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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

Running Head: Palbociclib versus capecitabine in metastatic breast cancer.

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ABSTRACT

Background:

Palbociclib plus endocrine therapy (ET) is the standard treatment for hormone receptor-positive and human epidermal growth factor receptor 2-negative, metastatic breast cancer (MBC). However, its efficacy has not been compared with that of chemotherapy's in a phase III trial.

Patients and Methods:

PEARL is a multicentre, phase III randomised study in which patients with aromatase inhibitors (AIs)-resistant MBC were included in two consecutive cohorts. In cohort 1 (C1), patients were randomised 1:1 to palbociclib plus exemestane or capecitabine. On discovering new evidence about oestrogen receptor-1 (*ESR1)* mutations inducing resistance to AIs, trial was amended to include cohort 2 (C2), in which patients were randomised 1:1 between palbociclib plus fulvestrant and capecitabine. The stratification criteria were disease site, prior sensitivity to ET, prior chemotherapy for MBC, and country of origin. Co-primary endpoints were progression-free survival (PFS) in C2 and in wild-type *ESR1* patients (C1+C2). *ESR1* hotspot mutations were analysed in baseline circulating tumour DNA.

Results:

From March-2014 to July-2018, 296 and 305 patients were included in C1 and C2, respectively. Palbociclib plus ET was not superior to capecitabine in both C2 (median PFS: 7.5 vs. 10.0 months; adjusted hazard ratio [aHR]: 1.13; 95% confidence Interval [CI]: 0.85-1.50) and wild-type *ESR1* patients (median PFS: 8.0 vs. 10.6 months; aHR: 1.11; 95% CI: 0.87-1.41). Most frequent grade 3-4 toxicities with palbociclib plus exemestane, palbociclib plus fulvestrant, and capecitabine were neutropenia (57.4%, 55.7% and 5.5%), hand/foot syndrome (0%, 0% and 23.5%), and diarrhoea

(1.3%, 1.3% and 7.6%). Palbociclib plus ET offered better quality of life (aHR for time to deterioration of global health status: 0.67; 95% CI: 0.53-0.85).

Conclusions:

There was no statistical superiority of palbociclib plus ET over capecitabine with respect to PFS in MBC patients resistant to AIs. Palbociclib plus ET showed a better safety profile and improved quality of life.

Trial registration number

ClinTrials.gov reference NCT02028507

Key words: palbociclib; capecitabine; metastatic breast cancer; hormone receptor-positive; HER2-negative; endocrine therapy

HIGHLIGHTS:

- Palbociclib plus fulvestrant did not provide evidence of PFS superiority over capecitabine in MBC patients resistant to AIs.
- Palbociclib plus ET did not show PFS superiority over capecitabine in wild-type *ESR1* MBC patients resistant to AIs.
- Palbociclib plus ET was better tolerated and offered better quality of life than capecitabine.

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INTRODUCTION

Until recently, single agent endocrine therapy (ET) was the recommended choice of treatment for most women with hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). Unfortunately, not all patients respond to ET due to primary or acquired resistance. In the past decade, new targeted therapies, mainly cyclin dependent kinase 4/6 (CDK4/6) inhibitors, in combination with ET have significantly improved progression-free survival (PFS)[1-7] and overall survival (OS)[8-10] compared with ET alone in patients with treatment-naïve or pre-treated MBC.

The PALOMA-3 trial[4] showed that palbociclib plus fulvestrant significantly improved PFS as opposed to fulvestrant plus placebo (hazard ratio [HR]: 0.46; $P<0.0001$) in patients who experienced cancer relapse or progression during or within 12 months of completing adjuvant ET or while they were on ET or within 1 month of prior ET for MBC. Consequently, palbociclib plus fulvestrant was approved by the Food and Drug Administration and the European Medicines Agency for these patients. That trial showed that adding palbociclib to fulvestrant significantly delayed disease progression compared with fulvestrant alone in patients resistant to aromatase inhibitors (AIs). However, we still considered necessary to analyse the efficacy differences between palbociclib plus ET and other current standard of care in MBC patients resistant to AIs, such as chemotherapy.

In 2014, the GEICAM Spanish Breast Cancer Group started the PEARL trial in collaboration with the Central European Cooperative Oncology Group (CECOG). This trial compared palbociclib plus ET with capecitabine in a population of postmenopausal patients very similar to those in the PALOMA-3 trial. We selected capecitabine as the chemotherapy agent as it is considered to be one of the most active drugs available for MBC, with median PFS ranging from 2.8 to 5.9 months (which was even higher in patients with hormone receptor-positive disease) and OS times of 9.3 to

18.1 months in previously treated MBC patients.[11-14]. We combined palbociclib with exemestane in the initial study design; however, after the emerging evidence that patients pre-treated with AIs may develop *ESR1* mutations that generate resistance to AIs, we introduced a second cohort for which palbociclib was combined with fulvestrant[15, 16].

METHODS

STUDY DESIGN

The PEARL trial, a multicentre, international, open-label, controlled, randomised phase III study with two successive cohorts of similar characteristics, was performed in four countries (37 sites): Spain (GEICAM), Austria, Hungary, and Israel (CECOG). Cohort 1 patients were randomised 1:1 to receive palbociclib (125 mg/d for 3 weeks followed by 1 week off) plus exemestane (25 mg/d) or capecitabine (according to the approved label: 2,500 mg/m^2/d [2000 mg/m^2/d in patients >70 years old] for 2 weeks followed by 1 week off). The study hypothesis endorsed the superiority of palbociclib plus exemestane over capecitabine (expected PFS, HR: 0.686, with a 5% significance level). In December-2015, new data suggested that exemestane in patients who have progressed on AIs could be a suboptimal option because *ESR1* mutations may confer AI therapy resistance in patients previously exposed to AIs (with a frequency of mutations of 29%-37%) [15-17]. One of the studies suggested that fulvestrant may be effective in patients with *ESR1* mutation-positive tumours [16]. In May-2016, a protocol amendment with a modification of trial design and objectives was approved before any efficacy data were available. Therefore, a subsequent cohort 2 was introduced, in which patients were randomised 1:1 to receive palbociclib (same schedule as cohort 1) plus fulvestrant (500 mg intramuscular injection on days 1 and 15 of cycle 1; then on day 1 of subsequent 28-day cycles) or capecitabine (same schedule as cohort 1). At that time 296 patients were already recruited in cohort 1 (from an initial planned sample of 348 patients). The new study hypotheses endorsed the superiority of palbociclib plus fulvestrant over capecitabine and palbociclib plus ET

over capecitabine in patients with wild-type *ESR1* (expected PFS, HR: 0.667, with a 5% significance level) (Material S1).

Randomisation was performed centrally at the GEICAM headquarters. In both the cohorts, stratification criteria were disease site (visceral/non-visceral), sensitivity to prior ET (relapse after 24 months of adjuvant ET or response [complete or partial] or stabilisation after 24 weeks of the most recent ET in the context of advanced disease [yes/no]), prior chemotherapy for MBC (yes/no), and country of origin. The treatment continued until either objective disease progression, according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [18], symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. As-per-protocol dose reductions of palbociclib and capecitabine were allowed in case of toxicity. Upon completion of the study treatment, patients were monitored for survival every 6 months.

Research protocol was approved by every site's institutional review board and every country´s regulatory agency. All the patients signed written informed consents. Safety and efficacy data were continuously evaluated by an independent data monitoring committee. The data were analysed by a statistician employed by GEICAM.

PATIENTS

Postmenopausal women with hormone receptor-positive and HER2-negative AI-resistant MBC (defined as 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 for advanced disease) were included. Patients had to have measurable disease assessable by computed tomography (CT)/magnetic imaging resonance (MRI) according to RECIST v1.1 or at least one lytic or mixed bone lesion. One chemotherapy line for MBC was permitted. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG) of 0 or 1, life expectancy of 12 weeks or more, and adequate organ function.

Patients who received prior treatment with CDK4/6, mammalian target of rapamycin (mTOR) or phosphoinositide 3-kinase (PI3K) inhibitors, capecitabine, or patients with visceral crisis were excluded. Patients were required to have a corrected QT interval (QTc) < 480 msec and no family or personal history of long or short QT syndrome, Brugada syndrome, Torsade de Pointes, or known history of QTc prolongation.

TRIAL ASSESSMENTS

Baseline disease assessments (performed within 4 weeks before randomisation), required a CT or MRI scan of the chest, abdomen, and pelvis. Assessments were performed every 8 weeks for 120 weeks and then every 12 weeks until documented progressive disease, initiation of a new anticancer therapy, or patient dropout. Patients who discontinued study treatment for reasons other than progressive disease had tumour assessments every 12 weeks.

Haematology and biochemistry tests were performed before each cycle; haematology testing was additionally performed on day 14 of cycles 1 and 2 in the palbociclib arms. Adverse events (AEs) were assessed and graded at each cycle according to National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) version 4.0.

Patients completed the European Organization for Research and Treatment of Cancer core quality-of-life (EORTC QLQ-C30; v3.0)[19], breast cancer-specific (EORTC QLQ-BR23; v1.0)[20], and the EuroQoL Health Utilities Index EQ-5D-3L[21] questionnaires at baseline, at every two cycles for the first seven cycles, then at every three cycles till the end of treatment, and once again at the post-treatment visit.

Patients were required to have a mandatory plasma sample drawn for exploratory biomarker analyses in circulating tumour DNA (ctDNA) obtained before treatment onset. With the protocol amendment to include cohort 2, the *ESR1* mutational status assessment was a predefined analysis required to evaluate the primary objective of the study. The results were blinded to patients and investigators (Material S2).

In addition, formalin-fixed paraffin-embedded tumour samples were collected prior to study entry to genetically identify intrinsic breast cancer (BC) subtypes (Luminal A and B, HER2-enriched, Basal-like and Normal-like) using the HTG EdgeSeq Oncology Biomarker Panel (Material S3).

OBJECTIVES AND ENDPOINTS

The initial primary objective was to compare PFS with palbociclib plus exemestane and that with capecitabine treatment. After the protocol amendment to include cohort 2, the two new co-primary objectives were: to compare PFS of patients treated with a) palbociclib plus fulvestrant versus capecitabine regardless of *ESR1* mutational status and b) palbociclib plus ET (exemestane or fulvestrant) versus capecitabine in patients with wild-type *ESR1* in ctDNA at study entry. PFS was defined as the time from randomisation to the first documentation of progressive disease based on investigators´ assessments according to RECIST v1.1 or to death from any cause.

Secondary objectives included, among others, PFS with palbociclib plus ET versus capecitabine regardless of *ESR1* mutational status, objective response rate (ORR), clinical benefit rate (CBR) (defined as ORR plus stable disease rate of at least 24 weeks of duration), response duration (RD), OS, safety, and patient-reported outcomes (PROs). Concerning PROs, we reported the time to deterioration for the global health status from the EORTC QLQ-C30, defined as the time from randomisation to first detection of a deterioration event (marked with a decrease of ≤10 points from the baseline).

Additionally, we explored the independent prognostic and predictive value of intrinsic subtypes.

STATISTICAL ANALYSIS

A total of 193 PFS events were required in cohort 2 to have 80% power to detect a difference between capecitabine (estimated median PFS of 6 months) and palbociclib plus fulvestrant (median PFS of 9 months [4]), for a HR of 0.667, with a 5% significance level. The target sample size was

300 patients. To detect the same difference between capecitabine and palbociclib plus ET in patients with wild-type *ESR1* and assuming an 80% ctDNA collection/detection rate and 30% of the patients with *ESR1* mutations, the required sample size was also 300 patients. The study was designed to have two interim analyses and a final analysis. The final PFS analysis was planned when 193 events in cohort 2 were observed. A modification of Hochberg's method[22] was used for two primary treatment comparisons to provide the control of experiment-wise Type 1 error rate at a two-sided 5% significance level.

The Kaplan-Meier method was used to estimate the median PFS; 95% confidence intervals (CIs) were provided for estimates of interest. The Cox proportional-hazards model was used to calculate the unadjusted and adjusted HR (aHR) (by stratification factors and number of involved sites) and 95% CI. Efficacy analyses were based on two populations: all randomised patients (intention-to-treat [ITT] population) and all randomised patients with wild-type *ESR1* in ctDNA at study entry (wild-type *ESR1* population). Safety analysis was performed on all patients who received ≥1 dose of study therapy. PROs analysis was performed on patients with baseline and one or more quality of life (QoL) questionnaires completed. Time to deterioration was analysed using Cox regression models.

RESULTS

PATIENTS AND TREATMENT

A total of 601 patients were included in this study from March 2014 to July 2018. Cohort 1 included 296 patients (153 on palbociclib plus exemestane and 143 on capecitabine) and cohort 2 included 305 patients (149 on palbociclib plus fulvestrant and 156 on capecitabine). Efficacy analyses included all the patients, but safety analyses excluded 13 patients (10 on capecitabine and three on palbociclib plus ET) never receiving study treatment. *ESR1* mutations were assessed in 557 patients (92.7%), 91% of which were from the capecitabine arms and 94% were from the palbociclib plus ET arms; 164 of them (29%) had *ESR1* mutations (Fig. 1).

All the baseline demographics and disease characteristics were balanced between the arms across both the cohorts, except for the number of involved sites (greater in the capecitabine arm in cohort 2) (Table 1).

At the cut-off date for the primary analysis (January 14, 2019), 80 patients were still on the study treatment: 10 (6.7 %) were on palbociclib plus exemestane, 37 (24.8%) on palbociclib plus fulvestrant, and 33 (11%) on capecitabine. The median relative dose-intensity in cohort 1 was 82.6% for capecitabine, 100% for exemestane, and 95.2% for palbociclib, and that in cohort 2 was 79.5% for capecitabine, 100% for fulvestrant, and 92.9% for palbociclib. The median time on study therapy in cohort 1 was higher for capecitabine, 7.9 months (range: 0.2-50.5), than for palbociclib plus exemestane, 6.3 months (range: 0.5-52.3). However, in cohort 2 the median time on study was 6.3 months for capecitabine (range: 0.2-26.4) and 7.8 months for palbociclib plus fulvestrant (range: 0.8-31.1). The main reason for permanent discontinuation of the treatment was disease progression. In both the cohorts, the proportion of patients who discontinued due to progressive disease was smaller in the capecitabine arm (65.7% in cohort 1, 58.6% in cohort 2) than in the palbociclib plus exemestane (81.3%) and palbociclib plus fulvestrant arms (68.5% in cohort 2) (Table S1).

EFFICACY

The median follow-ups of cohort 2 and the wild-type *ESR1* population were 13.5 months (range: 0.0-30.7) and 18.9 months (range: 0.0-56.3), respectively. The median PFS in cohort 2 was 7.5 months (95% CI: 5.7-10.9) in the palbociclib plus fulvestrant arm and 10.0 months (95% CI: 6.3-12.9) in the capecitabine arm (aHR: 1.13; 95% CI: 0.85-1.50; *P*=0.398). The median PFS in the wild-type *ESR1* population were 8.0 months (95% CI: 6.5-10.9) in the palbociclib plus ET arm and 10.6 months (95% CI: 7.4-13.0) in the capecitabine arm (aHR: 1.11; 95% CI: 0.87-1.41; *P*=0.404) (Fig. 2). PFS subgroup analyses by stratification factors and other baseline characteristics in cohort 2 and in the wild-type *ESR1* population (Fig. 3) as well as in the overall population regardless of *ESR1* mutational status (Fig. 1S) confirmed the non-superiority of palbociclib plus ET over capecitabine.

Regarding the study's secondary endpoints of efficacy, the median PFS in all patients from cohort 1 + cohort 2 was 7.4 months (95% CI: 5.9-9.3) in the palbociclib plus ET arm and 9.4 months (95% CI: 7.5-11.3) in the capecitabine arm (aHR: 1.11; 95% CI: 0.92-1.34; *P*=0.380) (Fig. S2). The aHR for PFS in the mutant *ESR1* population was 1.12 (95% CI: 0.78-1.60; *P*=0.540) as shown in Fig.S3. The ORR in cohort 2 was 26.7% for palbociclib plus fulvestrant versus 33.3% for capecitabine. In patients with *ESR1* wild-type, ORR was 27.8% for palbociclib plus ET versus 36.9% for capecitabine. The CBR was very similar between the arms in cohort 2 and the patients with *ESR1* wild-type. The median RD in cohort 2 was 9.4 months in the palbociclib plus fulvestrant arm and 12.9 months in the capecitabine arm (HR: 0.69; 95% CI: 0.33-1.46; *P*=0.335). Finally, the median RD in the wild-type *ESR1* population was 9.7 months in the palbociclib plus ET arm and 11.2 months in the capecitabine arm (HR: 0.75; 95% CI: 0.44-1.25; *P*=0.269) (Table S2).

PATIENT-REPORTED OUTCOMES

The questionnaires completion rate was similar across the arms, surpassing 82% till cycle 13. The median time to deterioration in global health status was 8.6 months in patients treated with palbociclib plus ET versus 6.2 months in those treated with capecitabine (aHR: 0.67, 95% CI: 0.53-0.85; *P*=0.001) (Fig. 4).

SAFETY

Safety information is shown in Table 2 and Table S3. The most frequent grade 3-4 toxicities in the palbociclib plus exemestane, palbociclib plus fulvestrant, and capecitabine arms, were neutropenia [(57.4%, 55.7%, 5.5%, respectively) with febrile neutropenia (1.3%, 0.7%, 1.4%, respectively)], hand/foot syndrome (0%, 0%, 23.5%, respectively), diarrhoea (1.3%, 1.3%, 7.6%, respectively), fatigue (1.3%, 0.7%, 5.5%, respectively), and anaemia (0.7%, 2.0%, 3.5%, respectively). The incidence of non-haematologic toxicity grade ≥3 was higher for patients on capecitabine (38.8%) than for those on palbociclib plus exemestane (6.7%) or palbociclib plus

fulvestrant (6.0%). Notably, grade 1-2 alopecia was reported in 11.0% of the patients on palbociclib plus ET as opposed to 3.8% of the patients on capecitabine.

Serious AEs related to the study treatment were reported by 10.4% of the patients on capecitabine, 4.0% of the patients on palbociclib plus exemestane, and 3.4% of the patients on palbociclib plus fulvestrant.

Forty-six patients on capecitabine (15.9%) dropped out due to AEs as compared with nine patients (6%) on palbociclib plus exemestane and 10 patients (6.7%) on palbociclib plus fulvestrant.

Of the 17 deaths observed during the study treatment, 11 were due to progressive disease, two occurred while patients were on palbociclib plus ET (pneumonitis and sepsis), and four occurred while the patients were on capecitabine (diarrhoea, general health status worsening, colitis, and sudden death). Diarrhoea, general health status worsening, and colitis were considered toxic deaths according to the investigators' assessments.

EXPLORATORY OBJECTIVES

Prognostic/predictive value of intrinsic BC subtypes: Subtypes were obtained for 455 patients (94.4% of the 482 patients assessed) with metastatic (30%) or primary tumour tissue (70%) available (Table 1); 75.7% of cohort 2 and 79.6% of the wild-type *ESR1* patient population. Most patients (93.2%) had luminal tumours. Cohort 2 patients with luminal tumours showed a median PFS of 7.7 and 10 months with palbociclib plus fulvestrant and capecitabine, respectively (HR: 1.07; 95% CI: 0.77-1.49; *P*=0.681). Patients with non-luminal tumours (*n*=20) had a median PFS of 3.3 and 13.7 months with palbociclib plus fulvestrant and capecitabine, respectively (HR: 5.87; 95% CI: 1.60-21.55; *P*=0.008). Patients with wild-type *ESR1* luminal tumours presented a median PFS of 9.3 and 11.0 months with palbociclib plus fulvestrant and capecitabine, respectively (HR: 1.01; 95% CI: 0.77-1.33; *P*=0.930). Patients with non-luminal tumours (*n*=25) on palbociclib plus ET and capecitabine had a median PFS of 2.3 and 13.7 months, respectively (HR: 7.36; 95% CI: 2.05-26.37; *P*=0.002) (Fig. S4).

DISCUSSION

The PEARL trial did not provide evidence of PFS superiority of palbociclib plus fulvestrant or of palbociclib plus ET in patients without *ESR1* mutations over capecitabine in AI-resistant MBC patients. However, it is worth noticing that compared with capecitabine, palbociclib plus ET was associated with a significant delay in QoL deterioration, less treatment discontinuations due to AEs, and a lower proportion of patients with related serious AEs.

The initial study design of the PEARL trial was modified after some compelling evidence that ESR1 mutations (present in up to 37% of patients pre-treated with AIs) could produce resistance to additional AI therapy, but not to fulvestrant[15-17]. Since in the initial design the endocrine arm was exemestane plus palbociclib, we added a second cohort of patients in which the endocrine arm was fulvestrant plus palbociclib, to avoid the potential negative influence of ESR1 mutations in patients treated with AIs. In fact, we identified 29% of ESR1 mutations in the patients included in this trial. Of note, this modification was made before any results were available.

The combination of palbociclib plus fulvestrant has been approved by several regulatory agencies for the treatment of patients with hormone receptor-positive/HER2-negative AI-resistant MBC based on the PALOMA-3 trial´s results, which clearly showed the efficacy of palbociclib in delaying resistance to fulvestrant. However, it did not provide information on the potential benefit of palbociclib plus fulvestrant with respect to other available therapeutic options (i.e., everolimus plus ET or chemotherapy) in this specific patient population. Given the poor performance of the fulvestrant-placebo arm in the PALOMA-3 trial (median PFS: 4.6 months), many oncologists might prefer other alternatives. The PEARL trial included patients with relatively similar characteristics to those in the PALOMA-3 trial, however, the median PFS of ET plus palbociclib in the PEARL trial was somewhat lower. The most plausible explanation for this apparent discrepancy is the different characteristics of the population included in these two trials, with the patients in PEARL having a

worse prognosis. Other studies exploring the combination of ET with CDK4/6 inhibitors as second line therapy showed better results with median PFS of 16.4 months in the MONARCH-2[6] and 25.3 months in the MONALEESA-3[5] trials. However, these data are not comparable to those of the PEARL study because the populations are quite different. For instance, only one prior line of ET was permitted and prior chemotherapy for MBC was not allowed in the MONARCH-2 and MONALEESA-3 studies, while there were no such limitations in the PEARL trial.

Considering the limited efficacy of palbociclib plus ET in this patient population (8- and 9.5-month PFS in the PEARL and PALOMA-3 trials, respectively), the high efficacy of the combination of ET and CDK 4/6 inhibitors in AI-sensitive MBC patients (with median PFS of around 2 years), and the demonstration of OS benefit in the only first-line trial that has reported this outcome so far [9], PEARL's findings indirectly suggest that palbociclib combinations are less effective in pre-treated MBC patients and should be used earlier in the treatment timeline, while capecitabine can be left for later lines. This statement agrees with the results from the meta-analysis by Giuliano et al[23]. This analysis showed that no chemotherapy regimen was significantly better than CDK4/6 inhibitors plus hormone therapies in the first- or second-line setting, supporting the treatment guideline recommendations for the use of ET plus targeted agents in earlier lines of treatment in women with hormone receptor-positive/HER2-negative MBC.

In addition, while the PEARL trial did not meet its co-primary objectives, it still provides evidence and suggestions for the management of hormone receptor-positive AI-resistant MBC. While patient´s PFS with capecitabine and palbociclib plus ET were similar, capecitabine´s toxicity was higher, and patients had earlier QoL deterioration with this chemotherapy. Thus, the endocrine combination could be the best choice for these patients. Capecitabine, albeit having higher AEs, remains an appropriate alternative where health care costs are restricted.

Efficacy results of the PEARL study were consistent across patient subgroups except for the small proportion of patients with genetically defined non-luminal tumours, for which capecitabine

was associated with a significantly better PFS. However, these results should be interpreted with caution and further validated in independent cohorts, because the non-luminal population represented only 5.2% of the patients in the PEARL trial.

Potential limitations of the study are: 1) the capecitabine outcome was better than that initially anticipated (9 months compared with 6 months in the protocol assumptions); 2) the open-label study design may lead to unclear interpretations, e.g. more patients were censored before initiating the study treatment in the capecitabine arm than in the palbociclib plus ET arm (3.3% and 1.0% respectively); 3) the subtype classification for the exploratory objective was performed in 70% of patients in the primary tumour, which might have changed in the metastatic disease in a proportion of patients. Finally, there are several strengths of the PEARL study that should be considered: 1) this is a well conducted academic, multicentre, international trial; 2) the sample size with 601 patients is high; 3) the prospective collection of plasma samples to assess *ESR1* mutations was conducted.

In conclusion, palbociclib plus ET did not improve PFS compared with capecitabine in patients with AI-resistant MBC, however, it was better tolerated and showed improved QoL.

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Authors' contributions

M. Martín, C. Zielinski, E. Carrasco, C. Huang, M. Koehler, and X. Huang conceived the study design. M. Martin, M. Ruiz Borrego, E.M. Ciruelos, M. Muñoz, B. Bermejo, M. Margeli, A. Anton,

Z. Kahan, T. Csöszi, L. Murillo, S. Morales, E. Alba, E. Gal-Yam, L. Calvo, J. de la Haba-Rodriguez, M. Ramos, I. Alvarez, A. Garcia-Palomo, J. A. Garcia-Sáenz, J. I. Chacón, and M. Gil-Gil contributed to data collection. M.I. Casas analysed the data. N. Turner, A. Guerrero-Zotano, and Claire Swift contributed to biological sample analysis and the interpretation of these data. M. Martín, C. Zielinski, E. Carrasco, R. Caballero, M. I. Casas, M. Gil-Gil, C. Huang, M. Koehler, M. Corsaro, and X. Huang interpreted the results. M. Martín, C. Zielinski, E. Carrasco, and R. Caballero contributed to manuscript preparation. All authors contributed to the review of the manuscript and approved the final version.

M. Martín had full access to all the data from the study and was responsible for the final decision to submit for publication.

Access to Data

The study is still ongoing and other secondary endpoints are yet to be analysed. Thus, the data cannot be shared at this point.

Role of the Funding Source

This work was supported by two funding companies: Pfizer inc. (that provided palbociclib and exemestane and the study grant) and AstraZeneca (that provided fulvestrant). The trial sponsor is 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.

Declaration of Potential Conflicts of Interest

Miguel 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. Christoph 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. Manuel Ruiz Borrego has received speaker fees and advisory grants from Pfizer, Novartis, and Lilly. Eva 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. Nicholas 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. Montserrat Muñoz has received travel and congress assistance support from Roche, Novartis, Pfizer and Eisai. Begoña Bermejo has received advisory board honoraria from Genentech, Novartis, Merck Sharpe and Dohme, speakers' honoraria from Genentech, Eisai and she has received travel and congress assistance support from Pfizer. Mireia Margelí has received advisory board fees from

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A complete list of the PEARL trial collaborators is provided in the Supplementary Appendix.

This study has been previously presented at San Antonio Breast Cancer Symposium; 2019 Dec 10-14; San Antonio, TX. Philadelphia (PA): AACR; Published at Cancer Res 2020;80(4 Suppl):Abstract nr GS2-07.Cancer Res February 14 2020 80 (4 Supplement) GS2-07-GS2-07; DOI: 10.1158/1538-7445.SABCS19-GS2-07 Published February 2020. Final PFS results were presented as a poster discussion at the American Society of Clinical Oncology (ASCO) virtual meeting and the quality of life data has been presented as a poster at the virtual European Society of Medical Oncology (ESMO) Breast Cancer Meeting.

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ONLINE-ONLY SUPPLEMENT MATERIAL:

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