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Efficacité et tolérance du Palbociclib dans le cancer du sein avancé présentant des récepteurs hormonaux positifs et prétraité par Everolimus : Analyse des données de l'Autorisation Temporaire d'Utilisation (ATU) à l'Institut de Cancérologie de l'Ouest

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Palbociclib plus fulvestrant after everolimus in Hormone Receptor-positive (HR+) metastatic breast cancer: Efficacy and tolerance data from the French Temporary Authorization for Use at the Institut de Cancérologie de l'Ouest.

Presented at ESMO 2017 for the Breast cancer, Metastatic Poster Session by Pauline du Rusquec[1] (See appendix p30)

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SUMMARY

I. ABSTRACT

AIM: The CDK4/6 inhibitor palbociclib, combined with endocrine therapy is a new standard of treatment for Hormone Receptor-positive (HR+) Metastatic Breast Cancer (MBC). Before the European Medicines Agency approval, a Temporary Authorization for Use (TAU) has been set up in France restricted to patients pretreated with everolimus. We present the efficacy and tolerance of this combination in this population.

METHODS: From November 2015 to November 2016, all the patients receiving palbociclib + fulvestrant according to the TAU in our institution were prospectively included. Data from their medical records and Adverse Events (AEs) were collected.

RESULTS: 60 patients received at least one dose of palbociclib in combination with fulvestrant with a median age of 61 years. 50 patients (83.3%) had visceral metastasis and 10 (16.7%) had bone only disease. Patients had received a median of 5 (range 1 to 14) lines of treatment before palbociclib initiation, including endocrine therapy (median = 3) and chemotherapy (median = 2). Of note, 28 patients (46.7%) had received fulvestrant previously and all had been pretreated with everolimus. With a median follow-up of 10.3 months, median progression free survival (PFS) was 5.8 months (95% CI 3.9 to 7.3) and median overall survival was not reached. PFS was the same according to the presence of visceral metastasis or no (HR = 1.46; 95% CI 0.57 to 3.74; *P* = 0.42). Interestingly, patients treated previously with fulvestrant and subsequently re-challenged with fulvestrant and palbociclib had a PFS of 6.4 months, which was similar to patients who didn't receive fulvestrant previously (HR = 1.00; 95% CI 0.55 to 1.83; *P* = 1.00). The most common AE were neutropenia (n = 56), anemia (n = 39) and thrombocytopenia (n = 33). At the time of this analysis (April 2017), 40 patients received a further line of treatment after progression.

CONCLUSION: In this heavily pretreated population, the association of fulvestrant plus palbociclib provides an interesting median PFS of 5.8 months. Patients previously treated with fulvestrant seem to derive the same magnitude of benefit compared to fulvestrant naive patients.

II. ABBREVIATIONS

AE(s)	Adverse Event(s)
ANSM	National Agency for Safety of Medication
ATU	Autorisation Temporaire d'Utilisation
CDK 4/6	Cyclin-Dependant Kinase 4 and 6
ESR1	EStrogen Receptor 1
ET	Endocrine Therapy
HR	Hazard Ratio
HR+	Hormone Receptor–positive (HR+)
MBC	Metastatic Breast Cancer
mTOR	mechanistic Target Of Rapamycin
MONALEESA	Mammary ONcology Assessment of LEE011's Efficacy and SAfety
OS	Overall Survival
PFS	Progression Free Survival
PFS1	Progression Free Survival 1 (palbociclib)
PFS2	Progression Free Survival 2 (subsequent line of treatment)
TAU	Temporary Authorization for Use

III. INTRODUCTION

Hormone Receptor–positive (HR+) breast cancer is the most common subtype of breast cancer, and while endocrine therapy has long been a mainstay of therapy for these patients, treatment resistance ultimately develops. Therefore, better therapeutic options are needed.

The recent approval of CDK4/6 inhibitors in combination with Endocrine Therapy (ET) represents a breakthrough and a new standard of treatment in HR+ Metastatic Breast Cancer (MBC). In front line, the MONALEESA-2 trial and the PALOMA-2 trial have demonstrated the striking benefit of adding CDK4/6 inhibitor (ribociclib and palbociclib respectively) to first-line endocrine therapy in these patients [1,2]. The magnitude of benefit for the combination arm is similar in these both trials with a median PFS of 14.5 months versus 24.8 months with palbociclib (Hazard Ratio (HR) = 0.58; 95% CI 0.46 to 0.72; $P < 0.000001$) and a median PFS of 14.7 months versus median not reached with ribociclib (HR = 0.56; 95% CI 0.43 to 0.72; $P < 0.000001$). These results are reinforced by the PALOMA-3 trial which has demonstrated a PFS benefit of 5 months by combining palbociclib and fulvestrant versus fulvestrant alone in a more advanced setting: 4.6 months versus 9.5 months (HR = 0.46; 95% CI 0.36 to 0.59; $P < 0.0001$) [3]. In addition the MONARCH 2 trial has shown that abemaciclib, a third CDK4/6 inhibitor, combined with fulvestrant increased PFS from 16.4 versus 9.3 months; (HR = 0.55; 95% CI 0.45 to 0.68; $P < 0.001$) in patients who had progressed while receiving endocrine therapy [4].

Given their relative favorable profile of tolerance, the efficacy and toxicity of CDK4/6 inhibitors in a more advanced setting is a specific question for the community. Monotherapy with abemaciclib provided an impressive disease control rate of 67.4% in 132 patients pretreated with a median number of 5 lines with a significant toxicity in the MONARCH 1 trial [5]. However, in the PALOMA-3 trial, patients who received 3 lines or more of treatment didn't seem to derive any benefit from the addition of palbociclib to endocrine therapy [3,6]. This contrasts with the results of the BOLERO-2 trial where everolimus, an mTOR inhibitor associated with endocrine therapy, provided a PFS benefit whatever the number of previous line of treatment. Of note, in the PALOMA-3 trial and in the MONARCH-2 trial, none of the patients had received prior everolimus, which is a standard of care in the context of MBC resistant to ET.

In France, a Temporary Authorization for Use (TAU) was granted to palbociclib in November 2015 before the approval. Prescription was restricted to post-menopausal HR-positive HER2-negative advanced or metastatic breast cancer previously treated with an aromatase inhibitor and everolimus.

The patients should not present a symptomatic visceral disease and were not eligible for any ongoing clinical trial. 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 ET in that population.

IV. METHODS

1) ATU

The “Autorisation Temporaire d’Utilisation” (“Temporary Authorizations for Use”) or ATU procedure is an exceptional measure making available medicinal products that have not yet been granted a Marketing Authorization. The aim of ATUs is to provide early access to new promising treatments where a genuine public health need exists, i.e. in the treatment of patients suffering from serious disease and having reached a situation of therapeutic impasse. This regulatory provision, stipulated in the French Public Health Code, has actually been applied in France since 1994. Before instigating the treatment, patient had to be informed about the conditions of exceptional access. The patients had also to be informed that data will be collected, particularly relative to safety and that this data will be passed on the ATU holder and the ANSM (National Agency for Safety of Medication) and may be computerized.

2) Patients

TAU for palbociclib was requested after discussion during a breast tumor board. The medical data of all patients included in this TAU at Institut de Cancérologie de l’Ouest (ICO) were prospectively recorded and included in a database. Blood tests were performed before palbociclib initiation, at the beginning of each cycle, as well as Day 14 of the first two cycles, and as clinically indicated. Fulvestrant was administered every twenty-eight days at the dose of 500 mg after a loading dose. The starting dose of palbociclib was 125 mg per day orally for 3 weeks, followed by 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 palbociclib efficacy was evaluated every 2 cycles by CT-scan. Premenopausal patients received also Ovarian Function Suppression (OFS) by Luteinizing Hormone Releasing Hormone-agonists (LHRH-agonists).

3) Statistics

Characteristics of the population included point estimates (numbers and percentages) for the qualitative variables, mean, standard deviation and median with 95% confidence intervals for the quantitative variables. Safety data are presented in accordance with the terminology and gradation system CTCAE v4.0 (Common Terminology Criteria for Adverse Events version 4.0). Primary end point was the Progression Free Survival 1 (PFS1), defined as the time from the first administration of palbociclib to the date of disease progression. Secondary end-points were Overall Survival (OS), defined as the time from the first administration of palbociclib to the date of death from any cause, and Progression Free Survival 2 (PFS2) defined as the duration of the subsequent line of treatment if indicated. 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 a Wald test. All statistical tests were achieved with a p value of 5%. The missing data were not replaced.

V. RESULTS

1) Patient's clinical and pathological features

From November 2015 to November 2016, 60 patients have been eligible for a Temporary Authorization for Use of palbociclib and had received prior everolimus. Baseline patient's characteristics are described on **Table 1**.

Of note 31 patients had received adjuvant endocrine therapy and 12 were considered endocrine sensitive as their disease relapsed one year or more after adjuvant endocrine therapy completion.

2) Treatment management and Adverse Events (AEs)

At the time of the data cutoff, median follow-up was 10.3 months (range 0.9 – 19.5).

AEs considered related to palbociclib (treatment-related AEs) were observed in 59 patients. Safety details are detailed in **Table 2**. Grade 3 and 4 treatment-related neutropenia were observed in 46 and 13 patients respectively and were the unique serious AEs experienced by more than 10% of the population. One fatal febrile neutropenia was reported in a patient with a visceral disease after 8.6 months on palbociclib.

Palbociclib was suspended in 36 (60.0%) patients for adverse events; mainly neutropenia. Twenty (33.3%) patients had a dose reduction. Palbociclib was resumed to initial dose of 125 mg for 40 patients (66.7%) or reduced to 100 mg (n = 11; 18.3%) or 75 mg (n = 9; 15.0%) according to the guidelines.

3) Efficacy of Palbociclib

Median PFS1 was 5.8 months (95% CI 3.9 to 7.3) (**Figure 1**) and median OS was not reached. Best response was evaluable for 60 patients according to Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1). A partial response was confirmed in 16 patients (26.7%). The 44 remaining patients had a stable disease (n = 27; 45%) or progressive disease (n = 17; 28.3%) as best response.

Twenty-eight patients (46.7%) had received previously fulvestrant for metastatic disease. Interestingly, patients subsequently re-challenged with fulvestrant and palbociclib had a PFS of 6.4 months, which was similar to patients who didn't receive fulvestrant previously (HR = 1.00; 95% CI 0.55 to 1.83, *P* = 1.00) (**Figure 2**). Patients pretreated with fulvestrant were

statistically older (median 67 versus 57 year; $P = 0.0169$), had received more treatments for metastatic disease (median 7 versus 3 lines; $P < 0.0001$) and especially a longer duration of endocrine therapy (median 44.3 versus 26.3 months; $P = 0.0018$).

The median PFS was not modified according to the duration of previous everolimus use (HR = 0.82; 95% CI 0.46 to 1.46; $P = 0.50$).

Of note, 2 patients received exemestane and everolimus in a clinical trial in combination with LEE011 (ribociclib). They progressed rapidly after 1.41 and 2.86 months on palbociclib. These two patients were heavily treated, 6 and 8 prior treatments for metastatic disease, respectively.

The localization of the metastasis did not influence the benefit of the treatment: 10 patients (16.7%) had only bone disease and 50 (83.3%) had visceral metastases. The median PFS1 was similar in these 2 groups (HR = 1.27; 95% CI 0.56 to 2.84; $P = 0.57$).

LDH serum levels and lymphocytes count were known for 51 and 55 patients respectively. 24 patients (47.1%) had LDH serum level ≥ 250 UI/L (Upper Limit Normal) with a PFS1 of 3.4 months versus 7.3 months for those with LDH < 250 UI/L ($P = 0.05$). LDH serum level appears to be a significant prognostic factor for patient's outcome on palbociclib. 29 patients (52.7%) had less than normal lymphocytes count (<1.2G/L). Their PFS1 was 3.9 months versus 7.1 months for patients with lymphocytes count ≥1.2G/L but not statistically significant ($P = 0.23$).

A forest plot summarizes the main analyzes of subgroups studied (**Figure 3**).

4) 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 therapy at different doses levels: 125 mg (n = 32), 100 mg (n = 9) or 75 mg (n = 6) with no statistically difference on PFS1 (5.4, 5.4 and 6.6 months respectively; $P = 0.14$). Among these 47 patients, 7 received Best Supportive Care (BSC) and 40 received one or more line of treatment. The patients subsequently received mainly chemotherapy (n = 38) with a median PFS2 of 3.3 months (95% CI 2.2 to 5.0) (**Figure 4**).

VI. DISCUSSION

We show that the combination of fulvestrant plus palbociclib in MBC pretreated with a median of 5 lines of treatments including everolimus provides a median PFS of 5.8 months with a tolerable safety profile. To our knowledge, this is the biggest reported cohort of patients in that setting. Dhakal et al. have presented at ASCO meeting the results of a cohort of 23 patients pretreated with everolimus and receiving fulvestrant and palbociclib (**Appendix**: Outcome of palbociclib based therapy in hormone receptor positive metastatic breast cancer patients after treatment with everolimus; Ajay Dhakal, J Clin Oncol 35, 2017 (suppl; abstr 1054) ASCO 2017). The median PFS was 2.9 months (95% CI 2.0 to 4.2); objective response rate was 0% and clinical benefit rate was 17.4%. The data of this relative small cohort contrasts with our results. The population was similar in terms of rate of visceral metastasis (82% versus 83% in our cohort).

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 relapsed during prior endocrine therapy [6,7]. This trial has demonstrated a significant increase of PFS of 5.4 months with a median PFS of 9.5 months in the fulvestrant + palbociclib group versus 4.6 months in the fulvestrant + placebo group. This results differs somewhat with the 5.8 months PFS for patients treated with this combination in our cohort. Indeed in the PALOMA-3 trial only 14% of the patients had received 3 lines or more of endocrine therapy while 58.3% of our patients did. Notably none of the patients had received prior everolimus for MBC in the PALOMA-3 trial although it's 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 PFS compared to the PALOMA-3 trial.

Bone-only disease is a recognized good prognostic factor of metastatic breast cancer [8,9]. 16.7% of our patients had only bone metastases compared to 41.6% in the PALOMA-3 trial. Bone-only disease was not associated with a longer PFS and patients with visceral metastasis

had the same PFS. These results are in accordance with results of PALOMA-3 trial and support the use of ET plus CDK4/6 inhibitor even in the presence of visceral involvement. Chemotherapy should be reserved for patients with visceral crisis as the guidelines states [10,11]. Our results confirm this information even in heavily pretreated patients.

The safety profile of palbociclib in this more advanced setting can be superimposed on that of PALOMA-3 and prior palbociclib clinical trials. Grade 3 or 4 adverse events occurred in 46 patients (76.7% versus 73% in the PALOMA-3 trial). The most observed Grade 3 or 4 AEs were neutropenia (56.7% versus 65% for PALOMA-3), thrombocytopenia (8.3% versus 3%) and anemia (5% versus 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. Apart from the death by febrile neutropenia, all of our patients were able to resume treatment after the management of potential adverse events according to the TAU procedure of dose reduction. This information is really useful for clinicians as only few data are available in advanced setting. The safety profile is favorable and really matters in the context of advanced disease where quality of life is the first goal. Interestingly, CDK4/6 inhibitors don't seem to be similar in terms of toxicity. Abemaciclib presents a different safety profile compared to palbociclib and ribociclib with a less frequent hematological toxicity (23.6% Grade 3 neutropenia), but an increased digestive toxicity with a diarrhea occurring in 86.4% of patients including 13.4% of grade 3 [4]. 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 for PFS2 and had a PFS2 of 3.3 months (95% CI 2.2 to 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. Time from start to end of the immediate follow-up therapy were respectively 4.8 (3.7-6.0), 3.4 (2.4-6.1) and 3.4 (2.4-6.8) for chemotherapy (n = 124), endocrine therapy (n = 57) and targeted therapy (n = 44) in the fulvestrant plus palbociclib group (**Appendix**: Treatment Postprogression in Women With Endocrine-Resistant HR+ HER2– Advanced Breast Cancer Who Received Palbociclib Plus Fulvestrant in PALOMA-3; Nicholas C. Turner, P4-22-06, SABC 2016). These results are quite disappointing with very short PFS even with chemotherapy. The impressive results of CDK4/6 inhibitors in front line 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 still immature and warmly awaited.

Another important finding of our study is the possibility of re challenging patients with fulvestrant during the course of the disease. Indeed, 46.7% of our patients had already been treated by fulvestrant for their metastatic disease. This is a clear difference with the PALOMA-3 and MONARCH2 trial where previous treatment with Fulvestrant was an exclusion criterion. Patient re-challenged with fulvestrant plus palbociclib derived the same PFS than patients who had never received fulvestrant. From our point of view, this is important information. Resistance to ET in the metastatic setting finally occurs and many efforts are made to overcome this process. Recently, the emergence of Estrogen Receptor 1 (ESR1) mutations in patients progressing while receiving aromatase inhibitor has been established as frequent mechanism of resistance [12,13]. As shown by Jill M. Spoerke et al, ESR1 mutation is not associated with resistance to fulvestrant as it acts as a Selective Estrogen Receptor Degrader (SERD) [14]. In the PALOMA-3 trial the presence of ESR1 was not associated with the benefit of adding palbociclib or not: ESR1 plasma mutations were found in 25.3% of patients. Fulvestrant plus palbociclib improved PFS compared with fulvestrant plus placebo in both ESR1 mutant (HR = 0.43; 95% CI 0.25 to 0.74; $P = 0.002$) and ESR1 wild-type patients (HR = 0.49; 95% CI 0.35 to 0.70; $P < 0.001$) and the benefit from palbociclib was seen despite ESR1 mutation status (interaction $P = 0.74$) [15].

VII. CONCLUSION

In this everolimus pretreated population, we show that the association of fulvestrant plus palbociclib provides an interesting median PFS 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. The approval of palbociclib, ribociclib and forthcoming abemaciclib is a breakthrough for HR+ MBC. Several questions are raised, including the real effect on overall survival and the best sequence to use.

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IX. CONFLICT OF INTEREST STATEMENTS

None.

X. APPENDICES

Table 1. Characteristics of the patients	
Characteristics	n
Age	
Median	46 y
Range	(24y – 75y)
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	
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	
Age at initiation of the treatment	
Median - yr	61y
Range - yr	(28y-81y)
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
Thrombopenia	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

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

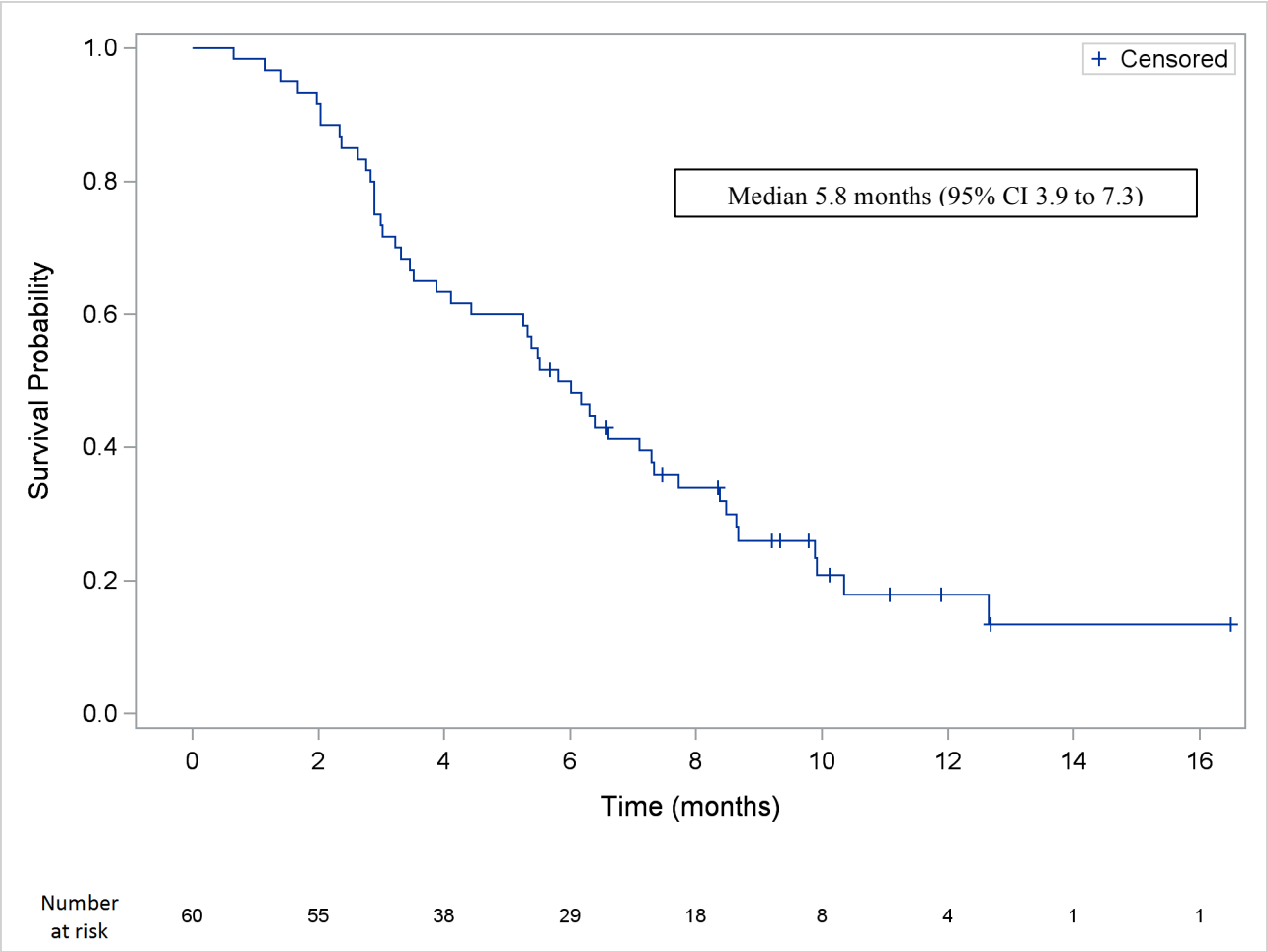


Figure 2. Comparison of progression-free survival according to fulvestrant pretreatment

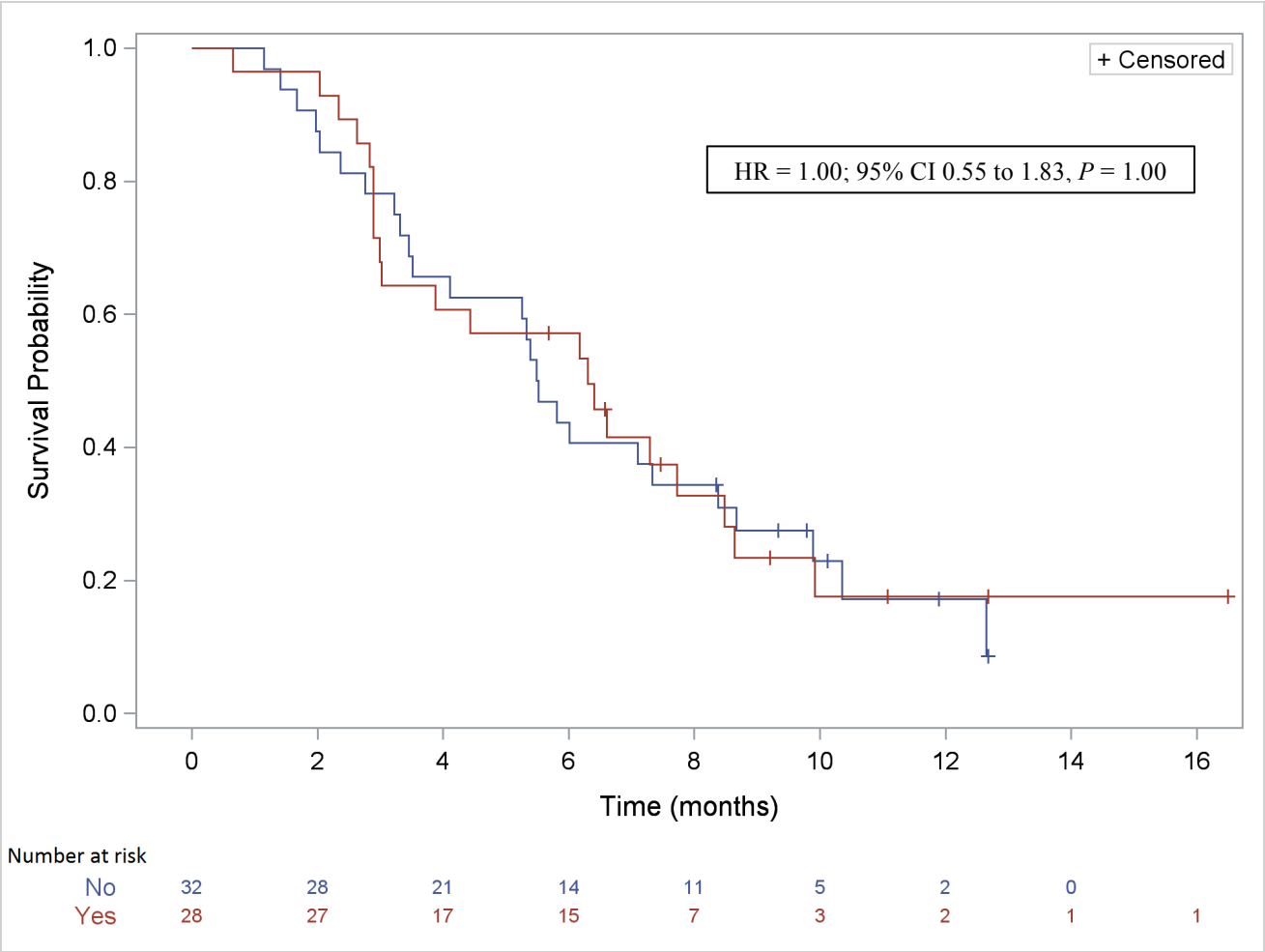


Figure 3. Subgroup analyses

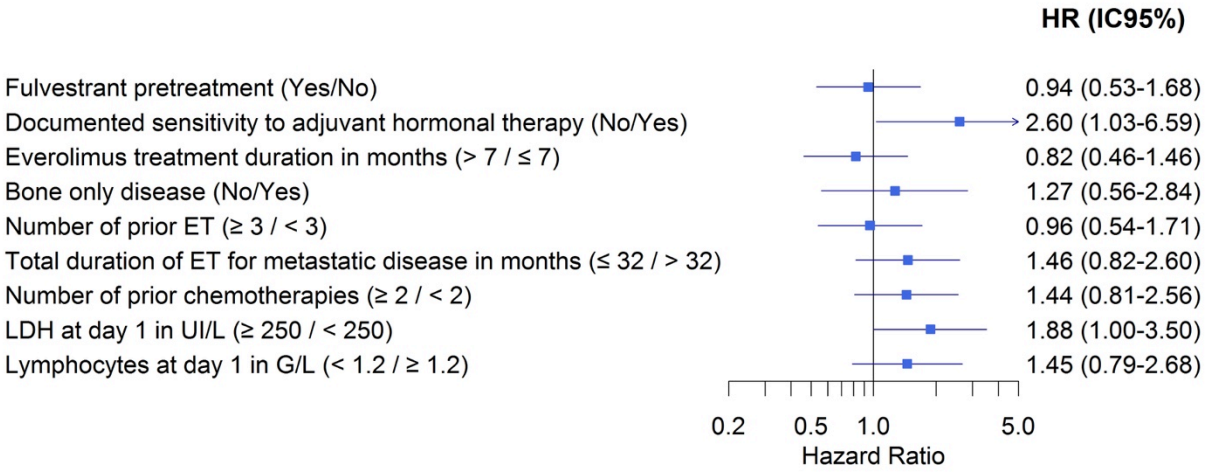
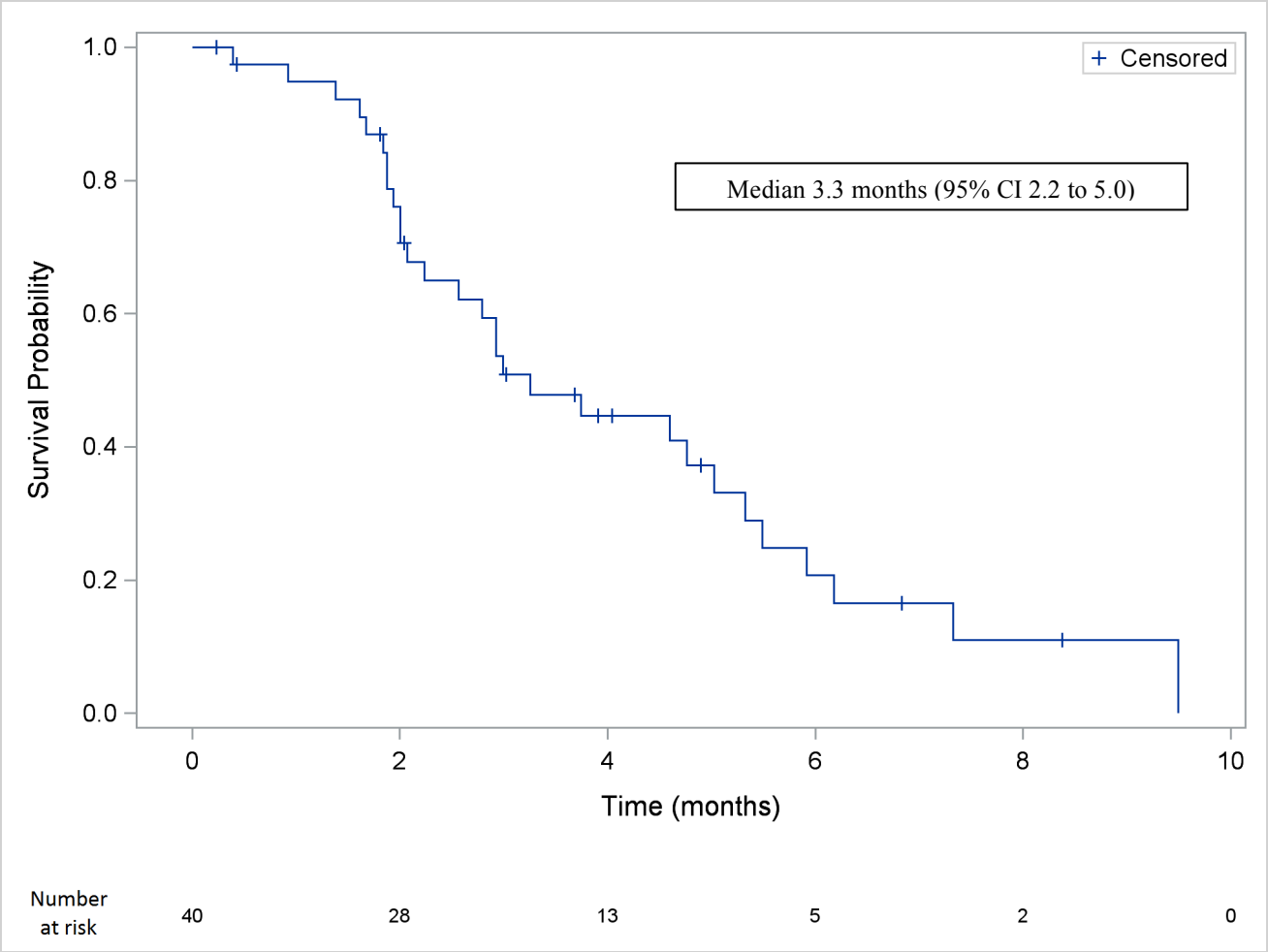


Figure 4. Progression Free Survival on subsequent line (cancer specific treatment) (PFS2)



Outcome of Palbociclib Based Therapy in Hormone Receptor Positive Metastatic Breast Cancer Patients After Treatment With Everolimus

Ajay Dhakal, Christina Matthews, Fan Zhang, Ellis G Levine, Stephen B Edge, Kilian E Salerno, Tracy O'Connor, Amy P Early, Thaer Khoury, Kazuaki Takabe, Jessica S Young, Mateusz Opyrchal

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UNDERSTAND PREVENT & CURE CANCER

Introduction

Resistance mechanisms to CDK 4/6 inhibition are not well defined. Outcome data on hormone receptor positive (HR+) metastatic breast cancer patients (MBCP) treated with palbociclib after treatment with everolimus are lacking. The PALOMA 3 trial showing benefit of palbociclib plus fulvestrant compared to fulvestrant alone in HR+ MBCP after progression on endocrine therapy excluded women previously treated with everolimus. The aim of our study was to investigate the outcomes of HR+ MBCP with prior everolimus treatment on palbociclib based therapy.

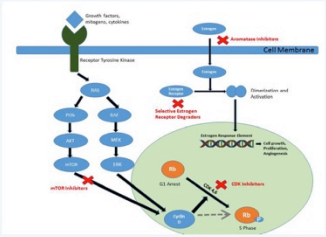


Fig: Simplified representation of relevant pathways in HR+ breast cancer.

Materials & Methods

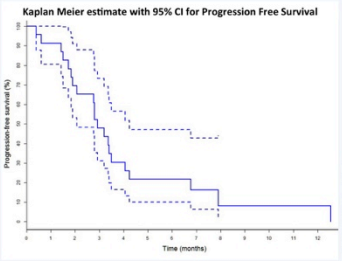
This is a retrospective, single institute review of HR+, HER 2 non-amplified MBCP from Jan 2014 - Nov 2016 treated with palbociclib after treatment with everolimus. Women who received everolimus for less than 1 month or palbociclib for less than 14 days were excluded. Progression free survival (PFS) was defined as the time from the initiation of palbociclib to the date of progression as determined by treating physician based on radiological, biochemical and/or clinical criteria. Response rates were determined based on available radiological data. Clinical benefit was defined as a complete response (CR), partial response (PR) or stable disease (SD) of at least 24 weeks.

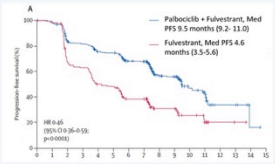
Results

23 patients with mean age 67 years (42 to 81) were identified. 95% of the patients were postmenopausal, 81% had ECOG performance status 0 or 1, 83% had visceral metastases, 95% had more than 2 lines of prior endocrine therapy, 82% have shown prior sensitivity to endocrine therapy, 82% have received prior chemotherapy, of which 84% were in metastatic setting. Median duration of everolimus therapy was 6 months. Kaplan Meier estimate showed median PFS of 2.9 months (95% CI 2.0-4.2); median PFS of palbociclib cohort of PALOMA 3 trial was 9.5 months (95% CI 9.2-11.0). Fisher's exact test comparing study cohort with palbociclib cohort of PALOMA 3 showed statistically significant differences in objective response (CR or PR) rates of 0/23 (0%) vs. 66/347 (19%, p = 0.02) & clinical benefit ratio of 4/23 (17.4%) vs. 231/347 (66.5%, p = 0.00).

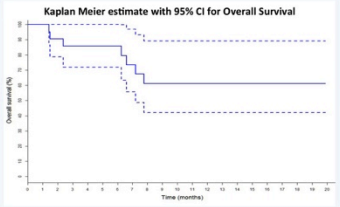
Variables	Study Cohort	Palbociclib Cohort of Paloma 3	p value
Population	23	347	
Complete response	0 **0%**	0 **0%**	
Partial Response	0 **0%**	66 **19%**	
Stable disease	5 **21.7%**	213 **61%**	
Progressive disease	18 **78.2%**	58 **17%**	
Objective tumor response	0 **0%**	66 **19%**	0.02*
Clinical Benefit#	4 **17.4%**	231 **67%**	0.00*

** Fisher's Exact test # CR, PR or SD of at least 24 weeks*





Progression Free Survival (PFS) with 95% CI of Study Cohort (Left) showing Median PFS 2.9 (2.0-4.2) months while Palbociclib cohort from PALOMA 3 (above, blue) 9.5 (9.2- 11.0) months.



Overall Survival (OS) with 95% Confidence Interval of Study Cohort has not been reached at the time of analysis.

Conclusion

Outcomes with palbociclib in HR+ everolimus treated MBCP were worse when compared to the palbociclib cohort of PALOMA 3 trial. Treatment with everolimus may lead to resistance to CDK inhibition. Further studies including more patients are necessary to confirm these findings. The data would provide further evidence to allow best sequencing of therapies in HR+ metastatic breast cancer patients.

Variables	Study Cohort	Palbociclib Cohort of Paloma 3
Population	23	347
Median age	**68** (42-81)	**57** (30-88)
Race		
• White	20 **88%**	252 **73%**
• Asian	1 **4%**	74 **21%**
• Black and others	2 **8%**	21 **6%**
Menopausal status		
• Pre or Peri-menopausal	1 **4%**	72 **21%**
• Post -menopausal	22 **96%**	275 **79%**
Number of previous line of endocrine therapy		
• 1	0 **0%**	60 **46%**
• 2	1 **4%**	140 **40%**
• 3 or more	22 **96%**	47 **14%**
Previous sensitivity to endocrine therapy		
• No	4 **18%**	73 **21%**
• Yes	19 **82%**	274 **79%**
Previous chemotherapy		
• Yes	19 **83%**	242 **70%**
• No	4 **17%**	105 **30%**
Reason for previous chemotherapy		
• Perioperative	3 **16%**	139 **57%**
• Metastatic disease with or without perioperative	16 **84%**	113 **43%**
Reason for termination of Everolimus		
• Intolerance	4 **17%**	NA NA*
• Progression	16 **70%**	NA NA
• Both/Others	3 **13%**	NA NA
Median number of chemo or hormonal therapies between Everolimus and Palbociclib	**1** (0-6)	NA NA
Metastasis		
• Visceral with or without non-visceral	19 **83%**	206 **59%**
• Non-visceral	4 **17%**	141 **41%**
Performance status		
• 0	1 **6%**	206 **59%**
• 1	12 **75%**	141 **41%**
• 2	3 **19%**	0 **0%**

** Not Applicable*

Reference:
Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3). Lancet Oncol. 2016 Apr;17(4):425-39. doi: 10.1016/S1470-2045(15)00613-0.

Treatment Postprogression in Women With Endocrine-Resistant HR+ HER2– Advanced Breast Cancer Who Received Palbociclib Plus Fulvestrant in PALOMA-3

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P4-22-06

BACKGROUND

- Palbociclib (IBRANCE®) is an orally bioavailable small-molecule inhibitor of cyclin-dependent kinases 4 and 6 for the treatment of hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2–) advanced or metastatic breast cancer (ABC or MBC, respectively) in combination with endocrine therapy (ET).[1]
- In the PALOMA-3 study (NCT01942135), palbociclib combined with fulvestrant demonstrated a significant improvement in investigator-assessed progression-free survival (PFS) vs placebo + fulvestrant in women with HR+, HER2– ABC whose disease had progressed on prior ET.[2] The study was stopped early at an interim analysis (December 5, 2014) because it had met the prespecified efficacy boundary.[3]
- Here, we assessed effectiveness of standard postprogression therapies after discontinuation of study treatment in PALOMA-3 to determine if the significant PFS benefit conferred by palbociclib + fulvestrant extends to subsequent treatment.

OBJECTIVES

- The objectives of this study were to:
  - Describe the pattern of disease progression
  - Describe the patterns of subsequent therapies
  - Assess the effect of study treatment on subsequent therapies
- Data are presented on the most mature PFS result (cutoff date of October 23, 2015)

METHODS

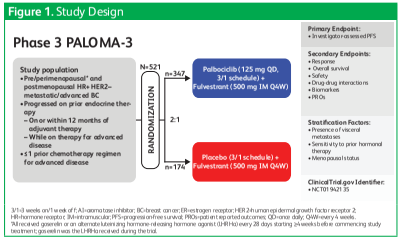
Study Population

- Key Inclusion Criteria
  - Women aged 18 years or older with HR+, HER2– metastatic or locally ABC who relapsed or had disease progression on prior ET (aromatase inhibitors for postmenopausal women and tamoxifen for pre-/perimenopausal women)
  - One prior line of chemotherapy (CTX) for ABC was allowed.
- Key Exclusion Criteria
  - Active brain metastases and symptomatic visceral spread that could lead to life-threatening complications

Study Design and Treatment

- The study design and treatment regimen have been described in detail elsewhere **(Figure 1)**.[2,3]

Figure 1. Study Design



3/1=3 weeks on/1 week off; AI=aromatase inhibitor; BC=breast cancer; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IM=intramuscular; PFS=progression-free survival; PROs=patient-reported outcomes; QD=once daily; Q4W=every 4 weeks.
*Received goserelin or an alternate luteinizing hormone-releasing hormone agonist (LHRHa) every 28 days starting ≥4 weeks before commencing study treatment; goserelin was the LHRHa received during the trial.

- Study treatment was continued until objective disease progression (confirmed per Response Evaluation Criteria in Solid Tumors v1.1), unacceptable toxicity, or study withdrawal.[2]
- Crossover between treatment groups was not allowed; however, patients could continue treatment as assigned at randomization beyond disease progression at the investigator's discretion if it was considered to be in the best interest of the patient and providing no new anticancer treatment was initiated.
- Patients who discontinued treatment because of disease progression were assessed every 3 months until death for information on poststudy treatment, subsequent disease progression, the type of new anticancer therapy given, and the duration of its use.

Statistical Analyses

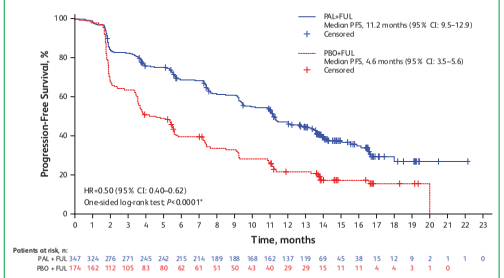
- An updated analysis of PFS was performed based on an October 23, 2015 cutoff date.
- Time to end of next-line therapy is defined as the time from randomization to the event defined as end or discontinuation of next-line therapy, progression on next-line therapy, or death from any cause.
  - Patients for whom end or discontinuation of next-line therapy or progression on next-line therapy had not been observed were censored at the last time known to be alive.
  - If a patient experienced multiple types of events (eg, a patient progressed on the next-line therapy and then discontinued the therapy), the time of the earliest event was used.
- The statistical analysis cutoff date for the time to end of next-line therapy analysis was October 23, 2015.
- Time to end of next-line therapy was summarized using the Kaplan-Meier method and the hazard ratio was estimated using Cox proportional hazards regression.
- One-sided *P* values were based on the log-rank test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization.
- Statistical analyses were performed using SAS® Version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients and Updated PALOMA-3 Efficacy Analysis

- As of October 23, 2015, the median follow-up was 15.8 months for patients who had been treated with palbociclib + fulvestrant (palbociclib group) and 15.3 months for patients who had received placebo + fulvestrant (placebo group).
- A total of 333 PFS events were observed; 200 events on palbociclib and 133 on placebo.
- Median PFS on palbociclib was 11.2 months (95% CI: 9.5–12.9) vs 4.6 months (3.5–5.6) on placebo; hazard ratio, 0.50 (95% CI: 0.40–0.62); one-sided log-rank test, *P*<0.0001 **(Figure 2)**.

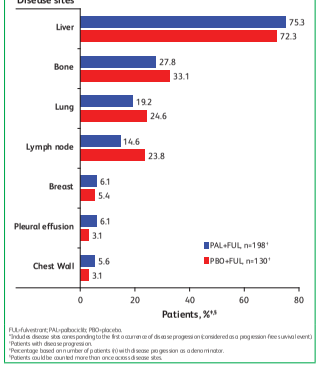
Figure 2. Progression-Free Survival: Updated Analysis of ITT Population



CI=confidence interval; FUL=fulvestrant; HR=hazard ratio; ITT=intent to treat; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.
*Stratified by the presence of visceral disease and sensitivity to prior hormone therapy.

- In both treatment groups, the most common sites of disease progression were liver (149 [75.3%] and 94 [72.3%]) and bone (55 [27.8%] and 43 [33.1%]) in the palbociclib and placebo groups, respectively **(Figure 3)**.
- One patient in each treatment group (<1% of the total study population) developed new brain metastases.
- There were 328 (63.0%) patients with disease progression, 198 (57.1%) in the palbociclib group and 130 (74.7%) in the placebo group.
- Postprogression systemic therapy was received by 290 patients, 172 (86.9%) in the palbociclib group and 118 (90.8%) in the placebo group.

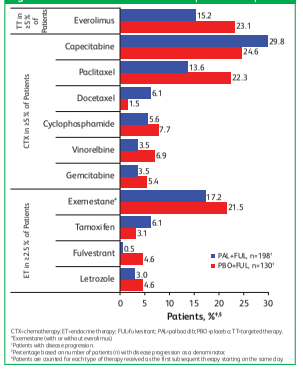
Figure 3. Sites of Disease Progression Occurring in ≥2.5% of Patients in Either Treatment Group



FUL=fulvestrant; PAL=palbociclib; PBO=placebo.
*Includes disease sites corresponding to the first occurrence of disease progression (considered as a progression-free survival event).
†Patients with disease progression.
‡Percentage based on number of patients (n) with disease progression as denominator.
§Patients could be counted more than once across disease sites.

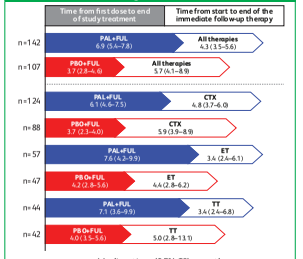
- The most commonly used postprogression regimens among patients were everolimus (30 [15.2%] palbociclib group and 30 [23.1%] placebo group), capecitabine (57 [28.8%] and 32 [24.6%]), paclitaxel (22 [11.1%] and 23 [17.7%]), and exemestane—with or without everolimus—(34 [17.2%] and 28 [21.5%]) **(Figure 4)**.

Figure 4. Most Common First Subsequent Therapies



CTX=chemotherapy; ET=endocrine therapy; FUL=fulvestrant; PAL=palbociclib; PBO=placebo; TT=targeted therapy.
*Exemestane (with or without everolimus).
†Patients with disease progression.
‡Percentage based on number of patients (n) with disease progression as denominator.
§Patients are counted for each type of therapy received as the first subsequent therapy starting on the same day.

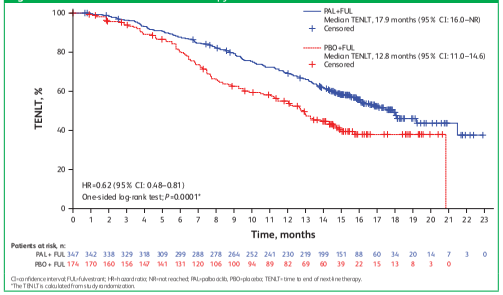
Figure 5. Kaplan-Meier Estimates of Treatment Durations For Patients on Poststudy Therapy for Disease Progression



CI=confidence interval; CTX=chemotherapy; ET=endocrine therapy; FUL=fulvestrant; PAL=palbociclib; PBO=placebo; TT=targeted therapy.

- For patients with poststudy disease progression, the median times until the start of subsequent follow-up treatment were longer in the palbociclib group than in the placebo group, and the end of the immediate follow-up therapy was also later in the palbociclib group, regardless of posttreatment modality **(Figure 5)**.
- Of the 290 patients who progressed on study and received next-line treatment, 193 had discontinued their immediately subsequent line of therapy.
- Proportionally, fewer patients in the palbociclib vs placebo group discontinued next-line treatment (32.6% vs 46.0%), likely reflecting the shorter median follow-up of patients on next-line of treatment.
- Analysis of time to end of next-line treatment showed that the hazard ratio between treatment groups was 0.62 (95% CI, 0.48–0.81; one-sided *P*=0.0001) in favor of palbociclib treatment **(Figure 6)**, similar to the favorable outcome for the updated analysis of the ITT population **(Figure 2)** and supporting the concept that palbociclib treatment has no effect on the benefit of subsequent treatments.

Figure 6. Time to End of Next-Line Therapy



CI=confidence interval; FUL=fulvestrant; HR=h azard ratio; NR=not reached; PAL=palbociclib; PBO=placebo; TENLT=time to end of next-line therapy.
*The TENLT is calculated from study randomization.

CONCLUSIONS

- The current analysis demonstrates that the treatment effect of palbociclib combined with fulvestrant is retained through the immediate next line of treatment postprogression, and that progression after palbociclib treatment has no effect on the therapeutic benefit derived from subsequent treatments.

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Efficacy of palbociclib plus fulvestrant in advanced HR+ Metastatic Breast Cancer pretreated with everolimus: Real-life data from the French Temporary Authorization for Use (TAU) at the Institut de Cancérologie de l'Ouest

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Background

The CDK4/6 inhibitor palbociclib, combined with endocrine therapy is a new standard of treatment for Hormone Receptor-positive (HR+) Metastatic Breast Cancer (MBC). Before the European Medicines Agency approval, a Temporary Authorization for Use (TAU) has been set up in France restricted to patients pretreated with everolimus.

We present the efficacy data of this combination in this population.

Methods

From November 2015 to November 2016, all the patients receiving palbociclib + fulvestrant according to the TAU in our institution were prospectively included. Data from their medical records and Adverse Events (AEs) were collected.

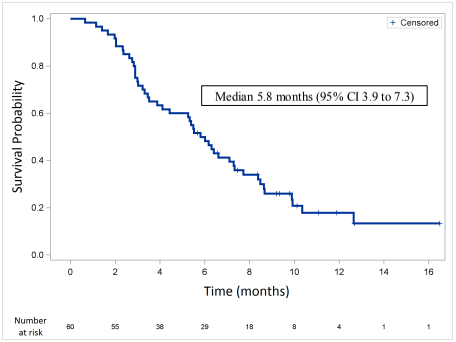
Results

60 patients received at least one dose of palbociclib in combination with fulvestrant with a median age of 61 years. 50 patients (83.3%) had visceral metastasis and 10 (16.7%) had bone only disease. Patients had received a median of 5 (range 1 to 14) lines of treatment before palbociclib initiation, including endocrine therapy (median = 3) and chemotherapy (median = 2). Of note, 28 patients (46.7%) had received fulvestrant previously and all had been pretreated with everolimus. With a median follow-up of 10.3 months, median progression free survival (PFS) was 5.8 months (95% CI 3.9 to 7.3) and median overall survival was not reached. PFS was the same according to the presence of visceral metastasis or no (HR = 1.46; 95% CI 0.57 to 3.74; P = 0.42). Interestingly, patients treated previously with fulvestrant and subsequently re-challenged with fulvestrant and palbociclib had a PFS of 6.4 months, which was similar to patients who didn't receive fulvestrant previously (HR = 1.00; 95% CI 0.55 to 1.83; P = 1.00). The most common AE were neutropenia (n = 56), anemia (n = 39) and thrombocytopenia (n = 33). At the time of this analysis (April 2017), 40 patients received a further line of treatment after progression.

Population

Characteristics		n
Age		
	Median	46 y
	Range	(24y – 75y)
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		
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		
Age at initiation of the treatment		
	Median - yr	61y
	Range - yr	(28y-81y)
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%)

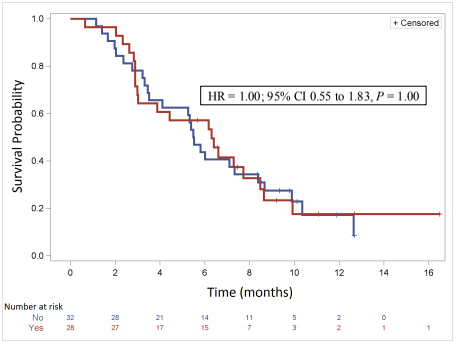
Efficacy of Palbociclib



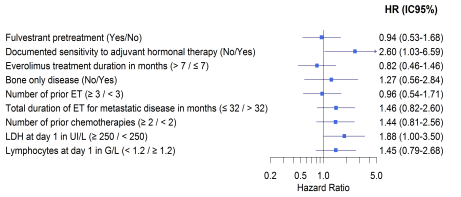
Adverse Events according CTCAE v.4.0

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
Thrombopenia	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

Impact of fulvestrant pretreatment



Subgroup analyses



Conclusion

In this heavily pretreated population, the association of fulvestrant plus palbociclib provides an interesting median PFS of 5.8 months. Patients previously treated with fulvestrant seem to derive the same magnitude of benefit compared to fulvestrant naive patients.

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NOM : DE L'ESTANG DU RUSQUEC PRENOM : Pauline

Titre de Thèse :
Efficacité et tolérance du Palbociclib dans le cancer du sein avancé présentant des récepteurs hormonaux positifs et prétraité par Everolimus : Analyse des données de l'Autorisation Temporaire d'Utilisation (ATU) à l'Institut de Cancérologie de l'Ouest

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RESUME

Introduction :
Le palbociclib, inhibiteur de CDK4/6, est un nouveau standard de traitement, en combinaison avec l'hormonothérapie, dans le cancer du sein métastatique. Nous présentons les résultats d'efficacité et de tolérance en association avec le fulvestrant chez les patientes de l'Institut de Cancérologie de l'Ouest (ICO) pendant son Autorisation Temporaire d'Utilisation.
Méthodes :
Entre novembre 2015 et novembre 2016, toutes les patientes de l'ICO (Nantes et Angers) prétraitées par everolimus pour un cancer du sein avancé présentant des récepteurs hormonaux positifs, et ayant reçu au moins une dose de palbociclib plus fulvestrant et ont été prospectivement incluse dans cette cohorte. Les évènements indésirables ont été recueillis à chaque visite.
Résultats :
60 patientes ont été incluses dans cette analyse. L'âge médian était de 61 ans. 50 patientes (83.3%) avaient des métastases viscérales et 10 (16.7%) avaient uniquement des métastases osseuses. Les patientes avaient précédemment reçu une médiane de 5 lignes thérapeutiques (1-14), dont 3 lignes d'hormonothérapie et 2 de chimiothérapie. 28 patientes (46.7%) avaient déjà reçu du fulvestrant pour leur maladie métastatique. Après un suivi médian de 10.3 mois, la survie sans progression était de 5.8 mois (IC 95% : 3.9-7.3) et la survie globale n'était pas atteinte. La survie était identique quelque soit la localisation des métastases (HR = 1.46; IC 95% : 0.57- 3.74; P = 0.42). Les patientes qui avaient déjà reçu du fulvestrant avaient une survie identique à celles qui ne l'avaient jamais reçu. (HR = 1.00; IC 95% : 0.55-1.83; P = 1.00). Les effets indésirables les plus fréquents étaient la neutropénie (n=56), l'anémie (n=39) et la thrombopénie (n=33). Au moment de cette analyse, 40 patientes avaient reçu une nouvelle ligne thérapeutique après progression sous palbociclib.
Conclusion :
Dans cette cohorte de patientes qui avaient reçu de nombreux traitements au préalable pour leur maladie métastatique, la survie sans progression était de 5.8 mois. Les patientes avaient un bénéfice identique du palbociclib, qu'elles aient déjà reçu ou non du fulvestrant.

MOTS-CLES

PALBOCICLIB, FULVESTRANT, CANCER DU SEIN, METASTATIQUE, RECEPTEURS HORMONAUX POSITIFS