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Clinical Trial

Health-related quality of life in patients with locally recurrent or metastatic breast cancer treated with etirinotecan pegol versus treatment of physician's choice: Results from the randomised phase III BEACON trial

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KEYWORDS
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Quality of life

Abstract ***Background:*** Health-related quality of life (HRQoL) enhances understanding of treatment effects that impact clinical decision-making. Although the primary end-point was not achieved, the BEACON (BrEAst Cancer Outcomes with NKTR-102) trial established etirinotecan pegol, a long-acting topoisomerase-1 (TOP1) inhibitor, as a promising therapeutic for patients with advanced/metastatic breast cancer (MBC) achieving clinically meaningful benefits in median overall survival (OS) for patients with stable brain metastases, with liver metastases or $\geq$ 2 sites of metastatic disease compared to treatment of physician's choice (TPC). Reported herein are the findings from the preplanned secondary end-point of HRQoL.
Patients and methods: HRQoL, assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (version 3.0) supplemented by the breast cancer-specific Quality of Life Questionnaire (QLQ-BR23), was evaluated post randomisation in 733 of 852 patients with either anthracycline-, taxane- and capecitabine-pretreated locally recurrent or MBC randomised to etirinotecan pegol (n = 378; 145 mg/m^2 every 3 weeks (q3wk)) or single-agent TPC (n = 355). Patients completed assessments at screening, every 8 weeks (q8wk) during treatment, and end-of-treatment. Changes from baseline were analysed, and the proportions of patients achieving differences ($\geq$5 points) in HRQoL scores were compared.
Results: Differences were seen favouring etirinotecan pegol up to 32 weeks for global health status (GHS) and physical functioning scales ($P < 0.02$); numerical improvement was reported in other functional scales. The findings from HRQoL symptom scales were consistent with adverse event profiles; etirinotecan pegol was associated with worsening gastrointestinal symptoms whereas TPC was associated with worsened dyspnoea and other systemic side-effects. Analysis of GHS and physical functioning at disease progression showed a decline in HRQoL in both treatment arms, with a mean change from baseline of −9.4 and −10.8 points, respectively.
Conclusion: There was evidence of benefit associated with etirinotecan pegol compared with current standard of care agents in multiple HRQoL measurements, including global health status and physical functioning, despite worse gastrointestinal symptoms (e.g. diarrhoea). Patients in both arms had a decline in HRQoL at disease progression.
Study number: NCT01492101.

1. Introduction

While there are different treatment approaches for women with advanced/metastatic breast cancer (MBC) depending on the molecular phenotype, chemotherapy remains fundamental to the management of most patients. With advances in the treatment of MBC, more women are living longer with their disease [1–3]. Nevertheless, the treatment of MBC remains essentially palliative rather than curative, with more than 500,000 women dying annually from the disease worldwide [4–5]. The median survival of patients with MBC is approximately 24 months, but varies widely between prognostic subgroups [6–10].

The key aims in treating women with MBC are to prolong survival and maintain or improve QoL. As the focus of treatment is primarily palliative, the impact of both the disease and its treatment on patients' functional abilities has led to the incorporation of patient-reported clinical outcome (PRO) measures into clinical trials [11]. Health-related quality of life (HRQoL) incorporates domains related to physical, mental, emotional, and social functioning that go beyond the direct measures of health and focusses on the QoL consequences of health status [12]. Increasing evidence shows that overall outcomes for patients with MBC improve when therapy is not just focussed on the disease but also on minimising disease-related and treatment-related symptoms [13]. Despite PRO measures rarely being used for drug approval, the effect of an intervention on HRQoL is significant for both patients and clinicians [14–15].

The international phase III BEACON (BrEAst Cancer Outcomes with NKTR-102) trial randomly assigned patients with heavily pre-treated MBC either to etirinotecan pegol (NKTR-102), or to single agent treatment of physician's choice (TPC) comprising specific cytotoxics commonly used in this setting [16]. Etirinotecan pegol is a novel, long-acting polymer-engineered pegylated topoisomerase-1 (TOP1) inhibitor designed to provide continuous exposure to SN38, the active moiety of irinotecan, at the site of the tumour through altered pharmacokinetics and exploitation of the enhanced permeability and retention (EPR) effect [17]. Preclinical experiments and initial clinical studies have demonstrated a marked contrast in the pharmacokinetic profile of SN38 after treatment with

etirinotecan pegol compared to irinotecan that translated to enhanced antitumour activity and improved tolerability, namely reduced and delayed myelosuppression and gastrointestinal toxicities [17–20]. The primary end-point of BEACON was not achieved; nevertheless, overall survival (OS) did numerically favour etirinotecan pegol, although this did not achieve statistical significance [16]. The comparison of HRQoL outcomes was a planned secondary outcome of the trial; it was hypothesised that HRQoL would improve in patients treated with etirinotecan pegol compared to those in the TPC control arm.

2. Methods

2.1. Patients and study design

From December 2011 to August 2013, the open-label, randomised, multi-centre BEACON trial enrolled 852 women with locally recurrent or MBC who had previously received an anthracycline (unless contraindicated or not medically appropriate), a taxane and capecitabine. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and have received a minimum of two prior cytotoxic regimens for advanced disease with the last dose of chemotherapy within 6 months of randomisation and no more than five prior cytotoxic regimens for breast cancer in all settings. Patients with stable brain metastases (symptomatically and on imaging) were eligible, provided local therapy (surgery, whole brain or stereotactic radiation) had been completed and corticosteroids for this indication had been discontinued at least 3 weeks before randomisation. The study was conducted at 139 community and academic centres, worldwide including in North America, Europe and the Republic of Korea; nearly half the patients were enrolled in North America.

Patients were randomly assigned via a central randomisation system in a 1:1 ratio to etirinotecan pegol (145 mg/m^2 once every 21 d as a 90-min intravenous (i.v.) infusion on day 1 of each treatment cycle) or single-agent TPC (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or *nab*-paclitaxel) administered according to local practice or in accordance with local product labelling. Prior to randomisation, the Investigator established and centrally registered as part of the informed consent process, the TPC that would be offered to the patient. Treatment continued until disease progression, the development of unacceptable toxicity or withdrawal of patient consent. Dose delays, reductions and discontinuations were defined for etirinotecan pegol but made according to the prescribing information or local practice guidelines pertaining to TPC.

The trial was conducted under the principles of the International Conference on Harmonisation Good Clinical Practice standards and in accordance with the Declaration of Helsinki, U.S. Food and Drug Administration regulations and all other applicable regulations. All patients provided written informed consent prior to any study-related procedures. Approval was obtained from the relevant institutional review board (IRB) or independent ethics committee (IEC) at each site. The study is registered on ClinicalTrials.gov (NCT01492101).

2.2. HRQoL assessment

HRQoL was evaluated using two validated questionnaires designed to assess both disease-related symptoms and the side-effects of treatment as well as their impact on everyday life, namely the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its associated breast cancer-specific QoL questionnaire, the EORTC QLQ-BR23 (BR23). All patients were eligible for HRQoL assessment. Questionnaires were completed at Screening, Cycle 1 (baseline at the start of the study treatment) then every 8 weeks (±7 d) prior to radiological tumour assessment while on study treatment and at the End-of-Treatment visit (within 30 d ± 7 d from last dose of study treatment). At the discretion of the investigator, earlier radiological assessment could be made if progression was suspected clinically, in which case the patient would be asked to complete a HRQoL questionnaire (EORTC QLQ-C30 with BR23 subscale) prior to that radiological assessment. Safety was assessed in all patients who received at least one dose of assigned treatment. Adverse events (AEs) were assessed from the first dose of treatment until 30 d after the last dose, and were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The EORTC QLQ-C30 questionnaire is a 30-item, cancer-specific, multi-dimensional self-administered questionnaire that has been validated in cross-cultural settings [21]. It comprises five multi-item functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning); a two-item Global Health Status (GHS) scale; and nine symptom scales and items (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The supplemental BR23 questionnaire comprises 23 items grouped into four functioning (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom (systemic side-effects, breast symptoms, arm symptoms, upset by hair loss symptoms) scales [22]. Items were scaled and scored according to the EORTC Scoring Manual [23]. Most items are answered based on a four-point scale ranging from 1 (not at all) to 4 (very much). The two items assessing global health and overall quality of life are responded to in seven

categories ranging from 1 (very poor) to 7 (excellent). Raw scores were transformed to a linear scale ranging from 0 to 100. For scores measuring function, a higher score represents a 'better' level of functioning, while for scores measuring symptoms, a higher score represents 'worse' level of symptoms.

2.3. Statistical considerations

The sample size was based on the primary study endpoint, OS. Patients were evaluable for the HRQoL analysis if they completed their baseline and at least one follow-up questionnaire. At each assessment point, summary statistics of absolute scores and changes from baseline were calculated by treatment group, including best and worst changes, for each subscale. Change from baseline over time was analysed by repeated measures linear mixed effects (Mixed effect Model Repeat Measurement or MMRM) [24,25] for domains/symptoms with multiple questions and generalised linear mixed models (GLMM) for domains/symptoms with a single question [26]. In the MMRM analysis, change from baseline was the dependent variable and treatment group, visit, and treatment group-by-visit interaction, the three predefined stratification factors (geographic region, prior eribulin, and receptor status) as fixed effects, and baseline value were the covariates. Minimal Important Difference (MID) thresholds, using a threshold of 5 points, were used to categorise patients as improved (+5), stable (>−5 to <+5), or worsened (−5). Treatment comparison of the proportion of patients in each category was conducted using a proportional odds model and odds ratios were calculated with QoL status as the dependent variable coded as 3, 2 and 1 for improved, stable, and worsened respectively; the independent variables included treatment arm, geographic region, prior use of eribulin, and receptor status. To meet criteria for improved or worsened, a subsequent confirmatory assessment at $\geq$ 4 weeks was required. Chi-square test was used to report *P*-values from a proportional odds model. Questionnaire completion rates were calculated as a percentage of eligible subjects who completed a questionnaire at each scheduled time point per the study protocol for each treatment group.

3. Results

3.1. Patient characteristics

Baseline demographic and disease characteristics of the 852 patients (etirinotecan pegol, n = 429; TPC, n = 423; Fig. 1) randomised were generally well balanced between treatment groups as previously reported [16] (Table 1). The median age was 55 years, and median time since diagnosis of locally recurrent or metastatic disease was 2.5 years. Almost all patients had a good performance status (ECOG 0-1), although a slightly higher proportion of those in the etirinotecan pegol arm had an ECOG PS of 0 than in the TPC arm (41% versus 32%, respectively). Over two-thirds of the population in both treatment arms had hormone receptor (ER or PR) positive and approximately 28% had triple-negative breast cancer (TNBC) disease. The most common sites of metastatic disease were bone (57%), liver (54%) and lung (38%); sixty-seven patients (8%) had a history of brain metastases. The median number of prior regimens for metastatic disease in each treatment group was three; 38 [9%] patients randomised to etirinotecan pegol had received five or more prior regimens in the metastatic setting versus 20 [5%] patients in the TPC arm.

Patients in both treatment groups received a median of three treatment cycles on protocol. The most commonly administered drug in the TPC arm was eribulin (40%), followed by vinorelbine (23%), gemcitabine (18%), nab-paclitaxel (8%), paclitaxel (4%), ixabepilone (4%) and docetaxel (3%). Baseline HRQoL scores were comparable between the treatment arms (Table 1); of note, mean GHS and physical functioning scores were similar between the two arms. Mean GHS scores were 61.4 (standard deviation [S.D.] = 21.76) and 58.0 (S.D. = 20.43) for etirinotecan pegol and TPC, respectively; mean physical functioning scores were 74.5 (S.D. = 19.72) and 72.3 (S.D. = 19.74), respectively.

3.2. HRQoL compliance results

Almost all randomised patients completed the baseline HRQoL questionnaire in both the etirinotecan pegol (98%, 422/429) and TPC arms (97%, 409/423) (Table 2); and most (86%, 733/852) completed at least one post-baseline HRQoL questionnaire (etirinotecan pegol: 378 [88%], TPC: 355 [84%]). Compliance for completion of questionnaires at each visit during the treatment period was 95% (range 87%–96%). As expected, the number of patients completing the questionnaire decreased over time, and by week 32, 16% (69/429) patients in the etirinotecan arm and 14% (59/423) patients in the TPC arm completed the questionnaire. By week 40, less than 10% of patients completed the questionnaire [9% (79/852) overall, 11% (48/429) patients in the etirinotecan arm and 7% (31/423) patients in the TPC arm], supporting a primary analysis in which data were assessed up to week 32 as preplanned in the protocol.

3.3. Global health status and functioning

The primary assessment of HRQoL occurred up to 32 weeks following randomisation. Findings from the GHS and five functioning domains (physical, role, emotional, cognitive and social) of the EORTC QLQ C-30 showed that HRQoL deteriorated slightly in both

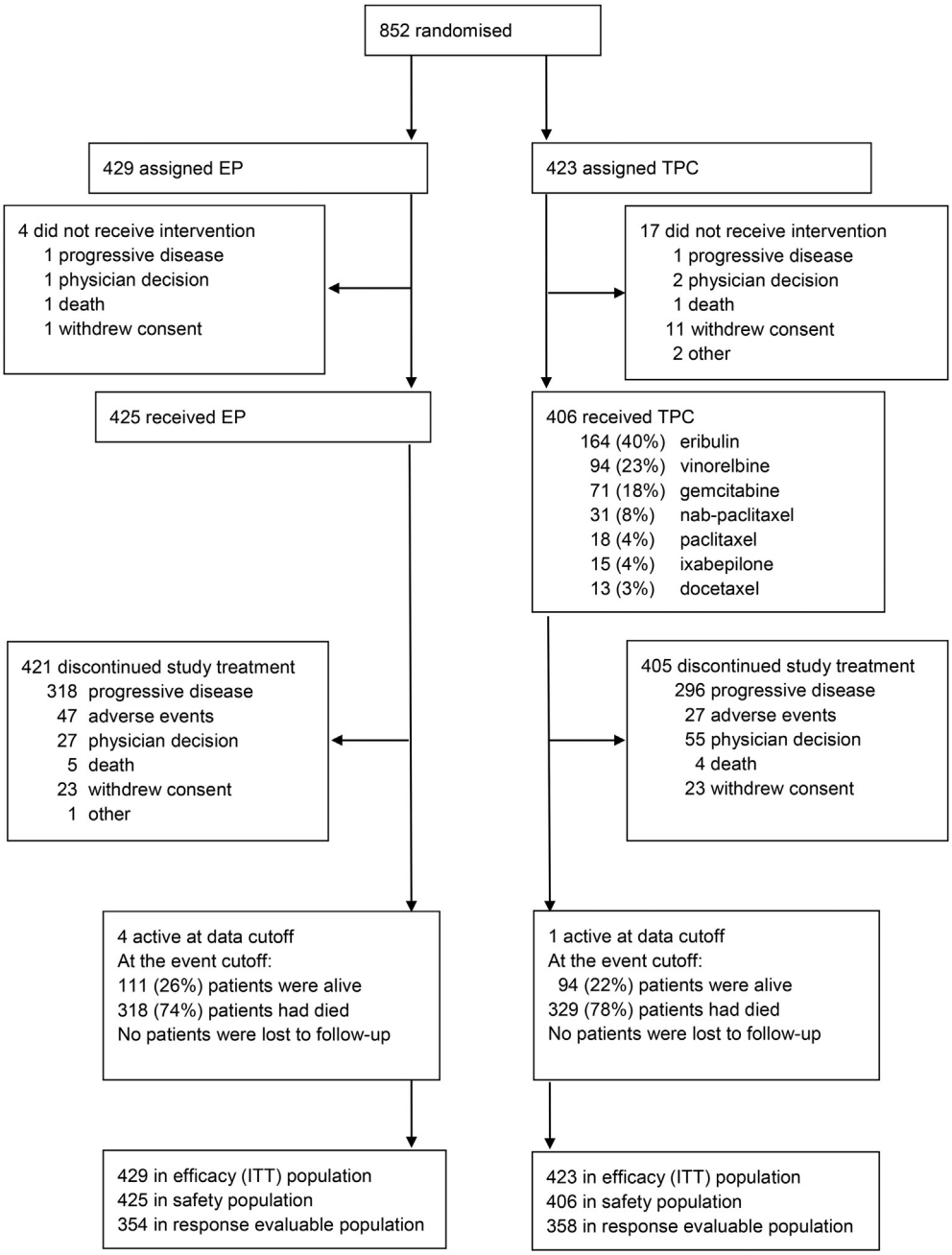

Fig. 1. Consort diagram: BEACON trial.

study arms over time. Differences between groups at each assessment time consistently favoured patients in the etirinotecan pegol arm up to week 32 and became more marked over time up to that point. Fig. 2A and B shows GHS and physical functioning mean symptom scores over time. At week 32, using MMRM analysis, the mean difference in GHS favouring patients in the etirinotecan pegol arm was 8.2 points. The individual functioning domains generally favoured patients in the etirinotecan pegol arm: physical by 5.7 points, role by 2.1 points, emotional by 3.9 points and cognitive by 5.1 points but social by −0.5 points. A longitudinal analysis of the MMRM for the change from baseline up to 32 weeks showed that etirinotecan pegol was statistically superior in its effect on GHS and the physical functioning domain (Fig. 3). There was also numerical superiority favouring patients in the etirinotecan pegol arm in the other functional domains. Similar trends were also observed in the four scales (body image, sexual functioning, sexual enjoyment, and future perspective) with the BR23. At the time of disease progression, analysis of the GHS and physical functioning domains showed a decline in HRQoL for patients in both arms, although this was less pronounced for those in the etirinotecan pegol arm; the mean change from baseline was −7.97 and −9.83 in GHS and physical functioning,

Table 1
Baseline characteristics and health-related quality of life in the intent-to-treat population of the BEACON trial.

Characteristic	Etirinotecan pegol (n = 429)	TPC (n = 423)
Age (years)	55 (28–84)	55 (32–80)
ECOG PS		
0	175 (41%)	134 (32%)
1	252 (59%)	285 (67%)
≥2	2 (<1%)	4 (<1%)
Time since initial breast cancer diagnosis (years)	5.8 (0.6–29.3)	5.4 (0.8–31.9)
Time since diagnosis of locally recurrent or metastatic disease (years)	2.5 (0.3–19.7)	2.5 (0.2–22.9)
Stage IV disease at diagnosis	70 (16%)	75 (18%)
Current breast cancer status		
Locally recurrent	4 (<1%)	8 (2%)
Metastatic	425 (99%)	415 (98%)
Visceral disease at enrolment	319 (74%)	324 (77%)
History of brain metastases	36 (8%)	31 (7%)
Metastatic sites at enrolment		
Brain	19 (4%)	18 (4%)
Liver	229 (53%)	227 (54%)
Lung	155 (36%)	168 (40%)
Bone	246 (57%)	243 (57%)
Hormone receptor status (ER or PR)		
Positive	295 (69%)	290 (69%)
Negative	133 (31%)	133 (31%)
Unknown	1 (<1%)	0
HER2 status[a]		
Positive	30 (7%)	32 (8%)
Negative	395 (92%)	387 (91%)
Unknown	4 (<1%)	4 (<1%)
Triple-negative disease	119 (28%)	117 (28%)
Prior anthracycline	410 (96%)	406 (96%)
Anthracycline refractory[b]	58 (14%)	57 (13%)
Prior taxane	429 (100%)	423 (100%)
Taxane refractory[b]	178 (42%)	157 (37%)
Prior capecitabine	429 (100%)	423 (100%)
Capecitabine refractory[b]	306 (71%)	315 (74%)
Prior eribulin	71 (17%)	72 (17%)
Number of prior regimens for locally recurrent or metastatic disease (range)	3 (1–6)	3 (1–6)
1[c]	1 (<1%)	2 (<1%)
2	122 (28%)	120 (28%)
3	147 (34%)	161 (38%)
4	114 (27%)	118 (28%)
5	40 (9%)	20 (5%)
6+[c]	5 (1%)	2 (<1%)
EORTC QLQ-C30 GHS and functioning scores,[d] mean (S.D.)	n = 378	n = 355
Global health status	61.4 (21.76)	58.0 (20.43)
Physical functioning	74.5 (19.72)	72.3 (19.74)
Role functioning	71.8 (26.81)	67.3 (26.93)
Emotional functioning	72.4 (21.86)	71.9 (20.06)
Cognitive functioning	82.5 (18.70)	81.2 (19.04)
Social functioning	73.0 (26.69)	71.0 (25.06)
EORTC QLQ-C30 symptom scores[d], mean (S.D.)		
Fatigue	46.0 (25.04)	48.3 (23.75)
Nausea and vomiting	8.6 (13.39)	9.9 (16.17)
Pain	32.3 (27.20)	35.3 (28.01)
Dyspnoea	24.5 (27.44)	23.6 (26.20)
Insomnia	29.3 (28.94)	31.5 (27.11)
Appetite loss	24.3 (27.55)	26.6 (27.89)
Constipation	24.3 (27.55)	26.6 (27.89)
Diarrhoea	6.3 (13.64)	5.6 (11.14)
Financial difficulties	26.4 (31.29)	21.9 (28.95)
EORTC QLQ-BR23 scores,[d] mean (S.D.)		
Body image	69.5 (28.94)	69.9 (27.91)
Sexual functioning	14.1 (19.24)	13.3 (18.91)
Sexual enjoyment	36.1 (29.25)	34.2 (30.77)
Future perspective	36.1 (29.25)	34.2 (30.77)
EORTC QLQ-BR23 symptom scores,[d] mean (S.D.)		
Systemic side-effects	21.9 (16.37)	22.3 (15.15)
Breast symptoms	15.3 (21.55)	15.8 (20.79)
Arm symptoms	20.8 (23.40)	22.2 (22.75)
Upset about hair loss symptoms	33.2 (34.15)	30.5 (33.29)

Data are n (%) or median (range) unless otherwise designated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; ER, oestrogen receptor; HER2, human epidermal growth factor receptor type 2; PR, progesterone receptor; S.D., standard deviation; TPC, treatment of physician's choice.
[a] HER2 status was determined regardless of hormone receptor status.
[b] Refractory disease was defined as disease progression while receiving therapy in the metastatic setting within 8 weeks of the last dose of the last regimen.
[c] These patients were entered into the protocol in violation of the entry criteria which stipulated that patients must have received between 2 and 5 regimens for locally recurrent or metastatic disease.
[d] Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms.

Table 2
Health-related quality of life EORTC QLQ-C30 global health status questionnaire.

Assessment	Etirinotecan Pegol (n = 429)	TPC (n = 423)	Total (n = 852)
Baseline	422 (98%)	409 (97%)	831 (98%)
Completed ≥ 1	378 (88%)	355 (84%)	733 (86%)
Week 8	337 (78%)	311 (73%)	648 (76%)
Week 16	181 (42%)	159 (38%)	340 (40%)
Week 24	116 (27%)	90 (21%)	206 (24%)
Week 32	69 (16%)	59 (14%)	128 (15%)
Week 40	48 (11%)	31 (7%)	79 (9%)
Week 48	29 (7%)	19 (5%)	48 (6%)
Week 56	26 (6%)	15 (4%)	41 (5%)

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; TPC, treatment of physician's choice.

respectively for patients in the etirinotecan pegol arm and −10.83 and −11.74, respectively for those in the TPC arm.

Fig. 4A shows the percentage of patients with a change from baseline of 5 points, either improved (≥5)

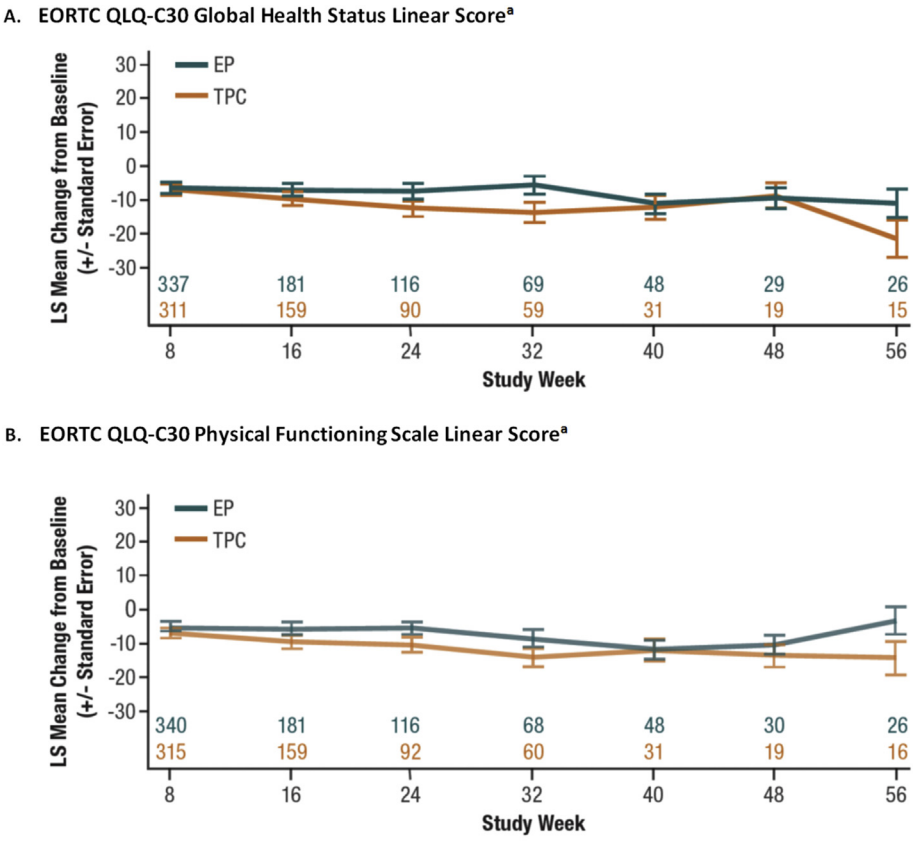

Fig. 2. **Global health status and physical functioning mean symptom scores over time**. Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EP, etirinotecan pegol; ITT, intent-to-treat; LS mean, least-squares mean; MMRM, Mixed effect Model Repeat Measurement; TPC, treatment of physician's choice.

or worsened (≤-5), between treatment groups for the functioning scales. All categories were similar between the treatment arms for GHS and physical functioning, although numerically more patients had improved physical functioning on the etirinotecan arm. Only a small proportion of patients had change from baseline ≥5 points in the same direction on at least two consecutive assessments, and MID analysis of GHS and all functioning domains did not show statistically significant differences between the two treatment arms.

Post hoc analysis of change in GHS and the functioning domains following the onset of grade 3 or higher AEs showed that QoL deteriorated significantly. Overall, patients without any grade 3 or higher AE consistently had better GHS and scores in all five functioning domains of the QLQ C-30 than those who had grade ≥3 AEs (all with *P*-value <0.05 by MMRM analysis).

3.4. Symptom scales

Ten symptom scales were collected: six single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) in the QLQ C-30 and four symptom scales (systemic therapy side-effects, breast symptoms, arm symptoms, upset by hair loss symptoms) in BR23. Symptoms scales (Fig. 4B) closely matched the AE profiles previously reported for each group [16] with a higher percentage of patients in the etirinotecan pegol group having worsening of gastrointestinal symptoms, i.e. nausea and vomiting (18% versus 9% with TPC, OR = 2.3), appetite loss (18% versus 12%, OR = 1.5), and diarrhoea (14% versus 5%, OR = 1.9); by contrast, a greater percentage of patients in the TPC group had worsening of dyspnoea (12% versus 8% with EP, OR = 0.6) and systemic side-effects (23% versus 14%, OR = 0.6). A higher proportion of patients in the etirinotecan arm had improvement in dyspnoea (14% versus 8% in TPC arm, respectively).

3.5. Brain metastases subgroup

Favorable HRQoL with etirinotecan pegol was also observed in the subgroup of patients with stable brain metastases at baseline. Although the sample size (n = 67) was small, the point estimate of the difference between the treatment groups favouring etirinotecan pegol was greater than 10 points for GHS (15.0), role

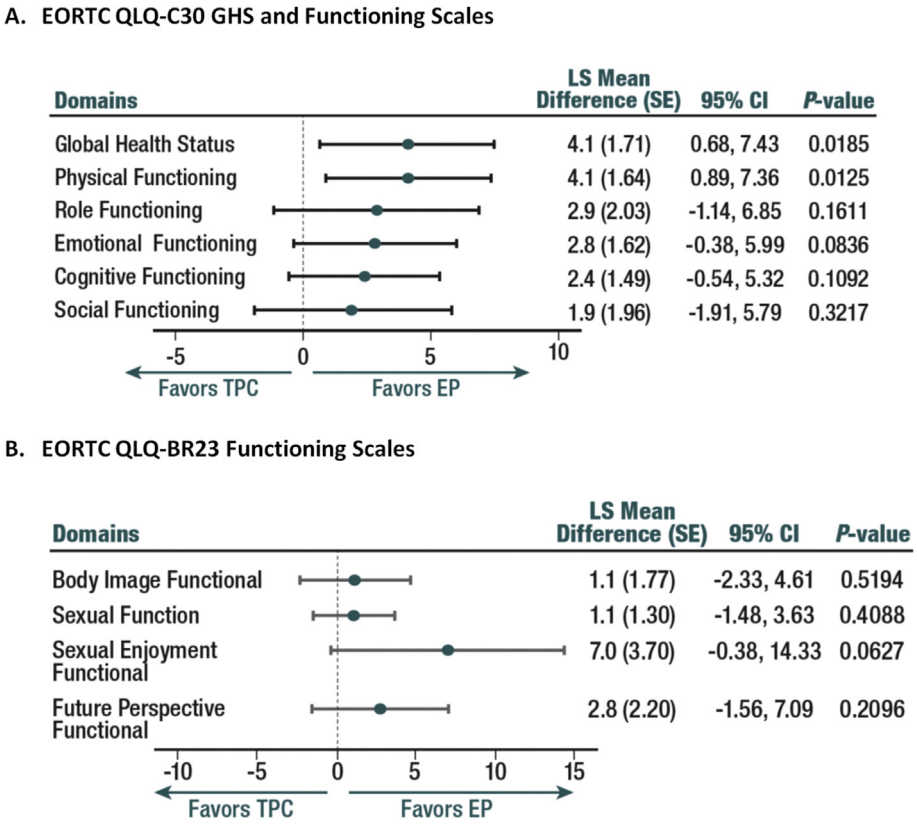

Fig. 3. **Mean change from baseline of the EORTC QLQ-C30 and EORTC QLQ-BR23 scales over 32 weeks using MMRM.** Abbreviations: EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EP, etirinotecan pegol; LS mean, least squares mean; MMRM, Mixed effect Model Repeat Measurement; SE, standard error; TPC, treatment of physician's choice.

functioning (11.6), cognitive functioning (12.1), and greater than 5 points for the other functioning domains (Table 3). Etirinotecan pegol was associated with worse symptoms of diarrhoea, nausea and vomiting, and appetite loss; by contrast, patients in the TPC treatment arm had worse symptoms of dyspnoea, fatigue, and constipation. The systemic side-effects symptom scale was improved 13.5 points in patients treated with etirinotecan pegol compared with TPC.

4. Discussion

The current analysis shows that in the BEACON trial, etirinotecan pegol treatment was associated with improvements in HRQoL as measured by the well-established EORTC instruments, QLQ-C30 and QLQ-BR23. Improvements in both GHS and physical functioning reached statistical significance over a 32-week time period as estimated using an MMRM- test. The pattern was less consistent after week 32, most likely a function of the sample size decreasing consistently over time with less than 10% of patients providing an assessment on or after week 40. There was a clear difference in quality of life according to the presence (or absence) of grade 3 or higher AEs; patients without any grade $\geq$3 adverse events consistently had better HRQoL as measured by GHS and all five functioning domains of the EORTC QLQ-C30 questionnaire regardless of treatment arm.

Two toxicities are worthy of additional discussion. First, dyspnoea (frequently a symptom of progression in patients with advanced breast cancer) improved in patients receiving etirinotecan pegol but deteriorated in those receiving TPC; this may reflect more effective treatment of lung metastases, which were present at baseline in 36% and 40% of patients in the etirinotecan pegol and TPC arms, respectively [16]. Alopecia is a potentially troubling toxicity for patients with advanced cancer. Although there was no statistical difference in the change from baseline in patients reporting being upset by hair loss, the overall incidence of alopecia in the etirinotecan pegol arm was less than half that in the TPC arm (10% and 23%, respectively) [16]. Finally, more patients withdrew from the etirinotecan pegol arm than the TPC arm due to adverse events (47 and 27, respectively), even though the incidence of grade 3 or worse events was significantly lower among patients treated with etirinotecan pegol (204 [48%] versus 256 [63%], respectively; odds ratio 0·54 [95% CI 0.41–0.71];

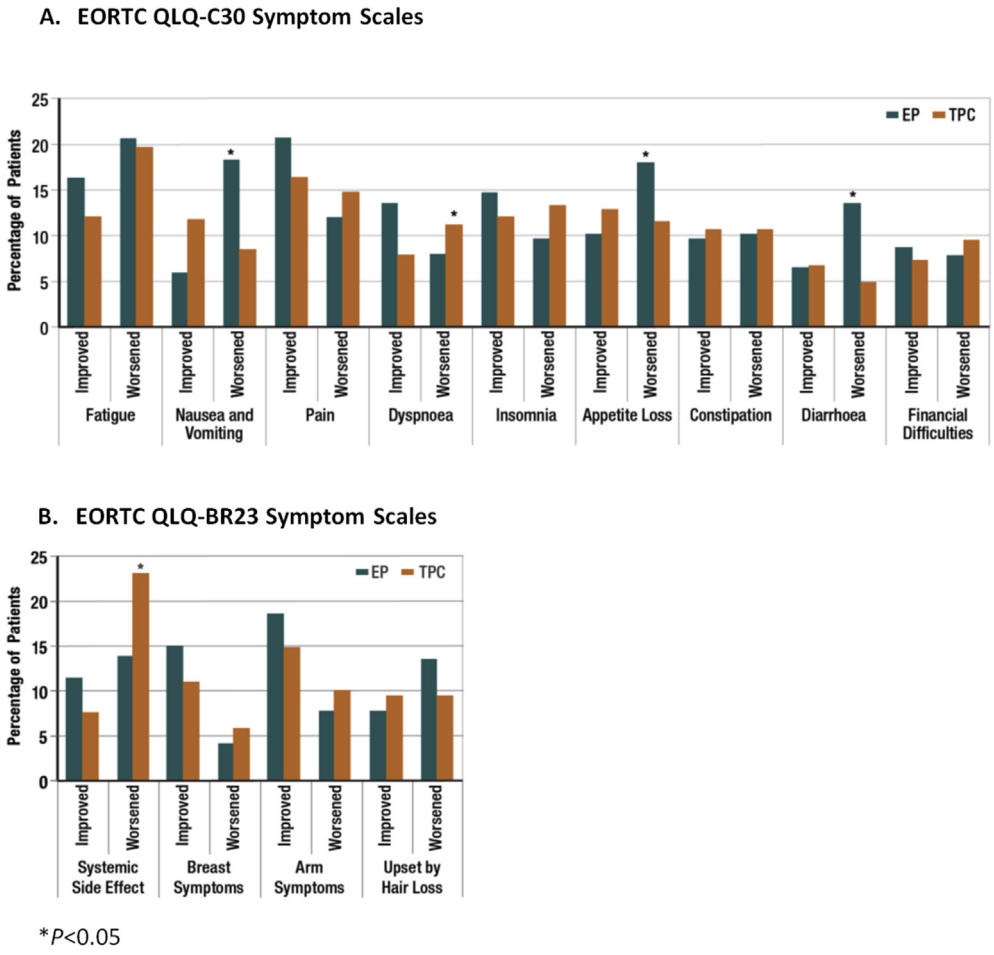

Fig. 4. **Summary of status of EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales using 5-point change threshold.** Abbreviations: EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EP, etirinotecan pegol; TPC, treatment of physician's choice. Note: A threshold of 5 score points of change from baseline in the linear transformed score was used to classify status as Improved (+5), Stable (>−5 to <5), or Worsened (−5). The first post-baseline status meeting Improved or Worsened with a subsequent confirmatory assessment in 4 weeks or later is counted. Proportional odds model was used to test the difference in proportion between treatment groups for each scale. The QoL status was the dependent variable and coded as 3, 2, and 1 for Improved, Stable, and Worsened, respectively. The independent variables will include treatment arm, geographic region, prior use of eribulin and receptor status.

$p < 0{\cdot}0001$). The higher AE discontinuation rate in the etirinotecan pegol arm may in part be a consequence of strict dosing guidelines reflecting its long elimination half-life, including mandatory cessation of dosing for repeated grade 2 diarrhoea and grade 2 neutropenia, which did not apply to the TPC arm.

As previously reported BEACON did not achieve its primary end-point; although there was a 2.1-month improvement in survival for patients treated with etirinotecan pegol compared to those receiving TPC that emerged early and persisted, this difference did not reach statistical significance (median 12.4 months versus 10.3 months for TPC; HR 0.87, 95% CI 0.75−1.02; $P = 0.084$) [16]. The trend for improvement in survival with etirinotecan pegol was noted across all subgroups. Importantly, in the preplanned subgroup of patients with stable brain metastases at study entry, etirinotecan pegol treatment was associated with a statistically significant 5.2-month improvement in median overall survival (10.0 months compared to 4.8 months in the TPC arm, $n = 67$, HR 0.51, $P < 0.01$). Similar results between treatment groups were observed for progression-free survival (PFS) (HR = 0.93, 95% CI 0.80−1.1) but more than twice as many patients were withdrawn from the TPC arm (55 compared to 27 patients) due to physician's decision; this includes patients withdrawn from the study due to clinical progression without radiographic progression. The ORR was very similar for the etirinotecan pegol and TPC arms (16% and 17%, respectively).

Based on these data, and a previous randomised phase II clinical trial [27], etirinotecan pegol is an active

Table 3
Health-related quality of life in brain metastases at baseline subgroup.

Domain	Treatment Difference (SE)[a]	95% CI[a]
EORTC QLQ-C30 global health status and functional domains[b]		
Global health status	15.0 (7.76)	−0.57, 30.51
Physical functioning	8.2 (6.62)	−5.06, 21.45
Role functioning	11.6 (8.86)	−6.19, 29.44
Emotional functioning	7.1 (6.22)	−5.38, 19.52
Cognitive functioning	12.1 (6.13)	−0.27, 24.4
Social functioning scale	8 (7.54)	−7.12, 23.21
EORTC QLQ-C30 and BR23 symptom scales[c]		
Fatigue symptom	−5.4 (6.62)	−18.7, 7.89
Nausea and vomiting symptom	13.7 (8.38)	−3.08, 30.52
Pain symptom	−15.9 (8.47)	−32.82, 1.09
Dyspnoea symptom	−4.9 (6.9)	−18.85, 9.12
Appetite loss symptom	5.4 (9.1)	−12.81, 23.7
Constipation symptom	−11.2 (8.21)	−27.67, 5.28
Diarrhoea symptom	5 (7.97)	−10.97, 21
Systemic side-effects mptom	−13.5 (4.54)	−22.55, −4.37

Abbreviations: CI, confidence interval; EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MMRM, Mixed effect Model Repeat Measurement; TPC, treatment of physician's choice; SE, standard error.

[a] Difference in mean change from baseline over 32 weeks using MMRM.

[b] Positive value for functioning scales favours etirinotecan pegol and negative value favours TPC.

[c] Negative value for symptoms favours etirinotecan pegol and positive value favours TPC.

agent in women with heavily pre-treated advanced breast cancer. Recognisable advantages of etirinotecan pegol are its non-cross-resistant mechanism of action and non-overlapping toxicity profile, specifically the lack of significant myelosuppression or neuropathy that frequently affect patients with heavily pre-treated disease. Importantly, the BEACON trial demonstrated that etirinotecan pegol was associated with significantly fewer grade 3 or higher adverse events compared to TPC (48% and 63%, respectively; $P < 0.001$). The improvement in many aspects of HRQoL, together with the tolerability and efficacy findings from the BEACON trial, reinforces that etirinotecan pegol is a potentially important new agent in the treatment of patients with metastatic breast cancer. Notably, although gastrointestinal AEs and symptoms were more pronounced with etirinotecan pegol, overall HRQoL, as reflected by GHS, was better in those patients suggesting that the benefits of a more effective treatment may outweigh treatment toxicities.

In the management of women with advanced breast cancer, where clinical outcomes with various treatment options may be similar and improvements modest, HRQoL provides crucial information beyond that of standard efficacy outcomes, especially where no single standard of care exists. There remains a need for new agents to treat advanced breast cancer that should preferably belong to a novel class, or have a novel mechanism of action, and impact survival while maintaining or improving QoL, being well-tolerated, and supported by a sound body of evidence. Based on the data reported to date, etirinotecan pegol is a promising agent whose efficacy and favourable safety profile are reflected in improved HRQoL for patients with advanced breast cancer compared to cytotoxics currently used in this setting. In June 2016, Nektar Therapeutics submitted a marketing authorization application (MAA) for conditional approval of Onzeald™ (etirinotecan pegol) in Europe for the treatment of adult patients with breast cancer and brain metastases. A decision on the conditional approval from the Committee for Medicinal Products for Human Use (CHMP) is expected in 2017.

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Conflict of interest statement

CJT and JO: advisor: Nektar Therapeutics. JC: advisor: Celgene, Roche; speaker: Celgene, Roche, Eisai, Novartis; stockholder: MedSIR. AA: advisor: Nektar Therapeutics, Roche, Bayer, Pfizer. VD: advisor: Roche, Novartis, Pfizer, Nektar, Eisai, Lilly; speaker: Roche, Pfizer, Novartis. CZ, UH, and MT: paid employees of Nektar Therapeutics. ALH: consultant, Nektar Therapeutics. HSR: research support to UC Regents from Eisai and from Nektar for this trial. EAP, LSS, S-AI, PG-P, DAY, DAP, AM, AM-A, and J-SA have declared no competing conflicts of interest.

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