European Journal of Cancer 168 (2022) 12–24

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Overall survival with palbociclib plus endocrine therapy versus capecitabine in postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer in the PEARL study

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https://doi.org/10.1016/j.ejca.2022.03.006

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Received 20 December 2021; received in revised form 25 February 2022; accepted 7 March 2022
Available online 13 April 2022

KEYWORDS
CDK4/6 inhibitor;
Palbociclib;
Endocrine therapy;
Hormone receptor-positive metastatic breast cancer;
Overall survival;
Capecitabine;
HER2−negative

Abstract ***Background:*** An earlier analysis of the PEARL phase III study showed that palbociclib plus endocrine therapy (ET) does not improve progression-free survival (PFS) over capecitabine in aromatase inhibitor-resistant, hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (MBC) patients. Here, we report the final overall survival (OS) analysis.
Methods: Postmenopausal patients (N = 601) were randomized 1:1 to capecitabine or palbociclib plus ET (exemestane, Cohort 1; fulvestrant, Cohort 2). OS was analysed in Cohort 2, the wild-type *ESR1* population and the overall population. Additionally, we analysed subsequent systemic therapies and explored PFS2 (time from randomization to the end of the first subsequent therapy/death).
Results: OS was 31.1 months for palbociclib plus fulvestrant and 32.8 months for capecitabine (adjusted hazard ratio [aHR] 1.10, 95% confidence interval [CI] 0.81−1.50, P = 0.550). In the wild-type *ESR1* population, OS was 37.2 months for palbociclib plus ET and 34.8 months for capecitabine (aHR 1.06, 95% CI 0.81−1.37, P = 0.683). In OS analyses, no subgroup showed superiority for palbociclib plus ET over capecitabine. OS in the overall population was 32.6 months for palbociclib plus ET and 30.9 months for capecitabine (P = 0.995). Subsequent systemic therapy was given to 79.8% and 82.9% of patients with palbociclib plus ET and capecitabine, respectively. Median PFS2 was similar between study arms (Cohort 2, P = 0.941; wild-type *ESR1* population, P = 0.827). No new safety findings were observed.
Conclusions: Palbociclib plus ET did not show a statistically superior OS compared to capecitabine in MBC patients progressing on aromatase inhibitors.
Trial registration: NCT02028507 (ClinTrials.gov), 2013-003170-27 (EudraCT).

1. Introduction

In 2020, an estimated 2.26 million new cases of invasive breast cancer were diagnosed, representing 11.7% of all cancer cases and approximately 685,000 patient deaths worldwide. Metastatic breast cancer (MBC) as initial presentation is uncommon (about 6%), but approximately 30% of patients will eventually develop recurrent advanced or metastatic disease [1]. Around 70% of patients with MBC have hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative tumours. The standard treatment for this subgroup includes endocrine therapy (ET), but not all patients respond to ET due to primary resistance and almost all have progressive disease sooner or later while on ET due to secondary resistance. For this reason, the use of chemotherapy in hormone-sensitive MBC patients is very common after ET failure. Capecitabine, an oral drug, is well tolerated and active in patients with MBC and one of the best options in patients with progression to prior therapies [2−5].

Multiple trials have shown that cyclin-dependent kinases 4/6 (CDK4/6) inhibitors in combination with ET significantly improve progression-free survival (PFS) [6−13] and overall survival (OS) [14−17] compared with ET alone, with manageable safety profiles and maintained quality of life (QoL) under therapy [18,19].

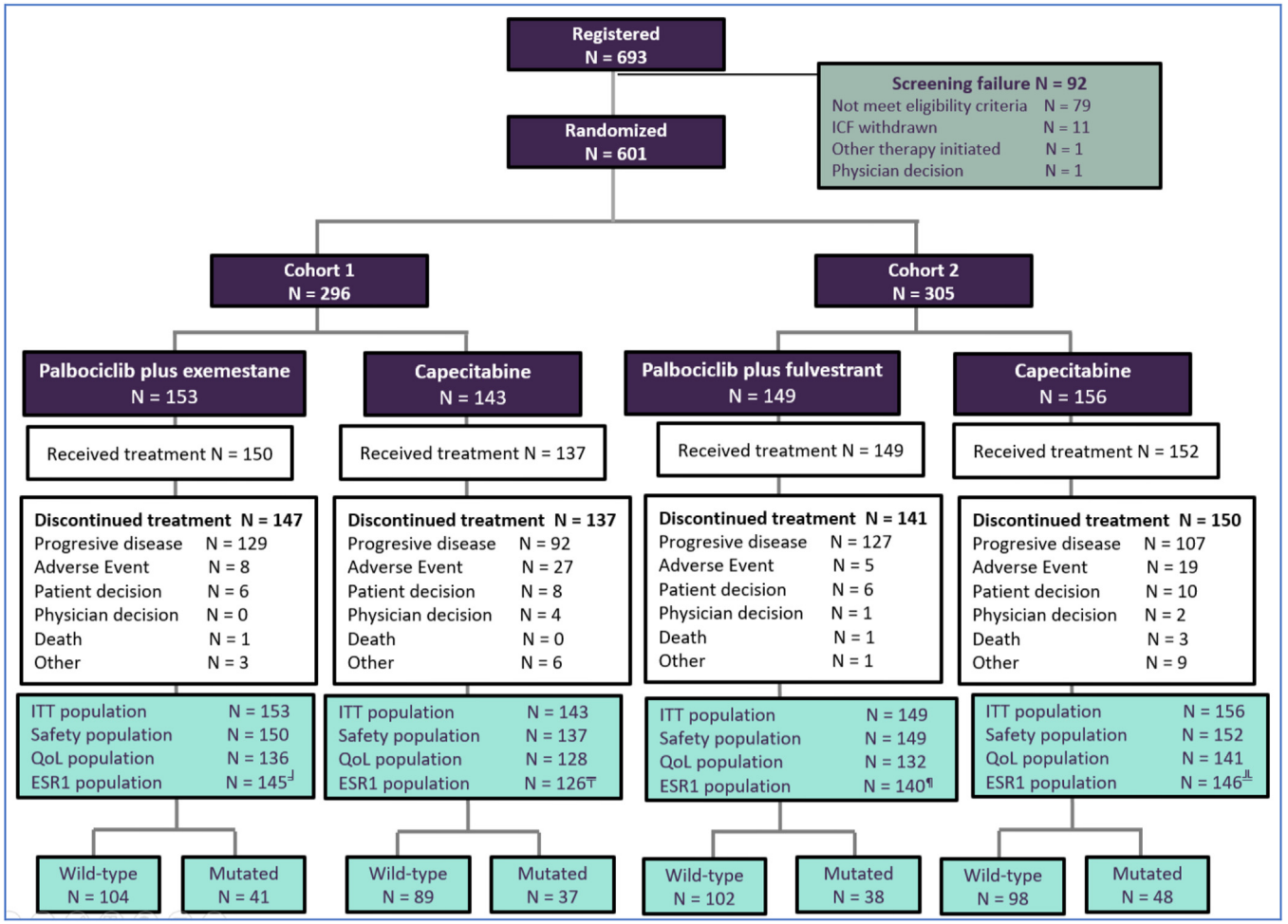


Fig. 1. Consort diagram. [Ŧ]No treatment N = 6 and sample not available N = 11. [ɻ]No treatment N = 2 and sample not available N = 6. [ǂ]No treatment N = 3 and sample not available N = 7. [¶]Sample not available N = 9 and samples with no results N = 2. In Cohort 1, two patients discontinued study therapy due to patient decision, but previously, these patients discontinued palbociclib (continuing with exemestane) due to adverse events. In Cohort 2, four patients discontinued study therapy due to progressive disease, one due to adverse events, and one due to patient decision, but previously, these six patients discontinued palbociclib (continuing with fulvestrant) due to adverse events. *ESR1*, oestrogen receptor 1; ICF, informed consent form; ITT population, intent-to-treat population; N, number of patients; QoL, quality of life.

The PEARL phase III study was designed to answer the important question of whether the efficacy of the combination of palbociclib with ET is superior to that of chemotherapy in postmenopausal hormone receptor-positive/HER2-negative MBC patients who progressed on an aromatase inhibitor (AI). In terms of PFS, the primary results of this study did not show superiority for palbociclib plus ET compared to capecitabine; however, it was better tolerated and showed a significant delay in the deterioration of QoL [20,21]. Here, we report the results of the OS analysis of the trial.

2. Materials and methods

2.1. Trial design

The PEARL study is a multicentre, international, open-label, controlled, phase III study with two successive cohorts. In Cohort 1, patients were randomized 1:1 to receive palbociclib (125 mg daily for three weeks followed by one week off) plus exemestane (25 mg daily) versus capecitabine (1250 mg/m^2 [1000 mg/m^2 in patients >70 years old] twice daily for two weeks followed by one week off). The trial was amended as previously reported [20] to add Cohort 2 in which patients were randomized 1:1 to receive palbociclib plus fulvestrant (500 mg on days 1 and 15 of cycle 1 and then on day 1 every four weeks) versus capecitabine. Stratification criteria were the site of disease (visceral/non-visceral), sensitivity to prior ET (relapse after 24 months of adjuvant ET or response [complete or partial] or stabilization after 24 weeks of the most recent line of ET in the context of advanced disease [yes/no]), prior chemotherapy for MBC (yes/no) and country of origin. The treatment continued until objective disease progression according to RECIST v1.1 [22], symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurred first. On the completion of study treatment, patients were monitored for survival every six months. Subsequent systemic therapies were collected in all patients discontinuing study therapy till death or trial closure. *ESR1* mutations were assessed in circulating free DNA (cfDNA) at study entry.

The study protocol and all amendments were approved by every site's institutional review board and every national regulatory agency. All patients gave written informed consent. A trial steering committee composed of representatives of the participating cooperative groups (GEICAM Spanish Breast Cancer Group and CECOG) oversaw the conduct of the study. Safety and efficacy at the interim analyses were evaluated by an independent data monitoring committee. The data were analysed by GEICAM's statisticians.

2.2. Patients

Postmenopausal women with hormone receptor-positive/HER2-negative MBC resistant to previous AIs (recurrence while on or within 12 months after the end of adjuvant treatment, or progression while on or within 1 month after the end of treatment of advanced disease) were included. Patients had to have measurable disease assessable by computed tomography/magnetic resonance imaging according to RECIST v1.1 [22] or at least one lytic or mixed bone lesion. Prior chemotherapy was permitted either in a (neo)adjuvant setting or first-line therapy for MBC. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, life expectancy of more than 12 weeks and adequate organ function.

Patients with the advanced, symptomatic and visceral spread that were at risk of life-threatening complications in the short term were excluded. Patients were required to have a corrected QT interval less than 480 ms and no family or personal history of long or short QT syndrome, Brugada syndrome, torsades de pointes or QTc prolongation.

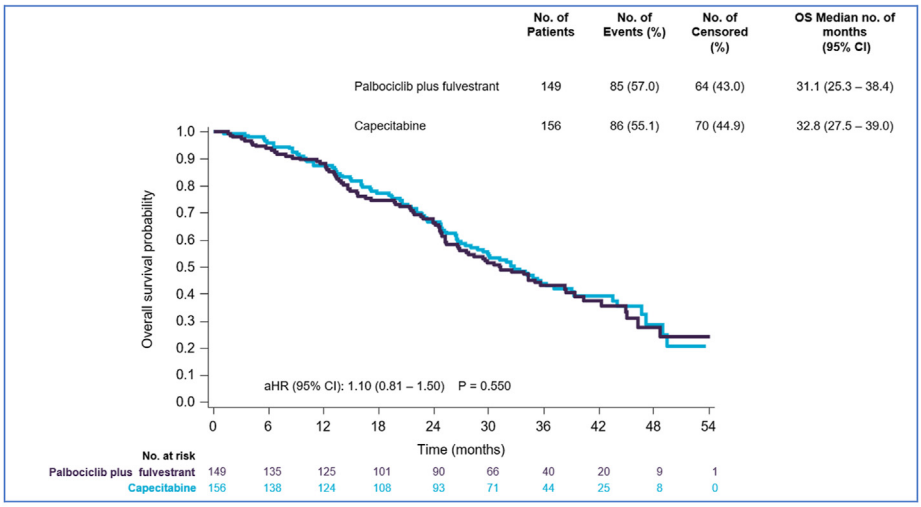
2.3. Outcomes

The results of the primary endpoint (PFS) and other secondary endpoints, such as objective response rate, clinical benefit rate, response duration and QoL, have been reported previously [20,21]. The pre-planned key secondary efficacy objectives were to compare OS of patients treated with (1) palbociclib plus fulvestrant versus capecitabine regardless of their tumour *ESR1* mutational status, (2) palbociclib plus ET versus capecitabine in patients with wild-type *ESR1* tumours (wild-type *ESR1* population) and (3) palbociclib plus ET versus capecitabine regardless of the tumour *ESR1* mutational status. OS was defined as the time from randomization to death from any cause. In addition, a post hoc exploratory analysis of PFS2, defined as the time from randomization to the end of the first subsequent therapy or death from any cause, was conducted.

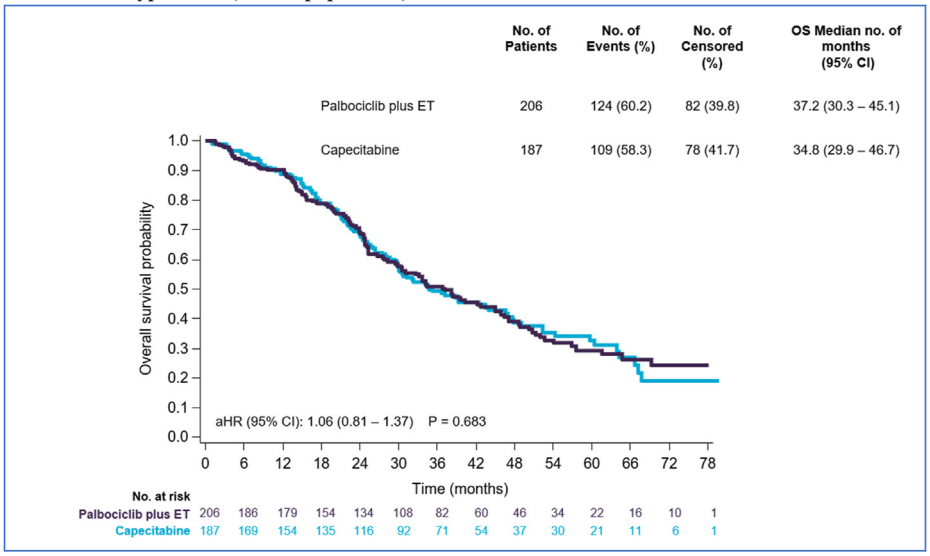
2.4. Statistical analysis

The sample size needed to analyse the primary endpoint of PFS also allowed the assessment of differences in the secondary endpoint of OS. This analysis was planned when approximately 152 deaths had occurred in Cohort 2 to have an 80% power to detect a difference between capecitabine (estimated median OS of 22 months) and palbociclib plus fulvestrant or palbociclib plus ET in the

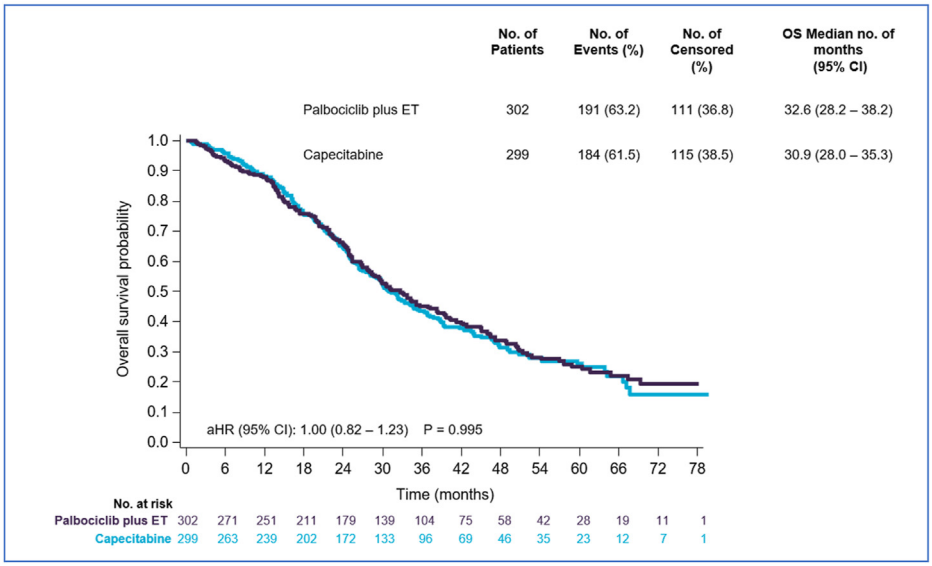
A Cohort 2



B Wild-type *ESR1* (overall population)



C Overall population (regardless of *ESR1* mutational status)



wild-type *ESR1* population (estimated median OS of 33 months), for a hazard ratio (HR) of 0.667 with a 10% significance level and one interim analysis of OS (at the time of the final PFS analysis). The target sample size in Cohort 2 was 300 patients. The sample size to detect the same difference in the wild-type *ESR1* population, assuming an 80% circulant tumour DNA (ctDNA) collection/detection rate and 30% of patients with *ESR1* tumour mutations was also 300 patients.

The Kaplan–Meier method was used to determine the median OS and PFS2, and 95% confidence intervals (CIs) were calculated for estimates of interest. The Cox proportional-hazards model was used to calculate unadjusted and adjusted HRs (aHR; by stratification factors and the number of involved sites) and 95% CIs.

3. Results

3.1. Patients

From March 2014 to July 2018, a total of 601 patients were enrolled at 37 sites in four countries (Spain, Hungary, Israel and Austria). Cohort 1 recruited 296 patients (153 on palbociclib plus exemestane and 143 on capecitabine), and Cohort 2 recruited 305 patients (149 on palbociclib plus fulvestrant and 156 on capecitabine). All patients were included in the efficacy analysis, but 13 patients were excluded from the safety evaluation as they never received study treatment. *ESR1* mutations were assessed in 557 patients (92.7%), and 393 of them (70.6%) were included in the wild-type *ESR1* population (187 treated with capecitabine and 206 with palbociclib plus ET; Fig. 1). Details of the patients included in the analysis were reported previously [20] and are shown in Supplementary Table A1.

At the cut-off date (January 11, 2021) for this OS analysis, 13 patients were still receiving study therapy: three in the palbociclib plus exemestane arm, eight in the palbociclib plus fulvestrant arm and two in the capecitabine arm. The median duration of study treatment in Cohort 1 was 6.3 (range: 0.4–73.5) months for palbociclib plus exemestane and 7.9 (range: 0.2–51.1) months for capecitabine; in Cohort 2, it was 8.3 (range: 0.7–51.6) months for palbociclib plus fulvestrant and 6.4 (range: 0.2–46.9) months for capecitabine.

3.2. Overall survival

The median follow-up periods of Cohort 2, wild-type *ESR1* population and overall population were 28.0 (range: 0.0–54.2) months, 30.3 (range: 0.0–79.7) months and 28.2 (range; 0.0–79.7) months, respectively. No significant differences were observed between the palbociclib plus ET and the capecitabine arms in any of the performed analyses. The median OS in Cohort 2 was 31.1 months with palbociclib plus fulvestrant versus 32.8 months with capecitabine (aHR 1.10, 95% CI 0.81–1.50, P = 0.550). Median OS in the wild-type *ESR1* population was 37.2 months with palbociclib plus ET versus 34.8 months with capecitabine (aHR 1.06, 95% CI 0.81–1.37, P = 0.683). Median OS in the overall population was 32.6 versus 30.9 months with palbociclib plus ET and capecitabine, respectively (aHR 1.00, 95% CI 0.82–1.23, P = 0.995; Fig. 2). None of the subgroup analyses showed superiority in OS for palbociclib plus ET compared to capecitabine, neither in Cohort 2 nor in the wild-type *ESR1* or overall populations (Fig. 3).

3.3. Subsequent treatments

Subsequent systemic therapy was given to 489 of the 601 randomized patients (81.4%): 126 in patients receiving palbociclib plus exemestane, 115 in those treated with palbociclib plus fulvestrant, and 248 in patients randomized to capecitabine (Table 1). The median number of subsequent lines of therapy was three in all study arms. The proportion of patients receiving subsequent chemotherapy was higher in patients treated with palbociclib plus ET (palbociclib plus exemestane, 78.4% and palbociclib plus fulvestrant, 73.2%) compared to patients receiving capecitabine (60.9%). Subsequent ET was received by 51.0% of patients treated with palbociclib plus exemestane, 41.6% of those treated with palbociclib plus fulvestrant and 71.2% of those treated with capecitabine (Table 1).

CDK4/6 inhibitors were received by 3.6% of patients treated with palbociclib plus ET and 23.1% and 55.1% of those treated with capecitabine in Cohort 1 and Cohort 2, respectively.

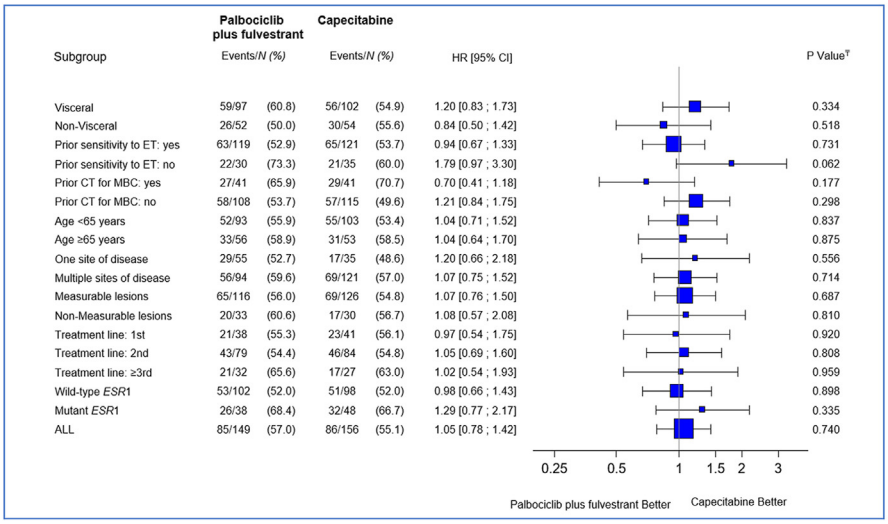
The first subsequent systemic therapy was capecitabine in 36.1% of patients treated with palbociclib plus ET and CDK4/6 inhibitors plus ET in 26.1% of patients treated with capecitabine (Table 2).

3.4. Progression-free survival 2

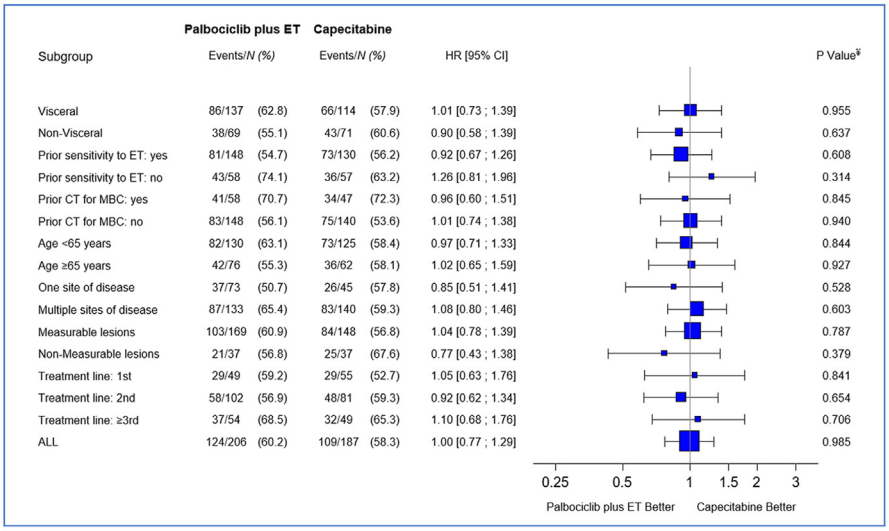
A total of 480 patients had a PFS2 event: 132 (86.3%) in the palbociclib plus exemestane arm, 115 (77.2%) in the palbociclib plus fulvestrant arm and 233 among patients treated with capecitabine (118 [82.5%] in Cohort 1 and 115 [73.7%] in Cohort 2; Supplementary Table A2). The median PFS2 in Cohort 2 was 17.8 months in the palbociclib plus fulvestrant arm versus 17.3 months in the

Fig. 2. Overall survival. Kaplan–Meier curves for OS are presented for (A) patients in Cohort 2: palbociclib plus fulvestrant versus capecitabine, (B) patients with wild-type *ESR1* from Cohort 1 + Cohort 2: palbociclib plus ET versus capecitabine, and (C) overall population of Cohort 1 + Cohort 2 regardless of *ESR1* mutational status: palbociclib plus ET versus capecitabine. Hazard ratios were adjusted for disease site, prior sensitivity to ET, prior chemotherapy for metastatic breast cancer, and the number of involved sites. aHR, adjusted hazard ratio; CI, confidence interval; *ESR1*, oestrogen receptor 1; ET, endocrine therapy; No, number; OS, overall survival.

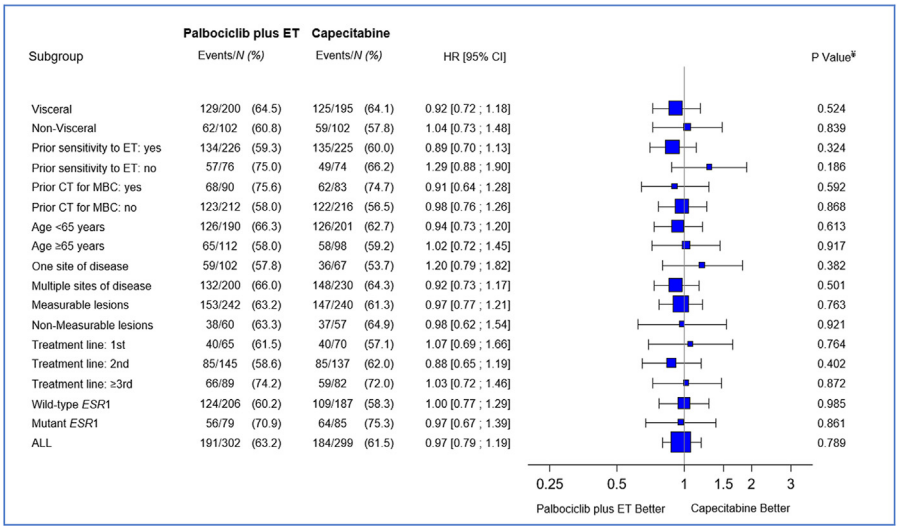
A Cohort 2



B Wild-type *ESR1* (overall population)



C Overall population (regardless of *ESR1* mutational status)



capecitabine arm (aHR 0.99, 95% CI 0.76–1.29, P = 0.941). In the wild-type *ESR1* population, the median PFS2 was 17.7 months in the palbociclib plus ET arm versus 17.7 months in patients treated with capecitabine (aHR 1.03, 95% CI 0.82–1.28, P = 0.827). Similar results were seen in the overall population with 16.7 months of PFS2 in the palbociclib plus ET arm versus 16.9 months in the capecitabine arm (aHR 1.01, 95% CI, 0.84–1.20, P = 0.943; Fig. 4).

3.5. Safety

The safety profile remained consistent with that in the primary analysis (Supplementary Table A3). The proportion of patients with at least one adverse event (AE) was 98.8% and was similar in all study arms. The most frequent grade 3–4-related AEs in the palbociclib plus ET and capecitabine arms were neutropenia (58.5% and 5.9%, with febrile neutropenia 1.0% and 1.4%, respectively), hand/foot syndrome (0% and 24.2%, respectively), diarrhoea (1.3% and 7.6%, respectively) and fatigue (1.0% and 5.5%, respectively). Serious AEs related to study treatments were reported by 4.0% of patients on palbociclib plus ET and 10.7% of patients on capecitabine. Study drug discontinuations due to AEs were reported for 7.7% of patients on palbociclib plus ET and 17.0% on patients treated with capecitabine.

4. Discussion

The current analysis of the PEARL trial showed that patients treated with palbociclib plus ET or capecitabine have a comparable OS. This finding is not unexpected since the PFS previously reported for both therapy approaches [20] were also similar. Besides, more than 80% of patients in all study arms received subsequent therapies, and there was significant cross-over between arms in subsequent lines (more than 36% in the palbociclib plus ET arms and 26% in the capecitabine arms). The initial study therapy (capecitabine or palbociclib plus ET) also did not have an impact on PFS2. This suggests that both are options of similar therapeutic efficacy for the population meeting the inclusion criteria of the trial, although palbociclib plus ET was associated with a better QoL than capecitabine [21].

The PEARL trial, together with other similar studies, provides relevant information regarding the current expected outcome of MBC patients with hormone receptor-positive/HER2-negative tumours that have become resistant to AIs. The eligibility criteria in the PEARL trial were similar to those of the PALOMA-3 study [23,24]. Not surprisingly, the median OS rates with palbociclib plus ET were also very similar in the PEARL (32.6 months) and PALOMA-3 (34.8 months) studies. Another trial with inclusion criteria very close to those of the PEARL and PALOMA-3 studies is the BOLERO-2 trial [25]. The median OS with everolimus plus exemestane in this trial was 31.0 months, again similar to that of the two previously mentioned studies [26]. Other trials in hormone receptor-positive/HER2-negative MBC resistant to ET have been recently reported. The MONARCH-2 study showed a median OS of 46.7 months with abemaciclib plus fulvestrant in patients progressing on ET [14], although the population in this trial had a better prognosis than those in the PEARL, PALOMA-3 and BOLERO-2 studies. In MONARCH-2, 30% of patients had not previously received AIs, and prior chemotherapy for metastatic disease was not allowed. In the MONALEESA-3 trial, comparing ribociclib plus fulvestrant with placebo plus fulvestrant, the median OS of the subset of patients progressing on ET was 40.2 months, but prior chemotherapy for metastatic disease was again not allowed [16]. The young-PEARL trial is a randomized phase II study comparing palbociclib plus ET with ovarian function suppression versus capecitabine in premenopausal MBC patients [27]. This trial, in which in contrast to the PEARL trial half of the patients were treated in first line and no prior AI was used, found that palbociclib plus ET improved PFS versus capecitabine. OS results have not been published yet and are awaited.

The PALOMA-3 study reported a median time from randomization to the end of the immediate subsequent line of therapy after disease progression of 18.8 months for the palbociclib plus fulvestrant arm. This is very similar to the PFS2 observed in the PEARL study in both study arms. The first subsequent lines of therapy were also very similar in the palbociclib plus ET arms of the PEARL study and the palbociclib plus fulvestrant arm of the PALOMA-3 trial (2.3% and 2.0% received CDK4/6 inhibitors and 54% and 56% of patients received chemotherapy, respectively) [23].

In conclusion, in hormone receptor-positive/HER2-negative MBC patients with prior AI therapy, capecitabine and palbociclib plus ET were associated with the

Fig. 3. Forest plot of overall survival hazard ratios by subgroups. Exploratory analyses of overall survival in subgroups and their respective hazard ratios are presented for (A) patients in Cohort 2: palbociclib plus fulvestrant versus capecitabine, (B) patients with wild-type *ESR1* from Cohort 1 + Cohort 2: palbociclib plus ET versus capecitabine, and (C) overall population of Cohort 1 + Cohort 2 regardless of *ESR1* mutational status: palbociclib plus ET versus capecitabine. P-values from Mann–Whitney test (continuous variables) or chi-square test (categorical variables). ₸Unadjusted Cox P-value comparing palbociclib plus fulvestrant versus capecitabine in each subgroup. ¥Unadjusted Cox P-value comparing palbociclib plus ET versus capecitabine in each subgroup. CI, confidence interval; CT, chemotherapy; *ESR1*, oestrogen receptor 1; ET, endocrine therapy; HR, hazard ratio; MBC, metastatic breast cancer; N, number of patients.

Table 1
Subsequent therapy lines.

Variables	Cohort 1		Cohort 2	
	PAL/EXE	CAP	PAL/FUL	CAP
	(N = 153)	(N = 143)	(N = 149)	(N = 156)
Patients randomized but not treated, N (%)	3 (2.0)	6 (4.2)	0	4 (2.6)
Patients on study therapy at the cut-off date, N (%)	3 (2.0)	0	8 (5.4)	2 (1.3)
Patients who discontinued study therapy, N (%)	147 (96.1)	137 (95.8)	141 (94.6)	150 (96.2)
Subsequent therapy, N (%)				
Yes	126 (82.4)	117 (81.8)	115 (77.2)	131 (84.0)
No	27 (17.6)	26 (18.2)	34 (22.8)	25 (16.0)
Number of subsequent lines, N (%)				
1	16 (10.5)	29 (20.3)	28 (18.8)	33 (21.2)
2	26 (17.0)	19 (13.3)	32 (21.5)	26 (16.7)
3	25 (16.3)	23 (16.1)	26 (17.4)	27 (17.3)
≥4	57 (37.3)	43 (30.1)	29 (19.5)	37 (23.7)
No subsequent lines of therapy received				
On study therapy	3 (2.0)	0	8 (5.4)	2 (1.3)
Ongoing on study therapy line[a]	2 (1.3)	3 (2.1)	0	8 (5.1)
Other reasons[b]	24 (15.7)	26 (18.2)	26 (17.4)	23 (14.7)
Median number of subsequent lines	3	3	2	3
Subsequent chemotherapy, N (%)				
Yes	120 (78.4)	90 (62.9)	109 (73.2)	92 (59.0)
No	33 (21.6)	53 (37.1)	40 (26.8)	64 (41.0)
Type of subsequent chemotherapy, N (%)				
Pyrimidine analogues	107 (69.9)	28 (19.6)	89 (59.7)	27 (17.3)
Capecitabine	106 (69.3)	6 (4.2)	87 (58.4)	6 (3.8)
Gemcitabine	21 (13.7)	20 (14.0)	10 (6.7)	15 (9.6)
Methotrexate	13 (8.5)	9 (6.3)	2 (1.3)	4 (2.6)
Fluorouracil/tegafur/uracil	11 (7.2)	10 (7.0)	4 (2.7)	5 (3.2)
Azacitidine	1 (0.7)	1 (0.7)	0	0
Taxanes	65 (42.5)	57 (39.9)	51 (34.2)	55 (35.3)
Vinca alkaloids	58 (37.9)	54 (37.8)	30 (20.13)	37 (23.7)
Other anti-tubulin agents	50 (32.7)	40 (28.0)	29 (19.5)	38 (24.4)
Anthracyclines	39 (25.5)	40 (28.0)	30 (20.1)	34 (21.8)
Alkylating agents	26 (17.0)	23 (16.1)	18 (12.1)	12 (7.7)
Platinum agents	18 (11.8)	15 (10.5)	18 (12.1)	14 (9.0)
Other	5 (3.3)	2 (1.4)	0	3 (1.9)
Subsequent endocrine therapy, N (%)				
Yes	78 (51.0)	97 (67.8)	62 (41.6)	116 (74.4)
No	75 (49.0)	46 (32.2)	87 (58.4)	40 (25.6)
Type of subsequent endocrine therapy, N (%)				
Selective oestrogen receptor degraders	52 (34.0)	63 (44.1)	7 (4.7)	107 (68.6)
Fulvestrant	52 (34.0)	62 (43.4)	7 (4.7)	107 (68.6)
Aromatase inhibitor	40 (26.1)	77 (53.8)	52 (34.9)	54 (34.6)
Exemestane	21 (13.7)	58 (40.6)	37 (24.8)	38 (24.4)
Letrozole	9 (5.9)	12 (8.4)	11 (7.4)	12 (7.7)
Anastrozole	11 (7.2)	7 (4.9)	5 (3.4)	4 (2.6)
Tamoxifen	21 (13.7)	13 (9.1)	13 (8.7)	8 (5.1)
Other	1 (0.7)	4 (2.8)	2 (1.3)	0
Other subsequent therapy, N (%)				
Yes	49 (32.0)	78 (54.5)	59 (39.6)	103 (66.0)
No	104 (68.0)	65 (45.5)	90 (60.4)	53 (34.0)
Type of other subsequent therapy, N (%)				
PI3K, mTOR or AKT inhibitor	32 (20.9)	51 (35.7)	41 (27.5)	39 (25.0)
Everolimus	24 (19.0)	51 (35.7)	31 (20.8)	29 (18.6)
Other	38 (24.8)	3 (2.1)	13 (8.7)	10 (6.4)
CDK4/6 inhibitor	5 (3.3)	33 (23.1)	6 (4.0)	86 (55.1)
Palbociclib	5 (3.3)	26 (18.2)	5 (3.4)	78 (50.0)
Abemaciclib	0	5 (3.5)	1 (0.7)	5 (3.2)
Ribociclib	0	2 (1.4)	0	4 (2.6)
Bevacizumab	13 (8.5)	7 (4.9)	14 (9.4)	4 (2.6)
Other	4 (2.6)	4 (2.8)	6 (4.0)	13 (8.3)

Note: AKT, protein kinase B; CAP, capecitabine; CDK4/6 cyclin-dependent kinases 4/6; EXE, exemestane; FUL, fulvestrant; mTOR mammalian target of rapamycin; N, number of patients; PAL, palbociclib; PI3K, phosphatidylinositol 3-kinase.

[a] Patients discontinuing study therapy due to a reason different than progression and receiving another therapy for cancer.

[b] Randomized patients who did not initiate study therapy, withdrew consent, were lost to follow-up or died.

Table 2
First subsequent therapy lines.

Variables	Cohort 1		Cohort 2	
	PAL/EXE	CAP	PAL/FUL	CAP
	(N = 153)	(N = 143)	(N = 149)	(N = 156)
First subsequent therapy, N (%)				
CT alone	71 (46.4)	39 (27.3)	67 (45.0)	27 (17.3)
CT followed by maintenance ET (± other therapy)	7 (4.6)	2 (1.4)	4 (2.7)	1 (0.6)
CT plus other therapy	5 (3.7)	7 (4.9)	8 (5.4)	2 (1.3)
ET alone	24 (19.0)	33 (23.1)	6 (4.0)	15 (9.6)
ET plus other therapy	17 (11.1)	32 (22.4)	29 (19.5)	76 (48.7)
Other therapy	0	1 (0.7)	1 (0.7)	2 (1.3)
Duration of first subsequent therapy (months)				
Median	5.3	4.9	5.7	4.9
Min–Max	0.0–45.1	0.2–47.6	0.0–30.0	0.0–37.7
Type of first subsequent therapy, N (%)				
Chemotherapy				
Pyrimidine analogues	54 (35.3)	8 (5.6)	58 (38.9)	8 (5.1)
Capecitabine (± other therapy)	53 (34.6)	4 (2.8)	56 (37.6)	3 (1.9)
Gemcitabine	1 (0.7)	0	0	0
Methotrexate	1 (0.7)	2 (1.4)	0	1 (0.6)
Fluorouracil	1 (0.7)	3 (2.1)	1 (0.7)	0
Taxanes	13 (8.5)	18 (12.6)	12 (8.1)	9 (5.8)
Vinca alkaloids	11 (7.2)	12 (8.4)	4 (2.7)	7 (4.5)
Other anti-tubulin agents	1 (0.7)	7 (4.9)	1 (0.7)	6 (3.8)
Anthracyclines	7 (4.6)	8 (5.6)	5 (3.6)	3 (1.9)
Alkylating agents	3 (2.0)	2 (1.4)	5 (3.6)	1 (0.6)
Platinum agents	2 (1.3)	1 (0.7)	4 (2.7)	3 (1.9)
Endocrine therapy				
Selective oestrogen receptor degraders	32 (20.9)	37 (25.9)	4 (2.7)	79 (50.6)
Fulvestrant	31 (20.3)	37 (25.9)	4 (2.7)	78 (50.0)
Aromatase inhibitor	11 (7.2)	27 (18.1)	27 (18.1)	13 (8.3)
Exemestane	6 (3.9)	21 (14.7)	19 (12.8)	9 (5.8)
Letrozole	1 (0.7)	3 (2.1)	6 (4.0)	4 (2.6)
Anastrozole	4 (2.6)	3 (2.1)	2 (1.3)	0
Tamoxifen	5 (3.3)	1 (0.7)	7 (4.7)	0
Other therapy				
PI3K, mTOR or AKT inhibitor	14 (9.2)	18 (12.6)	26 (17.4)	16 (10.3)
Everolimus	7 (4.6)	18 (12.6)	15 (10.1)	7 (4.5)
CDK4/6 inhibitor	3 (2.0)	15 (10.5)	4 (2.7)	65 (41.7)
Palbociclib	3 (2.0)	12 (8.4)	4 (2.7)	59 (37.8)
Abemaciclib	0	1 (0.7)	0	4 (2.6)
Ribociclib	0	2 (1.4)	0	2 (1.3)
Bevacizumab	5 (3.3)	4 (2.8)	6 (4.0)	0

Note: AKT, protein kinase B; CAP, capecitabine; CT, chemotherapy; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; Max, maximum; Min, minimum; mTOR, mammalian target of rapamycin; N, number of patients; PAL, palbociclib; PI3K, phosphatidylinositol 3-kinase.

same OS and the same PFS2. Therefore, from our point of view, the choice of one over another therapy should depend on other considerations, such as cost of therapy, tolerability and quality of life.

Funding

This work was supported by two companies: Pfizer Inc provided palbociclib, exemestane and the study grant (no grant number applicable) and AstraZeneca provided fulvestrant. The trial sponsor is the GEICAM Spanish Breast Cancer Group.

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.

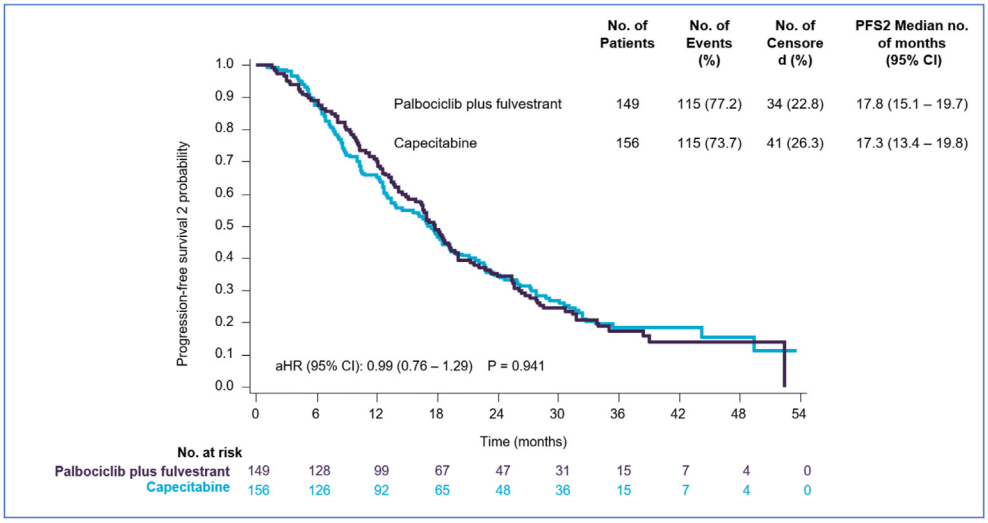
Access to data

The database of this study is available from the corresponding author on reasonable request.

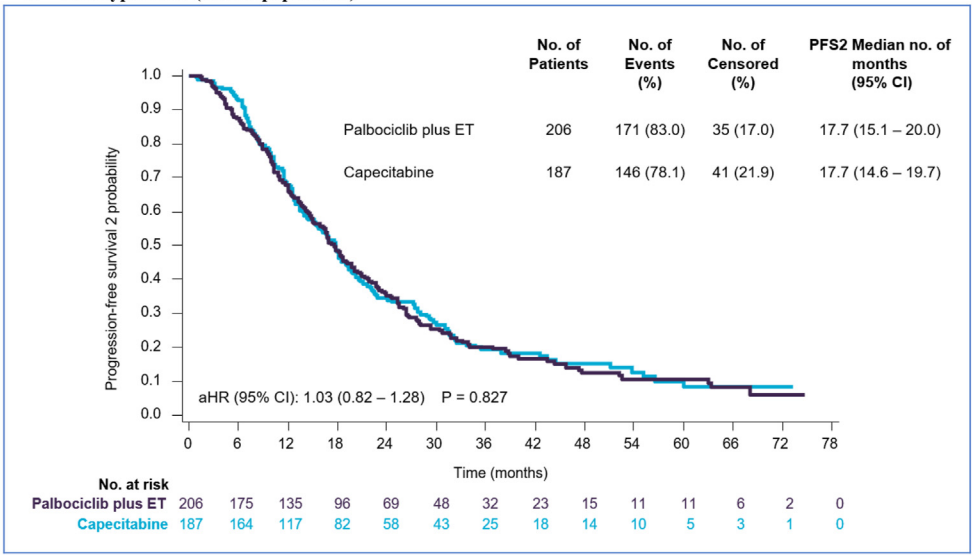
Author contributions

M. Martín, C. Zielinski and E. Carrasco: conceptualization. M. Martín, E. Carrasco, M. Casas and X. Huang: methodology and writing manuscript original draft. E. Carrasco and M. Casas: software (electronic case report form design). M. Casas: formal analysis. M. Martín, M. Ruiz-Borrego, E. Ciruelos, M. Muñoz, B. Bermejo, M. Margelí, T. Csöszi, A. Antón, S. Morales, E. Alba, L. Calvo, J. de la Haba-Rodríguez, M. Ramos, L. Murillo, A. Santaballa, J. L. Alonso, P. Sánchez-Rovira, Z. Kahan and

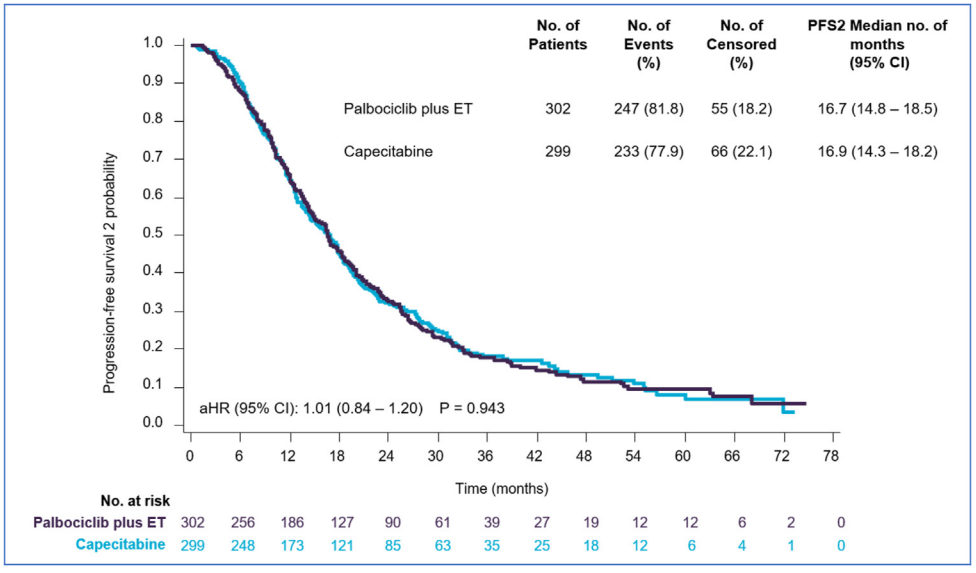
A Cohort 2



B Wild-type *ESR1* (overall population)



C Overall population (regardless of *ESR1* mutational status)



M. Gil-Gil: data collection and curation. M. Martín, C. Zielinski, M. Ruiz-Borrego, E. Carrasco, E. Ciruelos, M. Muñoz, B. Bermejo, M. Margelí, T. Csöszi, A. Antón, S. Morales, E. Alba, L. Calvo, J. de la Haba-Rodríguez, M. Ramos, L. Murillo, A. Santaballa, J. L. Alonso, P. Sánchez-Rovira, M. Corsaro, X, Huang, Z. Kahan and M. Gil-Gil: resources. N. Turner: biological sample analysis and interpretation of these data. All authors: reviewing and editing manuscript. M. Martín, C. Zielinski and E. Carrasco: supervision. M. Martín and E. Carrasco: project administration. E. Carrasco and M. Martín: funding acquisition.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M. Martín has received consulting fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Taiho Oncology and Pfizer; speakers' honoraria from AstraZeneca, Amgen, Roche/Genentech, Novartis, Daiichi-Sankyo and Pfizer; contracted research fees from Roche, Novartis and PUMA. C. Zielinski has received consulting fees and speaker's honoraria from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Imugene, Ariad, Pfizer, Merrimack, Merck KGaA, Fibrogen, AstraZeneca, Tesaro, Gilead, Servier, Shire, Eli Lilly and Athenex. His institution, Central European Cancer Center, Wiener Privatklinik Hospital, has received fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, AstraZeneca and Merck KGaA. M. Ruiz-Borrego has received speaker fees and advisory grants from Pfizer, Novartis and Lilly. E. Carrasco, 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, Celgene, 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. M. Ciruelos has received advisory board honoraria from Lilly, Novartis, MSD, AstraZeneca, Pfizer and Roche; speakers' honoraria from Roche, Lilly and Pfizer; travel and congress assistance support from Pfizer and Roche. M. Muñoz has received advisory board honoraria from Pierre Favre and Seagen; honoraria for expert testimony from Novartis, Roche and Eisai; travel and congress assistance support from Roche, Novartis, Pfizer and Eisai. B. Bermejo has received advisory board honoraria from Roche, Novartis and MSD; speakers' honoraria from Roche, Novartis, MSD, Pfizer and Pierfabre; travel and congress assistance support from Pfizer. M. Margelí has received advisory board fees from Roche, Novartis, Pfizer and Eisai. Her institution, ICO-Badalona. B-ARGO (Badalona Applied Research Group in Oncology) Hospital Universitari Germans Trias i Pujol, Badalona, has received funding research from Roche, Pfizer, Novartis, Lilly, AstraZeneca, Eisai and Kern, and she has received travel and congress assistance support from Roche. A. Antón has received advisory board fees from Bayer Spain, Lilly and Gilead. N. Turner has received advisory board honoraria from Astra Zeneca, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, Bicycle Therapeutics, Taiho, Zeno pharmaceuticals and Repare; therapeutics and research funding from Astra Zeneca, BioRad, Pfizer, Roche/Genentech, Clovis, Merck Sharp & Dohme and Guardant Health. E. Alba has received advisory board fees from Roche, Novartis, Pfizer, Lilly, Bristol-Myers Squibb, Genomic Health and Nanostring. He has received travel support from Celgene. His institution, Hospitales Regional y Virgen de la Victoria, Málaga, has received funding research from Roche, Pfizer, Sysmex, Merck Sharp & Dohme and Nanostring. J. de la Haba-Rodríguez has received speaker's honoraria from AstraZeneca, Pfizer, Novartis and Lilly. M. Ramos has received honoraria from Novartis, Roche and Pfizer. M. Corsaro is employed by Pfizer and has company stock options. X. Huang is employed by Pfizer and has company stock options. Z. Kahan has participated in advisory boards of and received speaker fees or travel support from Pfizer, Roche, AstraZeneca and Novartis. M. Gil-Gil has received honoraria from Pfizer, Ferrer International and Esteve Pharma. All remaining authors have declared no conflicts of interest. A complete list of the PEARL trial collaborators is provided in the Supplementary Appendix.

Acknowledgements

We thank the PEARL study steering committee and independent data monitoring committee members, the patients who took part in this study and their families, as well as all the participating investigators. We also thank the support staff at each study site and at both the GEICAM

Fig. 4. Subsequent progression-free survival (PFS2). Details of events considered for the PFS2 analysis are shown in Supplementary Table A2. Kaplan–Meier curves for PFS2 are presented for (A) patients in Cohort 2: palbociclib plus fulvestrant versus capecitabine, (B) patients with wild-type *ESR1* from Cohort 1 + Cohort 2: palbociclib plus ET versus capecitabine, and (C) overall population of Cohort 1 + Cohort 2, regardless of *ESR1* mutational status: palbociclib plus ET versus capecitabine. Hazard ratios were adjusted for disease site, prior sensitivity to ET, prior chemotherapy for metastatic breast cancer, and the number of involved sites. aHR, adjusted hazard ratio; CI, confidence interval; *ESR1*, oestrogen receptor 1; ET, endocrine therapy; No, number; PFS, progression-free survival.

and CECOG headquarters. We thank the Elsevier Language Editing Services for the English editing service.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.03.006.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.

[2] Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer 1999;17(2):485.

[3] Oshaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001;12(9):1247–54.

[4] Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer 2005;23(4):792–9.

[5] Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S, et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. Br J Cancer 2002;86(9):1367–72.

[6] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375(20):1925–36.

[7] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018;29(7):1541–7.

[8] Johnston S, Martin M, Di Leo A, Im S-A, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer 2019;5(1):5.

[9] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17(4):425–39.

[10] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018;36(24):2465–72.

[11] Sledge Jr GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35(25):2875–84.

[12] Tripathy D, Im S-A, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19(7):904–15.

[13] Albanell J, Martínez MT, Ramos M, O'Connor M, de la Cruz-Merino L, Santaballa A, et al. Randomized phase II study of fulvestrant plus palbociclib or placebo in endocrine-sensitive, hormone receptor-positive/HER2–advanced breast cancer: GEICAM/2014–12 (FLIPPER). Eur J Cancer 2022;161:26–37.

[14] Sledge Jr GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor–positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial. JAMA Oncol 2020;6(1):116–24.

[15] Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381(4):307–16.

[16] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med 2020;382(6):514–24.

[17] Hortobagyi GN, Stemmer SM, Burris III HA, Yap YS, Sonke GS, Hart L, et al. LBA17 Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2–) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Ann Oncol 2021;32. S1290–S1.

[18] Harbeck N, Iyer S, Turner N, Cristofanilli M, Ro J, Andre F, et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. Ann Oncol 2016;27(6):1047–54.

[19] Rugo HS, Dieras V, Gelmon KA, Finn RS, Slamon DJ, Martin M, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol 2018;29(4):888–94.

[20] Martin M, Zielinski C, Ruiz-Borrego M, Carrasco E, Turner N, Ciruelos EM, et al. Palbociclib in combination with endocrine therapy versus capecitabine in hormonal receptor-positive, human epidermal growth factor 2-negative, aromatase inhibitor-resistant metastatic breast cancer: a phase III randomised controlled trial-PEARL. Ann Oncol 2021;32(4):488–99.

[21] Kahan Z, Gil-Gil M, Ruiz-Borrego M, Carrasco E, Ciruelos E, Muñoz M, et al. 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. Eur J Cancer 2021;156:70–82.

[22] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.

[23] Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379(20):1926–36.

[24] Cristofanilli M, Rugo HS, Im S-A, Slamon DJ, Harbeck N, Bondarenko I, et al. Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): updated analyses from PALOMA-3 2021;39(15_suppl.):1000.

[25] Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer 2011;366(6):520–9.

[26] Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. Ann Oncol 2014;25(12):2357–62.

[27] Park YH, Kim TY, Kim GM, Kang SY, Park IH, Kim JH, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2019;20(12):1750–9.