Supplementary Table S1).

Effect of treatment on PRO scores

Proportion of patients experiencing clinically meaningful within-patient change from baseline

Clinically meaningful within-patient worsening

The TPC arm generally had higher proportions of patients with a clinically meaningful worsening than the SG arm in the primary domains of GHS/QoL, physical functioning, role functioning, and fatigue at most assessments up to C11D1 (Figure 1).

For the secondary domains, among the patients with clinically meaningful worsening, the proportion with worsening

Table 1. Demographics and baseline clinical characteristics (ITT population; *N* = 543).

Characteristics	SG (*N* = 272)		TPC (*N* = 271)	
	EORTC QLQ-C30 evaluable[a] (*n* = 236)	EORTC QLQ-C30 not evaluable (*n* = 36)	EORTC QLQ-C30 evaluable[a] (*n* = 210)	EORTC QLQ-C30 not evaluable (*n* = 61)
Age (years)				
Mean (SD)	56.9 (11.50)	58.5 (11.66)	55.6 (10.47)	56.1 (10.27)
Median	57.0	61.0	55.0	56.0
Female, *n* (%)	235 (99.6)	35 (97.2)	208 (99.0)	60 (98.4)
Race or ethnic group, *n* (%)				
White	164 (69.6)	20 (55.6)	136 (64.8)	42 (68.9)
Black	6 (2.5)	2 (5.6)	11 (5.2)	2 (3.3)
Asian	10 (4.2)	1 (2.8)	5 (2.4)	0 (0.0)
Others	0 (0.0)	0 (0.0)	3 (1.4)	2 (3.3)
Not specified	56 (23.7)	13 (36.1)	55 (26.2)	15 (24.6)
Geographic region, *n* (%)				
Europe	133 (56.4)	24 (66.7)	127 (60.5)	30 (49.2)
North America	103 (43.6)	12 (33.3)	83 (39.5)	31 (50.8)
Number of prior chemotherapy regimens in metastatic setting, *n* (%)				
2 lines	95 (40.3)	18 (50.0)	93 (44.3)	20 (32.8)
3/4 lines	141 (59.7)	18 (50.0)	117 (55.7)	41 (67.2)
Visceral metastasis, *n* (%)				
Yes	224 (94.9)	35 (97.2)	198 (94.3)	60 (98.4)
No	12 (5.1)	1 (2.8)	12 (5.7)	1 (1.6)
Endocrine therapy in metastatic setting for at least 6 months, *n* (%)				
Yes	208 (88.1)	27 (75.0)	185 (88.1)	49 (80.3)
No	28 (11.9)	9 (25.0)	25 (11.9)	12 (19.7)
Screening ECOG performance status, *n* (%)				
0	102 (43.2)	14 (38.9)	101 (48.1)	25 (41.0)
1	134 (56.8)	22 (61.1)	109 (51.9)	36 (59.0)
Time from metastatic breast cancer diagnosis to randomization (months)				
Mean (SD)	58.9 (39.16)	45.5 (27.72)	52.0 (30.53)	50.6 (31.25)
Median	49.9	42.0	47.7	45.3
Time from neoadjuvant/adjuvant chemotherapy to diagnosis (months)				
N	140	24	133	47
Mean (SD)	67.3 (61.17)	62.4 (43.18)	64.1 (53.70)	45.9 (45.94)
Median	52.6	52.2	46.7	37.2
Treatment of physician's choice, *n* (%)				
Capecitabine	—	—	19 (9.0)	3 (4.9)
Eribulin	—	—	107 (51.0)	23 (37.7)
Gemcitabine	—	—	43 (20.5)	13 (21.3)
Vinorelbine	—	—	41 (19.5)	22 (36.1)
Missing	—	—	0 (0.0)	0 (0.0)
Prior CDK inhibitor treatment duration, *n* (%)				
≤12 months	138 (58.5)	23 (63.9)	131 (62.4)	35 (57.4)
>12 months	95 (40.3)	11 (30.6)	77 (36.7)	25 (41.0)
Missing	3 (1.3)	2 (5.6)	2 (1.0)	1 (1.6)
Chemotherapy in neoadjuvant/ adjuvant setting, *n* (%)				
Yes	148 (62.7)	25 (69.4)	136 (64.8)	48 (78.7)
No	88 (37.3)	11 (30.6)	74 (35.2)	13 (21.3)
Total bilirubin levels at baseline				
N	236	34	210	61
Mean (SD)	8.3 (4.21)	10.2 (8.38)	9.2 (6.27)	9.5 (6.10)

[a]The EORTC QLQ-C30-evaluable population was defined as patients with ITT who completed at least one of the 15 domains/scales at baseline and at least one evaluable assessment at a post-baseline visit based on the EORTC QLQ-C30. Patients who did not meet this criterion were included in the EORTC QLQ-C30-nonevaluable population. An evaluable assessment for a given visit was defined as ≥ 1 non-missing domain score among the 15 domains for EORTC QLQ-C30 and ≥ 1 non-missing value among the 5 health status dimensions or VAS score for EQ-5D. The patient-reported treatment symptomatic toxicity, as assessed by the PRO-CTCAE, was evaluated in the safety population which was defined as all patients in the ITT group who received ≥ 1 dose of study treatment.
Abbreviations: CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; ITT, intent to treat; PRO, patient-reported outcome; SD, standard deviation; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

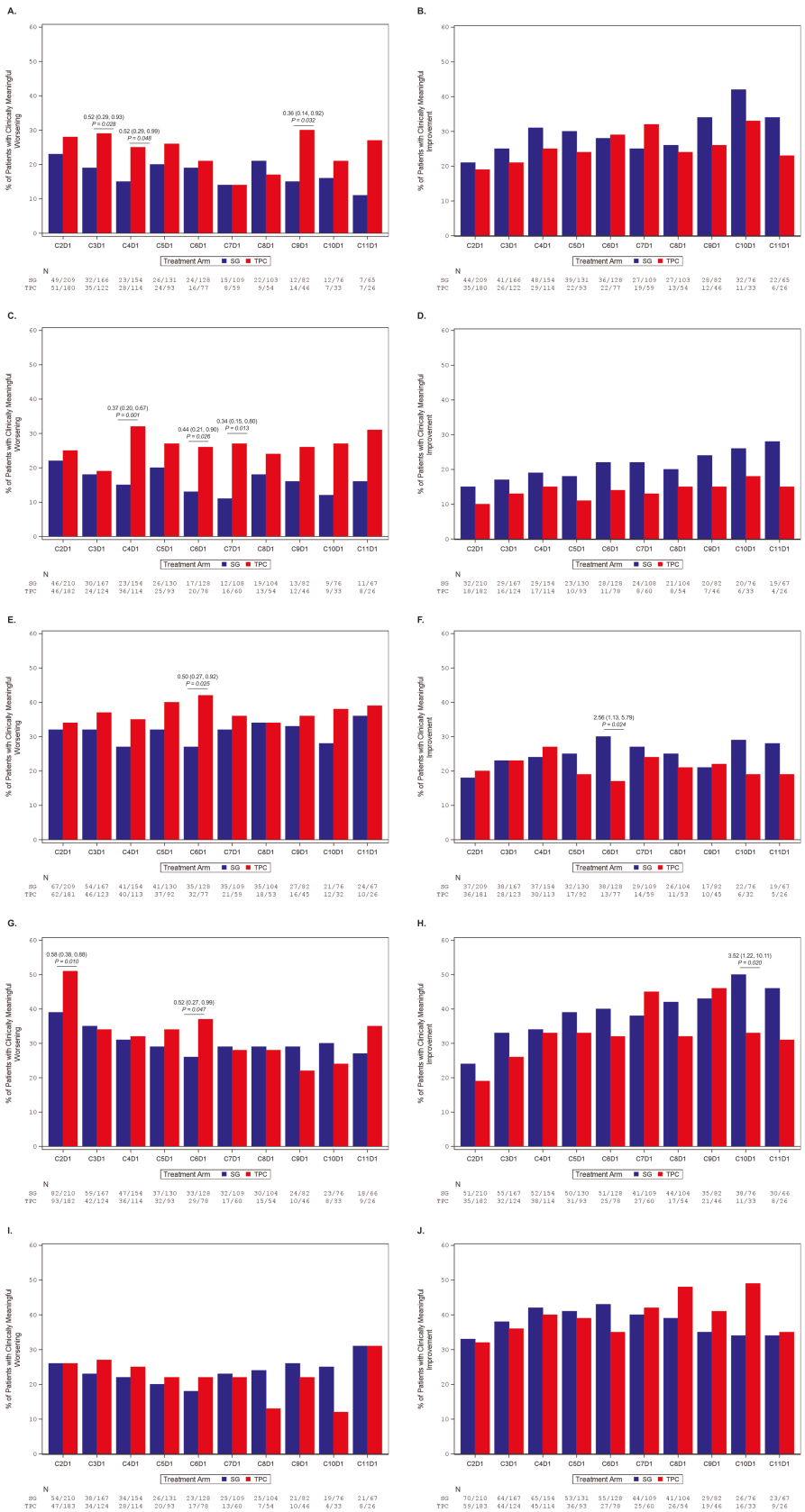

Figure 1. Proportion of patients experiencing clinically meaningful change from baseline on the primary PRO domains. Data show the proportions of patients in the PRO-evaluable population ($N = 446$, with 236 and 210 in the SG and TPC arms, respectively), who experienced clinically meaningful worsening or improvement on the primary domains (ie, reaching/exceeding the responder definition [RD] threshold of −10 or + 10 points for a global health/functioning domain or+10 or −10 points for a symptom domain). Data are shown to the visit where the number of evaluable patients was at least 25 in both arms (indicated by denominators of the fractions under the bars at cycle 11 day 1 [C11D1]). Odds ratios (95% CIs and *P*-values) between proportions of patients worsening/improving in the SG arm vs TPC arm by visit were calculated using logistic regression; values at visits where the SG arm was significantly different from the TPC arm are shown on each graph. Abbreviations: GHS/QoL, global health status/quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

for the social functioning and insomnia domains of EORTC QLQ-C30, and the EQ-VAS was higher in the TPC arm. SG had a higher proportion of patients with clinically meaningful worsening for the diarrhea domain. For all other secondary domains, the proportion of patients with meaningful worsening was comparable between arms (Supplementary Figure S3).

Clinically meaningful within-patient improvement

The SG arm generally had higher proportions of patients with a clinically meaningful improvement than the TPC arm at the individual level in the primary domains of GHS/QoL, physical functioning, role functioning, and fatigue at most assessments up to C11D1 (Figure 1). For the pain domain, the odds ratio for meaningful improvement did not favor the SG or TPC arm at any visit.

For the secondary domains, among the patients with clinically meaningful improvement, the proportion with improvement for the insomnia, appetite loss, and diarrhea domains of EORTC QLQ-C30 was higher in the TPC arm. SG had a higher proportion of patients with clinically meaningful improvement for the emotional functioning and dyspnea domains of EORTC QLQ-C30, the EQ-5D-5L health utility index, and the EQ-VAS. For all other secondary domains, the proportion of patients with meaningful improvement was comparable between arms (Supplementary Figure S3).

Time to first clinically meaningful worsening

The time to first clinically meaningful worsening or death, significantly favored the SG arm (ie, was longer than in the TPC arm) for the following primary EORTC QLQ-C30 domains: GHS/QoL (HR, 0.75; 95% CI, 0.61-0.92; $P = .006$), physical functioning (HR, 0.79; 95% CI, 0.64-0.97; $P = .022$), and fatigue (HR, 0.73; 95% CI, 0.60-0.89; $P = .002$; Table 2; Supplementary Figure S4).

Among the secondary domains, the time to first clinically meaningful worsening or death significantly favored the SG arm in emotional functioning, dyspnea, insomnia, financial difficulties, and EQ-VAS. The results did not differ between arms for the remaining secondary domains, except

Table 2. Time to first meaningful worsening or death.

	Median time to event (months)		Hazard ratio[b]	95% CI[b]
	SG ($n = 236$)	TPC ($n = 210$)		
EORTC QLQ-C30[a] ($N = 446$)				
Primary domains				
GHS/QoL	4.3	3.0	0.751	0.612-0.922**
Physical functioning	5.1	4.2	0.786	0.640-0.966*
Role functioning	2.6	2.8	0.912	0.745-1.117
Fatigue	2.2	1.4	0.732	0.598-0.894**
Pain	3.8	3.5	0.918	0.748-1.126
Secondary domains				
Emotional functioning	7.8	5.3	0.671	0.541-0.831**
Cognitive functioning	4.9	5.0	0.865	0.703-1.066
Social functioning	2.9	3.6	0.894	0.726-1.100
Nausea and vomiting	2.2	5.0	1.071	0.874-1.314
Dyspnea	5.8	4.5	0.742	0.602-0.915*
Insomnia	6.3	4.7	0.795	0.641-0.986*
Appetite loss	3.6	4.7	0.933	0.754-1.155
Constipation	3.9	5.0	1.027	0.834-1.265
Diarrhea	2.3	6.1	1.409	1.148-1.731**
Financial difficulties	9.8	8.0	0.765	0.614-0.952*
Summary score	5.1	5.5	0.924	0.751-1.136
EQ-5D-5L[a] ($N = 445$)	SG ($n = 238$)	TPC ($n = 207$)		
Health utility index	5.7	5.3	0.889	0.722-1.096
EQ-VAS	4.7	3.5	0.794	0.646-0.975*

[a]Assessments were made at baseline (ie, −3 to day 1), on day 1 of each treatment cycle (3 weeks per cycle for SG and 3-4 weeks per cycle for TPC) from cycle 2, at the end of treatment (EOT) visit (ie, ≥ 30 days after the last dose of the study drug and before the start of other treatments, or, in the event of premature study termination), and at the long-term follow-up visit (one visit after the EOT visit).
[b]Hazard ratios (95% CIs), estimated by stratified Cox regression analyses and labeled by asterisks, indicate domains for which time to first meaningful worsening, based on the responder definition (RD) threshold, significantly differed between arms. * $P < .05$; ** $P < .01$. Death was considered an event in the analysis. Patients whose baseline scores were so poor that it was impossible for the change score to exceed or equal the RD threshold for worsening were excluded.
Patients who never experienced clinically meaningful worsening were censored at the time of their last non-missing assessment. Death was treated as an event in the main analysis but censored at the time of the last non-missing PRO assessment in the sensitivity analysis. The Kaplan-Meier product-limit method was used to estimate the survival distribution functions for each treatment arm. Hazard ratios (HRs) of SG vs TPC on time to first worsening or death were estimated using stratified Cox proportional hazards regression models with treatment arm (SG vs TPC) as a covariate and the randomization stratification factors as stratification factors in the model. The Efron method was used to handle ties.
Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; GHS, global health status; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice; VAS, visual analog scale.

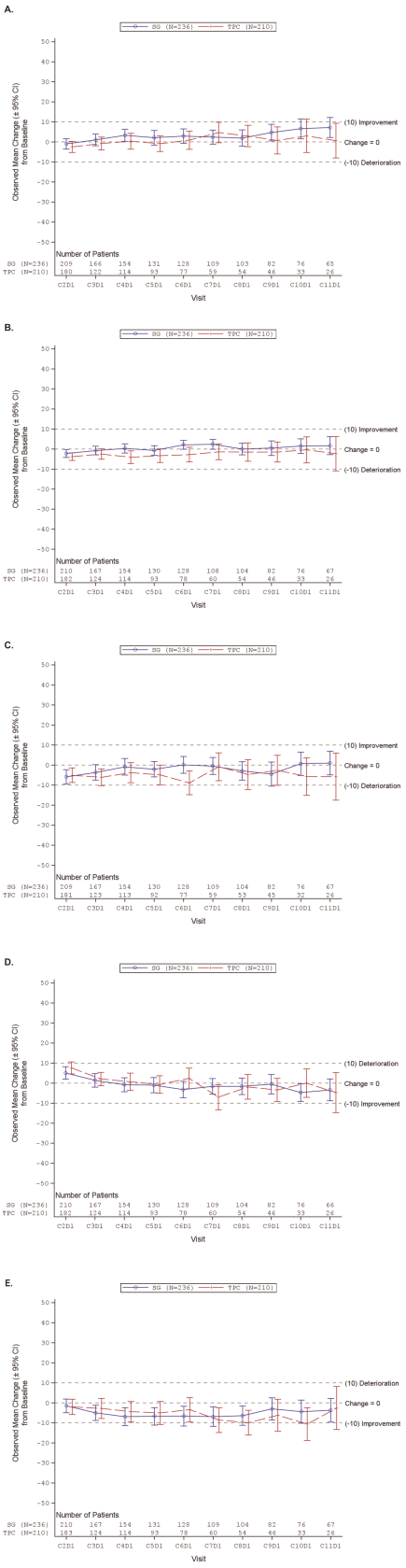

Figure 2. Observed changes from baseline in PRO scores for primary domains. Data show mean changes from baseline in the SG and TPC arms for the primary domains of interest (from the EORTC QLQ-C30), up to the visit where both arms had at least 25 evaluable patients (cycle 11 day 1 [C11D1]). The middle dotted line indicates the baseline level. Dotted lines labeled "improvement" and "deterioration" indicate the clinically important difference (CID) within an arm for the corresponding change in PRO score to be considered clinically meaningful. Note that an increase of 10 points from baseline indicates a meaningful improvement for global health-related and functional domains, whereas the same change indicates a meaningful worsening for symptom domains. Error bars indicate the 95% CI. Abbreviations: EOT, end of treatment; GHS/QoL, global health status/quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

for patient-reported diarrhea, which developed or worsened in patients with TPC more slowly than in patients with SG (Table 2).

Sensitivity analysis showed that the results were consistent when death was censored, with the exceptions of insomnia and financial difficulties which lost statistical significance, likely due to more censored subjects (Supplementary Table S2).

Observed changes from baseline

At the group level, mean EORTC QLQ-C30 scores for the primary focused domains were generally maintained in both arms during treatment up to C11D1 (**Figure 2**).

For secondary EORTC QLQ-C30 focused domains and the summary score, the mean EORTC QLQ-C30 scores were maintained during treatment in the SG arm, except for a meaningful worsening of diarrhea on several visits (Supplementary Figure S5). Mean scores in the TPC arm were also generally maintained during treatment, except for a meaningful improvement in appetite loss. For the EQ-5D-5L health utility index and EQ-VAS, observed mean changes were maintained during treatment in both study arms.

Least square mean changes from baseline

Overall, least square (LS) mean changes from baseline for the primary EORTC QLQ-C30 domains, based on mixed-effects models for repeated measures analyses of data up to the first 11 cycles of treatment, are shown in Table 3. For all primary focused domains, overall, within-group LS mean change from baseline in both treatment arms remained inside the thresholds for meaningful change (ie, did not exceed within-group CID of 10). For physical functioning, the difference in overall LS mean change from baseline between treatment arms was significant, in favor of the SG arm, although the difference was not clinically meaningful (ie, did not exceed the between-group CID of 5). For all the other primary focused domains, there was no significant between-arm difference in overall LS mean change from baseline.

LS mean change did not exceed the threshold for meaningful improvement for any secondary domain in the TPC arm. In the SG arm, the LS mean change of one secondary domain, emotional functioning, exceeded the threshold for meaningful improvement (10.37; 95% CI, 6.45-14.28]). LS mean changes for the secondary domains generally remained inside within-group thresholds for meaningful change (improvement or worsening) in both arms (Table 3). The between-arm difference in LS mean change was significant and meaningful for diarrhea, in favor of TPC. The between-arm difference in LS mean change was significant for physical functioning and significant and meaningful for dyspnea, in favor of SG. There were no significant or meaningful differences between the arms for the other secondary domains.

Table 3. Overall least square (LS) mean changes from baseline.

	LS mean change (95% CI)		Difference in mean change (95% CI)	Between-group CID[29]
EORTC QLQ-C30[a]	SG (n = 236)	TPC (n = 210)	SG vs TPC	
Primary domains				
GHS/QoL[b]	2.29 (−1.37, 5.94)	−0.13 (−4.04, 3.78)	2.42 (−0.66, 5.49)	4
Physical functioning[c]	0.44 (−2.95, 3.82)	−3.42 (−7.03, 0.18)	3.86 (0.87, 6.86)*	5
Role functioning[c]	−2.76 (−7.97, 2.45)	−5.87 (−11.38, −0.36)	3.11 (−1.15, 7.37)	6
Fatigue[d]	−0.06 (−4.69, 4.57)	3.26 (−1.63, 8.14)	−3.32 (−7.10, 0.47)	5
Pain[d]	−6.98 (−11.71, −2.25)	−5.35 (−10.38, −0.32)	−1.63 (−5.52, 2.25)	6
Secondary domains				
Emotional functioning[c]	10.37 (6.45, 14.28)	9.43 (5.27, 13.59)	0.94 (−2.39, 4.27)	3
Cognitive functioning[c]	−0.12 (−3.62, 3.39)	0.09 (−3.67, 3.84)	−0.20 (−3.26, 2.86)	3
Social functioning[c]	−0.28 (−5.12, 4.56)	−1.05 (−6.19, 4.08)	0.77 (−3.17, 4.72)	5
Nausea/vomiting[d]	1.55 (−1.35, 4.45)	0.12 (−2.97, 3.20)	1.44 (−0.91, 3.78)	3
Dyspnea[d]	−1.01 (−5.96, 3.94)	3.24 (−2.05, 8.53)	**−4.25 (−8.45, −0.06)***	4
Insomnia[c]	−8.24 (−13.44, −3.03)	−4.56 (−10.14, 1.03)	−3.68 (−8.10, 0.75)	4
Appetite loss[d]	−4.55 (−9.71, 0.60)	−1.27 (−6.71, 4.17)	−3.28 (−7.31, 0.75)	5
Constipation[d]	0.56 (−4.53, 5.66)	1.60 (−3.90, 7.10)	−1.04 (−5.51, 3.43)	5
Diarrhea[d]	9.47 (4.78, 14.17)	−0.91 (−6.03, 4.21)	**10.38 (6.32, 14.45)****	3
Financial difficulties[d]	0.90 (−3.11, 4.90)	0.04 (−4.14, 4.23)	0.85 (−2.45, 4.16)	3
Summary score[b]	0.40 (−2.41, 3.21)	−0.24 (−3.21, 2.74)	0.64 (−1.77, 3.05)	5
EQ-5D-5L[a]	SG (n = 238)	TPC (n = 207)	SG vs TPC	
Health utility index[a]	0.05 (0.02, 0.09)	0.03 (−0.00, 0.07)	0.02 (−0.01, 0.05)	0.08
EQ-VAS[a]	2.20 (−1.01, 5.41)	0.39 (−3.04, 3.82)	1.81 (−0.87, 4.48)	7

[a]Assessments were made at baseline (ie, −3 to day 1), on day 1 of each treatment cycle (3 weeks per cycle for SG and 3-4 weeks per cycle for TPC) from cycle 2, at the end of treatment (EOT) visit (ie, ≥ 30 days after the last dose of the study drug and before the start of other treatments, or, in the event of premature study termination), and at the long-term follow-up visit (one visit after the EOT visit).
[b]A higher score represents better QoL.
[c]A higher score represents better functioning.
[d]A higher score represents worse symptomatology.
The overall within-group least-square (LS) mean change from baseline and between-treatment difference in LS mean change were assessed using linear mixed-effects models for repeated measures (MMRM) with random intercept and time effects. The models used the change in PRO score from baseline as the dependent variable, included all post-baseline visits with ≥ 25 patients submitting an evaluable PRO assessment in both study arms, and included treatment arm (SG vs TPC), time (treated as a discrete variable), stratification factors, baseline PRO score, and treatment-by-time interaction as covariates. Differences between overall LS mean changes (95% CIs), estimated by linear MMRM and shown in bold, indicate meaningfully better scores in the SG arm than in the TPC arm based on the between-group CID. * $P < .05$; ** $P < .01$.
Abbreviations: CID, clinically important difference; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; GHS, global health status; QoL, quality of life; SG, sacituzumab govitecan; TPC, treatment of physician's choice; VAS, visual analog scale.

Assessment of PRO-CTCAE data

The percentages of patients experiencing worsening of PRO-CTCAE items to level 3 or worse during treatment were higher in the SG arm than in the TPC arm for diarrhea frequency and amount of hair loss (Figure 3). For other symptomatic treatment-related AEs, the percentages of patients experiencing worsening of PRO-CTCAE items to level 3 or worse during treatment were comparably low in both arms for decreased appetite, nausea, vomiting, constipation, abdominal pain, shortness of breath, and fatigue. The distribution of patients in each response category for PRO-CTCAE items is shown in Supplementary Figure S6.

Discussion

Patients with mBC often suffer reduced function and overall HRQoL as a result of the disease itself and side effects caused by prior and/or current treatments.[32] Efficacy data from the TROPiCS-02 study demonstrate that treatment with SG significantly and meaningfully prolonged PFS and OS compared with single-agent chemotherapy in patients with pretreated HR+/HER2− locally recurrent inoperable or mBC.[13] The present analysis shows that HRQoL does not deteriorate in patients treated with SG compared with patients treated with TPC. In conjunction with the previously published efficacy results, the observed HRQoL benefits strengthen the risk-benefit profile of SG over TPC as treatment for HR+/HER2− mBC.

At the individual level, the SG arm had significantly lower proportions of patients experiencing clinically meaningful within-patient worsening for social functioning, insomnia, and appetite loss than the TPC arm at one or more assessment visits, but a significantly higher proportion for diarrhea. Compared with the TPC arm, patients in the SG arm also took significantly longer to experience their first clinically meaningful worsening for 7 of the 15 EORTC QLQ-C30 domains—GHS/QoL, physical functioning, fatigue, emotional functioning, dyspnea, insomnia, and financial difficulties—and EQ-VAS.

At the group level, the results of the longitudinal analyses show a statistically significant difference in overall LS mean

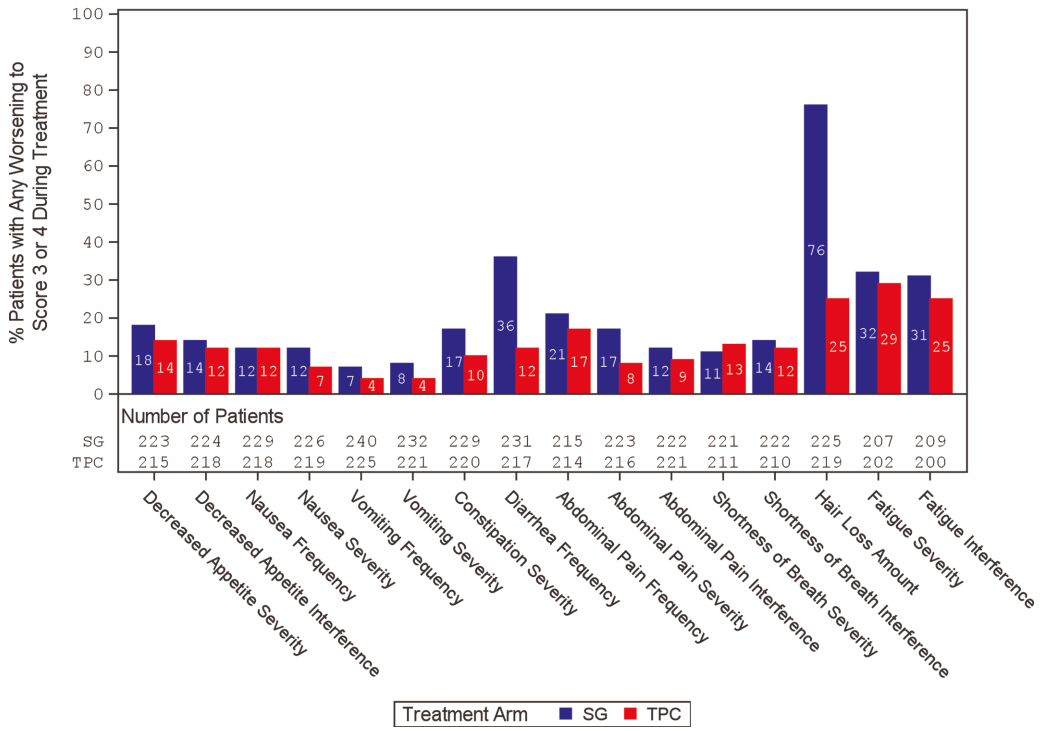

Figure 3. Proportion of patients with any worsening of level 3 or more during treatment. Data show proportions of patients in the safety population (excluding patients with a score of 3 or 4 at baseline), who showed worsening from baseline to a level of 3 or worse on 9 potentially relevant symptoms (decreased appetite, nausea, vomiting, constipation, abdominal pain, shortness of breath, fatigue, diarrhea, and hair loss) during treatment, as assessed by 16 items selected from the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), an instrument developed to identify cancer treatment-related adverse events. Numbers within bars indicate the percentage of patients showing any worsening of level 3 or greater during treatment. Abbreviations: SG, sacituzumab govitecan; TPC, treatment of physician's choice.

change in the physical functioning and dyspnea domains of the EORTC QLQ-C30 in favor of the SG arm and a similar overall LS mean change between treatment arms across the remaining primary and secondary PRO domains. The only exception was diarrhea, in which the SG arm was significantly worse than the TPC arm.

Analysis also showed that during treatment few patients in either arm reported worsening of PRO-CTCAE items to level 3 or more; 2 exceptions were diarrhea frequency and amount of hair loss, which favored the TPC arm. These exceptions were unsurprising as both items are part of the AE profile of SG. Diarrhea can be effectively managed according to established guidelines.[11,33]

These findings corroborate those of the ASCENT study on the effects of SG on HRQoL in the triple-negative mBC (mTNBC) setting,[16] extending them to the metastatic or locally recurrent inoperable HR+/HER2– mBC setting. In ASCENT, patients with refractory/relapsed mTNBC who had received ≥ 2 prior systemic therapies, including ≥ 1 in a metastatic setting, were randomized 1:1 to SG (n = 236) or TPC (n = 183; capecitabine, eribulin, vinorelbine, or gemcitabine) and HRQoL was assessed using EORTC QLQ-C30. Changes from baseline were greater with SG than TPC for 4 out of 5 primary focused domains: GHS/QoL, physical functioning, fatigue, and pain.[16] First clinically meaningful worsening took longer with SG than with TPC for physical functioning, role functioning, fatigue, and pain. Findings from TROPiCS-02 were largely consistent in that SG showed better changes from baseline and prolonged time to first HRQoL worsening or death.

The study findings should be interpreted with certain limitations in mind. First, 36 (13%) and 61 (23%) ITT patients in the SG and TPC arms, respectively, were excluded from the EORTC QLQ-C30-evaluable population because of missing data at baseline and/or all post-baseline visits. Baseline demographic and disease characteristics were generally similar between the evaluable and non-evaluable populations in both arms, with differences between the corresponding populations in several key disease characteristics. Specifically, the non-evaluable patients in the SG arm had a shorter time from mBC diagnosis to randomization (56 vs 46 months), and the non-evaluable patients in the TPC arm had a shorter time from neoadjuvant/adjuvant chemotherapy to mBC diagnosis (46 vs 64 months) and a greater proportion of patients receiving chemotherapy in a neoadjuvant/adjuvant setting (79% vs 65%) than the evaluable patients. Clinical outcomes were also worse for these non-evaluable patients in the TPC arm, with an overall response rate (ORR) of 1.6% vs 11.4% for the evaluable population, whereas the ORR was similar between the evaluable (16.9%) and non-evaluable (11.1%) populations within the SG arm. Collectively, these observations together with the higher baseline PRO scores in the TPC arm suggest that the findings of the present study should be considered representative of the patients with ITT who received SG but not TPC. The effects of TPC on PRO endpoints are likely to have been overestimated, as patients with worse prognosis were not considered in the analyses because they were missing baseline or all post-baseline PRO data.

Second, the results of this study may have favored the TPC arm as more patients discontinued treatment in the TPC arm

than the SG arm. The main cause of treatment discontinuation was disease progression, which was more likely to be associated with reduced functions and/or reduced HRQoL. PRO data were not collected for patients after they discontinued study treatment, so this effect could not be evaluated in the present analyses. Another cause of treatment discontinuation, AEs, may also have impacted the results, but the proportions of patients discontinuing treatment due to AEs were found to be small (< 7%) and similar in both treatment arms.

Additionally, SG and the different TPCs were administered on different schedules, and whether this had an impact on HRQoL is not known.

Conclusions

Compared with TPC, patients reported that treatment with SG maintained physical functioning and led to fewer symptoms of dyspnea. SG also significantly prolonged the time to first worsening in functioning (physical and emotional), symptoms/problems (fatigue, dyspnea, insomnia, financial difficulties), and overall HRQoL (GHS/QoL and EQ-VAS). In conclusion, treating patients with HR+/HER2– mBC who had previously progressed on 2 to 4 prior chemotherapy regimens with SG led to a QoL benefit compared with TPC, apart from diarrhea and hair loss. These AEs are part of the known safety profile of SG and can be effectively managed according to established guidelines.

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Conflict of Interest

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Data availability

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified

external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data request should be sent to datarequest@gilead.com.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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