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Original Research

Randomized phase II study of fulvestrant plus palbociclib or placebo in endocrine-sensitive, hormone receptor-positive/HER2–advanced breast cancer: GEICAM/2014–12 (FLIPPER)

J. Albanell [a,b,c,d,*], M.T. Martínez [e,b], M. Ramos [f,b], M. O'Connor [g,h], L. de la Cruz-Merino [i,b], A. Santaballa [j,b], N. Martínez-Jañez [k,b], F. Moreno [l,b], I. Fernández [m,b], J. Alarcón [n,b], J.A. Virizuela [o,b], J. de la Haba-Rodríguez [p,b,c], P. Sánchez-Rovira [q,b], L. González-Cortijo [r,b], M. Margelí [s,b], A. Sánchez-Muñoz [t,b], A. Antón [u,b,c], M. Casas [b], S. Bezares [b], F. Rojo [v,b,c]

[a] *Medical Oncology, Hospital Del Mar, IMIM, Barcelona, Spain*
[b] *GEICAM Spanish Breast Cancer Group, Madrid, Spain*
[c] *Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII, Spain*
[d] *Pompeu Fabra University, Barcelona, Spain*
[e] *Medical Oncology. Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria-INCLIVA, Valencia, Spain*
[f] *Medical Oncology, Centro Oncológico A Coruña, Coruña, Spain*
[g] *University Hospital Waterford, Waterford, Ireland*
[h] *Cancer Trials Ireland, Dublin, Ireland*
[i] *Medical Oncology, Hospital Universitario Virgen de La Macarena, Medicine Department-Universidad de Sevilla, Sevilla, Spain*
[j] *Medical Oncology, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[k] *Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[l] *Medical Oncology, Hospital Clínico Universitario San Carlos, Madrid, Spain*
[m] *Medical Oncology, Hospital Álvaro Cunqueiro, Vigo, Spain*
[n] *Medical Oncology, Hospital Universitari Son Espases, Palma de Mallorca, Spain*
[o] *Medical Oncology, Hospital Quirónsalud Sagrado Corazón, Sevilla, Spain*
[p] *Medical Oncology, Instituto Maimónides de Investigación Biomédica, Hospital Reina Sofía, Universidad de Córdoba*
[q] *Medical Oncology, Hospital Universitario de Jaén, Jaén, Spain*
[r] *Medical Oncology, Hospital Universitario Quirónsalud, Madrid, Spain*
[s] *Medical Oncology, B-ARGO Group, Catalan Institute of Oncology, Hospital Universitari Germans Trias I Pujol, Badalona, Spain*
[t] *Medical Oncology Intercenter Unit, Regional and Virgen de La Victoria University Hospitals, IBIMA, Malaga, Spain*
[u] *Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain*
[v] *Pathology Department, Fundación Jiménez Díaz, Madrid, Spain*

* *Corresponding author*: Medical Oncology Department, Hospital del Mar, 08003 Barcelona, Spain.
E-mail address: jalbanell@hospitaldelmar.cat (J. Albanell).

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Abstract ***Background:*** The potential benefit of adding palbociclib to fulvestrant as first-line treatment in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative endocrine-sensitive advanced breast cancer (ABC) patients remains uncharacterized.

Patients and methods: In this randomized (1:1), double-blind, phase II study, postmenopausal women with HR-positive, HER2-negative ABC with *de novo* metastatic disease or those who relapsed after >12 months of adjuvant endocrine therapy received palbociclib/fulvestrant or placebo/fulvestrant. Stratification was based on recurrent versus *de novo* metastatic disease and visceral involvement. The primary objective was one-year progression-free survival (PFS-1y) rate. The sample size was 190 patients. The two-sided alpha of 0.2, 80% of power to detect a difference between the arms, assuming PFS rates of 0.695 and 0.545 for palbociclib/fulvestrant and placebo/fulvestrant, respectively.

Results: In total, 189 patients were randomized to palbociclib/fulvestrant ([$n = 94$] or placebo/fulvestrant [$n = 95$]). 45.5% and 60.3% of patients had *de novo* metastatic disease and visceral involvement, respectively. PFS-1y rates were 83.5% and 71.9% in the palbociclib/fulvestrant and placebo/fulvestrant arms, (HR 0.55, 80% CI 0.36–0.83, $P = 0.064$). The median PFS were 31.8 and 22.0 months for the palbociclib/fulvestrant and placebo/fulvestrant arms (aHR 0.48, 80% CI 0.37–0.64, $P = 0.001$).

The most frequent grade 3–4 adverse events were neutropenia (68.1% vs. 0%), leucopenia (26.6% vs. 0%), anemia (3.2% vs. 0%), and lymphopenia (14.9% vs. 2.1%) for the palbociclib/fulvestrant and placebo/fulvestrant, respectively. The most frequent non-hematologic grade 3–4 adverse event was fatigue (4.3% vs. 0%).

Conclusions: Palbociclib/fulvestrant demonstrated better PFS-1y rates and median PFS than placebo/fulvestrant in HR-positive/HER2-negative endocrine-sensitive ABC patients.

1. Introduction

The development of cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) for patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC) has been a major therapeutic achievement. To date, three CDK4/6i have been approved for both first-line and second-line treatment of ABC [1]. There are slight differences in CDK4/I in their potency and selectivity that render each of them unique in terms of toxicity profiles, and efficacy. Pivotal trials have shown significant improvements in progression-free survival (PFS) for the three drugs when combined with a non-steroidal aromatase inhibitor (NSAI) [2–5]. Significant overall survival (OS) benefits have also been reported [6–11]. When combined with fulvestrant, the three drugs also significantly improved PFS in patients whose tumors progressed while receiving previous endocrine therapy (ET) [12–14]. As a consequence, fulvestrant combined with a CDK4/6i is a preferred option for second-line treatment in CDK4/6i-naïve patients or in those with early relapse.

Clinical trial data of CDK4/6i in combination with fulvestrant as first-line treatment for patients with endocrine-sensitive ABC are also required. Importantly, in a previous trial, patients with endocrine-naïve ABC had a higher PFS rate with fulvestrant than with anastrozole (FALCON trial) [15]. This result emphasizes the need to evaluate the combination of CDK4/6i plus fulvestrant as a first-line treatment for this subset of patients. To date, only two phase III studies evaluating the combination of CDK4/6i plus fulvestrant in endocrine-sensitive ABC, MONALEESA-3 [8] and PARFISAL [16], have been reported.

The FLIPPER trial design was based on the results from the FALCON and PALOMA-3 trials. PALOMA-3 compared palbociclib/fulvestrant vs. placebo/fulvestrant in women with HR-positive and HER2-negative ABC who had relapsed or progressed during previous

ET [12]. The results showed a significant improvement in PFS and OS with palbociclib to fulvestrant. Favorable OS was observed in most subgroups except among patients who were endocrine resistant or had prior chemotherapy for ABC [10]. FLIPPER is the first trial addressing the effectiveness of palbociclib/fulvestrant in endocrine-sensitive patients. The trial included patients with *de novo* ABC or those who had completed ≥5 years of (neo)adjuvant ET and relapsed ≥1 year after its completion. These two cohorts of patients were excluded in the PALOMA-3 trial. Its primary endpoint was the 1-year PFS rate, which was selected based on the expectation of prolonged PFS in both treatment arms.

2. Patients and methods

The FLIPPER is an international, multicenter, double-blind, placebo-controlled, randomized phase II study comparing the efficacy and safety of palbociclib/fulvestrant versus placebo/fulvestrant. It was conducted in compliance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by all participating institutions' independent ethics committees or institutional review boards. Written informed consent was obtained from all patients.

2.1. Patient eligibility

Eligible patients included postmenopausal women with HR-positive [17] HER2-negative [18] ABC. Patients had either a relapse after completing ≥5 years of ET in the adjuvant setting and remained disease-free for >12 months following its completion or *de novo* metastatic disease. Patients who had been scheduled for 5 years of adjuvant ET and voluntarily stopped the treatment after ≥3 years were also eligible as long as they remained disease-free for ≥3 years after ET discontinuation. Patients were required to have locoregional recurrence not amenable to therapy with curative intent or metastatic distant disease and at least one tumor lesion suitable for repeated assessment. Patients with bone disease only had to have at least one lytic or mixed lesion assessable by computed tomography scan or magnetic resonance imaging. Patients with a local recurrent disease could have received a "second adjuvant ET" for 5 years with recurrence after ≥12 months of its completion.

2.2. Study procedures

Baseline disease assessments were performed within four weeks before randomization. Tumor assessments occurred every 12 weeks from the start of treatment until documented progressive disease (PD), initiation of a new anticancer therapy, or patient dropout. Hematology and biochemistry tests were performed before the start of each cycle; hematology testing was additionally performed on day 14 of cycles 1 and 2.

Randomized patients were stratified by a) visceral versus non-visceral involvement and b) *de novo* metastatic versus recurrent BC. Patients were assigned (1:1) to receive palbociclib (125 mg/day, 28-day cycles; 3 weeks on, 1 week off) or matched placebo, and both arms received fulvestrant (500 mg on days 1, 14, 28, and every 28 days onward). Requirement dosing interruption and up to two dose reductions of palbociclib/placebo were allowed in cases of adverse events (AEs). Treatment continued until objective PD according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [19], clinical PD, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [20].

2.3. Outcomes

The primary outcome was to compare the 1-year PFS rate, defined as the rate of patients free of PD at 1 year (according to RECIST 1.1 and assessed by the investigators), between the palbociclib/fulvestrant and placebo/fulvestrant arms. The primary analysis was planned to be performed once all randomized patients had undergone a 1-year of follow-up. The trial was designed to have an 80% power to detect a difference between both arms, using a two-sided alpha of 0.2, assuming that the 1-year PFS rates were 54.5% and 69.5% for placebo/fulvestrant and palbociclib/fulvestrant, respectively. This was based on an expected median PFS of 13.7 months for placebo/fulvestrant and 22.9 months for palbociclib/fulvestrant, for a constant hazard ratio (HR) of 0.6 with a 20% significance level. This is a phase 2 study without registration purposes and according to ICH E9, the type I error (conventionally set at 5%), is acceptable to be higher in some cases [21]. . Based on these considerations, a target sample size of 190 patients was required (95 in each arm). No interim analyses were performed.

The secondary outcomes included median PFS, objective response rate (ORR), clinical benefit rate (CBR) defined as ORR plus stable disease ≥24 weeks rate, and safety profile. The final OS analysis will be performed when at least 60% of patients have died.

2.4. Statistical analyses

The Kaplan–Meier method was used to estimate the 1-year PFS rate and HR, and median PFS and median OS; 80% confidence intervals (CIs) were provided for estimates of interest. The Cox proportional hazards model was used to calculate the unadjusted and adjusted HR (aHR) and 80% CIs. The stratified Cochran–Mantel–Haenszel test was used to estimate the odds ratios (ORs) and 80% CIs and to test the association between the treatment arm and ORR or CBR. Efficacy analyses were based on all

randomized patients (intent-to-treat [ITT] population), and safety analyses were performed on all patients receiving ≥1 dose of study therapy.

3. Results

3.1. Study patients

Between February 2016 and January 2018, 189 patients were recruited at 32 institutions in two countries and randomly assigned to receive palbociclib/fulvestrant (94 patients) or placebo/fulvestrant (95 patients) (Fig. 1).

Baseline demographic and disease characteristics were similar between both arms except for progesterone receptor status (Table 1).

Considering the data cut-off date for the primary objective analysis, a total of 96 events of PFS had occurred (40 [42.6%] in the palbociclib/fulvestrant arm and 56 [58.9%] in the placebo/fulvestrant arm). Moreover, 35 (37.2%), 9 (9.6%), and 31 (32.6%) patients were still receiving palbociclib/fulvestrant, fulvestrant alone after palbociclib treatment discontinuation, and placebo/fulvestrant, respectively (Table 1S). The median relative dose intensities were 90% for palbociclib and 100% for fulvestrant in the palbociclib/fulvestrant arm and 99.7% for placebo and 100% for fulvestrant in the placebo/fulvestrant arm. The main reason for permanent study treatment discontinuation was PD in 39 (41.5%) patients in the palbociclib/fulvestrant arm and in 55 (57.9%) patients in the placebo/fulvestrant arm. Fifteen (15.6%) patients discontinued palbociclib due to AEs and continued with fulvestrant alone.

3.2. Efficacy

At the cut-off date (January 11, 2020), all randomized patients had undergone a 12-month follow-up. Median follow-up was 28.6 months. The study met its prespecified primary endpoint, the 1-year PFS rates were 83.5% (80% CI 78.5–88.5) and 71.9% (80% CI 65.8–77.9) in the palbociclib/fulvestrant and placebo/fulvestrant arms, respectively (HR 0.55; 80% CI 0.36–0.83; $P = 0.064$). This difference was statistically significant according to the two-sided alpha error of 0.2 (Fig. 2). The

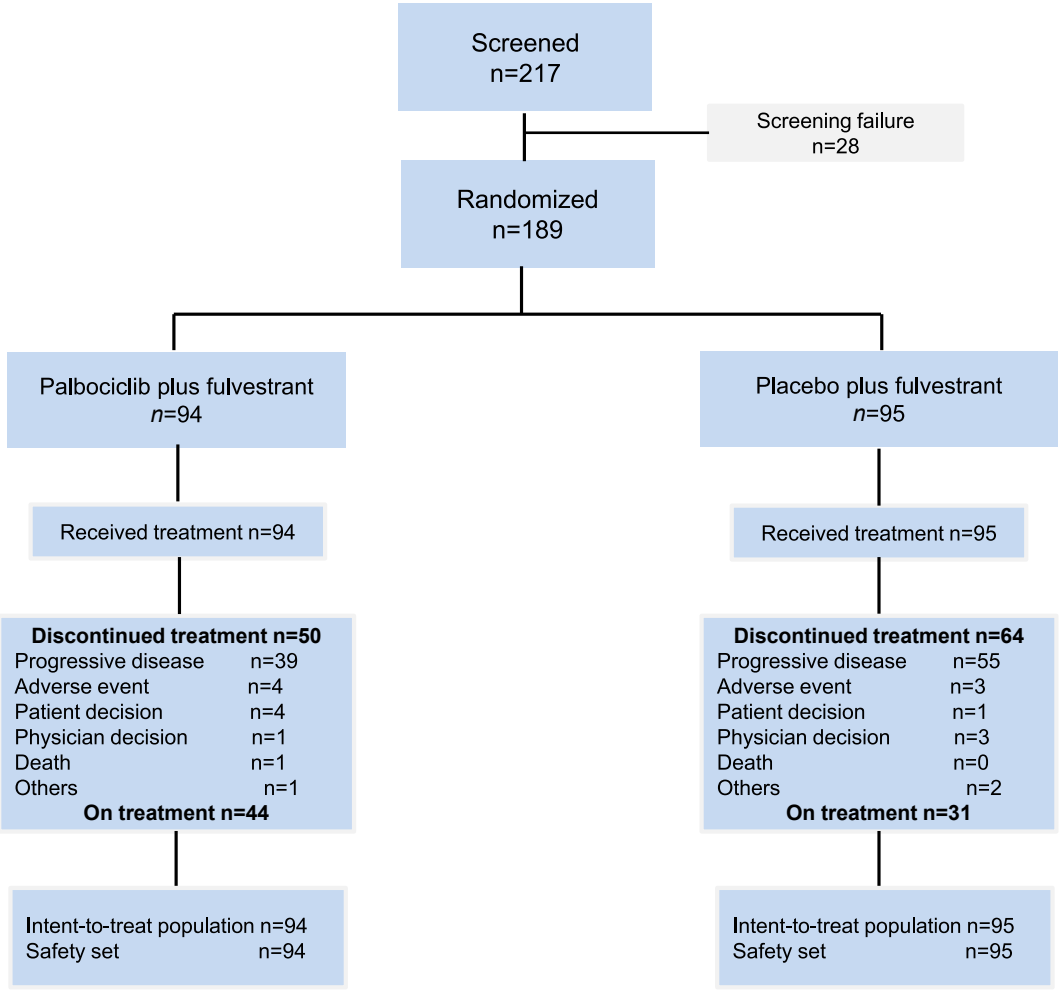


Fig. 1. Consort study flowchart. Screening failures (only those patients who signed the informed consent and were not enrolled in the study).

1-year PFS rates were also assessed according to the stratification factors (Fig. 3). Median PFS were 31.8 and 22.0 months in the palbociclib/fulvestrant and placebo/fulvestrant arms, respectively (aHR 0.48; 80% CI 0.37–0.64; $P = 0.001$) (Fig. 2). Subset analysis by stratification factors (Fig. 3) supported benefit regardless of visceral or non-visceral disease. In patients with *de novo* metastatic versus recurrent disease, the benefit appeared

Table 1
Patients' baseline characteristics (intention-to-treat population).[a]

	Palbociclib plus fulvestrant	Placebo plus fulvestrant	*P*-value
	n = 94	n = 95	
Demographics and disease characteristics			
Age			
Median (range), years	64 (38–81)	64 (42–82)	0.7174
<65 years, *n* (%)	47 (50.0)	50 (52.6)	
≥65 years, *n* (%)	47 (50.0)	45 (47.4)	
ECOG performance status[b], *n* (%)			
0	49 (52.1)	53 (55.8)	0.6136
1	41 (43.6)	40 (42.1)	
2	4 (4.3)	2 (2.1)	
Disease presentation at study entry, *n* (%)			
Metastatic *"de novo"*	44 (46.8)	42 (44.2)	0.7199
Recurrent disease	50 (53.2)	53 (55.8)	
Visceral disease[c], *n* (%)			
Yes	57 (60.6)	57 (60.0)	0.9285
No	37 (39.4)	38 (40.0)	
Measurable lesions, *n* (%)			
Measurable	63 (67.0)	64 (67.4)	0.9595
Non-measurable	31 (33.0)	31 (32.6)	
Most frequent disease sites, *n* (%)			
Bone	65 (69.1)	63 (66.3)	0.6770
Lymph node	47 (50.0)	55 (57.9)	0.2763
Breast	34 (36.2)	33 (34.7)	0.8368
Lung	32 (34.0)	32 (33.7)	0.9585
Pleura	25 (26.6)	22 (23.2)	0.5846
Liver	14 (14.9)	16 (16.8)	0.7140
Number of involved sites, *n* (%)			
1	23 (24.5)	23 (24.2)	0.8843
2	26 (27.7)	30 (31.6)	
≥3	45 (47.9)	42 (44.2)	
Tumor characteristics			
Receptor status[d], *n* (%)			
ER + PR+	70 (74.5)	84 (88.4)	**0.0135**
ER + PR−	24 (25.5)	11 (11.6)	
Time since the first diagnosis of BC M0 to randomization (years)	***n* = 50**	***n* = 53**	
Median (range) − years	10.9 (6.43–25.65)	12.96 (6.72–26.78)	
Time since the first diagnosis of M1 to randomization (months)			
Median (range) − months	1.22 (0.23–3.61)	1.08 (0.2–5.26)	
Subtype by IHC[e], *n* (%)			
Luminal B-like (HER2-)	56 (59.6)	56 (58.9)	0.9301
Luminal A-like	38 (40.4)	39 (41.1)	
Prior therapy			
Prior adjuvant or neoadjuvant therapies, *n* (%)			
Chemotherapy			
Neoadjuvant	5 (5.3)	6 (6.3)	
Adjuvant	36 (38.3)	38 (40.0)	
Both	4 (4.3)	3 (3.2)	
Endocrine therapy			
Adjuvant	49 (52.1)	54 (56.8)	
Both	1 (1.1)	0	
Prior endocrine therapy for EBC[f], *n* (%)			
Aromatase inhibitor	34 (36.2)	39 (41.1)	0.6381
Tamoxifen	33 (35.1)	37 (38.9)	0.7844

Table 1 (*continued*)

	Palbociclib plus fulvestrant	Placebo plus fulvestrant	*P*-value
	n = 94	n = 95	
Disease-free interval[g], *n* (%)			
≤36 months	15 (16.0)	14 (14.7)	0.6434
>36 months	35 (37.2)	40 (42.1)	

BC, breast cancer; EBC, early breast cancer; ER, estrogen receptor; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; IHC, immunohistochemistry; PR, progesterone receptor.

[a] There were no significant differences in baseline characteristics between the two treatment groups except for the progesterone receptor status.

[b] Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with 0 indicating no symptoms and higher score indicating greater disability.

[c] Visceral metastasis was defined as all lesions not included in the following list: breast, skin, subcutaneous tissue, lymph node, or bone.

[d] Documented positive hormone receptor status (≥1% of tumor cells with ER and/or PR expression by IHC) based on central laboratory determination on the most recent tumor biopsy.

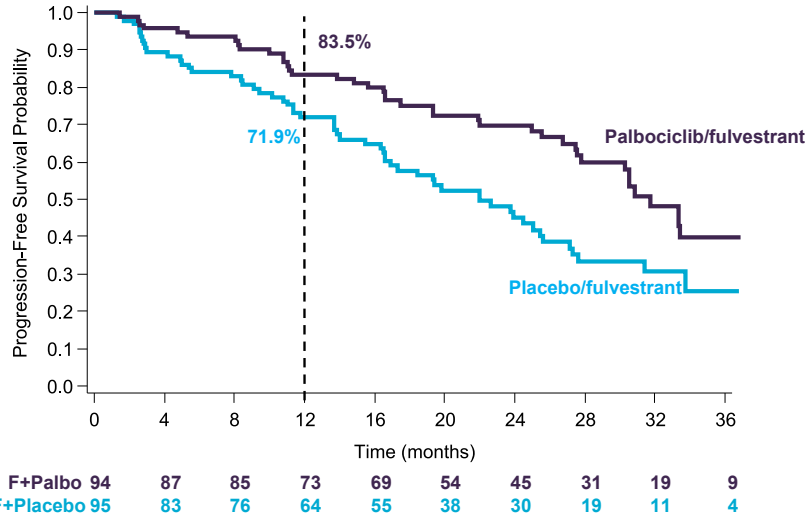
[e] Documented HER2-negative based on central laboratory determination on the most recent tumor biopsy. HER2-negative tumor was determined as IHC score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

[f] Four patients received GnRH agonists for EBC (three in the palbociclib/fulvestrant group and one in the placebo/fulvestrant group); on the first breast cancer diagnosis date, they were not postmenopausal patients.

[g] Disease-free interval was defined as the time from the completion of adjuvant endocrine therapy to recurrence.

significant only in the former group. Figure S1 shows a Forest plot analysis of the different subsets.

The ORR was 68.3% for the palbociclib/fulvestrant arm versus 42.2% for the placebo/fulvestrant arm (OR 2.9; 80% CI, 1.8–4.6, P = 0.004) (Table 2 and Figure S2). The CBR at 24 weeks was 90.4% versus 80% for the palbociclib/fulvestrant and placebo/fulvestrant arms, respectively (OR 2.3; 80% CI, 1.3–4.0, P =



	PFS rate at 1 year			Median PFS		
	No. of events (%)	No. of censored (%)	K-M estimates (80% CI)	No. of events (%)	No. of censored (%)	Median PFS no. of months (80% CI)
Palbociclib/ fulvestrant	15 (16.0)	79 (84.0)	**83.5 (78.5–88.5)**	40 (42.6)	54 (57.4)	**31.8 (30.3 –33.4)**
Placebo/ fulvestrant	26 (27.4)	69 (72.6)	**71.9 (65.8–77.9)**	56 (58.9)	39 (41.1)	**22 (18.5 –25.1)**
	HR (80% CI): 0.55 (0.36–0.83); *P*-value=0.064			aHR[¶] (80% CI): 0.48 (0.37–0.64); *P*-value=0.001		

Fig. 2. One-year progression-free survival rate (1-year PFS) and median PFS. Kaplan–Meier curves for PFS were represented for palbociclib plus fulvestrant versus placebo plus fulvestrant. Statistical design: hazard ratio 0.6, power 80%, two-sided alpha 0.2, ¶ Hazard ratios were adjusted by stratification factors: disease site (visceral vs. non-visceral) and (recurrent vs. *de novo* metastatic disease) and progesterone receptor status as covariates, CI, confidence interval; F, fulvestrant; HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival.

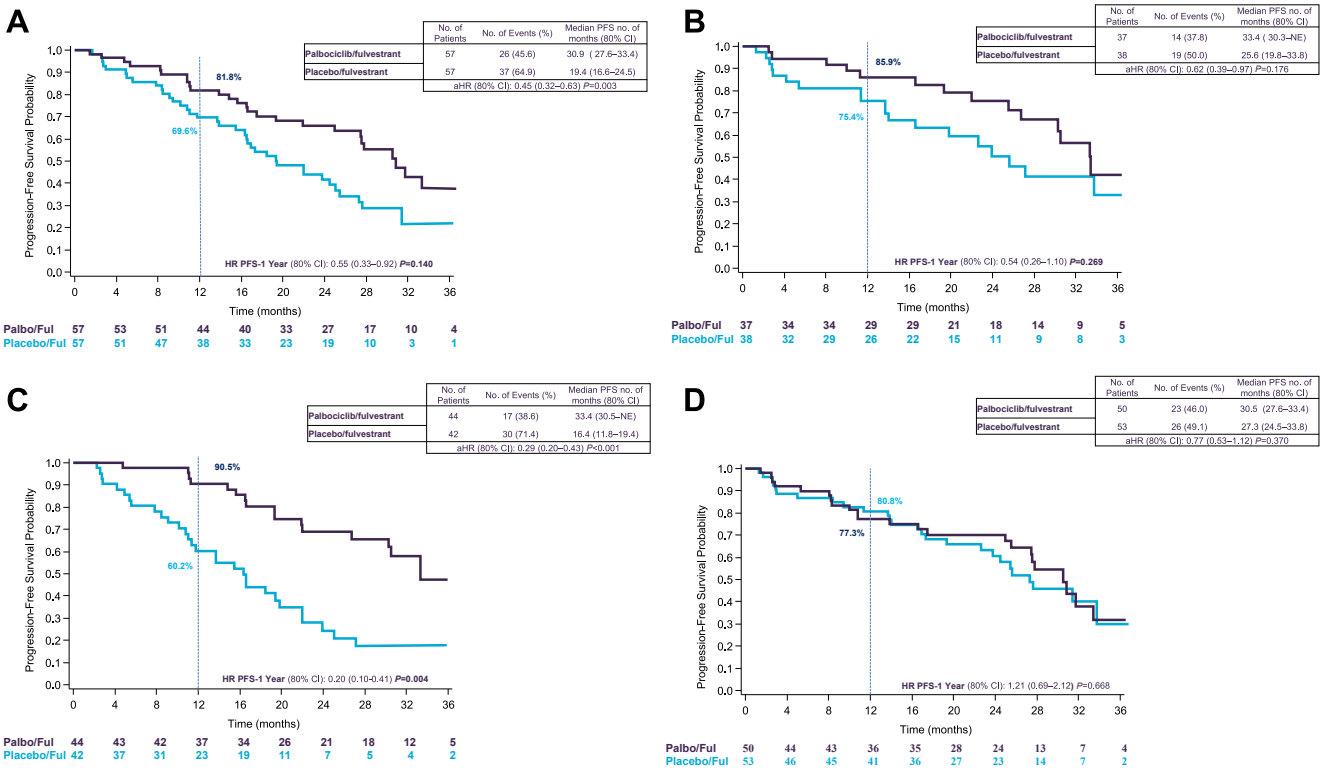


Fig. 3. One-year progression-free survival (PFS) rate and median PFS by the stratification factors. ∗Kaplan–Meier curves for PFS were represented for palbociclib plus fulvestrant versus placebo plus fulvestrant. Hazard ratios were adjusted by stratification factors: disease site (visceral vs. non-visceral) and (recurrent vs. *de novo* metastatic disease) and progesterone receptor status as covariates, **A** in subgroup visceral disease, **B** in subgroup non-visceral disease, **C** in subgroup *de novo* metastatic disease, and **D** in recurrent disease. Statistical design: hazard ratio 0.6, power 80%, two-sided alpha 0.2, CI, confidence interval; F, fulvestrant; aHR, adjusted hazard ratio; HR, hazard ratio; No, number; Palbo, palbociclib; PFS, progression-free survival.

0.048). In patients with visceral disease, the ORR was 67.4% for the palbociclib/fulvestrant arm versus 41% for placebo arm (OR 2.9; 80% CI, 1.65 − 5.04, P = 0.014), and the CBR at 24 weeks was 89.1% for the palbociclib/fulvestrant arm versus 79.5% for placebo arm (OR 2.3; 80% CI, 1.13 − 4.51, P = 0.127). The OS data were still immature at the time of this analysis. Only a 15% of ITT population had an OS event (14 events in fulvestrant/

Table 2
Summary of objective response rate and clinical benefit rate.

	Palbociclib plus fulvestrant	Placebo plus fulvestrant
	n = 94	*n* = 95
Best overall response, *n* (%)		
Complete response (CR)	1 (1.1)	4 (4.2)
Partial response (PR)	42 (44.7)	26 (27.4)
Stable disease (SD)	47 (50.0)	56 (58.9)
Stable disease ≥24 weeks	42 (44.7)	46 (48.4)
Progressive disease (PD)	3 (3.2)	9 (9.5)
Not evaluable[a]	1 (1.1)	0
Objective response rate, *n* (%)/patients with measurable disease		
CR + PR	43 (68.3)/63	27 (42.2)/64
Odds ratio (80% CI)	2.88 (1.79–4.62)	
P-value	0.004	
Clinical benefit rate at 24 weeks, n (%)		
CR + PR (at any time) + SD ≥ 24 weeks	58 (92.1)/63	49 (76.6)/64
Odds ratio (80% CI)	2.32 (1.33–4.03)	
P-value	0.048	

CI, confidence interval.
[a] No post-baseline response assessment.

palbociclib vs 16 events in fulvestrant/placebo). Double blinding has been maintained to allow ongoing follow-up to assess long-term outcomes.

3.3. Safety

Safety was assessed in all patients of the study population as all of them received at least one dose of treatment. Grade $\geq$ 3 AEs, irrespective of causality, were reported in 80.9% of patients in the palbociclib/fulvestrant arm and 37.9% in the placebo/fulvestrant arm. Non-hematologic grade $\geq$ 3 AEs were reported in 47.9% of patients treated with palbociclib/fulvestrant (7.4% related to treatment) versus. 37.9% in the placebo/fulvestrant arm (5.3% related to treatment) (Table S2). The most common AEs from any cause in $\geq$10% of the patients in either study arm are detailed in Table 3.

Serious adverse events (SAEs) occurred in 26.6% of patients in the palbociclib/fulvestrant arm and 20.0% in the placebo/fulvestrant arm. SAEs considered related to any study treatment that led to study drug discontinuation were reported in 3.2% and. 2.1% of patients in the palbociclib/fulvestrant and placebo/fulvestrant arms, respectively.

Permanent study treatment discontinuation associated with AEs was reported for 19 (20.2%) patients in the palbociclib/fulvestrant arm versus. five (5.3%) patients in the placebo/fulvestrant arm.

4. Discussion

The FLIPPER is the first study that aimed to evaluate palbociclib/fulvestrant versus placebo/fulvestrant as a first-line treatment for endocrine-sensitive ABC patients, considered as those with *de novo* metastatic disease and those whose disease relapsed >12 months after the completion of at least five years of (neo)adjuvant ET. The study demonstrated that palbociclib/fulvestrant significantly improved the one-year PFS rate compared with placebo/fulvestrant (83.5% vs 71.9%) in postmenopausal women with HR-positive/HER2-negative ABC, with a 45% reduction in the risk of one-year PD.

Median PFS was 31.8 and 22.0 months in the palbociclib/fulvestrant and placebo/fulvestrant arms, respectively, corresponding to a 48% reduction in the risk of PD. Patients treated with palbociclib/fulvestrant combination also had significantly better ORR and CBR at 24 weeks than those treated with placebo/fulvestrant. These data, albeit from a randomized phase II trial, support the benefit of adding palbociclib to fulvestrant as first-line treatment for postmenopausal women with HR-positive/HER2-negative ABC. This adds to the body of evidence collected in the MONALEESA-3 trial [8,12–14]. In the FLIPPER trial, we performed subset analyses on the benefit of adding palbociclib on either the one-year PFS or median PFS rates based on the stratification factors (visceral vs. non-visceral involvement and *de novo* metastatic vs. recurrent disease). Considering the exploratory nature of subset analyses, even more in a phase II study with relatively low patient numbers, the study suggests that patients with *de novo* metastatic disease might benefit more from the addition of palbociclib than those with recurrent disease. This result is hypothesis generating and raises the question of whether CDK4/6i could be safely omitted in patients with recurrent disease treated with fulvestrant. Additional subset analyses suggest a greater benefit from palbociclib/fulvestrant in patients with multiple sites of disease; however, this is not considered in clinical decision-making. The safety profile of palbociclib/fulvestrant was consistent with that reported in other clinical trials of palbociclib. Most AEs observed in the palbociclib/fulvestrant arm were of mild or moderate severity, except for those of hematologic origin, with no new safety signals reported. Although neutropenia was the most common all-grade and grade 3 or 4 AE, there were no reports of febrile neutropenia. The lack of reported severe liver or cardiac AEs and a generally low gastrointestinal toxicity may play a role in selecting patients based on pre-existing conditions or patient preferences.

In the FLIPPER trial, the ORR for the palbociclib/fulvestrant arm was 68.3% and the CBR at 24 weeks was 90.4%. The benefit in terms of PFS and ORR was similar in patients with and without visceral disease. These data confirm and extent the evidence supporting the capability of CDK4/6i combos to provide adequate response rates, even in patients with visceral or high tumor burden disease. The results are reassuring for considering CDK4/6i combined with endocrine therapy as upfront treatment for the majority of patients with HR positive/HER2 negative ABC. Two recent systematic reviews and meta-analysis support the superiority of CDK4/6i plus endocrine therapy over endocrine therapy alone in the vast majority of patients [22,23]. The authors also noted that in selected patients with low tumor burden and indolent endocrine-sensitive disease, particularly those with only-bone and very limited disease, endocrine therapy alone might still remain a valid option [22,23].

To date, only two phase III studies evaluating the combination of CDK4/6i plus fulvestrant in endocrine-sensitive ABC, MONALEESA-3 [8] and PARFISAL [16] have been reported. MONALEESA-3 tested fulvestrant with or without ribociclib in patients with HR-positive and HER2-negative ABC receiving treatment in a first-line setting (*de novo* or recurrence >12 months from the completion of (neo])adjuvant therapy) or in a second-line setting or with an early relapse [8,14]. The study showed that the addition of ribociclib significantly improved both PFS and OS in the general population and was consistent in both subsets (first- and second-line groups). PARSIFAL aimed to identify the best endocrine agent to be combined with palbociclib in this first-line setting. PARFISAL was not able to show an

Table 3
Summary of treatment-emergent adverse events from any cause that occurred in at least 10% of the patients in either study group (safety population)[a].

	Palbociclib plus fulvestrant			Placebo plus fulvestrant		
	$n = 94$			$n = 95$		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Any AE	94 (100)	75 (79.8)	8 (8.5)	94 (98.9)	36 (37.9)	1 (1.1)
Non-hematologic						
Fatigue	61 (64.9)	4 (4.3)	0	42 (44.2)	0	0
Hypertension	43 (45.7)	18 (19.1)	0	41 (43.2)	13 (13.7)	0
Arthralgia	31 (33.0)	0	0	27 (28.4)	2 (2.1)	0
Back pain	25 (26.6)	3 (3.2)	0	22 (23.2)	2 (2.1)	0
Respiratory infection	28 (29.8)	10 (10.6)	0	15 (15.8)	0	0
Chills	25 (26.6)	0	0	16 (16.8)	0	0
Hot flashes	18 (19.1)	0	0	23 (24.2)	0	0
Nausea	18 (19.1)	1 (1.1)	0	21 (22.1)	1 (1.1)	0
Constipation	18 (19.1)	0	0	18 (18.9)	0	0
Diarrhea	22 (23.4)	0	0	13 (13.7)	2 (2.1)	0
Weight gain	22 (23.4)	7 (7.4)	0	11 (11.6)	4 (4.2)	0
Cough	14 (14.9)	0	0	16 (16.8)	0	0
Overdose	12 (12.8)	0	0	17 (17.9)	0	0
Sinus tachycardia	14 (14.9)	0	0	14 (14.7)	0	0
Vomiting	13 (13.8)	0	0	15 (15.8)	0	0
Headache	10 (10.6)	0	0	16 (16.8)	0	0
Mucositis oral	19 (20.2)	1 (1.1)	0	7 (7.4)	0	0
Sinus bradycardia	13 (13.8)	0	0	13 (13.7)	0	0
Anorexia	15 (16.0)	0	0	9 (9.5)	0	0
Weight loss	11 (11.7)	0	0	13 (13.7)	1 (1.1)	0
Dyspnea	11 (11.7)	0	0	12 (12.6)	0	0
Urinary tract infection	12 (12.8)	0	0	11 (11.6)	1 (1.1)	0
Pain in the extremity	10 (10.6)	1 (1.1)	0	12 (12.6)	1 (1.1)	0
Alopecia	13 (13.8)	0	0	8 (8.4)	0	0
Dizziness	14 (14.9)	0	0	7 (7.4)	0	0
Hypothermia	12 (12.8)	0	0	8 (8.4)	0	0
Pruritus	12 (12.8)	0	0	6 (6.3)	0	0
Fever	11 (11.7)	0	0	5 (5.3)	0	0
Dry mouth	10 (10.6)	0	0	3 (3.2)	0	0
Hematologic						
Neutropenia	91 (96.8)	58 (61.7)	6 (6.4)	22 (23.2)	0	0
WBC decreased	88 (93.6)	23 (24.5)	2 (2.1)	24 (25.3)	0	0
Anemia	80 (85.1)	3 (3.2)	0	33 (34.7)	0	0
Lymphocytopenia	64 (68.1)	13 (13.8)	1 (1.1)	46 (48.4)	2 (2.1)	0
Thrombocytopenia	52 (55.3)	1 (1.1)	1 (1.1)	14 (14.7)	0	0
Biochemistry parameters						
Hyperglycemia	73 (77.7)	7 (7.4)	0	63 (66.3)	1 (1.1)	0
AST increased	53 (56.4)	2 (2.1)	0	31 (32.6)	0	0
ALT increased	46 (48.9)	3 (3.2)	0	33 (34.7)	0	0
AP increased	40 (42.6)	1 (1.1)	0	38 (40.0)	0	0
Hyperkalemia	21 (22.3)	2 (2.1)	1 (1.1)	18 (18.9)	2 (2.1)	0
Hypercalcemia	18 (19.1)	0	1 (1.1)	20 (21.1)	0	0
Hypocalcemia	25 (26.6)	1 (1.1)	1 (1.1)	12 (12.6)	0	0
Hypomagnesemia	22 (23.4)	1 (1.1)	1 (1.1)	13 (13.7)	0	0
Hypernatremia	23 (24.5)	0	0	11 (11.6)	0	0
Creatinine increased	23 (24.5)	0	0	10 (10.5)	0	0
Hypoalbuminemia	20 (21.3)	2 (2.1)	0	10 (10.5)	0	0
Hyponatremia	15 (16.0)	0	0	12 (12.6)	0	0
Hypermagnesemia	9 (9.6)	0	0	16 (16.8)	3 (3.2)	0
Hypokalemia	17 (18.1)	2 (2.1)	0	6 (6.3)	0	1 (1.1)

AE, adverse event; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase.
[a] Adverse events were coded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

improvement in PFS by adding palbociclib to fulvestrant versus letrozole/palbociclib. However, the role of palbociclib in the efficacy of the fulvestrant and palbociclib remained to be established in this setting The authors concluded that NSAI is the preferred combining agent to palbociclib in endocrine-sensitive disease, whereas fulvestrant in combination with CDK4/6i could be considered as first-line therapy in endocrine-sensitive patients who are intolerant to NSAI or with *PIK3CA* wild-type tumors.

Here, for the first time, the FLIPPER study demonstrated the benefit of palbociclib/fulvestrant as first-line treatment in patients with endocrine-sensitive, HR-positive, HER2-negative ABC. This trial must be interpreted in the context of the following limitations; this was a phase II trial instead of a phase III trial, the pragmatic primary endpoint (PFS rate at 1 year) was determined due to the long PFS expected for the control arm, and the focus of this trial was postmenopausal women. It is however reasonable to consider that palbociclib/fulvestrant could also benefit premenopausal women (adding ovarian suppression) and men.

At present, in the majority of patients with endocrine sensitive ABC, the first line consists of aromatase inhibitor (AI)/CDK4/6i. Although the FLIPPER data will not change this paradigm, it provides valuable data for considering palbociclib/fulvestrant instead of fulvestrant alone in patients unsuited for AI. Furthermore, our results establish this combination as a preferred control arm instead of fulvestrant alone for future trials in this setting considering the use of selective estrogen receptor degraders (SERDs).

List of where and when the study has been presented in part elsewhere

The study was presented in part at the 39th Annual San Antonio Breast Cancer Symposium in San Antonio, Texas, USA (poster within trial-in-progress category) and at the European Society of Medical Oncology Virtual Meeting 2020 (late breaking abstract, oral presentation in a Proffered Paper session).

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Trial registration number

Sponsor Study Code: GEICAM/2014-12.
EudraCT Number: 2015-002437-21.
ClinTrials.gov reference: NCT02690480.

Access to data

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

Role of the funding source

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Author contributions

J. Albanell: conceptualization and funding acquisition. J. Albanell and S. Bezares: methodology, supervision and project administration. M. Casas: formal analysis. J Albanell, M. T. Martínez, M. Ramos, M. O'Connor, L. de la Cruz-Merino, A. Santaballa, N. Martínez-Jañez, F. Moreno, I. Fernández, J. Alarcón, J. A. Virizuela, J. de la Haba-Rodríguez, P. Sánchez-Rovira, L. González-Cortijo, M. Margelí, A. Sánchez-Muñoz, A. Antón, F. Rojo: data collection, curation and resources. J. Albanell, M Casas and S. Bezares: writing manuscript original draft. All authors: reviewing and editing manuscript.

Conflict of interest statement

Joan Albanell has received consulting or advisory role fees from Roche, Pfizer, Amgen, MSD, Lilly and Daiichi-Sankyo; research funding or grant support trials by Roche, Pfizer, Amgen, MSD, Lilly, Daiichi-Sankyo; and travel and accommodation support from Roche, Pfizer, Amgen, MSD, Lilly and Daiichi-Sankyo. **Manuel Ramos** has received honoraria from Novartis, Roche, and Pfizer. **Luis de la Cruz-Merino** has received consulting or advisory role fees from MSD-Merck, Roche Farma, Bristol-Myers-Squibb, Pierre-Fabré, Amgen and Novartis; research funding from MSD-Merck, Roche Farma and Celgene; speaker's honoraria from MSD-Merck, Roche-Farma, Bristol-Myers-Squibb and Amgen; and grant support by Roche Farma and Bristol-Myers-Squibb. **Ana Santaballa** has received consulting or advisory role fees from GSK, Clovis, MSD, AstraZeneca, Roche and Pfizer; speakers' honoraria from GSK, Clovis, Roche, MSD, AstraZeneca and Pfizer;

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Appendix A. Supplementary data

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