



Fulvestrant and palbociclib combination in heavily pretreated hormone receptor-positive, HER2-negative metastatic breast cancer patients

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Received: 10 June 2019 / Accepted: 6 September 2019 / Published online: 14 October 2019
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Abstract

Purpose We report the results of a retrospective analysis of the fulvestrant and palbociclib combination within a temporary authorization of use (TAU) program in 77 heavily pretreated patients with hormone receptor-positive (HR+), HER2-negative metastatic breast cancer.

Methods All patients who received the fulvestrant and palbociclib combination within this TAU program were included. Toxicities were graded using the CTCAE v5 scale.

Results The majority of patients (62.3%) were previously treated with the mTOR inhibitor everolimus. The median number of previous treatments for their metastatic disease was 4. With a median follow-up of 14 months, the median progression-free survival (PFS) was 7.6 months. The median PFS significantly ($p < 0.0001$) decreased with the number of previous treatment lines in the metastatic setting. The median PFS was 5.5 months in patients who had previously progressed on everolimus compared to 9.3 months in the everolimus non-pretreated subgroup. No significant difference in median PFS was detected in patients according to age. The median overall survival rate was not reached. The clinical benefit rate was 64%, including 4% of complete responses, 26% partial responses, and 34% stable diseases for the entire cohort.

Conclusions The fulvestrant and palbociclib combination exerts an appreciable effect on metastatic heavily pretreated patients with a tolerable toxicity profile.

Keywords Endocrine therapy · CDK 4/6 inhibitors · Advanced breast cancer · Fulvestrant · Palbociclib

Introduction

Dysregulation of the cyclin-dependent kinases (CDK) 4/6–retinoblastoma (Rb) protein pathway has been shown to contribute to the development of endocrine resistance in breast cancer [1]. The targeting of this pathway has thus been considered of interest in recent years, and several CDK inhibitors have demonstrated efficacy for the

treatment of patients with hormonal receptor (HR)-positive and HER2-negative breast cancer. Palbociclib has been the first approved CDK4/6 inhibitor in combination with either letrozole in the first-line setting [2] or fulvestrant after one line of endocrine therapy [3]. The PALOMA 3 trial supported this approval, with randomly assigned patients who had relapsed or progressed during prior endocrine therapy, to receive either palbociclib and fulvestrant or placebo and fulvestrant. The results favored the palbociclib arm in terms of progression-free survival (PFS) (median PFS 9.2 months versus 5.2 months; hazard ratio 0.42; 95% confidence interval (CI): 0.32–0.56; $p < 0.001$) [3].

This single-center retrospective study reports the activity of palbociclib in combination with fulvestrant administered through a compassionate use program in France, known as temporary authorization of use (TAU). The TAU procedure was primarily implemented to improve early access to drugs under development or already authorized abroad, prior to its

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marketing authorization in Europe. In France, the present TAU was granted to palbociclib in November 2015 and restricted to postmenopausal patients with HR-positive HER2-negative metastatic breast cancer (MBC), previously exposed to multiple treatment lines, including mTOR inhibitors. This analysis assessed the efficacy and safety of palbociclib combined with faslodex in this heavily pretreated patient population.

Materials and methods

Between November 2015 and January 2017, the TAU of palbociclib was activated, though restricted to menopausal patients with HR-positive, HER2-negative MBC, previously treated with multiple treatment lines, including the combination of exemestane and everolimus. Patients received palbociclib 125 mg once a day 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 \geq 3 non-hematologic toxicities. Fulvestrant was given by intramuscular injections, with a recommended dose of 500 mg once a month, and an additional 500 mg dose for 2 weeks after the first dose. Clinical outcomes and adverse events (AEs) were recorded monthly, and treatment efficacy was evaluated every three cycles. Toxicities were graded using the CTCAE v5 scale.

We herein report toxicities of the fulvestrant and palbociclib combination, as well as PFS, overall survival (OS), clinical response, and the influence of previous treatment on efficacy.

Statistical analysis

All patients alive were followed up at least until 24 May 2018. PFS was defined as the time elapsed between the date of first administration of palbociclib and the date of progression, death or 24 May 2018 (date of analysis), whichever came first. Patients alive and free of any progression at the last follow-up were censored. OS was defined as the time between the date of first administration of palbociclib and the date of death from any cause or 24 May 2018, whichever came first. Both indicators were analyzed with the Kaplan–Meier method. The logrank test was used to compare groups. Median follow-up was estimated using the reverse Kaplan–Meier method [4]. Statistical analyses were carried out by means of the SAS 9.4 statistical software (SAS Institute, Cary, NC, USA).

Results

Overall, 77 patients (75 menopausal women and 2 men), with a median age of 66 years, were treated using the TAU procedure. Patient characteristics are provided in Table 1.

The median number of prior treatment lines was 4, with a median number of two lines of endocrine therapy and two lines of chemotherapy. Bone was the only metastatic site in 37.7% of patients (29/77), whereas 22.1% of patients (17/77) had exclusive visceral metastases. Only two exhibited central nervous system involvement, with one case of cerebral metastasis and one case of carcinomatous meningitis.

The median follow-up was 14 months (range 12.5–15.5). Five patients stopped treatment before the first evaluation. Treatment interruption was secondary to disease progression in 48 patients (62%) and related to toxicity for 10 patients (13%). At the date of analysis, 19 patients (25%) were still under treatment. The median duration of treatment was 122 days, with the best response evaluable in 72 patients. Three patients (4%) had a complete response, 20 patients (26%) partial response, 26 patients (34%) stable disease (for at least 24 weeks), and 23 patients (30%) had progressive disease.

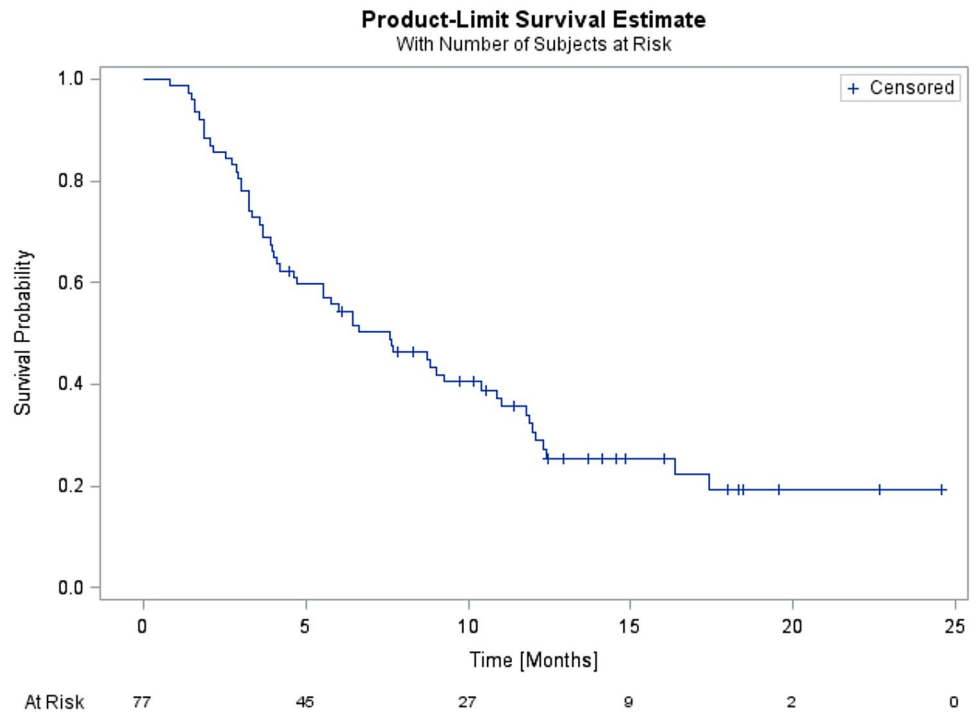
The median PFS was 7.6 (range 4.6–10.4) months for the entire cohort (Fig. 1), with the median OS not reached. Overall, 48 (62.3%) patients were pretreated with exemestane and everolimus combination. Of these 48, 22 patients stopped everolimus because of progression, whereas 26 interrupted the therapy due to toxicity. The median PFS in the everolimus non-pretreated subgroup was 9.3 (95% CI [6.0–12.3]) months, as compared to 5.5 (95% CI [3.0–11.0]) months in patients who had previously progressed under everolimus (Fig. 2). This difference was not statistically significant ($p = 0.19$). The median PFS

Table 1 Patient characteristics

Gender	Women	75	97.4%
	Men	2	2.6%
Age	65.6 \pm 11.5		
BMI	24.0 \pm 5.0		
WHO performance status	0	19	24.7%
	1	35	45.5%
	2	20	25.9%
	3	3	3.9%
Metastatic site	Bone exclusive	29	37.7%
	Visceral exclusive	17	22.1%
	Bone and visceral	29	37.7%
	CNS	2	2.6%
Number of previous treatment lines in metastatic setting	0–2	19	24.7%
	3–4	25	32.5%
	5–6	11	14.3%
	7–8	12	15.6%
	> 8	10	13.0%
Everolimus pretreated	No	29	37.7%
	Yes	48	62.3%

BMI body mass index

Fig. 1 PFS for the entire cohort



significantly ($p < 0.0001$) decreased with the number of previous treatment lines in a metastatic setting (Fig. 3). The median PFS was 10.5 months with ≤ 2 previous lines of treatment, 8.8 months with three to four previous lines, 7.6 months with five to six previous lines, 8.7 months with seven to eight previous lines, and 2.9 months with more than eight previous treatment lines. No significant

difference in median PFS was detected in patients according to age.

The most common grade 3/4 AEs were neutropenia in 48 patients (63%), with only one patient exhibiting febrile neutropenia, asthenia in 8 patients (10.4%), thrombopenia in 5 patients (6.5%) and anemia in 2 patients (2.6%). Because of toxicity, 24 patients (31%) had a dose reduction to 100 mg,

Fig. 2 PFS of patients without previous everolimus treatment and patients with previous progression on everolimus

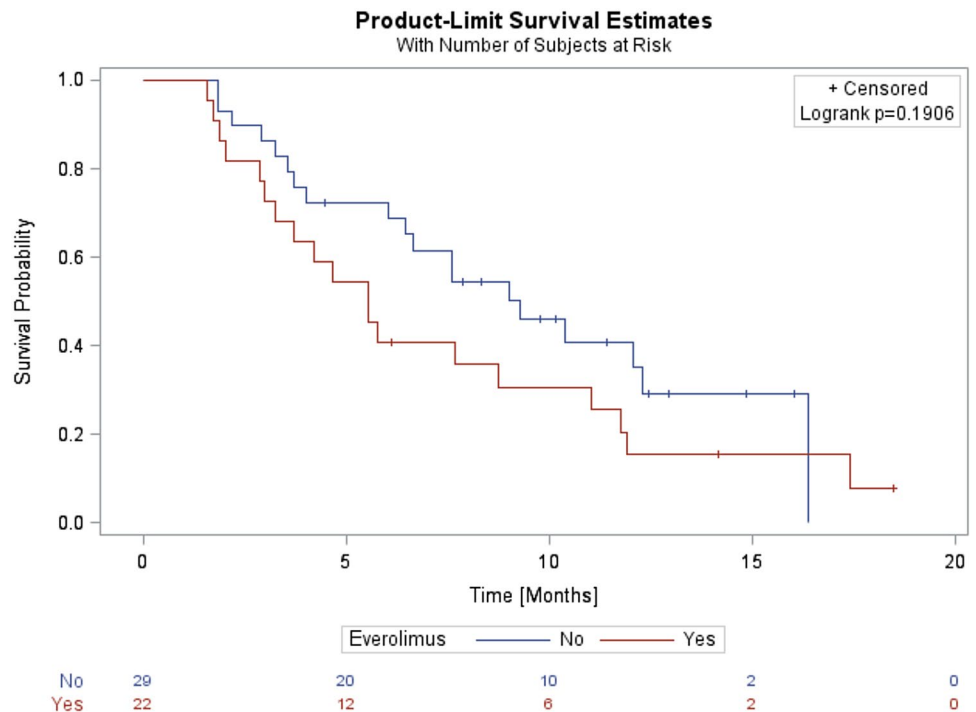
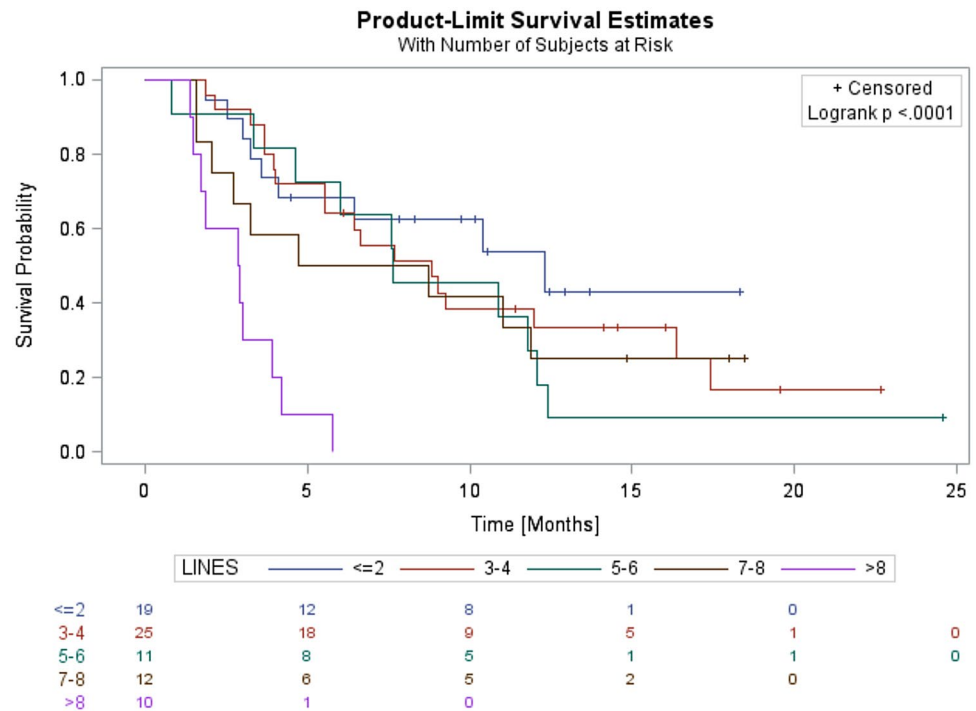


Fig. 3 PFS according to number of previous lines of treatment in metastatic setting



and four patients (5%) to 75 mg. Table 2 summarizes the toxicity profile in our cohort.

Discussion

Palbociclib is the first-in-class CDK4/6 inhibitor approved for HR-positive MBC. Pivotal registration trial PALOMA-3 assessed its efficacy in combination with fulvestrant in patients whose disease progressed during prior ET [3]. This trial met its primary endpoint with an improvement in PFS for the fulvestrant plus palbociclib arm versus fulvestrant plus placebo arm (9.5 versus 4.6 months, $p < 0.0001$, respectively). Secondary endpoints favored the combination arm with a higher response rate (25.0 versus 11.1%, $p = 0.0012$) than the control arm. Recently, an updated analysis showed a nonstatistically significant improvement in OS in the entire population (34.9 versus 28.0 months in the experimental arm versus the control arm, $p = 0.09$) [5].

Beyond first- and second-line, questions arise concerning the activity of CDK 4/6 inhibitors. The Phase II TREnd trial randomized 115 postmenopausal patients diagnosed with HR-positive, HER2-negative MBC to receive palbociclib

either alone or in combination with their current endocrine therapy (aromatase inhibitor or fulvestrant) [6]. These patients had progressed after one or two endocrine treatments. The median PFS was significantly longer with the combination of endocrine therapy and palbociclib (median PFS, 11.5 vs. 6 months for palbociclib alone; HR = 0.35 [0.18–0.7]; $p = 0.002$). The authors concluded that palbociclib was likely to reverse the acquired resistance to the identical endocrine agent used in the previous endocrine therapy lines.

Four retrospective studies evaluated the activity of the fulvestrant–palbociclib combination in heavily pretreated patients (Table 3). The Roswell Park Comprehensive Cancer Center reported data on 23 everolimus-pretreated patients [7]. There was no response, with a PFS of 2.9 months. The Jules Bordet Institut experience was reported with 34 patients [8]. The median PFS was 3.1 months with no difference between mTOR inhibitor-pretreated (3.5 months) and inhibitor-naïve patients (2.7 months; HR = 0.83). Data from 60 patients were analyzed in the René Gauducheau Cancer Center [9]. All patients were pretreated using everolimus, and the median PFS was 5.8 months. Lastly,

Table 2 Toxicity profile of the combination fulvestrant and palbociclib

	Grade	N	%
Neutropenia	1	2	2.6
	2	22	28.6
	3	38	49.4
	4	10	13.0
	Febrile neutropenia	1	1.3
Anemia	1	31	40.3
	2	8	10.4
	3	2	2.6
Thrombocytopenia	1	27	35.1
	2	3	3.9
	3	4	5.2
	4	1	1.3
Asthenia	1	6	7.8
	2	8	10.4
	3	8	10.4
Cutaneous toxicity	1	8	10.4
	2	4	5.2
Conjunctivitis	1	7	9.1
	2	4	5.2
Nausea	1	4	5.2
Headache	1	1	1.3
	2	1	1.3
Constipation	1	4	5.2
Diarrhea	1	1	1.3
	2	1	1.3
Dizziness	1	2	2.6
Herpes virus reactivation	1	2	2.6
	2	1	1.3
Alopecia	1	5	6.5
	2	1	1.3
Oral mucositis	1	5	6.5
	2	4	5.2

the UK compassionate access program experience was published, with 118 patients included [10]. Therein, palbociclib was associated with various endocrine treatments. After a median number of five previous treatments, the median PFS was 4.5 months, with a median OS of 15.8 months.

In the present study, PFS was longer for patients without previous everolimus exposure compared to those with previous progression on everolimus (9.3 versus 5.5 months). Owing to the small number of patients, this difference was not statistically significant ($p = 0.19$). Nevertheless, this result is different from what was observed in the Belgian study [8].

The efficacy of the fulvestrant + palbociclib combination was strongly related to the number of previous treatments, with a significant decrease of median PFS ($p < 0.0001$) with the number of previous treatment lines in the metastatic setting (Fig. 3). In the subset of patients with one to two previous treatment lines (19 patients), the median PFS was 10.5 months. This result is consistent with the median PFS of 9.9 months in patients treated with the fulvestrant and palbociclib combination in the PALOMA 3 trial, with a median number of previous metastatic treatments of one in a metastatic setting [3].

The haematologic safety profile of palbociclib in our study was very similar to that of PALOMA-3 trial [3]. Grade 3–4 neutropenia was reported in 62.4% of patients in our series and in 62% of PALOMA 3 patients, grade 3–4 thrombocytopenia in 6.5% of patients in our series and in 2.3% of PALOMA 3 patients, grade 3–4 anemia in 2.6% of patients in our series and in PALOMA 3 patients.

In conclusion, this single-center retrospective study revealed a median PFS of 7.6 months, with a favorable toxicity profile, in 77 heavily pretreated patients. The median PFS was significantly better for patients with few previous treatment lines in metastatic setting and seemed better without previous everolimus treatment. The median PFS was not influenced by age.

Table 3 Five retrospective studies evaluating the combination of endocrine treatment and palbociclib in heavily pretreated patient

	References	Patients number	Median age	Bone-only disease (%)	Median number of previous treatment	Previous treatment with everolimus (%)	PFS (months)
Roswell Park Center	[6]	23	68	17	≥ 3	100	2.9
Institut Jules Bordet	[7]	34	59	14.7	≥ 3	82.4	3.1
Centre Gauducheau	[8]	60	61	16.7	5	100	5.8
United Kingdom	[9]	118	59	6.8	5	–	4.5
Centre Paul Strauss	–	77	66	37.7	4	62.3	7.6

PFS progression-free survival

Author contributions MV and TP: conceived the study. HH and JL: collected and categorized the clinical data. MV, TP and XP: performed the statistical analyses and interpreted the results. HH: drafted the manuscript and all authors critically revised and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Thierry Petit is member of a Pfizer scientific board.

Ethical approval The study was approved by the Local Ethical Review Board, and complies with the current laws of France. The study has been performed in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Informed consent Informed consent was obtained from all individual participants included in the study.

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