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Original Research

Health-related quality of life with palbociclib plus endocrine therapy versus capecitabine in postmenopausal patients with hormone receptor–positive metastatic breast cancer: Patient-reported outcomes in the PEARL study

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Abstract ***Background:*** The PEARL study showed that palbociclib plus endocrine therapy (palbociclib/ET) was not superior to capecitabine in improving progression-free survival in postmenopausal patients with metastatic breast cancer resistant to aromatase inhibitors, but was better tolerated. This analysis compared patient-reported outcomes.
Patients and methods: The PEARL quality of life (QoL) population comprised 537 patients, 268 randomised to palbociclib/ET (exemestane or fulvestrant) and 269 to capecitabine. Patients completed the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-BR23 and EQ-5D-3L questionnaires. Changes from the baseline and time to deterioration (TTD) were analysed using linear mixed-effect and stratified Cox regression models, respectively.
Results: Questionnaire completion rate was high and similar between treatment arms. Significant differences were observed in the mean change in global health status (GHS)/QoL scores from the baseline to cycle 3 (2.9 for palbociclib/ET vs. −2.1 for capecitabine (95% confidence interval [CI], 1.4−8.6; P = 0.007). The median TTD in GHS/QoL was 8.3 months for palbociclib/ET versus 5.3 months for capecitabine (adjusted hazard ratio, 0.70; 95% CI, 0.55−0.89; P = 0.003). Similar improvements for palbociclib/ET were also seen for other scales as physical, role, cognitive, social functioning, fatigue, nausea/vomiting and appetite loss. No differences were observed between the treatment arms in change from the baseline in any item of the EQ-5D-L3 questionnaire as per the overall index score and visual analogue scale.
Conclusion: Patients receiving palbociclib/ET experienced a significant delay in deterioration of GHS/QoL and several functional and symptom scales compared with capecitabine, providing additional evidence that palbociclib/ET is better tolerated.
Trial registration number: NCT02028507 (ClinTrials.gov).
EudraCT study number: 2013-003170-27.

1. Introduction

Palbociclib, an orally bioavailable selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) [1], was approved for the treatment of hormone receptor−positive human epidermal growth factor receptor 2 (HER2)−negative metastatic/advanced breast cancer (MBC) as first or subsequent lines of therapy in combination with endocrine therapy (ET), based on the PALOMA-2 and PALOMA-3 trials. Both, PALOMA-2 including postmenopausal women and PALOMA-3 with women regardless of menopausal status, showed that palbociclib plus ET significantly improved progression-free survival (PFS) versus ET alone [2−4]. In PALOMA-3, patient-reported outcome (PRO) measures indicated that the addition of palbociclib to fulvestrant resulted in a significant improvement of overall global quality of life (QoL) and a significant delay in QoL deterioration [5]. In that study, menopausal status was a stratification factor, most patients were postmenopausal and no specific analysis was performed on QoL changes as per the menopausal status of the patient [3,5]. In PALOMA-2, palbociclib plus letrozole maintained QoL and significantly prolonged these effects in respondents [6]. Indeed, QoL changes

during anticancer therapies depend on the effectiveness and toxicities of the therapy [7,8]. Chemotherapy is generally considered as a treatment modality with more side-effects, hence more severe worsening of QoL than ET [9]. Various clusters of chemotherapy-related symptoms differentially influence functioning, which is why the impact of chemotherapy regimens on global QoL is not the same [8]. The ESMO Guideline and the ESMO Magnitude of Clinical Benefit Scale tool point to the importance of the impact of treatment on QoL in addition to efficacy and safety when deciding on therapies for patients with MBC [10,11].

PEARL is a phase III trial that compares palbociclib plus ET (palbociclib/ET) versus capecitabine in postmenopausal patients with MBC who progressed on an aromatase inhibitor. In the PEARL, although PFS was similar in the two arms, treatment with palbociclib/ET was better tolerated [12]; here, we report the findings on health-related QoL (HRQoL) based on PROs.

2. Patients and methods

PEARL is a multicentre, international, open-label, controlled and randomised phase III study with two treatment arms. Patients were randomised 1:1 to receive capecitabine versus palbociclib/ET; ET varied as per two consecutive cohorts of similar characteristics (exemestane in cohort 1 and fulvestrant in cohort 2). Treatment continued until objective disease progression in accordance with the Response Evaluation Criteria in Solid Tumours, version 1.1 [13], symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurred first. The detailed study design and characteristics of patients have been previously reported [12]. The comparison of HRQoL between treatment arms was a preplanned secondary objective.

The study protocol was approved by every site's institutional review board and every national regulatory agency. All the patients gave written informed consent.

2.1. PRO assessments

PRO measures of HRQoL were assessed using the European Organisation for Research and Treatment of Cancer core quality-of-life (EORTC QLQ-C30; v3.0) instrument [14], its breast cancer–specific module (EORTC QLQ-BR23; v1.0) [15] and the EQ-5D-3L [16] questionnaires. Patients were asked to complete each questionnaire at the baseline, every two cycles for the first 7 cycles, then every three cycles till the end of treatment and at the post-treatment visit. The questionnaires were completed by patients at the clinic before any study visit procedure.

The EORTC QLQ-C30 is a 30-item questionnaire composed of a global health status (GHS)/QoL, functional and symptom scales, and the EORTC QLQ-BR23 is a 23-item companion module consisting of functional and symptom scales (Table 1). Responses to all item measures were converted into linear scales ranging from 0 to 100 using a standard scoring algorithm [17]. For the GHS/QoL and functional scales, a higher score represents a better level of QoL/functioning. For symptomatic scales, a higher numerical score represents greater symptom severity.

The EQ-5D-3L is a standardised measure of health status that comprises a 5-item descriptive health state classifier and a single-item visual analogue scale (EQ-VAS) for self-rated health [16,18]. The EQ-5D-3L responses were linked to country-specific values published to derive a single summary index score based on the preferences of Spain [19].

Table 1
Item numbers and definition of the minimally important difference (MID) as change from the baseline (CFB) values by scales in the EORTC QLQ-C30 and QLQ-BR23 instruments.

Instruments, scales	Item number	MID[a]
EORTC QLQ-C30		
Functional scales		
Physical functioning	1–5	6
Role functioning	6–7	8
Emotional functioning	21–24	4
Cognitive functioning	20, 25	2
Social functioning	26–27	7
Quality of life		
Global health status/QoL	29–30	10
Symptom scales		
Fatigue	10, 12, 18	6
Nausea and vomiting	14–15	6
Pain	9, 19	4
Dyspnoea	8	6
Insomnia	11	3
Appetite loss	13	3
Constipation	16	6
Diarrhoea	17	6
Financial difficulties	28	3
EORTC QLQ-BR-23		
Functional scales		
Body image	9–12	5
Sexual functioning	14,15	5
Sexual enjoyment	16	5
Future perspective	13	5
Symptom scales		
Systemic therapy side-effects	1–4, 6, 7, 8	5
Breast symptoms	20–23	5
Arm symptoms	17,18,19	5
Upset by hair loss	5	5

EORTC QLQ-BR-23, European Organisation for Research and Treatment of Cancer breast-specific questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core questionnaire; GHS/QoL, global health status/quality of life; (Cocks K *et al.* Eur J Cancer 2012; 48:1713–1721 and Osoba D *et al.* J Clin Oncol 1998; 16: 139–144).

[a] A deterioration event is an increase of ≥ the MID from the baseline for the symptom scales and a decrease of ≥ the MID from the baseline for the functional scales and GHS/QoL.

3. Statistical analysis

PRO analyses were performed in cases with baseline and at least one post-baseline assessment. Completion rates were summarised by visit in the intention-to-treat population; a questionnaire was considered received if at least one question was answered. For partially completed multi-item scales, missing scores were equal to the average of the completed items if at least half of the items of that scale were answered but were not included in the analysis if less than that were completed.

Descriptive statistics, including 95% confidence interval (CI) for the means of actual values, and change from the baseline (CFB) were tabulated at the scheduled time points for each scale of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires as well as for the EQ-5D-3L index and VAS scores.

The means and 95% CIs of CFB, as well as the comparisons between treatment arms with their respective *P*-values, were analysed using a linear mixed model, with treatment arms, time points, treatment-time interaction terms and stratification criteria as factors and baseline scores as covariates. A random intercept−only model with a first-order autoregressive covariance structure was used. Baseline scores were compared between treatment arms using a t-test.

Time to deterioration (TTD), investigated in the entire study population and in subgroups as per therapy response, was defined as the time from the date of randomisation to the date of first increase ≥the minimally important difference (MID) from the baseline for the symptom scales or a decrease ≥the MID from the baseline for the GHS and functional scales, using an MID from 2 to 10 points [20,21] (Table 1). Patients with no definitive deterioration event were censored at their last available QoL assessment. In patients with no post-baseline assessment, TTD was censored on day 1.

The Kaplan-Meier method was used to estimate the distribution of TTD for each treatment arm and in accordance with therapy response. A log-rank test was performed to compare the TTD between treatment arms. Adjusted hazard ratios (aHRs) and 2-sided 95% CIs were estimated using a stratified Cox regression model for the comparison of palbociclib/ET versus capecitabine.

4. Results

4.1. Patients

From March 2014 to July 2018, 601 patients were included at 37 sites in Spain, Austria, Hungary and Israel. The QoL population comprised 537 patients (89.3%), 268 of them included in the palbociclib/ET arm and 269 in the capecitabine arm. Nevertheless, 34 patients in the palbociclib/ET arm and 30 in the capecitabine arm did not meet the criteria for being included in the QoL population. Baseline demographic and disease characteristics were well balanced between arms, except the number of involved sites which was greater in the capecitabine arm (Table S1).

4.2. Completion rates

The questionnaire completion rate was >82% until cycle 13 (Table S2). All PRO analyses were based on data of the 14th January 2019 cut-off date at a median follow-up time of 19.0 months.

4.3. EORTC QLQ-C30 and QLQ-BR23 scores

Baseline mean scores were similar in all dimensions among the treatment arms, with a GHS/QoL score of 62.1 (95% CI, 59.5−64.6) versus 59.7 (95% CI, 56.9−62.6) for palbociclib/ET and capecitabine (Table S3).

4.3.1. CFB as per treatment arm

Statistically significant increases in the mean CFB of the GHS/QoL scores were found in the palbociclib/ET arm at cycle 16 (5.7 [95% CI, 0.8−10.6]; P = 0.023) and the capecitabine arm at cycle 7 (4.1 [95% CI, 0.8−7.3]; P = 0.014); these improvements were generally maintained up to cycle 22 with a decrease at the post-treatment visits in both arms (Table 2).

Clinically meaningful improvements (≥MID point increase from the baseline for functional scales and ≥MID decrease for symptoms scales) were observed in both study arms at different time points for insomnia, pain and emotional functioning; while in the palbociclib/ET arm, such improvements evolved for cognitive functioning and financial difficulties, in the capecitabine arm, they evolved for appetite loss and upset by hair loss (Fig. S1).

4.3.2. Comparison of CFB between treatment arms

The overall CFB for all scales of the QLQ-C30 and QLQ-BR23 is presented in Fig. 1. Significant differences are observed for diarrhoea favouring palbociclib/ET (3.7 vs. 6.7; $P = 0.0318$) and for constipation (3.9 vs. −1.5; $P = 0.0051$) or upset by hair loss (8.3 vs. −2.0; $P = 0.0076$) favouring capecitabine.

As per the linear mixed model analysis, the change of the GHS/QoL score from the baseline to cycle 3 was 2.9 (95% CI, 0.2−5.6) for palbociclib/ET versus −2.1 (95% CI, −4.8 to 0.7) for capecitabine, with a mean difference of 5.0 (95% CI, 1.4−8.6; $P = 0.007$) (Table S4). No significant differences were observed between treatment arms at other time points (Fig. 2).

With regard to the various dimensions of the QLQ-C30 and QLQ-BR23 tools, there were statistically significant differences in CFB favouring palbociclib/ET in certain time points for physical, role and social functioning as well as body image and symptoms such as fatigue, nausea/vomiting and diarrhoea. On the other hand, statistically significant differences in CFB favouring capecitabine

Table 2
Baseline and on-treatment GHS/QoL scores in the EORTC QLQ-C30 scale by treatment arm.

Study visit	Palbociclib plus ET $n = 268$			Capecitabine $n = 269$		
	Mean (95% CI)	Mean CFB (95% CI)	*P*-value	Mean (95% CI)	Mean CFB (95% CI)	*P*-value
Baseline	62.1 (59.5; 64.7)	–	–	59.8 (57.1; 62.4)	–	–
Cycle 3	64.2 (61.5; 67.0)	2.1 (−0.8; 5.0)	0.148	58.3 (55.6; 61.1)	−1.4 (−4.3; 1.4)	0.326
Cycle 5	65.1 (62.1; 68.1)	3.0 (−0.1; 6.1)	0.056	61.2 (58.2; 64.2)	1.5 (−1.6; 4.5)	0.355
Cycle 7	62.9 (59.6; 66.1)	0.8 (−2.6; 4.1)	0.657	63.9 (60.7; 67.0)	4.1 (0.8; 7.3)	**0.014**
Cycle 10	62.7 (59.0; 66.3)	0.6 (−3.2; 4.3)	0.771	63.5 (60.0; 67.1)	3.8 (0.2; 7.4)	**0.041**
Cycle 13	65.2 (61.2; 69.2)	3.1 (−1.0; 7.2)	0.135	63.9 (60.1; 67.7)	4.1 (0.3; 8.0)	**0.036**
Cycle 16	67.8 (63.0; 72.7)	5.7 (0.8; 10.6)	**0.023**	63.1 (58.9; 67.3)	3.3 (−1.0; 7.6)	0.129
Cycle 19	68.6 (63.3; 73.8)	6.5 (1.2; 11.8)	**0.017**	61.6 (57.0; 66.2)	1.9 (−2.8; 6.5)	0.431
Cycle 22	67.6 (61.6; 73.6)	5.5 (−0.6; 11.6)	0.076	65.2 (60.2; 70.3)	5.5 (0.4; 10.6)	**0.036**
Post-treatment	56.6 (53.6; 59.7)	−5.5 (−8.6; −2.3)	**0.001**	56.7 (53.6; 59.7)	−3.1 (−6.3; 0.0)	0.053

Bold indicates the statistically significant P-values.
The baseline is defined as the last observed measurement on or before the date of the first dose of the study drug. The positive values indicate improvement, whereas the negative values mean deterioration in global health status.
The linear mixed model was used without covariates to compare scores between visits and the baseline.
CI, confidence interval; CFB, change from the baseline; EORTC QLQ-BR-23, European Organisation for Research and Treatment of Cancer breast-specific questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core questionnaire; ET, endocrine therapy; GHS/QoL, global health status/quality of life.

were seen for dyspnoea, insomnia, constipation, sexual functioning, systemic therapy side-effects, arm symptoms and upset by hair loss (Table S4).

4.3.3. Time to deterioration

Median TTD was superior in most dimensions of the QLQ-C30 and QLQ-BR23 instruments in the palbociclib/ET arm compared with the capecitabine arm. Notably, the median TTD in GHS/QoL, using an MID = 10, was 8.3 months in patients treated with palbociclib/ET versus 5.3 months with capecitabine (aHR, 0.70; 95% CI, 0.55–0.89; $P = 0.003$) (Fig. 3A). The stratified analysis by therapy response showed that TTD by means of GHS/QoL scores was significantly worse in patients treated with capecitabine whether they were non-responders (aHR, 1.7; 95% CI, 1.1–2.5) or responders (aHR, 1.6; 95% CI, 1.1–2.5) than that of responder patients treated with palbociclib/ET. No significant difference was seen in that respect among non-responders versus responders in the palbociclib/ET arm (aHR, 1.2; 95% CI, 0.8–1.9) (Fig. 3B).

Similar improvement was seen in the palbociclib/ET arm for some other QLQ-C30 scales (physical, role, cognitive and social functioning and fatigue, nausea/vomiting, pain, appetite loss and diarrhoea) and for systemic therapy side-effects in the QLQ-BR23 scale (Fig. 4A). The HRQoL comparison between the study arms in responder and non-responder patients indicated that among non-responders, the risk of deterioration was lower in most dimensions in the palbociclib/ET arm (Fig. 4B and C).

4.4. EQ-5D-3L

The summary of EQ-5D-3L levels by visit in each treatment arm for all dimensions recorded in this questionnaire is shown in Fig. S2. The proportions of patients reporting 'no problems' or 'some problems' for any dimension at the baseline were similar between treatment arms except for pain/discomfort (worse for capecitabine) (Table 3).

Baseline EQ-5D-3L index scores were similar between the palbociclib/ET and the capecitabine arms. No statistically significant differences were observed in the EQ-5D-3L index scores on treatment between the palbociclib/ET (0.72 [95% CI, 0.69–0.74]) and the capecitabine arms (0.71 [95% CI, 0.69–0.73]), $P = 0.672$ (Table 3).

CFB in the EQ-5D-3L index score per time point is shown in Fig. S3. The mean CFB to cycle 3 was 0.03 for palbociclib plus ET versus −0.01 for capecitabine, resulting in a mean difference of 0.03 (95% CI, 0.00–0.07; $P = 0.029$) (Table S5). No significant differences were found at any other time point.

Baseline mean EQ-5D-3L VAS scores were also very similar between the two study arms, and no statistically significant difference during treatment was observed between the palbociclib/ET (67.1 [95% CI, 65.3–69.0]) and capecitabine arms (66.6 [95% CI, 64.9–68.2]) ($P = 0.642$). The mean EQ-5D-3L VAS scores were minimally increased during the study period with no statistically significant differences from the baseline and worsened in both treatment arms at the post-treatment visit (Table 3).

5. Discussion

The impact of CDK4/6 inhibitors on treatment outcomes justifies its use as first-line therapy in hormone receptor–positive HER2-negative MBC. Although guidelines and evidence stress the use of modern ET in this setting before chemotherapy [22–24], analyses of various cancer databases show that chemotherapy is still

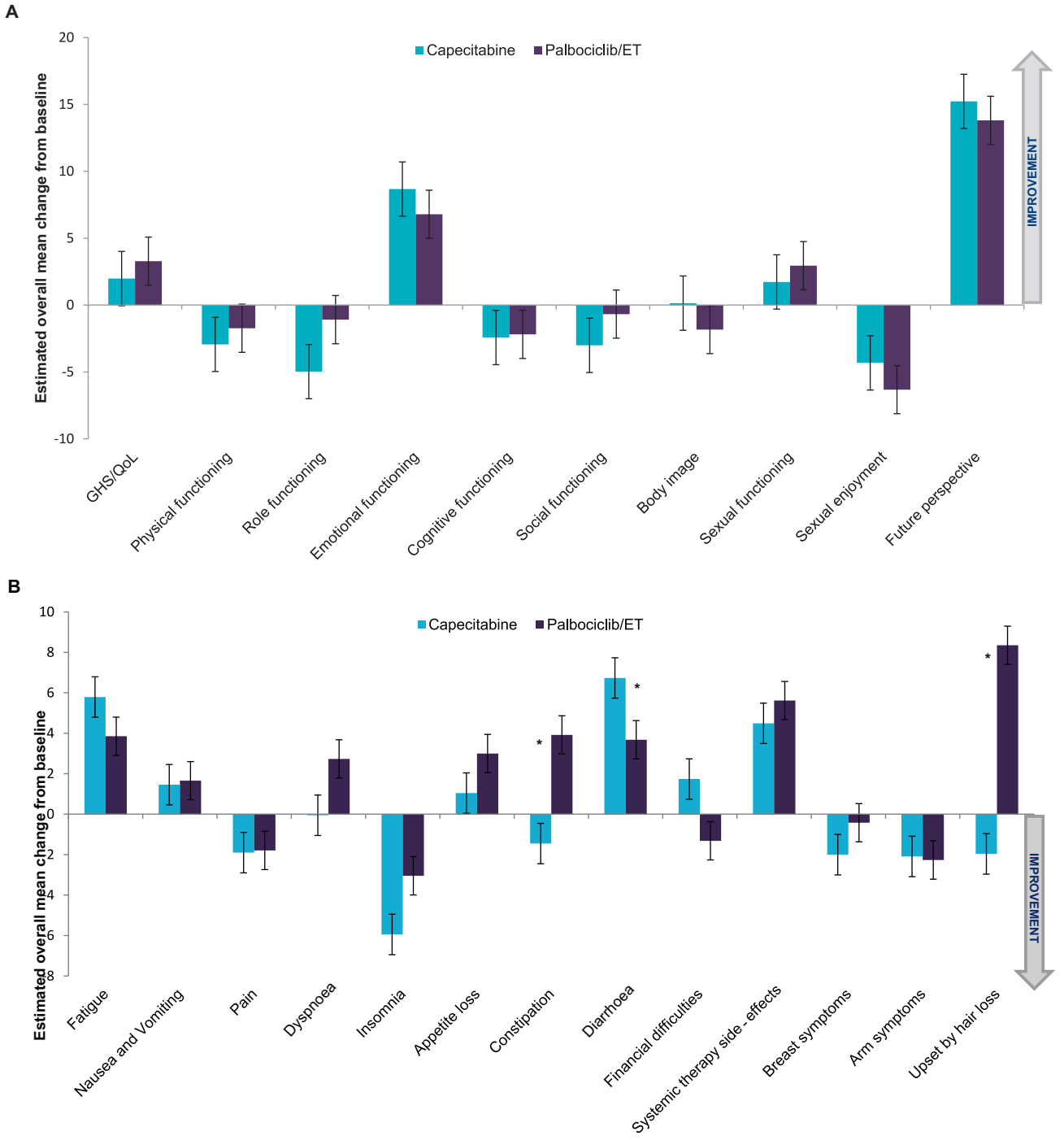

Fig. 1. **Overall change from the baseline in EORTC QLQ-C30 and BR23 scales.** Changes from the baseline were determined using a repeated-measures mixed-effect model. A, analysis of change from the baseline for GHS/QoL and functional scales; B, analysis of change from the baseline for symptom scales. ∗Statistically significant difference in change from baseline scores between treatment arms. EORTC QLQ-BR-23, European Organisation for Research and Treatment of Cancer breast-specific questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core questionnaire; GHS/QoL, global health status/quality of life.

a mainstay of anticancer therapy and is used as first-line therapy in about half of the cases [25–27]. Our results indicating that several components of HRQoL are significantly superior on palbociclib/ET than on capecitabine will contribute to the appropriate positioning of CDK4/6 inhibitors in the treatment armamentarium. Notably, the huge cost of adding CDK 4/6 inhibitors to ET may prevent its general use on the basis of improved QoL especially in low-income settings; in that situation, capecitabine could remain an option [28].

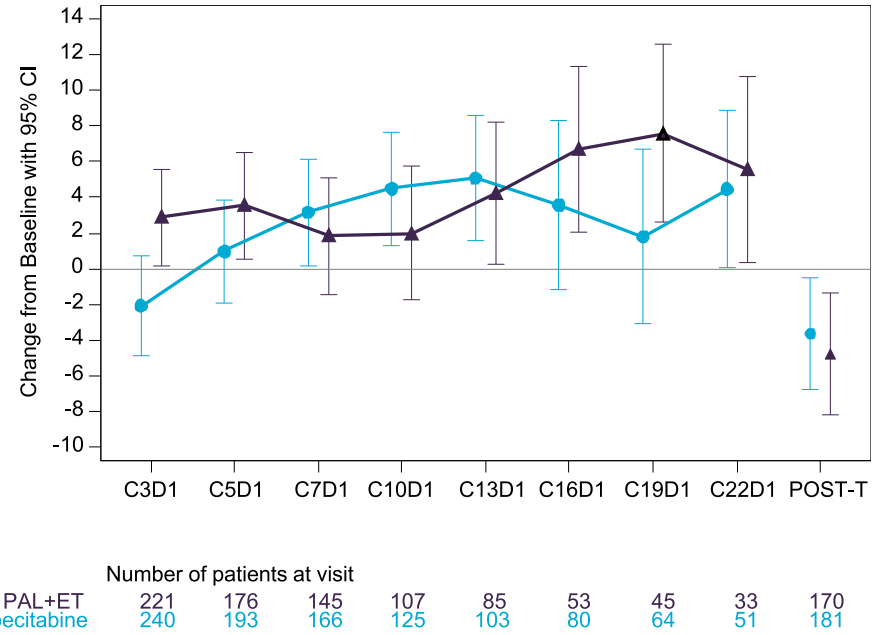

Fig. 2. **Change from baseline values in the GHS/QoL EORTC QLQ-C30 by treatment arm.** The baseline is defined as the last observed measurement on or before the date of the first dose of the study drug. The time profile provides the average estimates for the CFB for the interval from the baseline up to the respective cycle as assessed using a linear mixed model with treatment arms, time points, treatment-time interaction terms and stratification criteria as factors and baseline scores as covariates. Increases from the baseline mean improvement in GHS/QoL. C, cycle; CFB, change from the baseline; GHS/QoL, global health status/quality of life; CI, confidence interval; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core questionnaire; ET, endocrine therapy; PAL, palbociclib; Post-T, post-treatment visit.

Although patient-reported GHS/QoL levels were maintained in both treatment arms, specific advantages occurred on palbociclib/ET: early significant improvement was detected at cycle 3; TTD of self-reported GHS/QoL was extended by 29% (absolute 2.4 months). The PRO results reflected the side-effects of the specific treatment as determinants of different symptoms and functioning related to QoL. The lack of difference in EQ-5D-3L scores between the treatment arms could be due to, first, the generic nature of the tool as compared with the EORTC questionnaires and, second, to being less sensitive to changes in health status than other EQ-5D measures [29]. PEARL was the first randomised phase III study comparing the outcome (including QoL aspects) between modern ET with palbociclib versus capecitabine. Because PFS and overall response rate (ORR) were not different between the treatment arms [12], the QoL dimensions were primarily dependent on the tolerability of treatments. Most importantly, GHS/QoL showed a significant early improvement, and its deterioration and that of the specific functioning and symptom dimensions were significantly delayed in the palbociclib/ET arm; only sexual enjoyment and upset by hair loss, typical symptoms of hormone depletion, were worse in the investigational arm. The PRO analysis in our study helped to understand the patients' subjective appreciation of the compared treatment modalities and the impact these had on their HRQoL.

The recently reported Young-Pearl phase II study compared the treatment of premenopausal patients with palbociclib/ET (exemestane with leuprolide) versus capecitabine [30,31]. The PRO results were similar to ours: GHS/QoL was maintained in both arms, but some functioning dimensions and symptoms changed over time in accordance with treatment. While physical functioning improved from the baseline in the capecitabine arm the most, role and cognitive functioning improved in the other arm. The deterioration of symptoms such as nausea, diarrhoea and physical functioning was delayed by palbociclib/ET [31].

The QoL analyses of the PALOMA-2 and PALOMA-3 trials consistently demonstrated that the addition of palbociclib to standard first- and second-line ET did not compromise but enhanced the maintenance of QoL of postmenopausal patients [5,6]. Furthermore, because of greater therapeutic activity and longer disease control, deterioration in various dimensions was delayed; pain, a typical symptom related to advanced disease, decreased more and deteriorated later in both studies under palbociclib/ET. Similar to the findings in PALOMA-2, the deterioration of GHS/QoL was significantly delayed in patients having partial or complete response on palbociclib/ET versus patients treated with capecitabine irrespective of their therapeutic response [6].

Capecitabine is an oral antimetabolite agent registered as monotherapy for the treatment of patients with

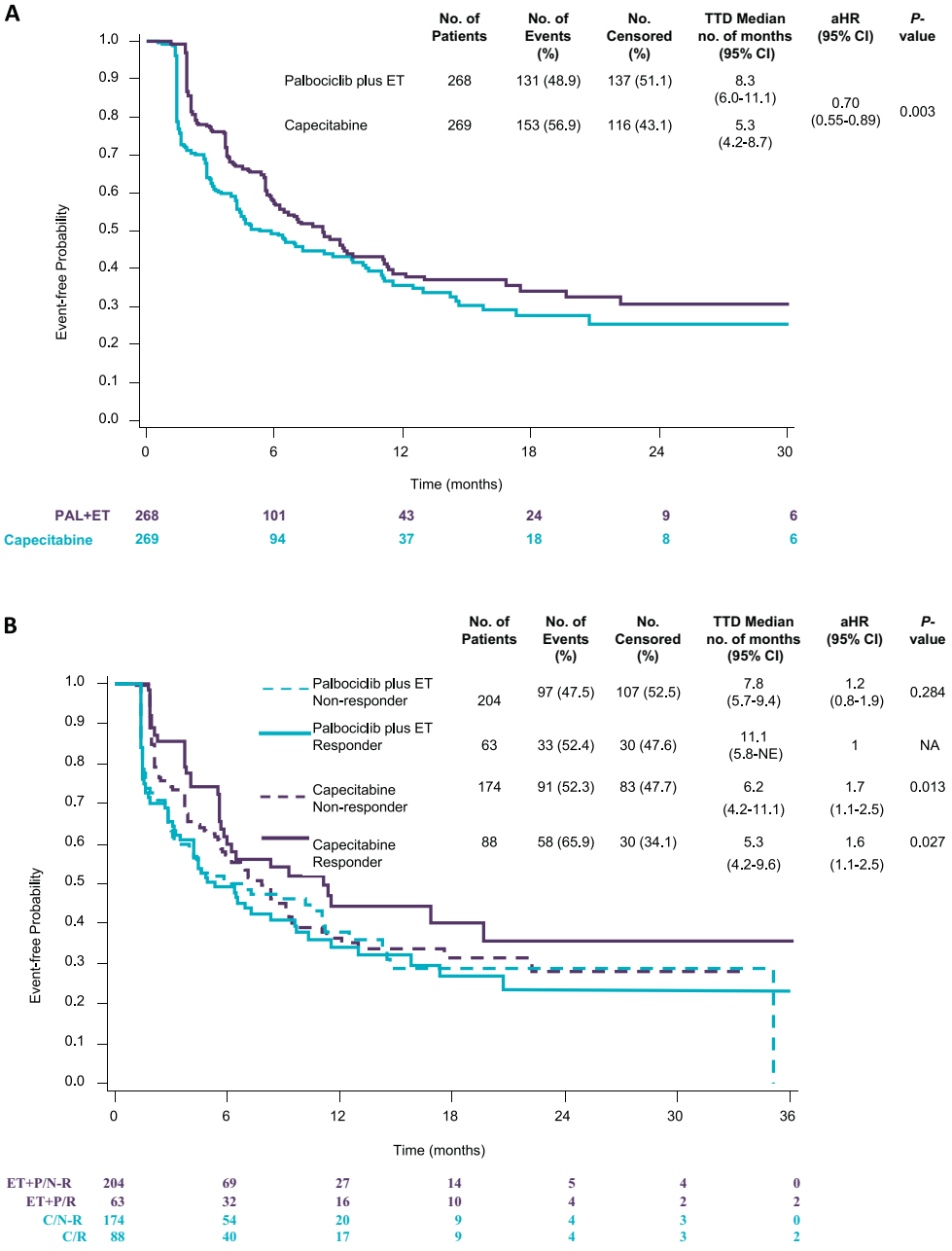

Fig. 3. **Kaplan-Meier estimates for time to deterioration in GHS/QoL based on the EORTC QLQ-C30 questionnaire data.** The adjusted hazard ratio was obtained using a stratified Cox proportional hazards model with treatment arm, the stratification factors (visceral, sensitivity to prior ET, prior chemotherapy for MBC) and number of involved sites as covariates. A, analysis in accordance with treatment arm; B, analysis in accordance with treatment arm and therapeutic response (responders showed partial or complete response, non-responders did not). aHR, adjusted hazard ratio; MBC, metastatic breast cancer; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core questionnaire; ET, endocrine therapy; GHS/QoL, global health status/quality of life; NA, not applicable; N-R, non-responder; PAL, palbociclib; R, responder; TTD, time to deterioration.

locally advanced or metastatic breast cancer after therapy with taxanes and anthracyclines or if these cannot be given [32]. Its toxicity profile is different from other cytotoxic agents, with the most side-effects being hand-foot syndrome, diarrhoea, fatigue, stomatitis and vomiting. A very attractive feature is that toxicity may be well controlled with dose-adjustment/delay while its efficacy is still being maintained [33]. Because of its favourable tolerability, the length of administration need not be different from that of ET. Most patients accept oral cancer therapies better than intravenous (i.v.) ones [7]. We believe that capecitabine is a unique chemotherapy option with good therapeutic activity and special impact on QoL. However, in recent literature reviews and network meta-analyses, the activity of some i.v. palliative chemotherapies was found superior to that

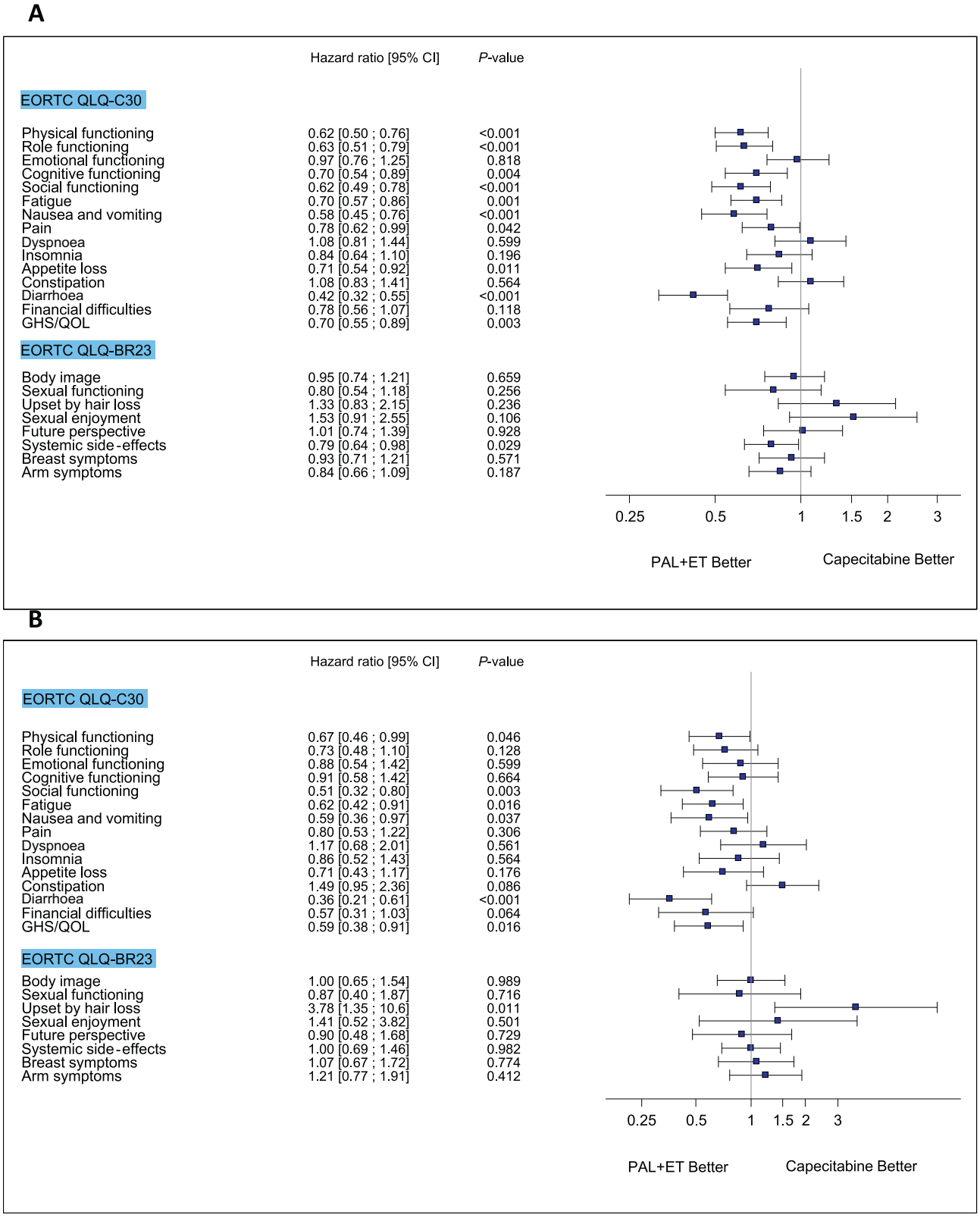

Fig. 4. **Forest plot: time to deterioration in the various scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.** Adjusted hazard ratios were obtained using a stratified Cox proportional hazards model with treatment arm, the stratification factors (visceral, sensitivity to prior ET, prior CT for MBC) and number of involved sites as covariates. A, analysis of all QoL population by treatment arm. B, analysis of responder patients by treatment arm (the responder had partial or complete response). C, analysis of non-responder patients by treatment arm (in non-responders, partial or complete response was absent). MBC, metastatic breast cancer; CI, confidence interval; EORTC QLQ-BR-23, European Organisation for Research and Treatment of Cancer breast-specific questionnaire; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core questionnaire; ET, endocrine therapy; GHS/QoL, global health status/quality of life; PAL, palbociclib.

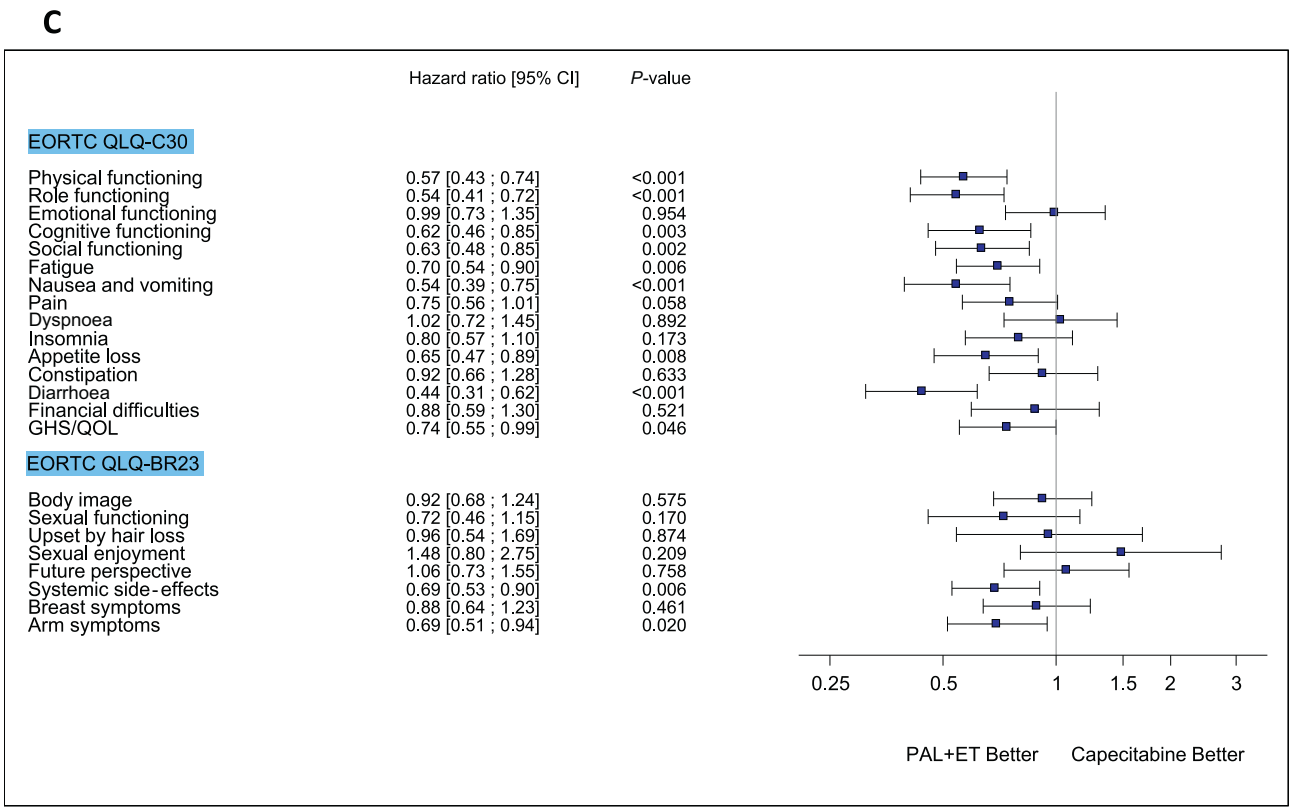

Fig. 4. (*continued*).

Table 3
EQ-5D-3L severity levels at the baseline and index and VAS scores at the baseline, during treatment and at the post-treatment visit by treatment arm.

	Palbociclib plus ET (n = 268)				Capecitabine (n = 269)				
EQ-5D-3L dimensions at the baseline	*n*	No problems *n* (%)	Some problems *n* (%)	Extreme problems *n* (%)	*n*	No problems *n* (%)	Some problems *n* (%)	Extreme problems *n* (%)	*P*-value[b]
Mobility	264	177 (67.0)	86 (32.6)	1 (0.4)	266	177 (66.6)	86 (32.3)	3 (1.1)	0.6236
Self-care	263	225 (85.6)	34 (12.9)	4 (1.5)	267	231 (86.5)	34 (12.7)	2 (0.8)	0.4474
Usual activities	263	156 (59.3)	94 (35.7)	13 (5.0)	267	146 (54.7)	110 (41.2)	11 (4.1)	0.6486
Pain/discomfort	267	90 (33.7)	164 (61.4)	13 (4.9)	267	98 (36.7)	142 (53.2)	27 (10.1)	**0.0214**
Anxiety/depression	265	118 (44.5)	130 (49.1)	17 (6.4)	267	103 (38.6)	148 (55.4)	16 (6.0)	0.8399
EQ-5D-3L index scores	***n***	**Mean**	**SD**	**95% CI**	***n***	**Mean**	**SD**	**95% CI**	***P*-value[c]**
Baseline	262	0.70	0.20	0.68–0.73	266	0.69	0.22	0.66–0.72	0.424
During treatment[a]	NA	0.72	NA	0.69–0.74	NA	0.71	NA	0.69–0.73	0.672
Post-treatment	166	0.63	0.25	0.59–0.67	179	0.65	0.23	0.61–0.68	0.437
EQ-5D-3L VAS scores	***n***	**Mean**	**SD**	**95% CI**	***n***	**Mean**	**SD**	**95% CI**	***P*-value[c]**
Baseline	263	67.4	18.4	65.2–69.6	265	66.8	19.2	64.5–69.2	0.730
During treatment[a]	NA	67.1	NA	65.3–69.0	NA	66.6	NA	64.9–68.2	0.642
Post-treatment	170	59.4	20.6	56.3–62.5	179	61.9	19.1	59.1–64.7	0.245

Higher EQ-5D index and VAS scores indicate better health status/QoL. The baseline is defined as the last observed measurement on or before the date of the first dose of the study drug.
CI, confidence interval; ET, endocrine therapy; SD, standard deviation; VAS, visual analogue scale. Bold source highlighted statistical significance.
[a] Estimated with a linear mixed model with treatment arms, time points, treatment-time interaction terms and stratification criteria as factors and baseline scores as covariates.
[b] Comparison between 'no problems' plus 'some problems' versus 'extreme problems'.
[c] Comparison between treatments arms.

of capecitabine in indirect comparisons with palbociclib/ET [23,24]. Obviously, the toxicity of these i.v. chemotherapy regimens being different probably would affect QoL dimensions in other ways and to a greater extent by impairing different symptom clusters than capecitabine [8]. Therefore, our findings regarding capecitabine's impact on QoL should not be generalised to other chemotherapy regimens.

PRO results may depend on the patient's country of origin and ethnicity. Chemotherapy and ET exerted slightly different effects on HRQoL and daily activity in patients from Europe versus the United States of America [9]. Our study population came from countries with similar values and lifestyles, and the country of origin was a stratification factor; nevertheless, the patient population of the Young-Pearl study was uniquely South Korean [31].

In conclusion, patients receiving palbociclib/ET experienced a significant delay in deterioration of GHS/QoL; multiple functional and symptom scales were more favourable as compared with capecitabine. These findings provide additional evidence that palbociclib/ET is better tolerated than capecitabine.

Author contributions

M. Martin: Conceptualisation, Methodology, data collection and curation, Resources, Supervision, Project administration, Funding acquisition; **E. Carrasco**, Conceptualisation, Methodology, Software (electronic case report form design)Writing – original draft, Supervision, Project administration, Funding acquisition; **M. Casas:** Formal analysis; **G. Rodrigálvarez**, Methodology, Resources, Writing – original draft, Project administration; **Z. Kahan:** data collection and curation, Resources; Writing – original draft, Supervision; **M. Gil-Gil:** data collection and curation, Resources; **M. Ruiz-Borrego:** data collection and curation, Resources; **E. Ciruelos:** data collection and curation, Resources; **M. Muñoz:** data collection and curation, Resources; **B. Bermejo:** data collection and curation, Resources; **M. Margelí:** data collection and curation, Resources; **A. Antón:** data collection and curation, Resources; **T. Csöszi:** data collection and curation, Resources; **L. Murillo:** data collection and curation, Resources; **S. Morales:** data collection and curation, Resources; **L. Calvo:** data collection and curation, Resources; **I. Lang:** data collection and curation, Resources; **E. Alba:** data collection and curation, Resources; **J. de la Haba:** data collection and curation, Resources; **M.l Ramos:** data collection and curation, Resources; **I.M. Álvarez-López:** data collection and curation, Resources; **E.Gal-Yam:** data collection and curation, Resources; **A. García-Palomo:** data collection and curation, Resources; **E. Álvarez:** data collection and curation, Resources; **S. González-Santiago:** data collection and curation, Resources; **C.A. Rodríguez:** data collection and curation, Resources; **S. Servitja:** data collection and curation, Resources; **M. Corsaro:** Resources; **C. Zielinski:** Resources, Supervision; **All authors:** Writing – review & editing.

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The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The content is solely the responsibility of the authors.

Conflict of interest statement

Z.K. has participated in advisory boards of and received speaker fees or travel support from Pfizer, Roche, AstraZeneca and Novartis. M.G-G.- has received honoraria from Pfizer and Eisai and has participated in advisory boards of Genentech and Daiichi Sankyo. He has received travel support from Pfizer, Novartis, Daiichi Sankyo, Roche and Kern. M.R.B. has received speaker fees and advisory grants from Pfizer, Novartis and Lilly. E.Ca., who has a stock and other ownership interests from Lilly, has received travel and accommodation support from Roche, and her husband, who has participated in consulting and advisory board activities with Bristol Myers Squibb, Novartis, Celgene, Roche Pharma, Janssen, Amgen, Incyte, AbbVie and Pfizer, has received travel and accommodation support from Celgene, Novartis and Bristol Myers Squibb. His institution has received research funding from Celgene, Janssen, Bristol Myers Squibb, Novartis, Roche/Genentech, Amgen, Pfizer and AbbVie. GEICAM has received research funding from Roche/Genentech, Bristol Myers Squibb, Novartis, Pfizer, Celgene, AstraZeneca, Merck Sharp & Dohme, Pierre Fabre and Takeda. E.Ci. has received advisory board honoraria from Lilly, Novartis, MSD, AstraZeneca, Pfizer and Roche and speakers' honoraria from Roche, Lilly and Pfizer, and she has received travel and congress assistance support from Pfizer and Roche. M.Mu. has received travel and congress assistance support from Roche, Novartis, Pfizer and Eisai. B.B. has received advisory board honoraria from Roche, Novartis and MSD and speakers' honoraria from Roche, Novartis, MSD, Pfizer and Pierre Fabre, and she has received travel and congress assistance support from Pfizer. M.Marg. has received advisory board fees from Roche, Novartis, Pfizer and Eisai. Her

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Appendix A. Supplementary data

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