Quality of life with talazoparib following platinum or multiple cytotoxic nonplatinum regimens in patients with advanced breast cancer and germline *BRCA1/2* mutations: patient-reported outcomes from the ABRAZO phase 2 trial

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Abstract

Background: Talazoparib (1 mg/day) exhibited promising efficacy and safety in patients with advanced breast cancer during ABRAZO (NCT02034916); this study evaluated patient-reported outcomes (PROs).

Patients and Methods: ABRAZO is a 2-cohort, 2-stage, phase 2 study of talazoparib in patients with advanced breast cancer following a response to prior platinum-based therapy (cohort 1 [C1], n = 49) or ≥3 platinum-free cytotoxic-based regimens (cohort 2 [C2], n = 35). PROs were assessed on day 1 (baseline), every 6 weeks for an initial 24 weeks, and every 12 weeks thereafter until progression, using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) and its breast cancer module, QLQ-BR23.

Results: GHS/QoL was maintained from baseline across all time points for both C1 and C2. For C1 and C2, median time to deterioration (TTD) of GHS/QoL (95% confidence interval [CI]) was 2.8 (2.1, 3.0) and 5.5 (4.2, 5.7) months, respectively. Median TTD for all QLQ-C30 functional scales for C1 and C2 ranged 2.1–3.1 months and 4.2–5.6 months, respectively; median TTD for all QLQ-BR23 symptoms scales ranged 2.6–4.0 months and 4.2–5.6 months, respectively. There were no statistically significant differences in estimated overall mean change from baseline in the GHS/QoL scale for both cohorts (C1: –2.6 [95% CI, –7.8, 2.5]; C2: 1.2 [95% CI, –5.5, 8.0]). Significant overall improvements in the breast symptoms, arm symptoms, and the future perspective of patients in C1 and C2 were observed despite the statistically significant and clinically meaningful overall deterioration among patients regarding their role functioning (in C1) and dyspnea symptoms (in C2).

Conclusions: Despite the statistically significant and clinically meaningful overall deterioration among patients regarding their role functioning (in C1) and dyspnea symptoms (in C2), patients

in both C1 and C2 reported significant overall improvements in their breast symptoms, arm symptoms, and future perspective, and their GHS/QoL was maintained from baseline.

Keywords

Poly(ADP-ribose) polymerase (PARP); Talazoparib; Breast cancer; Patient-reported outcomes; Quality of life; *BRCA1*; *BRCA2*

1. Introduction

Breast cancer susceptibility genes, *BRCA1* and *BRCA2* (*BRCA1/2*), are essential components in DNA double-strand break repair. Approximately 5% of unselected patients with breast cancer carry a germline *BRCA1/2* (g*BRCA1/2*) mutation [1]. Cancer cells with a *BRCA1/2* mutation are deficient in homologous recombination DNA repair, and the inhibition of poly(ADP-ribose) polymerase (PARP) results in synthetic lethality in these cells. This susceptibility has been exploited in *BRCA*-mutated tumors with the clinical development of several PARP inhibitors for a range of cancers [2]; in two clinical trials that investigated ovarian cancer patients treated with PARP inhibitors, no significant detrimental effect on their quality of life (QoL) was observed [3-5]. Efficacy and safety of the PARP inhibitor talazoparib as a single agent in patients with locally advanced or metastatic breast cancer with a g*BRCA* mutation were studied in a phase 2 clinical trial (ABRAZO, NCT02034916); primary results demonstrated 21%–37% objective response rates (ORR) by independent radiology facility (IRF); additional overall ORR by IRF have also been reported (triple-negative breast cancer, hormone receptor positive/human epidermal growth factor receptor 2 positive/negative: 26% and 29%, respectively; g*BRCA1*, g*BRCA2* mutation: 23% and 33%, respectively) [3].

Therapies that control disease are expected to maintain QoL; however, drug-related toxicity, even with molecularly targeted treatments, could diminish QoL among patients with

advanced breast cancer [7]. The maintenance of QoL is particularly important in the advanced breast cancer setting, where treatment is palliative, not curative.

Hence, when evaluating new treatments, it is imperative to evaluate the quality of the time gained by delaying disease progression via patient-reported outcomes (PROs). Here we report detailed PROs from the ABRAZO study and determine the effects of talazoparib treatment on QoL in patients with locally advanced or metastatic breast cancer carrying a *gBRCA* mutation who have received prior platinum-based therapy or ≥3 platinum-free cytotoxic-based regimens.

2. Methods

2.1 Study design and participants

This open-label, two-cohort, two-stage, international, phase 2 study assessed talazoparib in patients with locally advanced or metastatic breast cancer with a deleterious or a suspected deleterious g*BRCA1/2* mutation. Cohort 1 included those with a documented complete response or a partial response to a prior platinum-containing regimen for metastatic disease, with no disease progression on or within 8 weeks of the last dose of platinum therapy. Cohort 2 had received ≥3 prior cytotoxic chemotherapy regimens for metastatic disease and no prior platinum therapy for metastatic disease. Patients received continuous oral talazoparib 1 mg daily. A detailed study design was previously presented [6].

2.2 PRO assessments

PROs were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30, version 3.0) and its breast cancer module (QLQ-BR23).

Assessments were performed at baseline (≤7 days prior to cycle 1 day 1) and whenever tumor assessments were performed (ie, every 6 weeks for the initial 24 weeks from the date of cycle 1 day 1, then every 12 weeks or sooner if progression was clinically suspected, and at any unscheduled tumor assessment; always ±7 days). Patients were to complete these instruments in the clinic prior to having any tests and any discussion of their progress with healthcare site personnel.

EORTC QLQ-C30 is a 30-item questionnaire comprising five multi-item functional subscales, three multi-item symptom scales, a global health status (GHS)/QoL subscale, and six single-item symptom scales assessing other cancer-related symptoms. The questionnaire includes 4-point Likert scales, with responses from “not at all” to “very much” to assess functioning and symptoms, and two 7-point Likert scales for GHS/QoL [8]. EORTC QLQ-BR23 is a 23-item breast cancer–specific companion module to the EORTC QLQ-C30 that comprises four functional scales and four symptom scales. Responses to all items are converted to a 0–100 scale using a standard scoring algorithm [9]. For functional and GHS/QoL scales, higher scores represent a better level of functioning and QoL (a negative change from baseline reflects deterioration, and a positive change reflects improvement). For symptom scales, a higher score represents higher symptoms severity (a negative change reflects improvement, and a positive change reflects deterioration).

2.3 Statistical analyses

All PRO analyses included PRO-evaluable patients, defined as those in the intention-to-treat (ITT) population with a baseline and at least one postbaseline assessment before the end of study treatment. Completion rates were summarized by assessment time points. Summary statistics results are presented by cohort at baseline and at assessment time points.

We performed prespecified analyses of change from baseline in GHS/QoL, functional (QLQ-C30 and QLQ-BR23), and symptom (QLQ-C30 and QLQ-BR23) scales, and time to deterioration (TTD) on the GHS/QoL, functional (QLQ-C30), and symptom (QLQ-BR23) scales. For each cohort, statistical significance was interpreted using 95% confidence intervals (CIs) of the average change from the baseline score. Clinically meaningful change was defined as a 10-point or greater change from baseline in GHS/QoL, functional, and symptom score [10]. The TTD on GHS/QoL and functional scales was determined using Kaplan–Meier (KM) survival analysis methods from baseline to the first occurrence of a 10-point or greater decrease in functional score, disease progression, or death (whichever occurred first). Similarly, TTD on the breast cancer–specific symptom scale was determined using KM survival analysis methods from baseline to the first occurrence of a 10-point or greater increase in symptom score, disease progression, or death (whichever occurred first). Survival analyses methods included the KM approach for estimating the medians and percentiles and the Brookmeyer and Crowley method for computing 95% CIs.

The post hoc overall mean change from the baseline score was estimated based on a longitudinal mixed-effect random-intercept, random-slope model with variables of treatment, time, treatment by time, and baseline used as covariates. A restricted maximum likelihood method assuming an unstructured covariance matrix was used. All analyses were conducted using Statistical Analysis System software (SAS Institute, Cary, NC, USA). All *P* values are two-sided, unless stated otherwise.

Results

3.1 Patients

Between May 2014–February 2016, 84 patients were enrolled and included in the ITT population. Further information on the ITT population are available in Supplementary Fig. S1

and Table S1. The median age was 50 years for cohort 1 and 52 years for cohort 2. The median number of prior cytotoxic regimens received for advanced breast cancer was two for cohort 1 and four for cohort 2.

Up to week 36, when there were still more than 10 eligible patients, compliance was ≥53% in cohort 1 and ≥45% in cohort 2 (Supplementary Tables S2 and S3).

3.2 GHS/QoL

Baseline mean GHS/QoL scores were moderately high in both cohorts (Table 1). Baseline scores in the study were within range of published normative reference values (Table 1) [11]. Based on interpretation of the 95% CIs for the change from baseline analysis, GHS/QoL scores were maintained from baseline to the end of treatment across all time points within each cohort (Supplementary Fig. S2 and S3; Table S4).

Based on the repeated-measures mixed-effect model, there was no statistically significant overall change from baseline in GHS/QoL scores for either cohort (Table 2). The median TTD on the GHS/QoL scale was 2.8 (95% CI, 2.1, 3.0) months and 5.5 (95% CI, 4.2, 5.7) months for cohort 1 and cohort 2, respectively (Supplementary Table S5). See Fig. 1 for KM curves for TTD on the GHS/QoL scale for cohorts 1 and 2.

3.3 Functional scales (QLQ-C30)

Baseline functional scale scores indicated high functional levels in both cohorts and were generally consistent with normative reference values (Table 1). Based on interpretation of the 95% CIs, the changes from baseline within cohort 1 (Supplementary Fig. S2) indicated statistically significant deterioration in role functioning (at end of treatment) and emotional functioning (week 12).

The changes from baseline within cohort 2 (Supplementary Fig. S3) indicated statistically significant improvement in physical functioning (weeks 12 and 24), role functioning

(week 24), emotional functioning (week 12), and social functioning (weeks 18 and 24). No additional statistically significant change was observed for any other functional scale at any other assessment visit for cohorts 1 or 2.

Based on the repeated-measures mixed-effect model, there was a statistically significant and a clinically meaningful deterioration in the estimated mean overall change from baseline in role functioning for cohort 1 (Table 2). For cohort 2, there were statistically significant but not clinically meaningful improvements in the estimated mean overall change from baseline in role functioning and social functioning (Table 2).

The median TTD on all functional scales ranged from 2.1–3.1 months for cohort 1, and from 4.2–5.6 months for cohort 2 (Supplementary Table S5).

3.4 Symptom scales (QLQ-C30)

The mean baseline symptom scale scores indicated low symptom severity in both cohorts and were generally consistent with the reference values (Table 1), although constipation tended to be lower and diarrhea tended to be higher than the reference values in cohort 1.

Based on the interpretation from the 95% CIs, in cohort 1, there was a statistically significant deterioration from baseline in fatigue (weeks 6 and 12). There was a statistically significant improvement in dyspnea (week 24; Supplementary Fig. S2).

In cohort 2, statistically significant improvements were observed in fatigue (week 24), nausea/vomiting (week 18), and pain (week 24; Supplementary Fig. S3). No additional statistically significant change was observed for any other symptom scale at any other assessment visit for cohorts 1 and 2.

Based on the repeated-measures mixed-effect model, there was a statistically significant deterioration in the estimated mean overall change from baseline in fatigue for cohort 1 (Table 2); there were statistically significant but not clinically meaningful improvements in the estimated mean overall change from baseline in diarrhea (Table 2). In cohort 2, there were statistically

significant but not clinically meaningful improvements in the estimated mean overall change from baseline in nausea/vomiting, pain, and insomnia (Table 2). There was a statistically significant and a clinically meaningful deterioration in the estimated mean overall change from baseline in dyspnea in cohort 2.

3.5 Functional scales (QLQ-BR23)

Both cohorts tended to have numerically lower scores than normative reference values within all four scales, with the exception of sexual enjoyment in cohort 2, which was comparable to the reference value (Table 1). The sample sizes for sexual enjoyment were smaller than those for other scales because patients were asked to respond to this question only if they responded that they were sexually active in a previous question.

Based on interpretation of the 95% CIs, the change from baseline within cohort 1 indicated statistically significant improvements in body image (week 6), sexual functioning (week 18), sexual enjoyment (week 36), and future perspective (week 24; Supplementary Fig. S2).

The change from baseline within cohort 2 indicated statistically significant improvements in future perspective (weeks 6 and 12; Supplementary Fig. S3). No additional statistically significant change was observed for any other functional scale at any other assessment visit for cohorts 1 and 2.

Based on the repeated-measures mixed-effect model, there was a statistically significant and a clinically meaningful improvement in the estimated mean overall change from baseline in future perspective and a statistically significant improvement in sexual functioning in cohort 1 (Table 2). There were statistically significant but not clinically meaningful improvements in the estimated mean overall change from baseline in sexual enjoyment and future perspective in cohort 2 (Table 2).

3.6 Symptom scales (QLQ-BR23)

The sample sizes for the “upset by hair loss” symptom scale are much lower than those for the other symptom scales because this question was to be answered only if the patient experienced hair loss. All values from both cohorts were comparable to the reference values, with the exception of “upset by hair loss,” which was much higher in both cohorts than the reference values. (Table 1)

Based on interpretation of the 95% CIs, in cohort 1, a statistically significant deterioration in systemic therapy side effects was observed at the end of treatment. There were statistically significant improvements in breast symptoms and arm symptoms (week 6; Supplementary Fig. S2).

In cohort 2, a statistically significant improvement in breast symptoms was observed (weeks 6 and 18). In addition, a statistically significant improvement in arm symptoms was observed (week 48; Supplementary Fig. S3). No additional statistically significant change was observed for any other symptom scale at any other assessment visit for cohorts 1 and 2.

Based on the repeated-measures mixed-effect model, there were statistically significant improvements in the estimated mean overall change from baseline in breast symptoms and arm symptoms for both cohorts (Table 2).

The median TTD across all of the symptom scales ranged from 2.6–4.0 months in cohort 1 and from 4.2–5.6 months in cohort 2 (Supplementary Table S5).

4. Discussion

Preserving QoL in patients with advanced breast cancer is critical, especially when testing the efficacy of new therapies. Recently published European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale guidance emphasized the importance of a holistic assessment of the value of medicine that includes PROs in addition to efficacy and safety [12].

Presented herein are the first-ever detailed PROs regarding talazoparib in patients with advanced breast cancer. We show that the encouraging efficacy achieved with talazoparib is accompanied by maintaining patient-reported GHS/QoL.

The recent fourth European School of Oncology-ESMO international consensus guidelines for advanced breast cancer recommended a platinum regimen (if not previously administered and no suitable clinical trial is available) for *BRCA*-associated triple-negative or endocrine-resistant metastatic breast cancer previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting) [13, 14]. This recommendation was based on Tutt et al [14] who reported that carboplatin was associated with significantly better objective tumor response rates than docetaxel among patients with triple-negative breast cancer and with g*BRCA1/2* mutations. Nevertheless, it is important to also consider the potential detrimental QoL effects of platinum-based chemotherapy. Amadori et al [15] found that patients with advanced breast cancer treated with pemetrexed and carboplatin had significantly greater deterioration in GHS/QoL scores than those treated with vinorelbine and gemcitabine.

Patients receiving treatment for advanced breast cancer can be symptomatic, with significant impairment in daily activity and/or work productivity [16]. Because disease progression may negatively affect QoL, delaying progression could delay QoL deterioration, barring any significant detrimental treatment-related toxicity. A large proportion of patients with advanced breast cancer with bone metastases experience significant pain and have a high incidence of skeletal-related events [17]. Our results showed no significant deterioration of pain symptoms across all time points in cohort 1, and encouraging, statistically significant and clinically meaningful improvement in pain symptoms in cohort 2 at week 24. Such results further support the positive risk–benefit profile of talazoparib and show that talazoparib does not impose toxicities that interfere with patient GHS/QoL. However, it should be noted that a limitation of our study is the small sample size analyzed because of patient dropout.

5. Conclusion

The impact of living with incurable advanced breast cancer may go unrecognized by healthcare professionals. The unpredictable course of advanced breast cancer often leaves patients feeling vulnerable and distressed, with no sense of control over their future [18]. GHS/QoL was maintained from baseline in both cohorts; in addition, significant overall improvements in the breast symptoms, arm symptoms, and the future perspective of patients in both cohorts were observed despite the statistically significant and clinically meaningful overall deterioration among patients regarding their role functioning (cohort 1) and dyspnea symptoms (cohort 2). Published positive PRO results from another PARP inhibitor [19] and recently presented positive PRO results from a randomized, two-arm, phase 3 trial (NCT01945775) that compared talazoparib with physician's choice of cytotoxic chemotherapy (PCT) in patients with *gBRCA1/2* advanced breast cancer (talazoparib vs PCT for ORR [63% vs 27%, respectively] and median progression-free survival [8.6 vs 5.6 months, respectively]) [20] provide very encouraging outlooks regarding the effects of PARP inhibitors on QoL of patients with advanced breast cancer.

Contributions

SAH, RGWQ, NCT, ALH, MER, and AMW designed this phase 2 trial in collaboration with the study sponsor (Medivation LLC, a Pfizer company). Site investigators recruited patients, contributed to patient care, and collected patient data. SAH, RGWQ, and AMW guided the initial drafting of the manuscript, with input from all other authors. SAH, NCT, MLT, HSR, AM, JE, EG, LAM, JB, PAF, HB, ALH, MER, and AMW contributed to the review of the data and the manuscript. HB and RGWQ contributed to the data analysis and reporting. All authors had full access to the study data, contributed to the revision and approval of the manuscript, and participated in the decision to submit the manuscript for publication.

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Conflict of interest statement

SAH reports research funding (to her institution) from Amgen, Bayer, BioMarin, Boehringer Ingelheim, Cascadian Therapeutics, Dignitana, Roche/Genentech, GlaxoSmithKline, Lilly, Medivation (acquired by Pfizer in September 2016), Merrimack, Novartis, OBI Pharma, Pfizer, Puma Biotechnology, and Sanofi; and travel, accommodations, and expenses from Bayer, Lilly, Novartis, and OBI Pharma. RGWQ and HB are employees of and own stock in Pfizer.
NCT reports advisory board honoraria and research funding from Pfizer and BioMarin. MLT reports a consulting or advisory role for AstraZeneca, Tesaro, PharmaMar, and Vertex; research

funding (to her institution) from AbbVie, Biothera, Calithera Biosciences, Genentech, Medivation (acquired by Pfizer in September 2016), Novartis, OncoSec, Pfizer, PharmaMar, Sanofi, Tesaro, and Vertex. HSR reports honoraria from Genomic Health; speakers bureau fees from Genomic Health; research funding (to her institution) from Celsion, Clovis Oncology, Eisai, Genentech, GlaxoSmithKline, Lilly, MacroGenics, Merck, Novartis, OBI Pharma, Pfizer, and Plexxikon; and travel, accommodations, and expenses from Bayer, Novartis, OBI Pharma, Pfizer, and Roche/Genentech. JE reports consulting fees from Novartis, Pfizer, Roche, and Eisai; contracted research from Celgene; and honoraria from Pfizer, Roche, TEVA, and Pierre Fabre. JB reports an advisory board or consulting role for Medivation (acquired by Pfizer in September 2016), Clovis, and Tesaro, and travel expenses and research funding (to her institution) from AstraZeneca and PharmaMar. PAF reports honoraria from Amgen, Novartis, Pfizer, and Roche; a consulting or advisory role for Novartis, Pfizer, and Roche; and research funding from Amgen and Novartis. ALH reports leadership at NeoGenomics Laboratories; stock and other ownership interests in NeoGenomics Laboratories; and consulting or advisory role for Basilea Pharmaceutica, Jazz Pharmaceuticals, Medivation (acquired by Pfizer in Sept 2016), and Nektar. MER reports honoraria from AstraZeneca; a consulting or advisory role for AstraZeneca and McKesson; research funding (to his institution) from AbbVie, AstraZeneca, BioMarin, Medivation (acquired by Pfizer in Sept 2016), Myriad Genetics, and Tesaro; and travel, accommodations, and expenses from AstraZeneca. AMW reports honoraria from AstraZeneca, Lilly, Novartis, and Roche; a consulting or advisory role for AstraZeneca, Lilly, Novartis, and Roche; speakers bureau fees from Roche; and research funding (to his institution) from Roche. All other authors (AM, EG, and LAM) have nothing to disclose.

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Fig. 1.

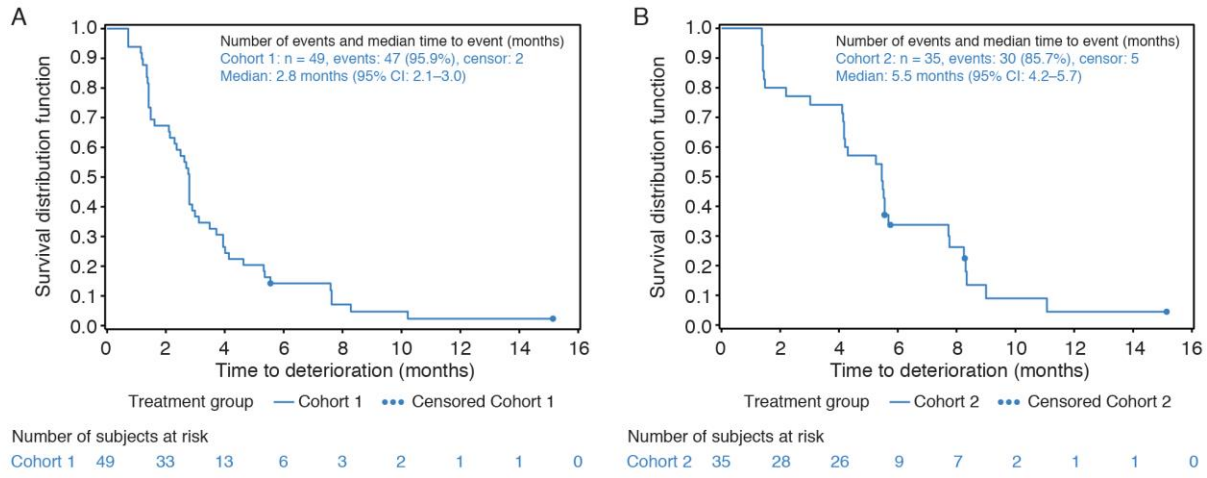
A
Survival distribution function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Number of events and median time to event (months)
Cohort 1: n = 49, events: 47 (95.9%), censor: 2
Median: 2.8 months (95% CI: 2.1–3.0)
0 2 4 6 8 10 12 14 16
Time to deterioration (months)
Treatment group — Cohort 1 ••• Censored Cohort 1
Number of subjects at risk
Cohort 1 49 33 13 6 3 2 1 1 0
B
Survival distribution function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Number of events and median time to event (months)
Cohort 2: n = 35, events: 30 (85.7%), censor: 5
Median: 5.5 months (95% CI: 4.2–5.7)
0 2 4 6 8 10 12 14 16
Time to deterioration (months)
Treatment group — Cohort 2 ••• Censored Cohort 2
Number of subjects at risk
Cohort 2 35 28 26 9 7 2 1 1 0

Table 1. Baseline EORTC QLQ-C30 and QLQ-BR23 scores and reference values (PRO analysis set)[a]

	Cohort 1 (n = 49)		Cohort 2 (n = 35)		Reference values[b,8]
EORTC domain/scale	**N[a]**	**Mean (95% CI)**	**N[a]**	**Mean (95% CI)**	**Mean (SD)**
QLQ-C30 GHS/QoL[c]					
GHS/QoL	47	65.1 (59.9, 70.2)	34	63.2 (56.6, 69.9)	60.2 (25.5)
QLQ-C30 functional scales[c]					
Physical functioning	47	80.6 (75.7, 85.4)	35	79.4 (74.3, 84.6)	81.6 (18.7)
Role functioning	47	75.5 (68.6, 82.4)	35	70.0 (61.8, 78.2)	67.4 (31.1)
Emotional functioning	47	73.2 (66.3, 80.2)	34	72.8 (66.1, 79.5)	65.9 (24.6)
Cognitive functioning	47	85.8 (80.7, 90.9)	34	87.3 (81.5, 93.0)	80.5 (23.2)
Social functioning	47	72.7 (64.8, 80.6)	34	74.0 (66.3, 81.8)	74.2 (28.4)
QLQ-C30 symptom scales[d]					
Fatigue	47	35.0 (27.9, 42.1)	35	36.3 (29.1, 43.6)	36.3 (27.0)
Nausea/vomiting	47	11.3 (6.3, 16.4)	35	11.4 (5.3, 17.6)	10.3 (19.7)
Pain	46	26.4 (18.5, 34.4)	35	32.4 (23.0, 41.8)	30.9 (29.6)
Dyspnea	47	24.8 (17.3, 32.3)	35	21.9 (13.6, 30.2)	20.4 (28.2)
Insomnia	47	31.2 (22.2, 40.2)	35	32.4 (21.5, 43.3)	33.1 (32.6)
Appetite loss	47	19.1 (11.3, 27.0)	35	18.1 (10.1, 26.1)	21.7 (31.0)
Constipation[c]	47	9.2 (3.9, 14.5)	34	20.6 (11.5, 29.6)	19.2 (28.8)
Diarrhea[c]	47	10.6 (4.5, 16.8)	34	4.9 (0.7, 9.1)	5.8 (15.2)
QLQ-BR23 functional scales[c]					
Body image	46	64.5 (55.2, 73.8)	35	67.5 (57.7, 77.2)	81.9 (22.6)
Sexual functioning	44	14.0 (8.6, 19.5)	33	15.7 (9.1, 22.3)	19.2 (23.2)
Sexual enjoyment	16	52.4 (32.8, 71.9)	12	33.3 (17.7, 49.0)	55.1 (25.6)
Future perspective	47	38.3 (28.3, 48.3)	35	34.3 (22.7, 45.9)	47.6 (34.1)
QLQ-BR23 symptom scales[d]					
Systemic therapy side effects	47	16.7 (12.4, 20.9)	35	15.2 (11.4, 19.0)	15.8 (14.3)
Breast symptoms	47	15.9 (9.9, 21.9)	35	18.5 (10.0, 26.9)	17.6 (16.7)
Arm symptoms	47	22.5 (15.4, 29.5)	35	19.7 (9.4, 30.0)	21.0 (21.1)
Upset by hair loss	8	58.3 (33.6, 83.0)	6	27.8 (13.5, 42.1)	5.3 (19.3)

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; PRO, patient-reported outcome; QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; QoL, quality of life; SD, standard deviation.

[a] PRO-evaluable population is defined as all patients who have completed ≥1 PRO question at baseline and ≥1 PRO question postbaseline.

[b] Reference values for patients with recurrent/metastatic across all lines of treatment are shown (reference 8).

[c] Larger values better.

[d] Larger values worse.

Table 2. Estimated mean overall change from baseline (mixed-effects model)

	Cohort 1		Cohort 2	
Domain/scale	**Overall**	**(95% CI)**	**Overall**	**(95% CI)**
EORTC QLQ-C30 GHS/QoL (positive changes correspond to better outcome)				
GHS/QoL	–2.6	(–7.8, 2.5)	1.2	(–5.5, 8.0)
EORTC QLQ-C30 functional scales (positive changes correspond to better outcome)				
Physical functioning	–3.2	(–7.6, 1.3)	1.3	(–2.0, 4.6)
Role functioning	–11.0	(–19.0, –2.9)	6.9	(3.1, 10.7)
Emotional functioning	–5.4	(–12.0, 1.2)	1.8	(–3.3, 6.9)
Cognitive functioning	–4.5	(–9.2, 0.2)	0.1	(–3.6, 3.9)
Social functioning	–0.9	(–8.0, 6.2)	8.3	(4.3, 12.3)
EORTC QLQ-C30 symptoms scales (negative changes correspond to better outcome)				
Fatigue	7.6	(2.1, 13.0)	–3.9	(–8.7, 0.9)
Nausea/vomiting		NE	–4.3	(–7.1, –1.6)
Pain		NE	–8.2	(–14.4, –2.0)
Dyspnea	–0.9	(–6.8, 5.0)	10.3	(1.3, 19.2)
Insomnia	–0.6	(–7.7, 6.6)	–7.2	(–12.9, –1.5)
Appetite loss	1.3	(–4.3, 7.0)	–0.8	(–7.6, 6.0)
Constipation		NE	–1.5	(–7.0, 3.9)
Diarrhea	–5.4	(–9.4, –1.4)	1.6	(–3.4, 6.6)
EORTC QLQ-BR23 functional scales (positive changes correspond to better outcome)				
Body image	5.6	(–0.2, 11.4)	3.6	(–2.7, 10.0)
Sexual functioning	5.6	(0.9, 10.3)	–0.3	(–5.8, 5.1)
Sexual enjoyment		NE	9.1	(1.8, 16.5)
Future perspective	11.1	(1.9, 20.2)	9.9	(1.8, 18.0)
EORTC QLQ-BR23 symptoms scales (negative changes correspond to better outcome)				
Systemic therapy side effects	0.6	(–2.6, 3.9)	0.9	(–2.1, 3.8)
Breast symptoms	–6.6	(–11.1, –2.2)	–8.7	(–13.0, –4.4)
Arm symptoms	–6.6	(–12.6, –0.6)	–4.4	(–8.0, –0.8)
Upset by hair loss		NE	–16.7	(–67.4, 34.1)

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; NE, not estimated; QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; QoL, quality of life.
Notes: Data in the table are color coded as follows: dark orange = clinically meaningful and statistically significant (deterioration); light orange = statistically significant (deterioration); green = clinically meaningful and statistically significant (improvement); light green = statistically significant (improvement).