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Original Research

Predictors of prolonged benefit from palbociclib plus fulvestrant in women with endocrine-resistant hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer in PALOMA-3

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KEYWORDS
Palbociclib;
Fulvestrant;
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HR+/HER2−;
Long-term response

Abstract ***Background:*** The addition of palbociclib to fulvestrant improved clinical outcomes over placebo-fulvestrant in endocrine-pretreated metastatic breast cancer (MBC) patients in PALOMA-3. Here, we examined factors predictive of long-term benefit.
Methods: Premenopausal-peri/postmenopausal patients with endocrine-resistant, hormone receptor−positive (HR+)/human epidermal growth factor receptor 2−negative MBC were randomised 2:1 to fulvestrant (500 mg) and either palbociclib (125 mg/d; 3/1 schedule; n = 347) or placebo (n = 174). Baseline characteristics, mutation status and HR expression levels were compared in patients with and without prolonged benefit (treatment duration ≥18 months).
Results: By August 2016, 100 patients (29%) on palbociclib-fulvestrant and 26 (15%) on placebo-fulvestrant demonstrated prolonged benefit, with long-term responders in both arms sharing common clinical characteristics. They usually had less disease burden at baseline versus those treated <18 months, such as having one disease site (40% vs 29% on palbociclib-fulvestrant and 69% vs 29% on placebo-fulvestrant), bone-only disease (32% vs 22% and 46% vs 17%) and were less heavily pretreated (69% vs 56% and 73% vs 60% had ≤2 prior therapies). Baseline tumour *ESR1* and *PIK3CA* mutation rates were lower among long-term responders in both arms; median oestrogen receptor H-scores were similar, whereas progesterone receptor H-scores were higher among long-term responders.
Conclusions: This exploratory analysis demonstrates that some patients with endocrine-resistant MBC derive significant and prolonged benefit when treated with palbociclib-fulvestrant, with fewer patients experiencing similar efficacy with placebo-fulvestrant. The current analysis did not identify specific molecular or clinical factors prognostic of long-term benefit with palbociclib-fulvestrant (ClinicalTrials.gov, NCT01942135).

1. Introduction

Endocrine therapy (ET) remains the current standard treatment for hormone receptor−positive (HR+), human epidermal growth factor receptor 2−negative (HER2−) breast cancer [1,2]. Although some patients have a prolonged clinical response to ET alone, many fail to benefit from ET alone or develop resistant disease [3,4]. Considerable effort has been made to improve the efficacy of endocrine-based therapies to delay the use of chemotherapy and optimise both the length and quality of life of patients [1].

Inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) enhance ET activity and significantly improve clinical outcomes in patients with breast cancer [5–9]. Palbociclib (IBRANCE®) is a first-in-class, orally bioavailable inhibitor of CDK4/6 approved for the treatment of HR+/HER2− metastatic breast cancer (MBC) in combination with fulvestrant in pre/perimenopausal and postmenopausal women with disease progression after ET and in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women [10]. In the phase 3, randomised, double-blind PALOMA-3 study, palbociclib plus fulvestrant demonstrated significantly improved efficacy versus placebo plus fulvestrant in patients with endocrine-resistant HR+/HER2− MBC, with median progression-free survival (PFS) of 11.2 versus 4.6 months, respectively (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.40–0.62; one-sided $P < 0.0001$) [11,12]. Although ET is more effective overall when combined with a CDK4/6 inhibitor [13–16], prolonged responses have been observed in subsets of patients with breast cancer receiving ET alone [17]. Therefore, the identification of clinical or molecular markers that predict which patients may derive the largest benefit from monotherapy versus a combination is vitally important to inform clinical decisions and could significantly improve the management of breast cancer. We, therefore, evaluated baseline characteristics of patients with HR+/HER2− MBC as predictors of prolonged benefit with palbociclib-fulvestrant or placebo-fulvestrant.

2. Methods

2.1. Patients

Eligible patients were women aged ≥18 years of any menopausal status with HR+/HER2− MBC whose disease had progressed on prior ET (i.e. aromatase inhibitors for postmenopausal women and tamoxifen for premenopausal women). Patients were allowed one prior line of chemotherapy in the advanced setting; those who received prior treatment with any CDK inhibitor, fulvestrant, everolimus or any phosphoinositide 3-kinase or mammalian target of rapamycin pathway inhibitor were excluded. Full eligibility criteria are reported elsewhere [5,7].

2.2. Study design

The design of the PALOMA-3 study (NCT01942135) was described previously [5,7]. Briefly, patients in this

trial were randomised 2:1 to receive fulvestrant (500 mg intramuscularly) and either palbociclib (125 mg/d orally for 3 weeks followed by 1 week off) or matching placebo. Premenopausal/perimenopausal women were required to receive luteinising hormone–releasing hormone agonist ≥4 weeks before study treatment and agree to switch to goserelin at randomisation. Randomisation was stratified by the presence of visceral metastasis, menopausal status at study entry (post vs pre/peri) and sensitivity to prior ET. Treatment continued until disease progression, unacceptable toxicity or study withdrawal. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by an institutional review board, or equivalent, for each site, and all patients provided informed consent before enrolment.

Baseline plasma samples were collected for circulating tumour DNA analysis and processed within 1 h as described previously [5]. BEAMing assays were used to detect mutations (Sysmex Inostics; Baltimore, MD, USA). *ESR1*-positive mutation status was defined as ≥0.1% for any nucleotide change; *PIK3CA*-positive mutation status was defined as ≥0.02%. H-scores were calculated as the sum of the percentage of cells at each level of the staining intensity multiplied by the staining intensity value; values could range from 0 to 300.

2.3. End-points

The primary end-point of PALOMA-3 was investigator-assessed PFS according to Response Evaluation Criteria in Solid Tumors v1.1 criteria. Secondary end-points included objective response (clinical response is reported as a radiologically confirmed response), clinical benefit response (defined as complete response, partial response or stable disease for ≥24 weeks), overall survival (OS) and safety. Tumour assessments were performed at baseline and every 8 weeks for the first year and every 12 weeks thereafter.

2.4. Statistical analysis

The long-term benefit patients were identified using the August 31, 2016, data set that collected demographics, baseline characteristics, exposure, time on treatment and safety data only. Long-term benefit was defined as treatment duration ≥18 months (without disease progression) by August 31, 2016; results by treatment duration ≥12 and < 12 months are also reported based on the August 31, 2016, data set. In addition, the most recent efficacy data cut-off of October 23, 2015, was used to evaluate the primary end-point (PFS) for these long-term benefit patients, which was the last efficacy data collection time point. Subgroup analyses of PFS were exploratory. The Kaplan–Meier method was used to estimate median PFS, and the two-sided log-rank test was used for comparisons of PFS. HRs and two-sided 95% CIs were estimated using the Cox proportional hazards model. Expression of oestrogen receptor (ER) and progesterone receptor (PR) was evaluated at a central laboratory by validated immunohistochemistry, and results were quantified using H-score methodology. Unless otherwise noted for efficacy data, all data were obtained from the August 31, 2016, cut-off.

3. Results

3.1. Patients and treatment exposure

Between September 26, 2013, and August 26, 2014, 521 patients from 144 centres in 17 countries were randomised to palbociclib-fulvestrant (n = 347) or placebo-fulvestrant (n = 174) in the PALOMA-3 study (Fig. A1). As of August 31, 2016, 100 (29%) of the 347 patients randomised to palbociclib-fulvestrant received treatment for ≥18 months, including 70 (20%) who received treatment for >2 years (26–39 cycles). In contrast, 26 (15%) of 174 patients in the placebo-fulvestrant arm received ≥18 months of treatment, and only 16 patients (9%) were treated for >2 years (27–38 cycles). Similarly, a greater proportion of patients in the palbociclib-fulvestrant versus control arm received ≥12 months of treatment (154 [44%] vs 38 [22%]). The mean overall time on treatment was 12.5 (standard deviation [SD], 9.3) months in the palbociclib-fulvestrant arm and 7.9 (8.1) months in the placebo-fulvestrant arm (Table A1). Mean (SD) duration of treatment among patients with prolonged benefit on palbociclib-fulvestrant was 25.2 (3.2) months versus 7.4 (5.1) months for those with <18 months of treatment. The mean (SD) of treatment among long-term responders in the control group was 24.6 (3.5) months versus 4.9 (4.1) months for patients with <18 months of treatment.

Patient demographics and baseline characteristics are shown in Table 1 and Table A2. In both arms, patients with long-term benefit tended to have less disease burden at baseline than those treated for shorter durations. Among patients treated with palbociclib-fulvestrant, 40% of those with prolonged benefit had a single site of disease involvement and 32% had bone-only disease compared with 29% and 22%, respectively, of those treated for <18 months. Among patients treated with placebo-fulvestrant, 69% of long-term responders had a single site of disease involvement and 46% had bone-only disease compared with 29% and 17%, respectively, of those treated for <18 months. Patients with prolonged benefit versus those treated for <18 months also typically had an earlier line of therapy (69% vs 56% in the palbociclib-fulvestrant arm and 73% vs 60% in the placebo-fulvestrant arm had received ≤2 prior therapies) and were sensitive to prior hormonal therapy (86% vs 76% in the palbociclib-fulvestrant arm and 81% vs 75% in the placebo-fulvestrant arm).

Table 1
Patient demographics and baseline characteristics.

Characteristics	≥18 months		<18 months	
	Palbociclib-fulvestrant (n = 100)	Placebo-fulvestrant (n = 26)	Palbociclib-fulvestrant (n = 245)	Placebo-fulvestrant (n = 146)
Age, years				
Median (range)	59 (34–82)	61 (35–79)	56 (30–88)	55 (29–80)
≥65	33 (33)	5 (19)	53 (22)	38 (26)
Race				
White	72 (72)	21 (81)	179 (73)	110 (75)
Asian	23 (23)	4 (15)	50 (20)	27 (19)
Black and other	5 (5)	1 (4)	15 (6)	8 (5)
ECOG performance status				
0	61 (61)	20 (77)	143 (58)	94 (64)
1	39 (39)	6 (23)	102 (42)	52 (36)
Menopausal status				
Premenopausal/perimenopausal	23 (23)	5 (19)	48 (20)	31 (21)
Postmenopausal	77 (77)	21 (81)	197 (80)	115 (79)
Sensitive to prior hormonal therapy	86 (86)	21 (81)	186 (76)	110 (75)
Visceral metastases	44 (44)	8 (31)	155 (63)	96 (66)
Bone-only disease	32 (32)	12 (46)	53 (22)	25 (17)
Measurable disease	69 (69)	15 (58)	197 (80)	122 (84)
Disease stage at initial diagnosis				
I	4 (4)	1 (4)	21 (9)	11 (8)
II	37 (37)	12 (46)	82 (33)	44 (30)
III	17 (17)	8 (31)	52 (21)	39 (27)
IV	29 (29)	3 (12)	57 (23)	32 (22)
Other/missing	5 (5)	2 (8)	8 (3)	6 (4)
Recurrence type				
Local/locoregional	10 (10)	3 (12)	24 (10)	15 (10)
Regional	2 (2)	1 (4)	13 (5)	6 (4)
Distant	68 (68)	21 (81)	159 (65)	98 (67)
Newly diagnosed	20 (20)	0	47 (19)	25 (17)
Disease-free interval, months				
<12	2 (2)	0	9 (4)	3 (2)
12–24	3 (3)	2 (8)	26 (11)	17 (12)
>24	59 (59)	18 (69)	131 (54)	82 (56)
Disease site				
Bone	81 (81)	20 (77)	183 (75)	109 (75)
Breast	21 (21)	1 (4)	39 (16)	17 (12)
Liver	18 (18)	4 (15)	109 (45)	77 (53)
Lung	26 (26)	4 (15)	74 (30)	40 (27)
Lymph node	31 (31)	6 (23)	107 (44)	57 (39)
Other	32 (32)	4 (15)	90 (37)	47 (32)
Disease sites, n				
1	40 (40)	18 (69)	71 (29)	42 (29)
2	33 (33)	4 (15)	62 (25)	46 (32)
3	9 (9)	3 (12)	64 (26)	30 (21)
4	14 (14)	1 (4)	32 (13)	19 (13)
≥5	4 (4)	0	16 (7)	9 (6)
Prior surgeries	75 (75)	23 (89)	208 (85)	123 (84)
Prior radiation therapy	63 (63)	21 (81)	172 (70)	109 (75)
Prior chemotherapy				
Neoadjuvant	17 (17)	1 (4)	49 (20)	31 (21)
Adjuvant	44 (44)	18 (69)	106 (43)	70 (48)
Advanced/metastatic	26 (26)	6 (23)	78 (32)	54 (37)
Tamoxifen only	3 (3)	0	2 (<1)	4 (3)
Aromatase inhibitors only	17 (17)	2 (8)	29 (12)	14 (10)
Tamoxifen and aromatase inhibitors	38 (38)	10 (39)	120 (49)	70 (48)
Prior therapies, n				
1	29 (29)	8 (31)	53 (22)	34 (23)
2	40 (40)	11 (42)	85 (35)	54 (37)
3	16 (16)	3 (12)	68 (28)	36 (25)
≥4	15 (15)	4 (15)	39 (16)	22 (15)

ECOG, Eastern Cooperative Oncology Group.
Data are n (%) unless noted otherwise.

Moreover, fewer patients with long-term benefit had measurable disease at baseline than patients treated for <18 months (69% vs 80% in the palbociclib-fulvestrant arm and 58% vs 84% in the placebo-fulvestrant arm). In the palbociclib-fulvestrant arm, fewer patients with prolonged benefit had prior surgeries at baseline compared with those treated for <18 months (75% vs 85%). Among patients receiving palbociclib-fulvestrant, the type of disease recurrence did not appear to affect the duration of benefit (Table 1 and Table A2). However, in the placebo-fulvestrant arm, none of the 25 patients newly diagnosed with metastatic disease received ≥12 months of treatment.

3.2. Efficacy

After a median follow-up of 14.0 months (95% CI, 13.9–14.5) in the palbociclib-fulvestrant group, in the intent-to-treat (ITT) population, median PFS was 11.2 months (95% CI, 9.5–12.9), which was more than double that of the placebo-fulvestrant group (4.6 months [95% CI, 3.5–5.6]) (HR, 0.497; 95% CI, 0.398–0.620; 1-sided $P < 0.0001$; Fig. 1A). Median PFS was significantly improved with the addition of palbociclib in patients with bone-only metastases (Fig. 1B), in patients with only one prior therapy (Fig. 1C), in patients with ≤2 disease sites (Fig. 1D) and in patients with prior sensitivity to hormonal therapy (Fig. 1E; all $P < 0.05$). Compared with the placebo-fulvestrant group, median PFS also improved significantly with the addition of palbociclib in patients without bone-only metastases (Fig. 2A), in patients with >1 prior therapy (Fig. 2B) and in patients with ≥3 disease sites (Fig. 2C; all $P < 0.0005$); improvements with palbociclib-fulvestrant versus placebo-fulvestrant in patients with no prior sensitivity to hormonal therapy were not significant (Fig. 2D). In the ITT population and in each of the subgroups analysed, the PFS benefit with palbociclib-fulvestrant was also observed in patients with ≥12 months and ≥18 months of treatment.

3.3. Baseline ESR1 and PIK3CA analysis

A total of 395 patients had baseline circulating free DNA evaluable for mutation analysis. Mutations in *ESR1* and *PIK3CA* have been implicated as mechanisms for endocrine resistance in MBC [18]. In both arms, the incidences of baseline *ESR1* and *PIK3CA* mutations were lower among patients treated for ≥18 months versus those treated for <18 months; however, the difference was more pronounced among patients treated with placebo-fulvestrant (Table 2). In the palbociclib-fulvestrant group, 19% of long-term responders versus 28% of patients treated for <18 months had *ESR1* mutations and 24% versus 37% had *PIK3CA* mutations at baseline, respectively. In comparison, 6% of patients with prolonged benefit on placebo-fulvestrant versus 33% of those treated for <18 months had *ESR1* mutations and 6% versus 39% had *PIK3CA* mutations, respectively (Table 2).

3.4. Baseline hormone receptor expression

Most patients with long-term benefit had a valid baseline assessment of ER and PR status. In the palbociclib-fulvestrant arm, 70% of long-term responders had a valid ER assessment at baseline and 69% had a valid PR assessment. Among patients treated with placebo-fulvestrant, 88% of those treated for ≥18 months had a valid baseline ER and PR assessment. As shown in Table 2, mean (SD) ER H-scores were similar among long-term responders and those treated for <18 months in both the palbociclib-fulvestrant arm (125 [73] and 100 [74], respectively) and the placebo-fulvestrant arm (101 [68] and 99 [74], respectively); similar results were observed in patients with and without ≥12 months of treatment. In contrast, mean (SD) PR H-scores were higher among long-term responders than those treated for <18 months with both palbociclib-fulvestrant (72 [76] vs 45 [63]) and placebo-fulvestrant (82 [74] vs 46 [58]). Median ER H-scores were similar among patients with and without prolonged benefit and were similar between treatment groups (Table 2). Median PR H-scores were higher among long-term responders, regardless of the treatment group, and were lower overall among patients in the palbociclib-fulvestrant versus the placebo-fulvestrant group.

4. Discussion

PALOMA-3 was a prospective, randomised, multicentre, placebo-controlled study evaluating palbociclib plus fulvestrant versus placebo plus fulvestrant in patients with HR+/HER2− MBC that had progressed on prior ET [7]. The study demonstrated improved PFS and objective response rates at predetermined time points with the combination; subgroup analyses have shown that the observed benefit was independent of menopausal status, previous ET, number of disease sites, previous lines of ET, sensitivity to previous hormonal therapy, previous chemotherapy [5,7] and presence of visceral metastases at baseline [19]. Furthermore, patients receiving the combined regimen experienced an improvement in the quality of life and a favourable toxicity profile [20–22]. However, a detailed retrospective biomarker analysis was unable to identify factors prognostic of response or benefit [5].

To identify potential predictors of prolonged benefit with palbociclib-fulvestrant, this exploratory analysis evaluated clinical and biological characteristics of the subset of patients with long-term benefit on the combination. No specific molecular or clinical factors prognostic of long-term benefit with palbociclib-fulvestrant

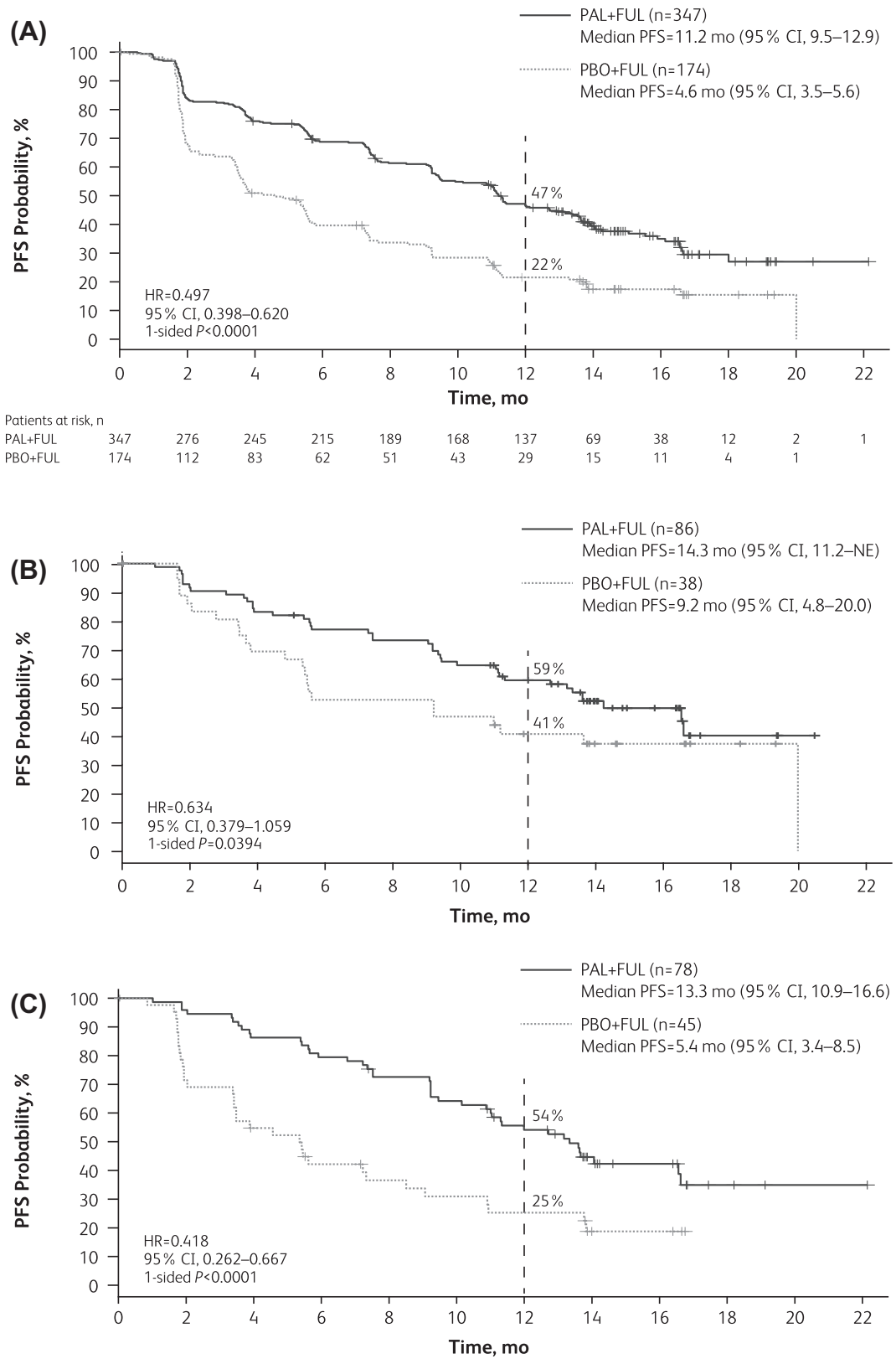

Fig. 1. Progression-free survival in the ITT population (A), in patients with bone-only metastases (B), with one prior therapy (C), one or two disease sites (D) and sensitivity to prior hormonal therapy (E). FUL, fulvestrant; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; PAL, palbociclib; PBO, placebo; PFS, progression-free survival; CI, confidence interval.

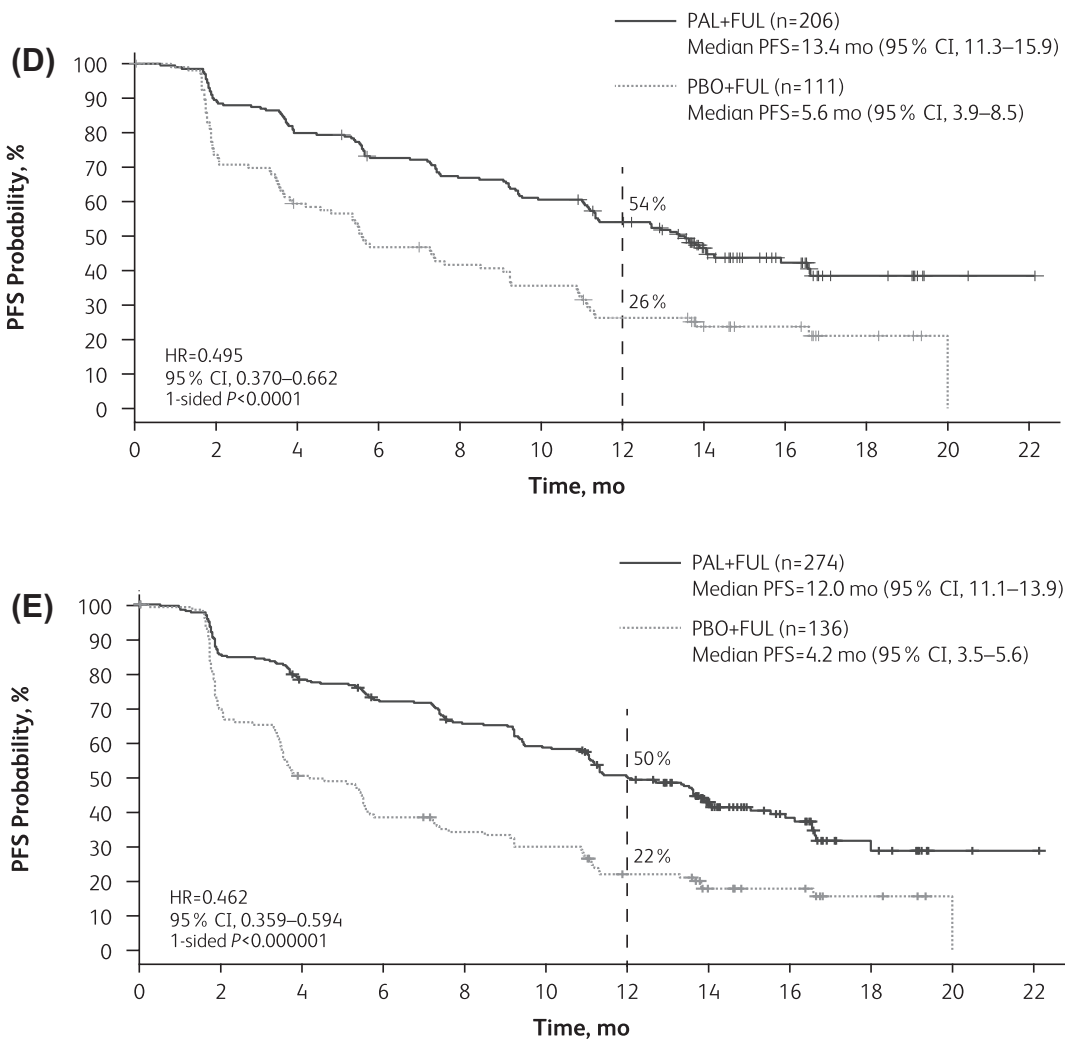

Fig. 1. (*continued*).

were identified. Notably, baseline *ESR1* and *PIK3CA* mutation status did not preclude patients from obtaining prolonged benefit from the combination. With extended follow-up, we continued to observe a remarkable difference in disease control and prolonged therapeutic benefit with the combination. Approximately one-third of patients who received palbociclib-fulvestrant had derived prolonged benefit from the combination and continued to receive treatment for a median of >2 years. Among patients receiving palbociclib-fulvestrant, 29% were without disease progression ≥18 months after enrolment compared with only 15% in the fulvestrant arm. Although substantially fewer patients achieved long-term benefit with placebo-fulvestrant, these patients did as well as patients who achieved long-term benefit with palbociclib-fulvestrant, as suggested by the similar mean durations of therapy. The data indicate that palbociclib can maintain ET benefit for a relatively long time in patients with HR+ MBC that progressed on prior ET and can reduce endocrine resistance in combination with ET.

The comparison between patients with and without prolonged benefit showed that there were no major differences in certain clinical characteristics, such as the menopausal status and type of prior ET. Nevertheless, patients achieving long-term benefit were more likely to have a lower disease burden at baseline; they tended to have fewer disease sites, non-visceral disease as indicated by a lower incidence of liver metastases, a higher incidence of bone-only disease and were less heavily pretreated. Furthermore, the efficacy of the combination regimen was superior to single-agent treatment across subsets of patients, including those with characteristics considered favourable for ET. Interestingly, the biomarker analysis showed that the baseline ER expression level had no impact on treatment duration, whereas the baseline PR expression level was higher among long-term responders in both arms. The frequencies of baseline *ESR1* and *PIK3CA* mutations were lower in patients with extended benefit, particularly in those treated with placebo-fulvestrant. Although the data are exploratory, not conclusive and cannot drive

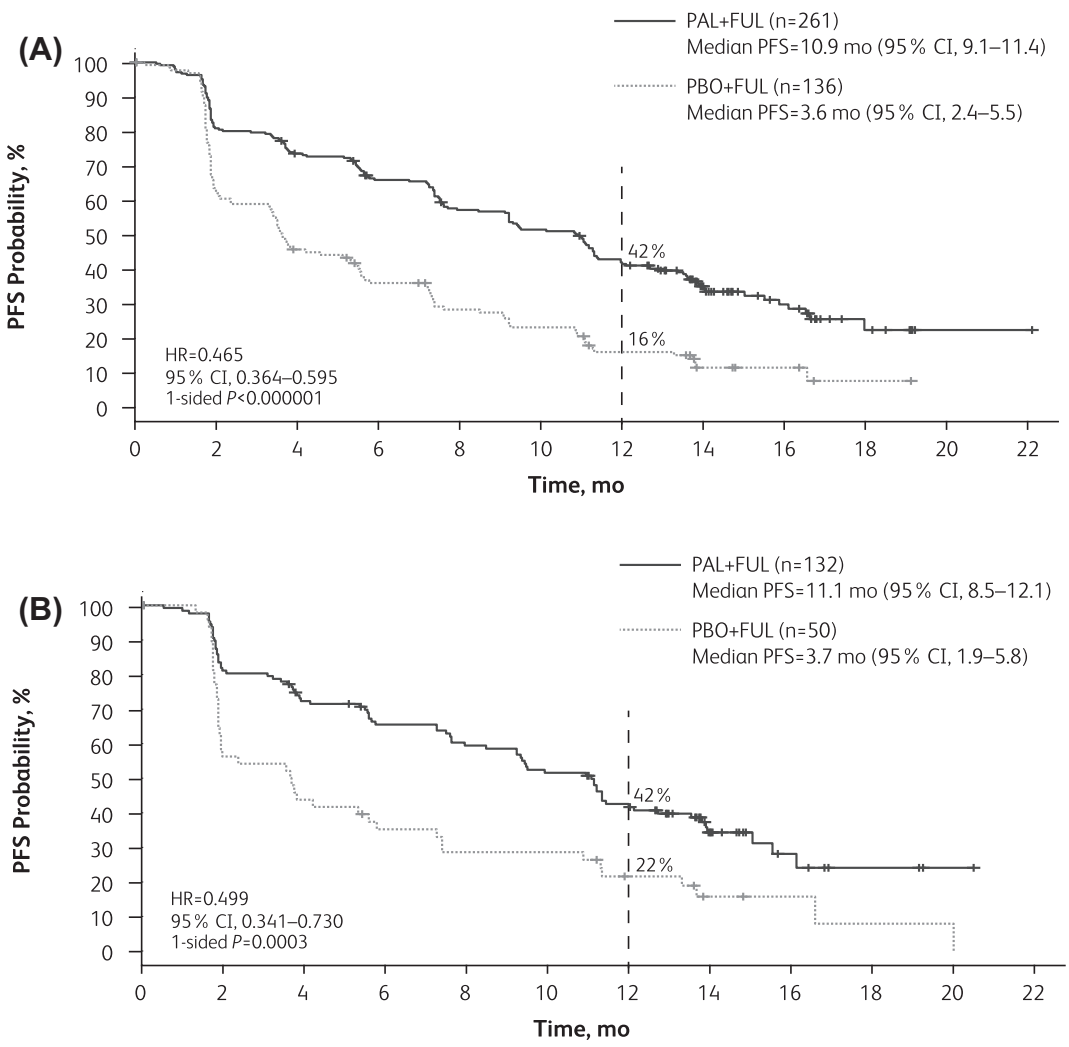

Fig. 2. Progression-free survival in patients without bone-only metastases (A), with >1 prior therapy (B), ≥3 disease sites (C) and no prior sensitivity to hormonal therapy (D). FUL, fulvestrant; HR, hazard ratio; PAL, palbociclib; PBO, placebo; PFS, progression-free survival; CI, confidence interval.

decision-making in treatment selection, there is interest in understanding and continuing to explore the prognostic role of molecular diagnostics and the disease site. It is also relevant to consider the impact of other therapeutic options on this specific setting to better understand the effect of the combination.

BOLERO-2 was a multicentre, double-blind, randomised, placebo-controlled, phase 3 study comparing exemestane plus everolimus with single-agent exemestane in patients with MBC [23]. The clinical characteristics of patients in this study were similar to those of patients in PALOMA-3. Patients enrolled in BOLERO-2 had previously received systemic therapy for metastatic disease, most commonly ET (primarily an aromatase inhibitor), but patients exposed to chemotherapy were also included [23]. Similar to PALOMA-3, the combination regimen demonstrated superior efficacy with improved PFS; however, no impact on OS was observed at the final planned PFS analysis, and after a median follow-up of 18 months, only 16.7% of patients were still receiving the planned study treatment [24,25]. Furthermore, patients treated with everolimus experienced significant treatment-related toxicity, with 55% of patients reporting grade III/IV toxicity, resulting in a median time of exposure to the everolimus combination of 23.9 weeks for the overall study group [24]. Considering the toxicity reported with everolimus, palbociclib-fulvestrant represents a highly appropriate and well-tolerated choice [26,27].

An alternative treatment option for this population is chemotherapy, primarily single-agent treatment with drugs such as capecitabine, eribulin and a taxane [28]. Treatment with these agents is typically associated with significant toxicity other than neutropenia (an adverse event commonly associated with palbociclib) and, in many cases, requires dose reductions and/or treatment discontinuation, primarily because of the onset of long-term, non-haematologic toxicity. Furthermore, some of

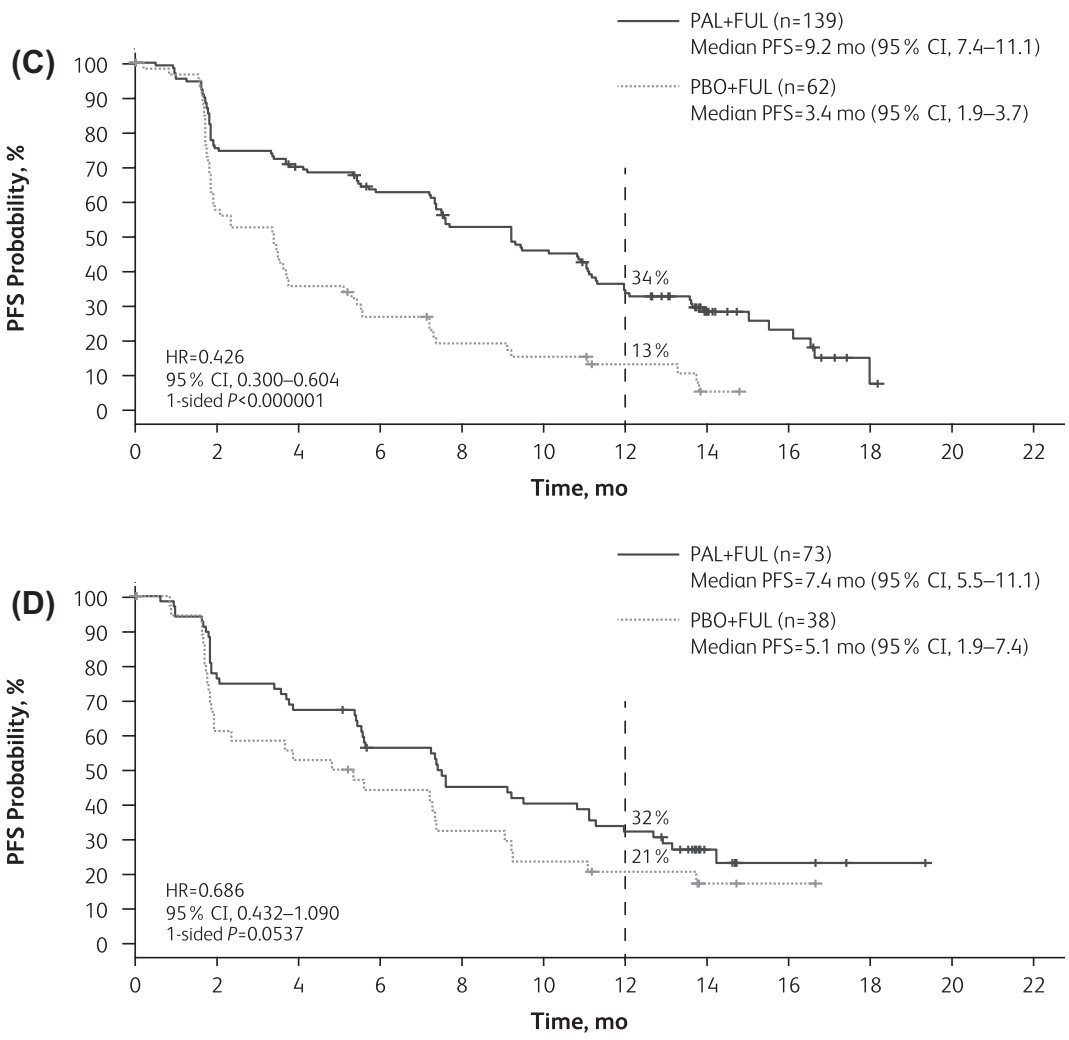

Fig. 2. (*continued*).

these agents require frequent infusions that have a substantial impact on costs and patient's quality of life. However, the current costs of targeted therapies such as palbociclib are higher than those of chemotherapy [29], and no head-to-head studies have been conducted to directly compare the efficacy, tolerability, quality of life or treatment compliance between chemotherapy and palbociclib combination therapy. Nevertheless, our analysis showed that, in a subset of patients who only had one line of prior therapy, including patients who

Table 2
Baseline mutation rate and hormone receptor expression.

	Palbociclib-fulvestrant				Placebo-fulvestrant			
	≥18 months	<18 months	≥12 months	<12 months	≥18 months	<18 months	≥12 months	<12 months
Mutation								
ESR1, n/N (%)	15/80 (19)	52/185 (28)	25/120 (21)	42/145 (29)	1/16 (6)	38/115 (33)	4/27 (15)	35/104 (34)
PIK3CA, n/N (%)	19/80 (24)	68/185 (37)	31/120 (26)	56/145 (39)	1/16 (6)	45/115 (39)	9/27 (33)	37/104 (36)
Median (range) H-score								
Oestrogen receptor	130 (0–250)	100 (0–280)	120 (0–250)	100 (0–280)	120 (0–260)	117 (0–180)	115 (0–260)	119 (0–280)
Progesterone receptor	40 (0–270)	6 (0–240)	30 (0–270)	6 (0–240)	70 (0–230)	10 (0–230)	50 (0–230)	10 (0–230)
Mean (SD) H-score								
Oestrogen receptor	125 (73)	100 (74)	118 (72)	98 (75)	101 (68)	99 (74)	94 (70)	101 (74)
Progesterone receptor	72 (76)	45 (63)	62 (72)	46 (65)	82 (74)	46 (58)	66 (69)	48 (60)

SD, standard deviation.
ESR1-positive mutation status was defined as ≥0.1% for any nucleotide change; *PIK3CA*-positive mutation status was defined as ≥0.02%.
H-score was calculated as the sum of the percentage of cells at each level of the staining intensity multiplied by the staining intensity value; values range from 0 to 300.

may have received chemotherapy in the MBC setting, median PFS was prolonged with the combination.

This analysis was exploratory in nature with limited statistical methods performed. Additionally, this analysis was limited by the small number of patients included overall and especially in the *ESR1* and *PIK3CA* analyses because evaluable baseline circulating free DNA samples were not available from all patients. Nevertheless, findings from this analysis provide novel clinical insights into the subset of patients with long-term benefit from palbociclib-fulvestrant.

In summary, this extended analysis of palbociclib plus fulvestrant in the context of the PALOMA-3 study indicates the possibility of significant long-term benefit for patients with HR+/HER2− MBC after failure of previous ET. Although no new biomarkers were identified for predicting long-term benefit other than those identified in previous studies (namely, low disease burden and limited treatment for advanced disease), it is possible that increased genomic variants associated with aggressive endocrine-resistant disease could aid future treatment selection, with potential implications for use of other therapies, including immune therapy [30].

Conflict of interest statement

Massimo Cristofanilli has been a consultant or on the advisory board for Dompé Farmaceutici, Cynvenio Biosystems, Newomics and Vortex Biosciences and received honoraria from Pfizer, Celgene, Dompé Farmaceutici and Agendia. Angela DeMichele has received honoraria from Pfizer, and her institution received research funding from Genentech, Pfizer, Incyte, Millennium, Bayer, Veridex, Calithera Biosciences, GlaxoSmithKline and Wyeth. Nicholas Turner has received honoraria from and been a consultant or on the advisory board for Pfizer, and his institution has received research funding from Servier, Pfizer, Eli Lilly, Roche and AstraZeneca. Dennis Slamon has served in a leadership position for BioMarin and has stock or other ownership interests in Pfizer. Seock-Ah Im has been a consultant or on the advisory board for AstraZeneca, Novartis, Roche and Spectrum and has received research funding from AstraZeneca. Norikazu Masuda has received honoraria from Chugai, AstraZeneca and Kyowa-Kirin, and his institution received research funding from Chugai, Pfizer, Novartis, Lilly, AstraZeneca and Kyowa-Kirin. Shailendra Verma has been a consultant or on the advisory board for Pfizer. Sherene Loi's institution has received research funding from Roche/Genentech, Pfizer, Novartis, Merck, Puma Biotechnology and Bristol-Myers Squibb. Marco Colleoni has been a consultant or on the advisory board for Pierre Fabre, Pfizer, OBI Pharma, Puma Biotechnology, Celldex and AstraZeneca and received honoraria from Novartis. Kathy Puyana Theall, Xin Huang, Yuan Liu and Cynthia Huang Bartlett are employees of and own stock in Pfizer. Carla Giorgetti was an employee of Pfizer when the manuscript was initiated.

Author contributions

Massimo Cristofanilli, Nicholas Turner, Dennis Slamon, Seock-Ah Im, Norikazu Masuda and Cynthia Huang Bartlett contributed to study concepts and study design. Massimo Cristofanilli, Angela DeMichele, Nicholas Turner, Dennis Slamon, Seock-Ah Im, Norikazu Masuda, Shailendra Verma, Sherene Loi and Marco Colleoni helped in data acquisition. Carla Giorgetti, Kathy Puyana Theall, Xin Huang, Yuan Liu and Cynthia Huang Bartlett were involved in quality control of data and algorithms. Xin Huang helped in statistical analysis. All authors were involved in the preparation, editing and reviewing of the manuscript and in data analysis and interpretation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.08.011.

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