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Original article

Real life efficacy of palbociclib and endocrine therapy in HR positive, HER2 negative advanced breast cancer

B. Porte [a], M. Carton [b], F. Lerebours [a], E. Brain [a], D. Loirat [a], L. Haroun [c], A. Bellesoeur [a], S. Bach Hamba [a], Y. Kirova [d], P. Cottu [a, *]

[a] Department of Medical Oncology, Institut Curie, Paris and Saint Cloud, France
[b] Department of Biostatistics, Institut Curie, Paris and Saint Cloud, France
[c] Department of Data, Institut Curie, Paris and Saint Cloud, France
[d] Department of Radiation Oncology, Institut Curie, Paris and Saint Cloud, France

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ABSTRACT

Background: Palbociclib is indicated for the treatment of hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC), in combination with endocrine therapy. Emerging real-life data suggest that the efficacy of a palbociclib-based therapy is highly conserved. We report the *Institut Curie* hospital experience.

Patients and methods: We retrospectively reviewed all patients with HR + HER2- ABC treated with a palbociclib-based therapy as first or second line for ABC, with an initial prescription from November 2016 to December 2018. Clinical, laboratory and imaging data were retrieved from electronic records. Data lock was December 31st, 2019. Descriptive analyses, univariate and multivariate Cox regression analyses were performed.

Results: We included 310 consecutive patients. Median age was 61.8 years old. Palbociclib was prescribed in first line in 225 patients (72.6%). Before palbociclib-based therapy initiation, 122 patients (39.3%) were endocrine naive, 96 (31.0%) endocrine sensitive and 92 (29.7%) endocrine resistant. Median follow-up was 20.7 months. Median progression free survival (PFS) was 23.4 months (95%CI: 21.6-NR) in endocrine naive patients, 22.7 months (95%CI: 14.7-NR) in endocrine sensitive, and 13.4 months (95%CI: 10.7 −20.8) in endocrine resistant. At 12 months from the initiation of palbociclib, 94.5% of patients were alive. By multivariate analysis, poor prognosis factors for PFS were identified in the endocrine naive/sensitive population: initial ECOG status 2, previous endocrine therapy for ABC, 3 metastatic sites or more. Toxicity profile was similar to previously published data.

Conclusion: In a non-selected population of patients with HR + HER2- ABC, the efficacy and safety data are strikingly similar to those previously reported.

1. Introduction

Breast cancer in the most common female cancer in France, with 58,459 new cases and 12,146 deaths in 2018 [1]. The hormone receptor-positive (HR+), HER2-negative (HER2-) subtype is the most frequent one, accounting for about 75% of all breast cancers [2]. In patients with HR + HER2-advanced breast cancer (ABC), endocrine therapy (ET) alone used to be the standard of care in first line setting [3]. However, all patients eventually suffer from progressive disease, and an extensive body of research has progressively unveiled the molecular features associated with resistance to ET [4]. The cyclin-D1/CDK4/6/Rb axis is commonly activated in luminal tumors [5], and this axis could be involved in resistance to ET [6].

Palbociclib is a highly selective serine/threonine kinase inhibitor of CDK4/6. In preclinical and early clinical trials, it has shown a moderate anti-tumor action with a cytostatic effect as a monotherapy [7] and a favorable toxicity profile [8]. Preclinical studies had shown a synergic action with endocrine therapy in breast cancer [9]. Palbociclib has been evaluated in two pivotal randomized, placebo-controlled, double-blind, international phase III clinical trials. The PALOMA-3 trial recruited 521 premenopausal

* Corresponding author.
E-mail address: paul.cottu@curie.fr (P. Cottu).

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and postmenopausal women after progression on previous ET(10). In the PALOMA-2 trial, 666 postmenopausal women were treated by palbociclib-letrozole or with placebo-letrozole in mostly endocrine sensitive patients in the first line setting [11]. Both trials demonstrated a striking and sustained benefit of palbociclib, leading to its approval for the treatment of HR + HER2- ABC in association with an aromatase inhibitor, or with fulvestrant for patients who have progressed under previous ET. For premenopausal women, a LH-RH agonist should be added [12]. Myelosuppression, particularly neutropenia, is the most frequent adverse event (AE). Indeed, a pooled analysis of the PALOMA-1, PALOMA-2 and PALOMA-3 trials has found that grade 3–4 hematological AE occur at the following frequencies: neutropenia 65.1%, leucopenia 26.7%, anemia 4.6%, and thrombocytopenia 1.9%. The most common non-hematologic AE was infections (54.7% all grades). However, febrile neutropenia was very rare (1.0%).

The rapidly growing clinical experience with palbociclib-based therapy has generated an increasing need for real-world (RW) data, in order to assess both efficacy and tolerability in real life settings. Very interestingly, early RW studies results were very close to those from the pivotal trials [13,14]. We report here the *Institut Curie* experience with palbociclib since the marketing authorization in France (November 2016). We aimed to assess efficacy and safety of palbociclib in first and second line in HR + HER2- ABC in real life condition, while also looking at prognosis factors for progression free survival, modalities of concomitant medical care, and efficacy and safety of post-palbociclib treatments.

2. Patients and methods

Eligible patients were premenopausal and postmenopausal women, aged 18 years-old and more, treated for a histologically proven ABC, by a palbociclib-based therapy in first or second line. Palbociclib must have been prescribed for the first time at *Institut Curie* (IC) between November 9th, 2016 (date of marketing authorization in the European Union) and December 31st, 2018. Patients must have had at least one follow-up consultation under palbociclib-based therapy. The use of electronically recorded medical data is authorized per current French regulation.

Patients electronic health records (EHR) were screened by the software ConSoRe®, by using key words “palbociclib” and “Ibrance”. We manually reviewed all files to ensure and validate eligibility. Clinical, laboratory, and imaging data were retrieved from EHRs. We collected characteristics of patients, of their cancers at initial diagnosis and at palbociclib initiation, and of first dosing of palbociclib, follow-up modalities, medical events under palbociclib, and finally details of subsequent treatment line. Toxicities were graded according to the CTCAE version 5.0. Imagining responses were assessed according to RESISTv1.1. Data lock was December 31st, 2019. Endocrine sensitive patients (ESP) were defined either by an absence of recurrence during adjuvant ET or during 24 months after its completion, or by an absence of progression during 6 months after the initiation of an ET for ABC, and endocrine resistant patients by the occurrence of a recurrence or progression in these timeframes [15].

Outcomes were progression free survival (PFS), overall survival (OS), and toxicity. We also looked at prognosis factors for PFS. Descriptive statistics were used to summarize patients' characteristics. Survival curves for PFS and OS with associated median survival with corresponding two-sided 95% confidence intervals (95% CI) were generated using the Kaplan–Meier method. Median follow-up was calculated using reverse Kaplan–Meier estimation. Survivals were compared using log-rank tests and Cox proportional-hazards models were used to estimate hazard ratios and 95%CI. Multivariate Cox proportional hazards models were constructed on the general population in a first time and in the endocrine naive patients (ENP) and ESP population in a second time using a backward step-by-step manual selection procedure to identify independent prognosis factors. All factors significant at a conservative 10% level in univariate analysis were included in multivariate analysis. The final model was reached when including only significant factors at a $p = 0.05$ significance level. All analysis were performed using R version 3.3.2 [16]. Statistical significance was defined by a two-tailed $p < 0.05$.

3. Results

From November 2016 to December 2018, 721 patients were screened for eligibility. Among them, 310 patients met eligibility criteria (Fig. 1).

Baseline demographic and clinical characteristics of patients are shown in Table 1. Median age was 61.8 years-old (range: 23.5–92.1). Among them, 253 patients (81.6%) were postmenopausal. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 160 patients (59.7%), 1 in 86 (32.1%), and 2 in

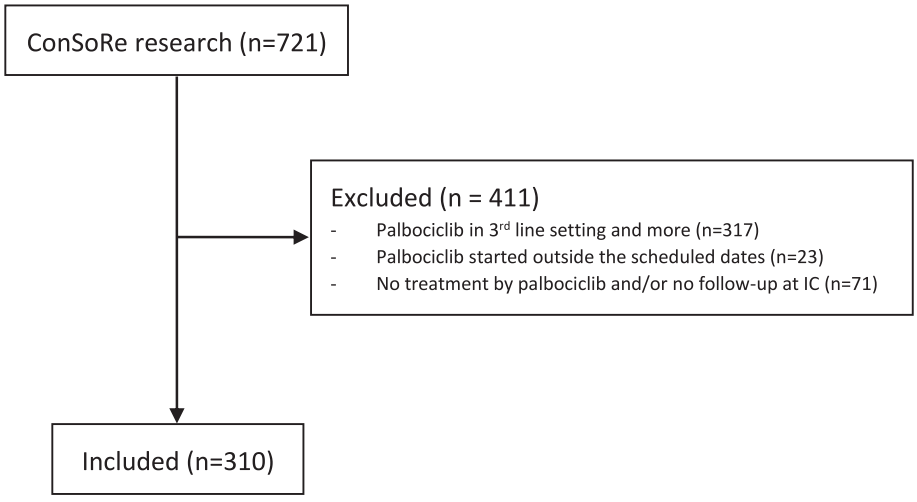

Fig. 1. Flow chart.

22 (8.2%) of patients. At first diagnosis of breast cancer, 227 patients (73.2%) had early stage disease while 83 patients (26.8%) had *de novo* disease. At diagnosis of ABC, there was at least one visceral lesion in 158 patients (51.0%) and 3 metastatic sites or more in 87 patients (28.1%). One hundred patients (32.3%) had bone-only metastatic disease. Before initiation of palbociclib, some patients have been treated by chemotherapy and/or ET. Indeed, at the early phase, 149 (65.5%) and 176 patients (77.5%) received chemotherapy and ET, respectively. At the metastatic phase prior initiation of palbociclib 30 patients (35.3%) had received chemotherapy and 70 (82.4%) ET. Among 188 patients pretreated by at least one ET, 96 (51.1%) were considered ESP (Table 1).

Palbociclib was prescribed in the 1st line setting in 225 patients (72.6%) and in the 2nd line setting in 85 (27.4%). The initial dose was 125 mg daily in 295 patients (95.2%), 100 mg daily in 14 (4.5%) or 75 mg daily in 1 (0.3%), 3 weeks out of 4 for all of them. Palbociclib was associated with an aromatase inhibitor in 207 patients (66.8%) or with fulvestrant in 103 (33.2%). For 10 patients (3.2%), ET was at first started alone and palbociclib was added after a median duration of 51.5 days. A LH-RH agonist was prescribed in 61 patients (19.7%). Among 229 patients with at least one bone lesion, denosumab was prescribed in 170 (74.2%). Among 47 patients aged 75 and more, 18 (38.3%) had an oncogeriatric assessment before initiation of palbociclib. After the first prescription of palbociclib, 222 patients (71.6%) had a consultation with a clinical nurse. This consultation aimed to make sure that the treatment's modalities were fully understood and to promote the patient's autonomy (Table 1).

During palbociclib-based treatment, at least one local treatment for a cancer lesion was performed in 94 patients (30.3%). A breast and loco-regional lymph nodes treatment (surgery and/or radiation therapy) was performed in 24 patients (28.9%) in patients with *de novo* ABC. A radiation therapy for a metastatic lesion was performed in 56 patients (18.1%), a vertebroplasty in 33 patients (10.6%) and finally, a surgery in for a metastatic lesion in 3 patients (1.0%).

At data lock, median follow-up was 20.7 months. Median progression free survival was 21.3 months (95%CI: 17.5–25.2) in the overall population, 23.0 months (95%CI: 20.8-NR) for patients in first line, 13.1 months (95%CI: 9.0–18.6) for patients in second line, 23.4 months (95%CI: 21.6-NR) for patients without previous ET, 22.7 months (95%CI: 14.7-NR) for patients who have shown endocrine sensitivity (HR = 1.2, 95%CI: 0.81–1.77, p = 0.0027), and 13.4 months (95%CI: 10.7–20.8) for patients who have shown resistance to previous ET (HR = 1.88, 95%CI: 1.29–2.73, p = 0.003) (Fig. 2). Results of the univariate and the multivariate analysis in the overall population are shown respectively in Supplementary Table 1 and Supplementary Table 2. In the ENP/ESP population, six favorable prognostic factors for PFS were identified by univariate analysis (Supplementary Table 3), and three poor prognostic factors for PFS were identified by multivariate analysis: initial ECOG performance status 2, HR = 3.96 (95%CI: 7.97–7.97), previous ET for ABC, HR = 2.38 (95%CI: 1.54–3.69), 3 metastatic sites or more, HR = 1.88 (95%CI: 1.26–2.82), p < 0.001 (Table 2).

Overall, 46 patients (14.8%) have died at data lock. Median overall survival was not reached. At 12 and 24 months from the initiation of palbociclib, 94.5% and 81.8% of patients were respectively alive. There was no difference in OS rate according to previous ET status (Supplementary Figure 1). Tumor response was assessed by imaging procedure, which was performed every 104.8 days in average. At least one CT-scan, one PET scan, one bone scintigraphy and one MRI were realized respectively in 230 patients (74.2%), 157 (50.6%), 116 (37.4%) and 72 (23.2%). According to imaging criteria, a complete response was observed in 28 patients (9.2%), a partial response in 151 (49.8%), a stable disease in 81 (26.7%), and a progression disease in 43 (14.2%). At least one lesion

Table 1
Baseline demographic and clinical characteristics.

Characteristics	N(%)
Median age (range) - yr	61.8 (23.5–92.1)
<60 yr - no. (%)	135 (43.5)
≥60 yr - no. (%)	175 (56.5)
Menopausal status - no. (%)	
Premenopausal	57 (18.4)
Postmenopausal	253 (81.6)
Initial ECOG performance status - no. (%)	
0	160 (59.7)
1	86 (32.1)
2	22 (8.2)
Histology[a] - no. (%)	
Invasive of no special type	231 (81.0)
Invasive lobular	47 (16.5)
Other	7 (2.5)
Estrogen receptor[a] (threshold: 10%) - no. (%)	
Positive	268 (99.3)
Negative	2 (0.7)
Progesterone receptor[a] (threshold: 10%) - no. (%)	
Positive	197 (81.4)
Negative	45 (18.6)
HER2[a] - no. (%)	
Positive	0 (0.0)
Negative	239 (100.0)
Breast cancer first diagnosis - no. (%)	
Early	227 (73.2)
Advanced	83 (26.8)
Stage at diagnosis - no. (%)	
Stade I	44 (14.2)
Stade II	93 (30.0)
Stade III	15 (4.8)
NA (localized only)	75 (24.2)
Stade IV	83 (26.8)
Visceral lesion - no. (%)	
Yes	158 (51.0)
No	152 (49.0)
Bone-only metastasis - no. (%)	
Yes	100 (32.3%)
No	210 (67.7%)
No. of metastatic sites - no. (%)	
1–2	223 (71.9)
≥3	87 (28.1)
Previous systemic treatment - no. (%)	
Endocrine therapy	188 (60.6)
Chemotherapy	157 (49.7)
Prior endocrine therapy - no. (%)	
Endocrine therapy-naïve	122 (39.3)
Sensibility to endocrine therapy	96 (31.0)
Resistance to endocrine therapy	92 (29.7)
Line - no. (%)	
First	225 (72.6)
Second	85 (27.4)
Initiation dose - no. (%)	
125 mg	295 (95.2)
100 mg	14 (4.5)
75 mg	1 (0.3)
3 weeks out of 4	310 (100.0)
Endocrine therapy - no. (%)	
Letrozole	195 (62.9)
Anastrozole	9 (2.9)
Exemestane	3 (1.0)
Fulvestrant	103 (33.2)
LH-RH agonist	61 (19.7)
Denosumab - no. (%)	170 (74.2)
Additional consultation - no. (%)	
Clinical nurse	222 (71.6)
Oncogeriatrician	18 (5.8)

HER2: Human Epidermal Growth Factor Receptor-2.
LH-RH: luteinizing-hormone-releasing-hormone.
[a] In the first histological exam.

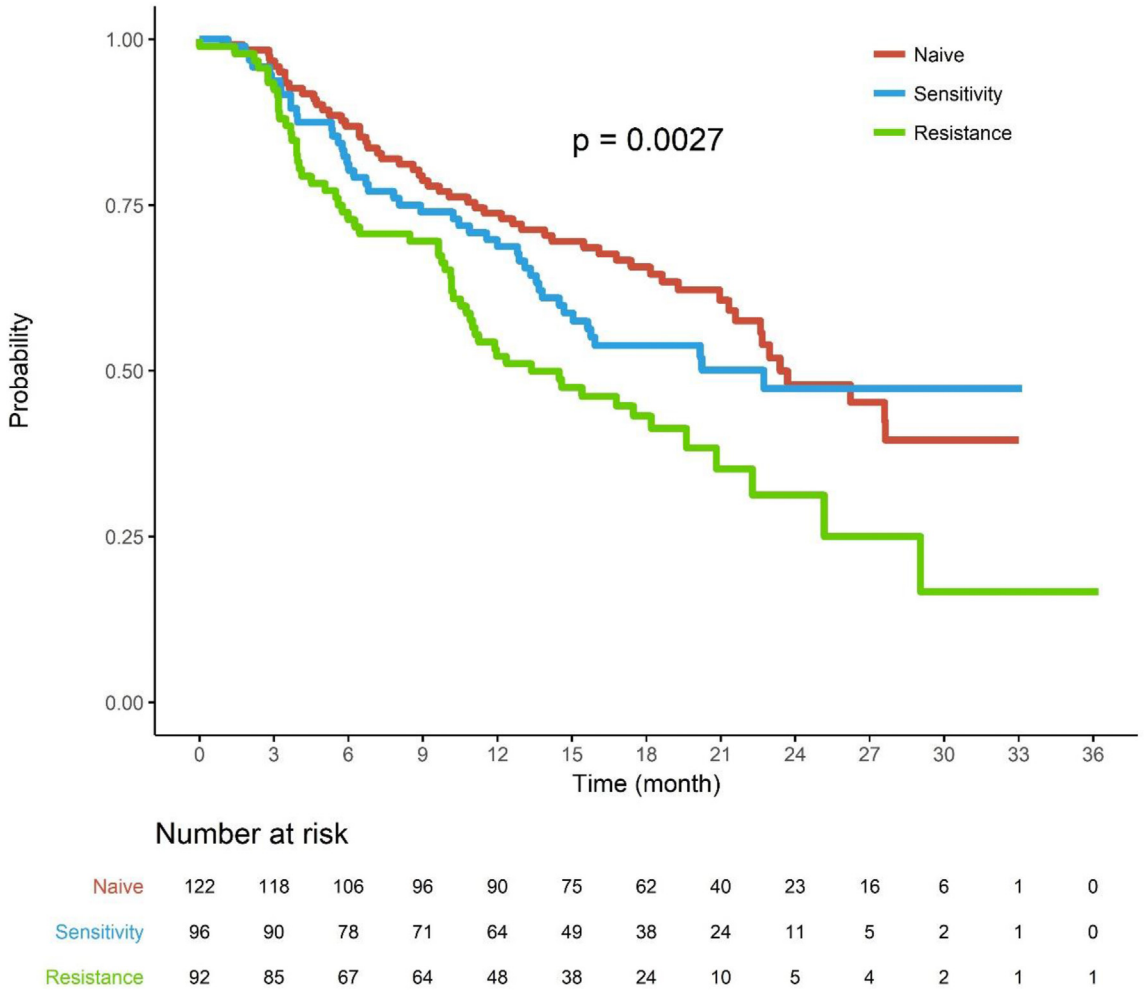

Fig. 2. Progression free survival according to sensitivity status to endocrine therapy.

Table 2
Multivariate Cox regression analysis of prognostic factors for progression-free survival in endocrine therapy-naive and endocrine therapy-sensitive population.

Prognostic factors	n	HR (95CI)	P value
ECOG status - no. (%)			<0.001
0	119	1	
1	63	1.4 (0.9–2.18)	
2	15	3.96 (1.97–7.97)	
Pretreated by endocrine therapy for advanced disease - no. (%)			<0.001
No	169	1	
Yes	49	2.38 (1.54–3.69)	
Metastatic sites - no. (%)			<0.001
1–2	151	1	
3 and more	67	1.88 (1.26–2.82)	

could be clinically evaluated (e.g. breast, lymph nodes and skin lesion) in 116 patients (62.6%). Among them, a complete response was observed in 94 patients (43.0%), a partial response in 54 (47.4%), a stable disease in 10 (8.8%), and a progression disease in 1 (0.9%) (Supplementary Table 4).

Medical clinical follow-up was performed every 59.4 days in average. ECOG statuses at the beginning and at the end of palbociclib are shown in Supplementary Table 5. Myelosuppression was monitored by a laboratory test performed every 22.1 days in average. Hematological grade 3–4 AE were neutropenia (72.3%), leukopenia (43.9%), anemia (3.2%) and thrombocytopenia (2.9%) (Supplementary Table 6A). Neutrophils polynuclear count decrease strongly with a nadir at 3 months after initiation of palbociclib, then ascent a less strongly, before levelling off (Fig. 3). Non-hematological AE are detailed in Supplementary Table 6B. At least one dose reduction occurred in 91 patients (29.4%), mostly because of hematological toxicity. Permanent discontinuation because of treatment toxicity was observed in 10 patients (5.7%). Transient grade 3–4 liver function tests elevation was observed in 1.3% of patients. The other AE of interest (all grades) were infections (16.5%), stomatitis (13.9%) and alopecia (13.9%) (Supplementary Table 6B). No toxic death was observed. During follow-up, 80 patients (25.8%) were hospitalized at least once. Among 108 hospitalizations under palbociclib, only 3 (2.8%) were assigned to

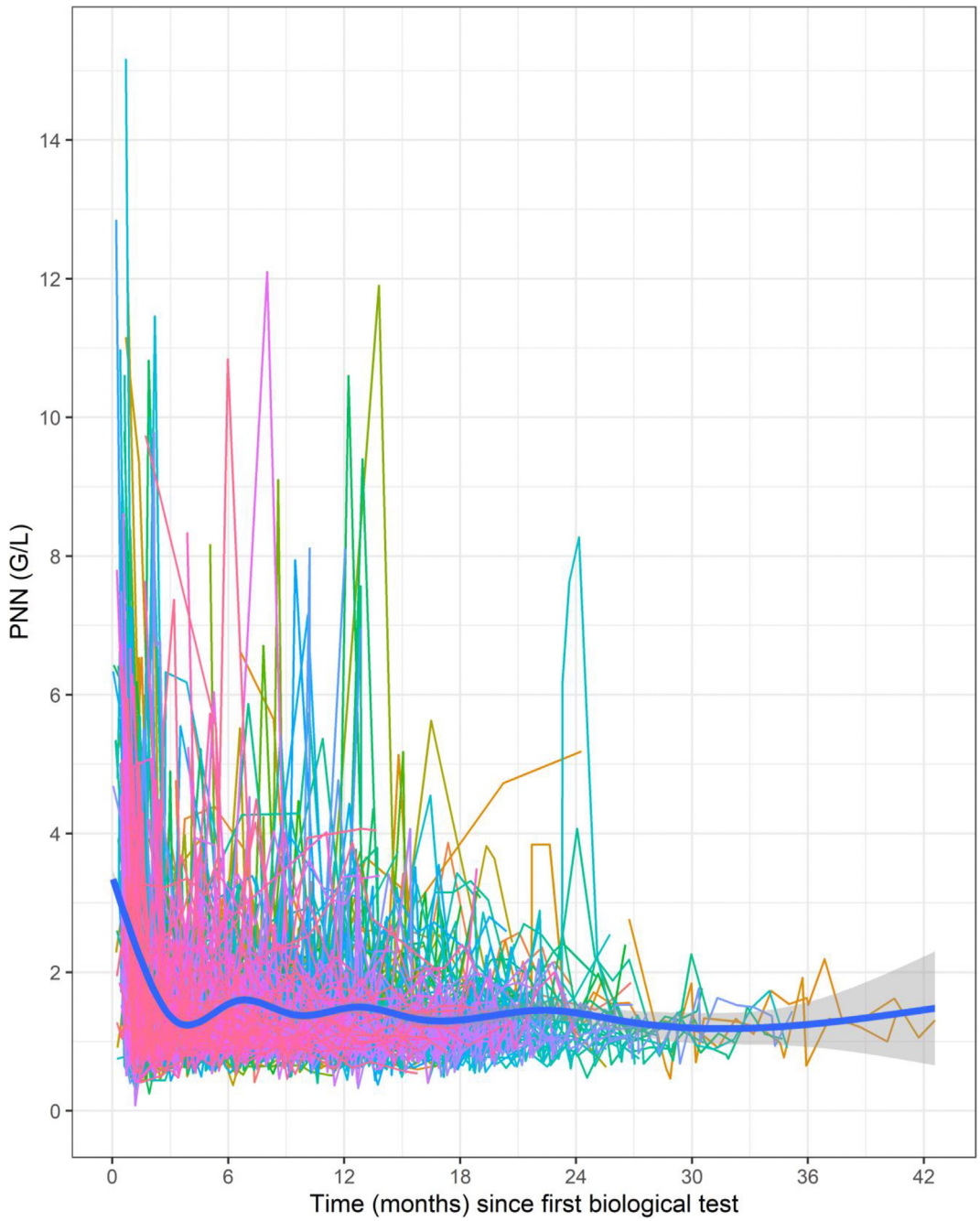

Fig. 3. Evolution of neutropenia from the initiation of palbociclib. Each colored line represents the individual evolution of neutrophil count since beginning of palbociclib. The larger blue line is constructed from regression analysis. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

palbociclib, 38 (35.2%) were assigned to a cancer complication or intercurrent event and 67 (62.0%) were assigned to a scheduled intervention.

Finally, 176 (56.8%) patients have stopped palbociclib, for progressive disease in 149 patients (84.7%), toxicity in 10 (5.7%), death in 3 (1.7%), loss to follow-up in 3 (1.7%) and other causes in 11 (6.2%). Among 170 potential candidates for a subsequent line of treatment, 7 (4.1%) did not start a new line because of a pejorative general condition, 2 (1.2%) had chosen not to, 4 (2.3%) were still waiting for a therapeutic decision at data lock, and finally 157 (92.4%) have started a post-palbociclib line. The subsequent line included of chemotherapy in 69 patients (44.0%), ET alone in 27 (17.2%), targeted therapy alone in 3 (1.9%) and, ET in combination with targeted therapy in 58 (36.9%). The targeted therapies were everolimus in 47 patients (77.0%), alpelisib in 7 patients (11.5%), and other miscellaneous treatments in 7 patients (11.5%). During this line, 13 patients (8.3%) were included in a clinical trial. Median PFS after palbociclib discontinuation was 6.4 months (95%CI: 4.8–8.9). There were no unexpected toxicities after palbociclib.

4. Discussion

In this institutional RW study, we report our experience in patients with HR + HER2- ABC treated with a palbociclib and ET

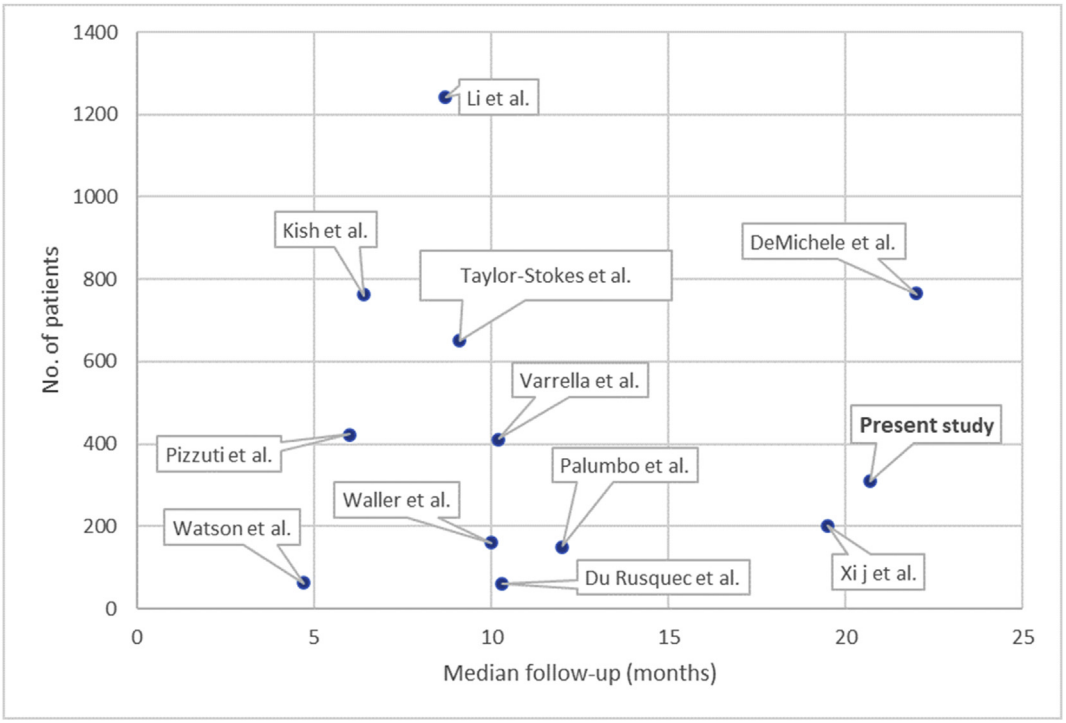

Fig. 4. Published retrospective cohorts with palbociclib in 1st and 2nd line. Each point represents a published retrospective cohort of patient treated by palbociclib-based therapy in first and/or second line setting for an advanced breast cancer according to number of patients and median follow-up.

combination according to palbociclib approval. We gathered information on patients and breast cancers characteristics, previous treatments that we administered for breast cancer, prescription and follow-up habits, events occurring under palbociclib and the subsequent treatment line. Demographic characteristics of this cohort population appear to be very similar to those of the general population [17]. We noticed that among 227 patients with secondary metastases, only 176 patients (77.6%) had received adjuvant ET, which is in line with current RW data on compliance to adjuvant ET [18]. Although 85 patients (27.4%) had a previous treatment for ABC, they were in good general condition with mostly 0–1 ECOG status. As expected, median PFS in first line (23.0 months) is similar to median PFS in the PALOMA-2's palbociclib group (24.8 months) [11]. But median PFS in second line (13.1 months) seems longer than in the PALOMA-3's palbociclib group (9.5 months). Indeed, patients in PALOMA-3 were much more heterogeneous, some of them being heavily pretreated [10]. In the present study, patients in third line setting or more were excluded. It is also striking that ENP patients (mostly *de novo* metastatic patients) and ESP patients have similar outcomes. This is in line with previous observations suggesting that patients with *de novo* ABC have a more favorable outcome [17]. In the general as well as in the ENP/ESP populations, the multivariate analysis has expectedly shown that a baseline ECOG status 2 and finally 3 metastatic sites or more are independent poor prognosis factors for PFS. These factors might be associated with individual disease natural course. Furthermore, previous exposure to chemotherapy and previous ET for an ABC are also independent poor prognosis factors for PFS respectively in general population and in ENP/ESP population. In PALOMA-2, the subgroup analysis suggested that palbociclib could have a better effectiveness in patients with bone-only lesions than in other patients. In this study, Cox univariate and multivariate does not have confirm this trend. It is currently acknowledged that we lack clinical and biological factors predictive of CDK4/6 inhibitors efficacy [19]. Most of the times, CDK4/6 inhibitors have shown similar benefit in all assessed sub-groups [20,21]. Our data add knowledge on the natural history of patients treated with a palbociclib based combination according to the present approval of the drug.

Hematological toxicity was very similar to previously published data. Liver toxicity is rare but can lead to permanent discontinuation of palbociclib and for one case, to hospitalization. In this cohort, at least one dose reduction occurred in 91 patients (29.4%), which seems lower than observed in the PALOMA trials (36.9%) [13]. Most patients experiencing progression under palbociclib during the study period received subsequent therapies. It is striking that post-palbociclib median PFS was very short (6.4 months), thus underlining the need for more active therapies in this rapidly emerging clinical setting. Recent results from the BYLieve trial strongly suggest that specific targeting of PIK3CA with alpelisib might be very efficient in this population [22]. Other preclinical data have recently shown that alternative mechanisms of the cell cycle machinery might be involved in resistance to CDK4/6 inhibition, paving the way for innovative drug development [23].

One of the secondary objectives was to observe routine medical practice in patients treated with a palbociclib-based combination. The medical burden seems moderate with a follow-up mostly ambulatory. Hospitalizations have been rare, often short for programmed intervention with 33 vertebroplasties and 12 breast surgeries (respectively 30.6% and 11.1% of hospitalizations). Another very interesting issue is initial dosing of palbociclib. We can notice some variations in prescriptions. Palbociclib was started at a lower dose in 15 patients (4.8%), was added to a previously started ET in 10 patients (3.2%) and was started as a maintenance treatment in 1 patient (0.3%). These prescriptions do not strictly follow current recommendations. Most often, it was explained by caution for patients deemed vulnerable because of advanced age, a local treatment temporary contraindicating palbociclib or an uncertain diagnostic. It is noteworthy that this individual, medically

reasonable, dose adaptation, does not seem to jeopardize palbociclib efficacy, in line with other recent real-world reports [13].

Other retrospective cohorts studying palbociclib in first and/or second line setting for the treatment of HR + HER2- ABC have been reported (Fig. 4). Only one of them has a longer follow-up duration [14]. First real-life cohorts of patients treated by palbociclib have confirmed a toxicity profile similar to randomized clinical trials [24,25]. With a longer follow-up, subsequent large US and international studies have shown similar PFS data and have suggested an OS benefit [13,14]. Other, more limited studies, were in line with those results [26-33].

We however acknowledge the limitations of this retrospective study. This is a monocentric, retrospective cohort with usual biases, implying that comparisons with data from prospective clinical trials must be extremely careful. There are some missing data. When patients have been firstly treated in another center for early breast cancer then treated in IC for ABC, we can notice missing data about early disease in some files. They were however few missing data at metastatic stage, except for the collection of non-laboratory test toxicities, which was not exhaustive. We also did not collected data about comorbidities and concomitant treatments that could be confounding factors. There was a low rate of patients lost to follow-up (1.7%), thus giving strength to the outcomes analyses.

In summary, this RW study helps to establish an accurate description of the population of patients with HR + HER2- ABC treated with a palbociclib and ET combination according to the current approval. First data of subsequent line shown no over toxicity profile. We have highlighted three poor prognostic factors in our general population: previous chemotherapy, ECOG status 2, and 3 metastatic sites or more; and in ENP/ESP population: ECOG 2, previous ET for ABC and 3 metastatic sites or more. Overall, we document here the natural course of the disease in this rapidly emerging clinical setting, in line with previously reported data, and highlight the urgent need to develop post CDK4/6 inhibitors therapies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.11.008.

Endocrine naive patients never received endocrine therapy for both early and advanced breast cancer. Endocrine sensitive patients were defined either by an absence of recurrence during adjuvant endocrine therapy or during 24 months after its completion, or by an absence of progression during 6 months after the beginning of an endocrine therapy for an advanced breast cancer. Endocrine sensitive patients were defined by a presence of one of these events.

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