Breast Cancer Research and Treatment (2018) 168:559–566
https://doi.org/10.1007/s10549-017-4623-8

BRIEF REPORT

# Efficacy of palbociclib plus fulvestrant after everolimus in hormone receptor-positive metastatic breast cancer

**Pauline du Rusquec[1] · Clément Palpacuer[2] · Loic Campion[2] · Anne Patsouris[3] · Paule Augereau[3] · Carole Gourmelon[1] · Marie Robert[1] · Laurence Dumas[4] · Folliard Caroline[5] · Mario Campone[1] · Jean-Sébastien Frenel[1]**

Received: 6 December 2017 / Accepted: 11 December 2017 / Published online: 15 December 2017
© Springer Science+Business Media, LLC, part of Springer Nature 2017

## Abstract

**Background** Palbociclib, a CDK4-6 inhibitor, combined with endocrine therapy (ET) is a new standard of treatment for Hormone Receptor-positive Metastatic Breast Cancer. We present the first real-life efficacy and tolerance data of palbociclib plus fulvestrant in this population.

**Methods** From November 2015 to November 2016, patients receiving in our institution palbociclib + fulvestrant according to the Temporary Authorization for Use were prospectively analyzed.

**Results** 60 patients were treated accordingly; median age was 61 years; 50 patients (83.3%) had visceral metastasis, and 10 (16.7%) had bone-only disease. Patients had previously received a median of 5 (1–14) lines of treatment, including ET (median 3) and chemotherapy (median 2); 28 (46.7%) received previously fulvestrant and all everolimus. With a median follow-up of 10.3 months, median progression-free survival (mPFS) was 5.8 months (95% CI 3.9–7.3). Patients pretreated with fulvestrant had a similar PFS of 6.4 months (HR 1.00; 95% CI 0.55–1.83; $P = 1.00$). The most common AEs (adverse events) were neutropenia (93%), anemia (65%), and thrombocytopenia (55%).

**Conclusion** In this heavily pretreated population including everolimus, fulvestrant plus palbociclib provides an mPFS of 5.8 months with the same magnitude of benefit for fulvestrant-pretreated patients.

**Keywords** Palbociclib · Fulvestrant · Everolimus · Metastatic breast cancer · HR positive · PALOMA-3

## Introduction

Hormone Receptor-positive (HR+) breast cancer is the most common subtype of breast cancer, and while endocrine therapy (ET) has long been a mainstay of therapy, treatment resistance ultimately develops [1].

The recent approval of CDK4/6 inhibitors in combination with ET represents a new standard of treatment in HR + Metastatic Breast Cancer (MBC). In frontline, the MONALEESA-2, the PALOMA-2, and the MONARCH 3 trials demonstrated the benefit of adding CDK4/6 inhibitor to ET [2–4]. The magnitude of benefit in favor of the combination arm was similar in these trials: with palbociclib, median progression-free survival (mPFS) of 14.5 months without versus 24.8 months; Hazard Ratio (HR) of 0.58 (95% CI 0.46–0.72; $P < 0.000001$), 14.7 months versus not reached; and HR of 0.56 (95% CI 0.43–0.72; $P < 0.000001$) with ribociclib and 14.7 months versus not reached; and a HR of 0.54 (95% CI 0.40–0.72; $P = 0.000021$) with

✉ Pauline du Rusquec
pauline.durusquec@ico.unicancer.fr

1 Medical Oncology Department, Centre René Gaudducheau, Institut de Cancérologie de l'Ouest (ICO), Saint-Herblain, France

2 Biometrics Department, Centre René Gaudducheau, Institut de Cancérologie de l'Ouest (ICO), Saint-Herblain, France

3 Medical Oncology Department, Centre Paul Papin, (ICO), Saint-Herblain, France

4 Pharmacy Department, Centre René Gaudducheau, Institut de Cancérologie de l'Ouest (ICO), Saint-Herblain, France

5 Pharmacy Department, Centre Paul Papin (ICO), Saint-Herblain, France

abemaciclib. These results are reinforced by the PALOMA-3 and the MONARCH 2 trials demonstrating the benefit of adding CDK4/6 inhibitor to fulvestrant in a more advanced setting: mPFS of 9.5 months versus 4.6 months (HR 0.46; 95% CI 0.36–0.59; $P < 0.0001$) with palbociclib; and mPFS of 16.4 months versus 9.3 months (HR 0.55; 95% CI 0.45–0.68; $P < 0.001$) with abemaciclib [5, 6].

In the MONARCH 1 trial, abemaciclib has provided an impressive disease control rate of 67.4% in 132 patients pretreated with a median number of five lines but with a significant gastrointestinal toxicity [7]. Abemaciclib has therefore been approved as a single therapy by the Food and Drug Administration. However, in post hoc subanalysis of the PALOMA-3 trial, patients who had received ≥ 3 lines of treatment did not derive any PFS benefit from the addition of palbociclib to endocrine therapy [5, 8]. This contrasts with the results of the BOLERO-2 trial where everolimus associated with ET provided a PFS benefit whatever was the number of previous endocrine line of treatment. Of note, in the PALOMA-3 and the MONARCH 2 trials, none of the patients had received prior everolimus, which is a standard of care in the context of MBC resistant to ET.

Given these data confirming efficacy and a correct profile of tolerance, CDK4/6 inhibitors represent an important path forward in HR + MBC. In France, a Temporary Authorization for Use (TAU) was granted to palbociclib in November 2015, but restricted to postmenopausal HR + HER2-negative MBC previously treated with everolimus. This population represents a unique subset of patients as no data issued from the randomized trial will be available. We report the efficacy and safety of palbociclib combined with fulvestrant (ET) in that population.

## Methods

### TAU

The TAU procedure is an exceptional measure making available in France medicinal products before their Marketing Authorization. This regulatory provision, stipulated in the French Public Health Code, has been applied in France since 1994. Before instigating the treatment, patients had to be informed about the conditions of exceptional access and that data will be collected, and will be passed on to the TAU holder and the ANSM (The National Agency for Safety of Medication), and may be computerized.

### Patients

TAU for palbociclib was requested after discussion during a breast tumor board. The medical data of all patients included in this TAU at the Institut de Cancérologie de l'Ouest (ICO) were prospectively recorded and included in a database. Fulvestrant was administered every 28 days at the dose of 500 mg after a loading dose. The starting dose of palbociclib was 125 mg per day 3 weeks on, 1 week off. Dose reduction to 100 mg (then 75 mg) was applied in case of grade 4 (or febrile grade 3) neutropenia or any grade 3 or more non-hematologic toxicity. Clinical outcomes and adverse events were monthly recorded, and the palbociclib efficacy was evaluated at every 2 cycles by CT-scan. Premenopausal patients received also Ovarian Function Suppression (OFS) by Luteinizing Hormone-Releasing Hormone-agonists (LHRH-agonists).

### Statistics

Our analysis was particularly focused on the PFS1, defined as the time from the first administration of palbociclib to the date of disease progression. Other endpoints were Overall Survival (OS), defined as the time from the first administration of palbociclib to the date of death from any cause, and PFS2 defined as the duration of the subsequent line of treatment if indicated. Safety data are presented in accordance with the terminology and gradation system CTCAE v4.0 (Common Terminology Criteria for Adverse Events version 4.0). Response evaluation was according to Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1). Survival curves were calculated using the Kaplan–Meier's method. Hazard ratio and 95% Confidence Intervals (95% CI) were calculated using a Cox model. The comparison of the different subgroups was carried out using the Wald test. Significance was defined at the $P < 0.05$ level.

## Results

### Patients' clinical and pathological features

From November 2015 to November 2016, 60 patients from our center were included in the TAU cohort. Baseline patient's characteristics are described in Table 1.

### Treatment management and adverse events (AEs)

Median follow-up was 10.3 months (range 0.9–19.5 months). AEs considered related to palbociclib were observed in 59/60 patients. Safety data are detailed in Table 2. The unique serious AEs experienced by more than 10% of our patients were grade 3 and 4 treatment-related neutropenia which were observed in 46 and 13 patients, respectively. One fatal febrile neutropenia was reported in a patient after

**Table 1** Characteristics of the patients

| Characteristics | *n* |
|---|---|
| Age | |
| Median | 46 years |
| Range | (24–75 years) |
| Stage at initial diagnosis | |
| Localized | 47 (78.3%) |
| Metastatic | 13 (21.7%) |
| Adjuvant endocrine therapy | |
| Yes | 31 (51.7%) |
| Median duration (months) | 49.8 (12–108) |
| Documented sensitivity to adjuvant endocrine therapy ($n = 31$) | |
| Yes | 12 (38.7%) |
| No | 19 (61.3%) |
| Prior therapies for metastatic disease | *n* |
| Number of prior lines of therapy for metastatic disease | |
| Median | 5 (1–14) |
| Prior endocrine therapy | |
| 1 or 2 | 25 (41.7%) |
| ≥ 3 | 35 (58.3%) |
| Median | 3 (1–7) |
| Total duration of endocrine therapy (months) | |
| Mean | 45.5 |
| Median | 32.3 (2.7–193.7) |
| Previous fulvestrant | |
| Yes | 28 (46.7%) |
| No | 32 (53.3%) |
| Duration of everolimus (months) | |
| Median | 7 (1.4–40.7) |
| Prior chemotherapy | |
| 0 or 1 | 28 (46.7%) |
| ≥ 2 | 32 (53.3%) |
| Median—no. (range) | 2 (0–8) |
| Palbociclib treatment | *n* |
| Age at initiation of the treatment | |
| Median, year | 61 years |
| Range, year | (28–81 years) |
| Metastatic sites | |
| Visceral | 50 (83.3%) |
| Bone only | 10 (16.7%) |
| LDH (UI/L) at day 1—no. (%) ($n = 51$) | |
| < 250 | 27 (52.9%) |
| ≥ 250 | 24 (47.1%) |
| Lymphocytes (G/L) at day 1—no. (%) ($n = 55$) | |
| < 1.2 | 29 (52.7%) |
| ≥ 1.2 | 26 (47.3%) |

**Table 2** Adverse events according CTCAE v4.0

| Event (*n*, %) | Any grade | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| Any adverse event | 59 (98.3%) | 46 (76.7%) | 13 (21.7%) | 1 (1.7%) |
| Neutropenia | 56 (93.3%) | 34 (56.7%) | 10 (16.7%) | 0 |
| Febril neutropenia | 2 (3.3%) | 0 | 1 (1.7%) | 1 (1.7%) |
| Anemia | 39 (65.0%) | 3 (5.0%) | 0 | 0 |
| Trombopenia | 33 (55.0%) | 5 (8.3%) | 2 (3.3%) | 0 |
| Fatigue | 10 (16.7%) | 2 (3.3%) | 0 | 0 |
| Alopecia | 3 (5.0%) | 0 | 0 | 0 |
| Nausea | 2 (3.3%) | 0 | 0 | 0 |
| Stomatitis | 2 (3.3%) | 1 (1.7%) | 0 | 0 |
| Gastrointestinal bleeding | 1 (1.7%) | 1 (1.7%) | 0 | 0 |
| Elevated transaminases | 1 (1.7%) | 0 | 0 | 0 |
| Skin (rash) | 1 (1.7%) | 0 | 0 | 0 |
| Renal failure | 1 (1.7%) | 0 | 0 | 0 |
| Vertigo | 1 (1.7%) | 0 | 0 | 0 |

8.6 months on palbociclib. Palbociclib was suspended in 36 (60.0%) patients for AEs mainly neutropenia. Twenty (33.3%) patients had a dose reduction to 100 mg ($n = 11$; 18.3%) or 75 mg ($n = 9$; 15.0%) according to the guidelines.

## Efficacy of palbociclib

The mPFS1 was 5.8 months (95% CI 3.9–7.3) (Fig. 1), and median OS was not reached. Best response was evaluable for all patients. A partial response was obtained in 16 patients (26.7%); 27 ($n = 45\%$) had a stable disease and 17 (28.3%) a progressive disease as the best response.

Twenty-eight patients (46.7%) had previously received fulvestrant. Interestingly, patients subsequently re-challenged with fulvestrant and palbociclib had a PFS of 6.4 months, which was similar to patients who did not receive fulvestrant previously (HR 1.00; 95% CI 0.55–1.83, $P = 1.00$) (Fig. 2). Patients pretreated with fulvestrant were statistically older (median 67 vs. 57 year; $P = 0.0169$), had received more treatments for metastatic disease (median 7 versus 3 lines; $P < 0.0001$) and especially for a longer duration of ET (median 44.3 vs. 26.3 months; $P = 0.0018$).

The mPFS was not modified according to the duration of previous everolimus use (HR 0.82; 95% CI 0.461.46; $P = 0.50$).

The PFS1 was similar for patients with bone-only disease or visceral disease (HR 1.27; 95% CI 0.56–2.84; $P = 0.57$). LDH serum levels (with a cutoff value of upper limit normal, 250 UI/L) and lymphocytes count (Normal vs low values) were known for 51 and 55 patients, respectively. No variables had a significant prognostic factor for patient's outcome on palbociclib, but LDH and lymphocytes' count were not far from significance.

A forest plot summarizes the main analyses of the subgroups studied (Fig. 3).

## Analysis of the subsequent line of treatment following palbociclib

At the time of this analysis, 13 patients were still on treatment. The remaining 47 patients completed palbociclib

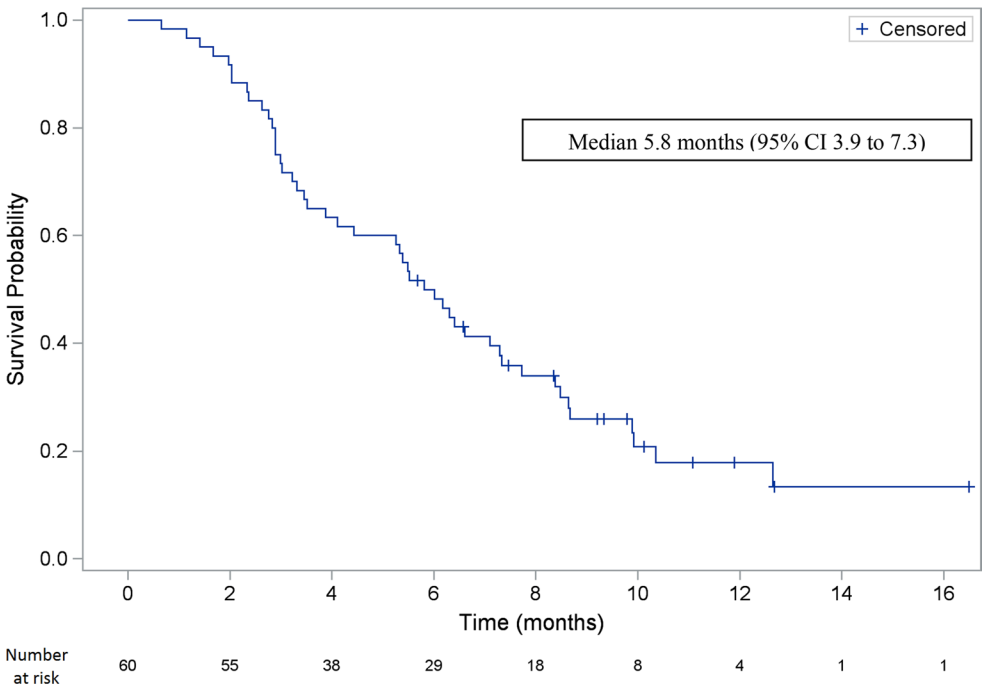


**Fig. 1** Progression Free Survival on fulvestrant + palbociclib (PFS1)

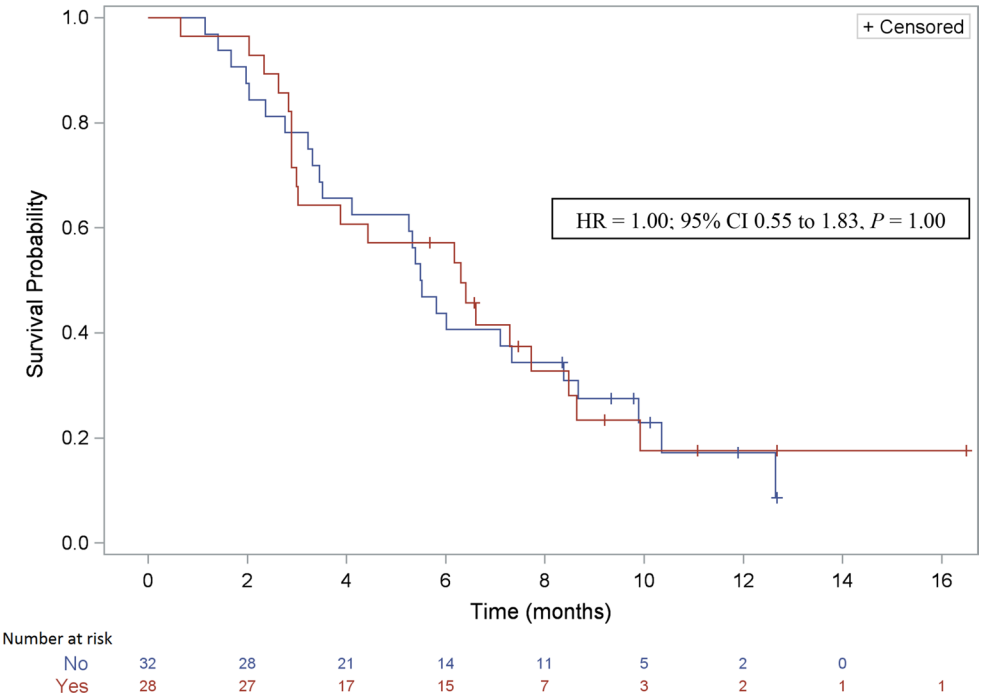


**Fig. 2** PFS1 according to fulvestrant pretreatment

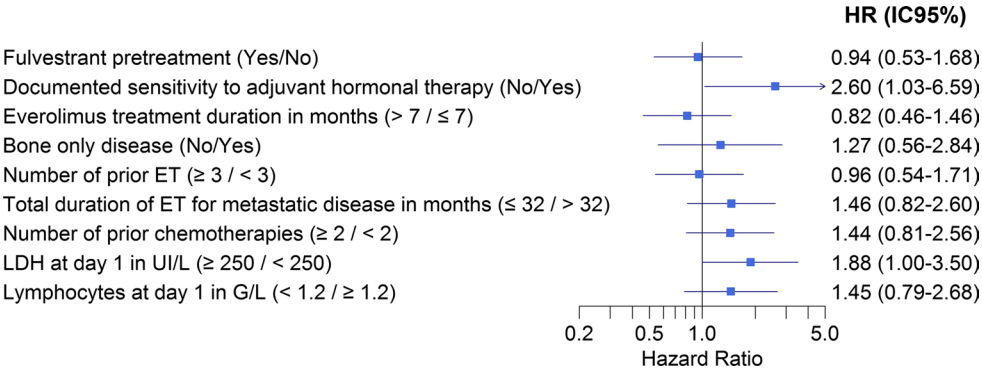


**Fig. 3** Subgroup analyses

therapy at different doses levels: 125 mg ($n = 32$), 100 mg ($n = 9$), or 75 mg ($n = 6$). Among these 47 patients, 7 received Best Supportive Care (BSC) only, and 40 received one or more line of treatment, mainly chemotherapy ($n = 38$) with a median PFS2 of 3.3 months (95% CI 2.2–5.0) (Fig. 4).

## Discussion

In this everolimus-pretreated population, palbociclib plus fulvestrant provides a mPFS of 5.8 months with a tolerable safety profile despite a median of 5 previous lines of treatment. To our knowledge, this is the largest reported cohort of patients in that setting.

Palbociclib is the first-in-class CDK4/6 inhibitor approved for HR + MBC. Pivotal registration trial PALOMA-3 assessed its efficacy in combination with fulvestrant in patients whose disease progressed during prior ET [8, 9]. This trial had shown a mPFS of 9.5 months in the combination arm versus 4.6 months in the fulvestrant arm. This result differs somewhat with the 5.8 months mPFS in our cohort. Indeed, in the PALOMA-3 trial, only 14% of the patients had received 3 lines or more of ET while 58.3% of our patients did. Notably none of the patients had received prior everolimus for MBC in this trial although it is a standard of care in the context of disease resistant to ET. This exclusion criterion was similar in the MONARCH 2 trial. In addition, only 33% of patients in the PALOMA-3 fulvestrant plus palbociclib subgroup had received chemotherapy (1 line or more) for metastatic disease although 78% of our cohort had received previous chemotherapy. Our population is a more advanced and pretreated one, explaining the 5.8 months mPFS compared with the PALOMA-3 trial.

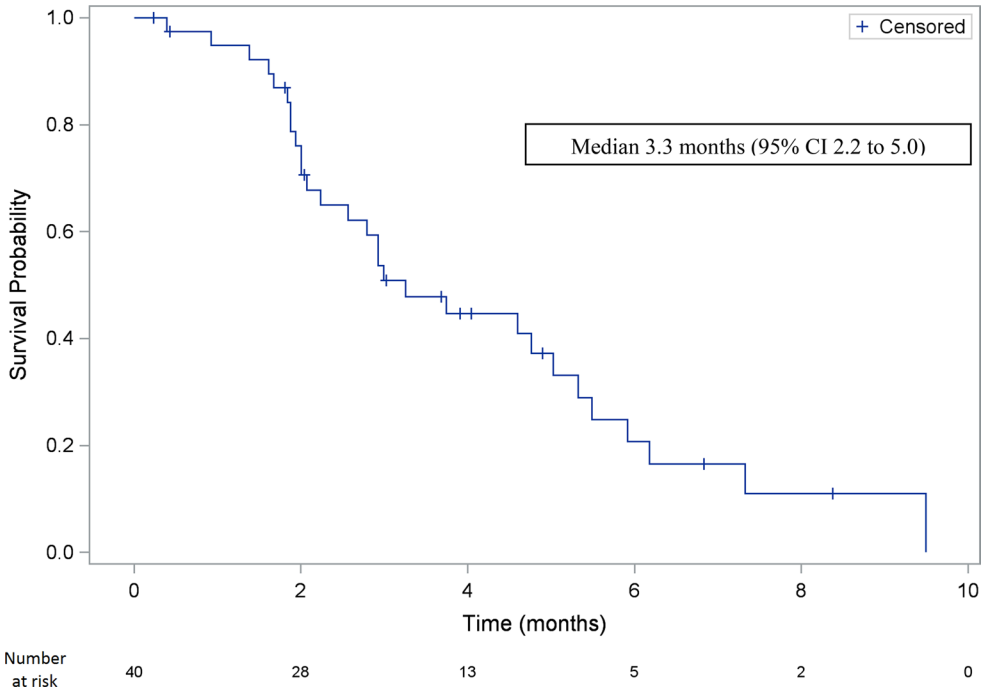


**Fig. 4** Progression Free Survival on subsequent line (cancer specific treatment) (PFS2)

Few clinical trials have evaluated the efficacy of ET after everolimus use in MBC. Dhakal et al. have presented the results of a retrospective cohort of 23 patients pretreated with everolimus and receiving fulvestrant and palbociclib [10]. The mPFS was 2.9 months (95% CI 2.0–4.2); no objective response was observed, and clinical benefit rate was of only 17.4%. These data contrast with our results. The population was similar in terms of rate of visceral metastasis (82% vs. 83% in our cohort), but few data were presented on the previous number of lines of treatment. The BELLE-3 trial assessed whether the addition of buparlisib (oral pan-class I PI3 K inhibitor) to fulvestrant improved PFS in treating patients with HR+, HER2-negative, aromatase inhibitor-treated, locally advanced MBC that progressed on or after treatment with everolimus [11]. 432 patients were randomized to a combination of daily buparlisib plus fulvestrant or placebo plus fulvestrant. Among these patients, 73% had visceral metastasis, 35% had received chemotherapy for metastatic disease, and 69% had received ≥ 2 lines of endocrine therapy for metastatic disease but were fulvestrant naïve. Median PFS for patients in the buparlisib arm was 3.9 months and only 1.8 months for those in the placebo arm. Thus, fulvestrant monotherapy after everolimus use provides a very modest PFS. This contrasts strikingly with the 5.8 months PFS obtained in combination with palbociclib in our study. Thus, two hypotheses can be raised. The first is that Palbociclib is potentially active as monotherapy in this ET-resistant population and represents the backbone of treatment. However, clinical data of Palbociclib as single agent are limited [12]. The second explanation is that adding palbociclib to fulvestrant may partially reverse the acquired resistance to ET. Preclinical evidence supports this hypothesis [13]. More recently, the Italian phase II, multicenter, open-label To Reverse Endocrine Resistance (TREnd) clinical trial has included 115 postmenopausal patients diagnosed with HR-positive, HER2-negative metastatic breast cancer whose disease had progressed after 1 or 2 endocrine treatments [14]. The patients were randomized to receive palbociclib either alone ($n = 58$) or in combination with their current endocrine therapy (aromatase inhibitor or fulvestrant) ($n = 57$). Around 75% of the patients had visceral metastasis, 97 had received ≤ 2 lines of previous ET, and around 30% had received previous chemotherapy for MBC. Despite Clinical Benefit Rate being similar in both groups, duration of clinical benefit was significantly longer for the combination (median PFS, 11.5 vs. 6 months for palbociclib alone; HR 0.35; 95% CI 0.18–0.7; $P = 0.002$). PFS was significantly longer for the combination for patients whose duration of the prior line of ET was > 6 months (median PFS, 11.5 vs. 6.5 months for palbociclib alone; HR 0.53; 95% CI 0.3–0.9; $P = 0.02$). The authors conclude that palbociclib could reverse the acquired resistance to the same endocrine agent used in the prior line of ET. In our population, 46.7% had already been treated by fulvestrant for metastatic disease. Patient re-challenged with fulvestrant plus palbociclib derived the same mPFS as patients who had never received fulvestrant. From our point of view, this is an important information.

The safety profile of palbociclib in our series is superimposable to that of PALOMA-3 and prior palbociclib clinical

trials. Grade 3 or 4 AEs occurred in 46 patients (76.7% vs. 73% in the PALOMA-3 trial). The most observed Grade 3 or 4 AEs were neutropenia (56.7% in our series, 65% for PALOMA-3), thrombocytopenia (8.3–3%), and anemia (5–3%). We did not report any grade 3 hepatic toxicity. As in the PALOMA-3 trial, no non-hematological grade 3 or more AE in more than 10% of patients were reported. All of our patients were able to resume treatment after the management of potential adverse events according to the TAU procedure of dose reduction; but one patient died of febrile neutropenia after more than 8 months of treatment at full dose. The safety profile is favorable and significant in the context of advanced disease where quality of life is the main goal. Interestingly, all CDK4-6 inhibitors do not seem to be similar in terms of toxicity. Abemaciclib has a different safety profile with a less-frequent hematological toxicity (23.6% Grade 3 neutropenia), but more digestive toxicity with a diarrhea (86.4% of patients including 13.4% of grade 3) [6]. Beyond the results of the phase 3 trials, this could impact the future choice of the molecule for clinicians.

We assessed the outcome of patients after progression with fulvestrant and palbociclib. Forty patients were evaluable and had a PFS2 of 3.3 months (95% CI 2.2–5.0). Thirty-eight patients received chemotherapy and 2 received ET. Similar data have been shown from the PALOMA-3 trial: 142 patients of the fulvestrant plus placebo group were evaluable for PFS2. Mean durations from the start to the end of the immediate follow-up therapy were, respectively 4.8 (3.7–6.0), 3.4 (2.4–6.1), and 3.4 months (2.4–6.8) for chemotherapy ($n = 124$), endocrine therapy ($n = 57$), and targeted therapy ($n = 44$) in the fulvestrant plus palbociclib group [15]. These results are quite disappointing with very short PFS even with chemotherapy. The impressive results of CDK4/6 inhibitors in frontline raise specific concerns about the management of subsequent lines of treatment. Indeed, even if there is a clear improvement in PFS with this combination, resistance finally occurs and could select a more aggressive phenotype impeding the efficacy of following treatment. Data showing that this combination increases the overall survival are eagerly awaited.

## Conclusion

In this everolimus-pretreated population, we show that the association of fulvestrant plus palbociclib provides a mPFS of 5.8 months with a favorable safety profile. Patients previously treated with fulvestrant seem to derive the same magnitude of benefit compared to fulvestrant-naive patients suggesting a potential reversion of the resistance to ET. The approvals of palbociclib, ribociclib, and abemaciclib represent a breakthrough for HR + MBC. However, many questions are raised, including the impact on overall survival, and the best sequence to use to help provide the best benefit for the patients with a minimal toxicity.

**Funding** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Compliance with ethical standards

**Conflict of interest** JSF and MC report receiving consulting fees from Pfizer; PA received fees for serving on advisory boards from Pfizer; PDR, JSF, AP, and MC received travel support from Pfizer.

## References

1. Augereau P, Patsouris A, Bourbouloux E, Gourmelon C, Abadie-Lacourtoisie S, Berton Rigaud D et al (2017) Hormonoresistance in advanced breast cancer: a new revolution in endocrine therapy. Ther Adv Med Oncol 9:335–346. https://doi.org/10.1177/1758834017693195
2. Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Paluch-Shimon S et al (2016) Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 375:1738–1748. https://doi.org/10.1056/NEJMoa1609709
3. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K et al (2016) Palbociclib and letrozole in advanced breast cancer. N Engl J Med 375:1925–1936. https://doi.org/10.1056/NEJMoa1607303
4. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J et al (2017) MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol. https://doi.org/10.1200/JCO.2017.75.6155
5. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N et al (2016) Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 17:425–439. https://doi.org/10.1016/S1470-2045(15)00613-0
6. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X et al (2017) MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol. https://doi.org/10.1200/JCO.2017.73.7585
7. Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D et al (2017) MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory $HR^+$/$HER2^-$ metastatic breast cancer. Clin Cancer Res. https://doi.org/10.1158/1078-0432.CCR-17-0754
8. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H et al (2015) Palbociclib in hormone-receptor–positive advanced breast cancer. N Engl J Med 373:209–219. https://doi.org/10.1056/NEJMoa1505270
9. Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A et al (2015) FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res 21:4760–4766. https://doi.org/10.1158/1078-0432.CCR-15-1185
10. Dhakal A, Matthews C, Zhang F, Levine EG, Edge SB, Salerno KE et al (2017) Outcome of palbociclib based therapy in hormone receptor positive metastatic breast cancer patients after treatment

with everolimus. J Clin Oncol 35:1054. https://doi.org/10.1200/JCO.2017.35.15_suppl.1054
11. Di Leo A, Ciruelos E, Janni W, Lonning PE, O'Regan R, Hubalek M et al (2015) BELLE-3: A phase III study of the pan-phosphatidylinositol 3-kinase (PI3 K) inhibitor buparlisib (BKM120) with fulvestrant in postmenopausal women with HR+/HER2– locally advanced/metastatic breast cancer (BC) pretreated with aromatase inhibitors (AIs) and refractory to mTOR inhibitor (mTORi)-based treatment. J Clin Oncol 33:TPS626. https://doi.org/10.1200/jco.2015.33.15_suppl.tps626
12. DeMichele A, Clark AS, Tan KS, Heitjan DF, Gramlich K, Gallagher M et al (2015) CDK 4/6 inhibitor palbociclib (PD0332991) in Rb + advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin Cancer Res 21:995–1001. https://doi.org/10.1158/1078-0432.CCR-14-2258
13. Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ et al (2009) PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res 11:1
14. Malorni L, Curigliano G, Minisini AM, Cinieri S, Tondini C, Arpino G et al (2017) A phase II trial of the CDK4/6 inhibitor palbociclib (P) as single agent or in combination with the same endocrine therapy (ET) received prior to disease progression, in patients (pts) with hormone receptor positive (HR+) HER2 negative (HER2 −) metastatic breast cancer (mBC) (TREnd trial). J Clin Oncol 35:1002. https://doi.org/10.1200/JCO.2017.35.15_suppl.1002
15. Turner N, Andre F, Cristofanilli M, Verma S, Iwata H, Loi S et al (2016) Abstract P4-22-06: treatment postprogression in women with endocrine-resistant HR+/HER2- advanced breast cancer who received palbociclib plus fulvestrant in PALOMA-3. Cancer Res 77:P4–P22