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The safety and efficacy of palbociclib in older patients with advanced breast cancer in a real-world setting

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Abstract

Aims: Palbociclib has been approved in combination with endocrine therapy (ET) for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC), regardless of age. Even though ABC is one of the most prevalent cancers in older patients, very few patients ≥ 65 years old were included in pivotal trials. Therefore, the current study evaluated the safety and efficacy of palbociclib in "real-world" routine treatment of unselected older patients with HR+/HER2- ABC.

Methods: Data were collected on patients > 70 years old who were treated with palbociclib plus ET for HR+/HER2- ABC in our institution. We analyzed safety data (CTCAE v4.0 criteria) and outcomes, such as progression-free survival (PFS) and overall survival (OS), as well as any associations between main geriatric characteristics and our results. Furthermore, we assessed safety at a national level by analyzing all palbociclib-related adverse events (AEs) reported in the French Pharmacovigilance Database (FPVD) during the same period.

Results: From February 2016 to July 2019, 52 patients were identified with a median age of 80.9 years, of whom 88% presented an AE. The most common grade 3-4 AE was neutropenia (64%). Median PFS and OS were nine months and not reached, respectively. The FPVD reports 227 cases of palbociclib-related AEs, with older and younger patients sharing similar characteristics.

Conclusion: Palbociclib is well tolerated in older patients with efficacy comparable to that in younger patients. However, the addition of palbociclib to ET should be evaluated individually in this older and frailer subgroup.

Keywords: Advanced breast cancer, palbociclib, older patients, tolerance, efficacy, pharmacovigilance

INTRODUCTION

Breast cancer (BC) is the most common cancer, accounting for 11.7% of all new diagnoses in 2020, and is responsible for 7% of all cancer-related deaths[1]. As such, breast cancer is a serious public health concern and can be responsible for considerable costs in healthcare services[2]. Pathogenesis of BC is multifactorial since estrogen exposure and numerous genetic, lifestyle, and molecular factors can be involved in BC development, metastasis, and treatment resistance[3]. Breast cancer is a very heterogeneous disease, and various subtypes have been described with different prognoses and treatment requirements[4,5]. The molecular classification is mostly based on hormone receptor (HR) and human epidermal growth factor receptor (HER2) expression and includes luminal, HER2-positive, and triple-negative types[4,6].

In older women, hormone receptor-positive (HR+)/human epidermal growth factor receptor-negative (HER2-) BC is the most common subtype, accounting for 70% of patients aged ≥ 75 years, and the incidence of HR+/HER2- BC appears to increase with age[7]. However, the population of older cancer patients is greatly heterogeneous. Some older patients with few comorbidities and good Eastern Cooperative Oncology Group (ECOG) performance status scores are considered equivalent to younger patients and treated identically. Others might be frailer, with multiple comorbidities and should not be treated the same as the overall population. It is well known that increased age and multiple comorbidities may have negative impacts on survival[8]. Social and cognitive factors also affect treatment decisions and patient compliance. Because of such concerns, women aged > 75 years with advanced breast cancer (ABC) may receive less aggressive treatments and have poorer survival rates than their younger counterparts[9].

Palbociclib is an oral cyclin-dependent kinases 4/6 inhibitor (CDK4/6i) that blocks G1 to S phase progression[10,11]. Randomized phase III trials, included in the Palbociclib Ongoing Trials in the Management of Breast Cancer (PALOMA) clinical trial program, have demonstrated that palbociclib combined with endocrine therapy (ET) significantly improves progression-free survival (PFS) compared to ET alone in both with treatment-naive (PALOMA-1 and PALOMA-2) and previously treated (PALOMA-3) HR+/HER2- ABC patients[12-15]. Overall survival (OS) was only improved in PALOMA-3 in association with fulvestrant in the subgroup with sensitivity to previous ET[16]. When it was combined with letrozole as first-line therapy, no benefit in OS has yet been found in a phase III trial. Based on these clinical trials, palbociclib was approved in Europe for ABC, regardless of age[17].

Nevertheless, these results can hardly be extrapolated to older patients due to their underrepresentation in pivotal clinical trials and the subsequent scarcity of specific data concerning efficacy and safety[18]. Indeed, in the PALOMA program (including PALOMA-1, PALOMA-2, and PALOMA-3 studies), patients between 64 and 75 years old represented only 37% of the population, while patients over 75 years of age represented only 9% of the population. The median age of patients receiving palbociclib in the PALOMA-2 and PALOMA-3 studies was 62 and 57 years, respectively[13,15].

In an exploratory pooled analysis, Rugo *et al.* focused on older patients included in the three PALOMA studies and suggested that palbociclib is well tolerated with no new safety concerns in older patients, while PFS improved similarly in younger and older patients[19]. The FDA also conducted a pooled analysis of older patients treated for treatment-naive HR+/HER2- ABC with all available CDK4/6is in pivotal trials (palbociclib in PALOMA-2, ribociclib in MONALEESA-2, and abemaciclib in MONARCH-3). Their study revealed that older women displayed similar outcomes when compared to younger patients, with increased but manageable toxicity[20]. However, patients included in clinical trials are often highly selected; almost all patients (99%) had an ECOG score of 0-1[20]. Thus, there is a growing need for data collected from unselected patients.

With these elements in mind, we decided to evaluate the safety and efficacy of palbociclib in routine practice for unselected older patients with HR+/HER2- ABC in a real-world setting. We herein present the safety and efficacy data of palbociclib collected from a cohort of older patients treated in the Paoli-Calmettes Institute (a French comprehensive cancer center) between December 2015 and July 2019 and compare the reported toxicity in this cohort to the data reported in the national French Pharmacovigilance Database (FPVD).

METHODS

Data from IPC cohort

Our monocentric retrospective patient cohort comprised patients of the Paoli-Calmettes Institute (IPC, Marseille, France), a French comprehensive cancer center. Currently, there is no consensus on the definition of "older" patients in the literature, as studies use various age cut-offs from over 65 years to over 75 or even 80 years to identify this population[7]. In the current study, we used an arbitrary age of 70 years to define older (≥ 70 years) or younger (< 70 years) patients. Eligibility criteria included age > 70 years old, diagnosis of ABC with HR+/HER2-phenotype, and treatment with the combination of palbociclib and ET (aromatase inhibitors or fulvestrant). The inclusion period for treatment initiation was from December 2015 (date of initial Temporary Authorization for Use in France) to July 2019 (follow-up data cut-off date). Patients who received palbociclib as part of a clinical trial were excluded. Patients were given palbociclib at 125, 100, or 75 mg daily, according to European recommendations and at the physician's discretion, until disease progression or unacceptable toxicity. Dose reduction was permitted in the case of toxicity in accordance with the European Medicine Agency's summary of product characteristics. Endocrine therapy (aromatase inhibitors or fulvestrant) was systematically associated with palbociclib. Previous treatments for ABC (including chemotherapy or ET) were collected, along with dose reductions and their causes (hematological or non-hematological).

The G8 score was prospectively collected in routine clinical practice and retrieved from patient medical files. A comprehensive geriatric assessment (CGA) was recommended to collect and evaluate geriatric characteristics for G8 scores ≤ 14[21]. Performance status (PS) was defined by the ECOG score. Other geriatric domains assessed were activities of daily living (ADL)[22], instrumental activities of daily living (IADL)[23], polypharmacy (defined as ≥ 3 concomitant treatments), and malnutrition (defined by body mass index (BMI) < 21, albumin < 35 g/L, and weight loss > 5% in one month or > 10% in six months).

Because this was a retrospective, non-interventional study and no patient-identifiable data were collected, formal informed consent was not required. This work was performed after approval by our institutional review board (IPC *Comité d'Orientation Stratégique-PALBO-IPC 2019-008*). All procedures were in accordance with the French ethical standards.

Endpoints and statistical analysis

The primary aim of our study was to evaluate the safety of palbociclib in a real-world setting in unselected older patients with ABC. Drug-related adverse events (AEs) were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Our secondary goal was to evaluate efficacy in terms of PFS and OS using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria[24]. PFS was defined as the time from the first palbociclib cycle until objective tumor progression or death from any cause, and OS was defined as the time from the first palbociclib cycle to death from any cause. The Kaplan-Meier method was used to analyze PFS and OS with two-sided 95% confidence intervals (95%CI). Patients without disease progression or death were censored at the date of the last follow-up. Associations between geriatric characteristics and efficacy data were assessed via univariate Cox models.

Data from the French pharmacovigilance database

The French pharmacovigilance network includes 31 regional pharmacovigilance centers that collect spontaneous reports of adverse drug reactions (ADRs) when notified by healthcare professionals and patients. All reported cases are validated by a pharmacologist according to chronological and symptomatic criteria and graded according to seriousness (factors used to define serious cases include death, life-threatening, hospitalization (initial or prolonged), disability, and congenital abnormalities). These cases are stored in a common computerized database using Medical Dictionary for Regulatory Activities (MedDRA) terminology for ADR coding. This database is called the "French Pharmacovigilance Database (FPVD)".

We reviewed all cases of ADRs with palbociclib (ATC L01XE33) recorded in the FPVD from August 2016 to December 2019. We compared patients and ADR characteristics (general information concerning patients, patterns of ADRs classified by system organ class (SOC), seriousness, date of onset, and evolution) for two different populations divided according to age (< 70 *vs.* ≥ 70 years).

RESULTS

Graphical abstract summarizes the results.

Patients

During the 44-month inclusion period, 52 older patients were included in the study, with the first and last patients initiating palbociclib in February 2016 and July 2019, respectively. Patient characteristics are listed in Table 1 and Supplementary Table 1. The median age at palbociclib initiation was 80.9 years (range, 70.4-95.3 years), with 44% of patients between 75 and 80 years and 56% of patients ≥ 80 years. All patients had metastatic or recurrent HR+/HER2- ABC. Palbociclib plus fulvestrant were used in 38 patients (73%) and aromatase inhibitors in 14 patients (27%). Patients were heavily pretreated, with a median of three (range, 0-9) previous treatments (chemotherapy or ET) for advanced metastatic disease. Twenty-four patients (46%) received at least two lines of ET, with a median of two lines of ET (range, 0-6) for advanced metastatic disease. Prior ET regimens for metastatic BC included combinations of exemestane and everolimus (56%), fulvestrant (40%), anastrozole (31%), letrozole (31%), tamoxifen (27%), and exemestane alone (21%). Eleven patients (21%) had at least two lines of chemotherapy to treat metastatic BC. Prior metastatic chemotherapy regimens included taxanes (37%), capecitabine (35%), eribulin (17%), vinorelbine (13%), and anthracyclines (8%). The G8 scores were only available for 33 patients (64%) with a median score of 10 (range, 3-15) [Table 2]. Of these, 30 patients had a G8 score ≤ 14, for whom CGA was recommended. CGAs were actually performed in 28 patients (54%). The ECOG scores were only available for 35 patients, with 40% of all patients having an ECOG score of 0 or 1. Most patients were independent for daily living but needed help for instrumental activities, with ADL > 4 in 75% and IADL > 6 in 36%. Approximately half of the patients (53%) were malnourished, while 75% were subjected to polypharmacy.

Table 1. Patient characteristics at baseline (*n* = 52)

Characteristics (*n* = 52)		*n* (%)
Age (years)		
	Median (range)	80.9 (70.4-95.3)
	75-80	23 (44%)
	> 80	29 (56%)
Metastatic status		
	Recurrent disease	34 (65%)
	Metastatic de novo	18 (35%)
Number of prior metastatic therapies (median (range))		
	Overall	3 (0-9)
	Chemotherapy	0 (0-6)
	ET	2 (0-6)
≥ 2 metastatic lines		27 (52%)
≥ 2 chemotherapy metastatic lines		11 (21%)
≥ 2 ET metastatic lines		24 (46%)
Endocrine therapies in combination with palbociclib		
	Fulvestrant	38 (73%)
	Letrozole	12 (23%)
	Anastrozole	1 (2%)
	Exemestane	1 (2%)
Prior metastatic chemotherapies		
	Taxane	19 (37%)
	Capecitabine	18 (35%)
	Eribulin	9 (17%)
	Navelbine	7 (13%)
	Anthracycline	4 (8%)
Prior metastatic endocrine therapies		
	Exemestane - Everolimus	29 (56%)
	Fulvestrant	21 (40%)
	Letrozole	16 (31%)
	Anastrozole	16 (31%)
	Tamoxifen	14 (27%)
	Exemestane	11 (21%)

ET: Endocrine therapy.

Treatment administration

The median treatment duration for palbociclib was 5.5 months (range, 0-2.6 months). Among the 34 patients who had to stop treatment, the causes of discontinuation were disease progression in 24 patients (71%), toxicity in 5 patients (15%), and death in 2 patients (6%). Most patients (89%) initiated full-dose palbociclib at 125 mg daily, but five patients (9%) and one patient (2%) started treatment at 100 and 75 mg daily, respectively. Twenty-one patients (40%) received dose reductions due to toxicity. These dose reductions occurred in a median of 1.4 months (range, 0.9-8.5 months), and the causes of dose reduction were hematological toxicity in 71% and non-hematological toxicity in 29% of patients.

Safety

Eighty-eight percent of all patients presented with an AE of any grade [Table 3]. No treatment-related deaths were reported. The most frequently reported treatment-related AEs were neutropenia (73%),

Table 2. Geriatric characteristics at baseline

Characteristics (*n* = 52)	***n* (%)**
CGA available (*n = 52*)	28 (54%)
ECOG score (*n = 35*)	
0	6 (17%)
1	15 (29%)
2	9 (17%)
3	5 (10%)
G8 score (*n = 33*)	
> 14	3 (9%)
ADL (*n = 28*)	
> 4	21 (75%)
IADL (*n = 28*)	
> 6	10 (36%)
Polypharmacy (*n = 28*)	21 (75%)
Malnutrition (*n = 26*)	14 (54%)

CGA: Comprehensive geriatric assessment; ECOG score: Eastern Cooperative Oncology Group score; ADL: activities of daily living; IADL: instrumental activities of daily living.

Table 3. Adverse events occurring during palbociclib treatment (*n* = 52)

Adverse events (*n* = 52)	**Any grade (%)**	**Grade ≥ 3 (%)**
All	46 (88%)	35 (67%)
Neutropenia	38 (73%)	33 (63%)
Febrile neutropenia	1 (2%)	1 (2%)
Asthenia	20 (38%)	5 (10%)
Anemia	16 (31%)	1 (2%)
Thrombocytopenia	10 (19%)	2 (4%)
Infection	10 (19%)	3 (6%)
Mucositis	8 (15%)	0
Nausea	8 (15%)	0
Diarrhea	6 (12%)	0
Anorexia	5 (10%)	0
Alopecia	5 (10%)	0
Skin rash	4 (8%)	0
Dry eye	2 (4%)	0
Epistaxis	2 (4%)	0
Vomiting	1 (2%)	0
Palmar-plantar erythrodysesthesia	1 (2%)	0
Dysgeusia	1 (2%)	0
Blurred vision	1 (2%)	0

asthenia (39%), anemia (31%), thrombocytopenia (19%), and digestive issues such as nausea (15%) and diarrhea (12%). Grade 3-4 AEs were reported in 35 patients (67%). The most common grade 3-4 AE was neutropenia (64%). Only one case of febrile neutropenia was reported. Other grade 3-4 AEs reported included asthenia (10%), infection (6%), or thrombocytopenia (4%).

Efficacy

Median PFS was nine months [95%CI: six months to not reached (NR)] with palbociclib [Figure 1A] and median OS was not reached (95%CI: 22 months to NR) [Figure 1B]. Nineteen patients (36%) were still undergoing treatment as of the cut-off date for follow-up data. In subgroup analysis, none of the following geriatric characteristics were significantly associated with PFS: ECOG status [≤ 1 *vs.* > 1; HR = 0.42 (95%CI: 0.09-1.90); $P = 0.24$], G8 score [> 14 *vs.* ≤ 14; HR = 0.75 (95%CI: 0.09-6.26); $P = 0.79$], polypharmacy [no *vs.* yes; HR = 1.07 (95%CI: 0.32-3.53); $P = 0.91$], ADL [> 4 *vs.* ≤ 4; HR = 2.07 (95%CI: 0.21-20.49); $P = 0.52$], and IADL [> 6 *vs.* ≤ 6; HR = 2.40 (95%CI: 0.25-23.13); $P = 0.43$].

ADR characteristics from the French Pharmacovigilance Database

In total, 227 cases of AEs concerning patients treated with palbociclib were recorded in the FPVD during the inclusion period. Of these, 120 patients (53%) were under 70 years old (the median age was 62 years in this group) and 107 patients (47%) were 70 years or older. In the 70 years or older patient subgroup, 58 AEs (54%) were considered serious adverse events (SAEs) with one death and two life-threatening events compared to 84 SAEs in patients under 70 years (70%), including three deaths and five life-threatening events. The most frequently reported treatment-related SAEs were similar in both groups and were mainly hematological in nature, with 25 cases in the older group (43.1% of reported SAEs), including nine cases of neutropenia, one case of thrombocytopenia, seven cases of bicytopenia, and eight cases of pancytopenia. In the younger group, 33 SAEs (43.1% of reported SAEs) were hematological in nature, with 14 cases of neutropenia, 2 cases of thrombocytopenia, 2 cases of anemia, 6 cases of bicytopenia, and 9 cases of pancytopenia. The most frequently reported non-hematological SAEs were cardiovascular (10 cases in the older group and 11 cases in the younger group) and cutaneous (6 cases in the older group and 10 cases in the younger group) in nature. The details of the SAEs were similar across both groups, with median times to onset of 29 days (range, 2 days to 3 years) and 30 days (range, 1 day to 17 years), 59 (70%) and 46 (79%) patients discontinuing therapy due to SAEs, and favorable evolution in 44 (52.4%) and 37 patients (62.7%) in the older and younger groups, respectively.

DISCUSSION

Over the past decade, the association of palbociclib with ET has demonstrated significantly improved outcomes with acceptable toxicity in HR+/HER2- ABC. Thus, CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have become standard first- or second-line treatments for ABC. Nonetheless, data concerning efficacy and safety in older patients are scarce and mostly originate from subgroup analyses of phase III randomized trials, thereby limiting their application in unselected patients.

Throughout the PALOMA trials, grade 3-4 AEs occurred in 73%-75% of patients, with neutropenia being the most frequently reported AE[12,15]. In a pooled analysis of older patients included in the PALOMA trials, Rugo *et al.* reported all-grade and grade 3-4 neutropenia in 90% and 73% of patients > 75 years old treated with palbociclib, respectively. Moreover, grade 3-4 neutropenia was more frequent in patients ≥ 75 years old (73%) *vs.* < 65 years old (65%)[19]. In another pooled analysis, the FDA assessed CDK4/6is in older subgroups from multiple registration trials. A higher number of grade 3-4 AEs was reported in patients ≥ 75 years old compared to patients < 75 years old (88% *vs.* 73%, respectively), leading to higher rates of dose reduction/interruption (81.6% *vs.* 71.1%, respectively) and discontinuation (32% *vs.* 12.1%, respectively)[20]. Another meta-analysis of phase II and III studies also showed that palbociclib was associated with significantly increased rates of neutropenia in an older subgroup compared to their younger counterparts, with an ORR of 2.57. Leukopenia, anemia, back pain, asthenia, and infections were also more frequent in the older group[25]. Recently, results were reported from the French prospective study PALOMAGE and its safety analysis of palbociclib + ET in a real-life setting in women aged ≥ 70 years with HR+/HER2- ABC, where 807 patients were included with a median age of 79 years old. Of these, 68.3% had a G8 score of ≤ 14,

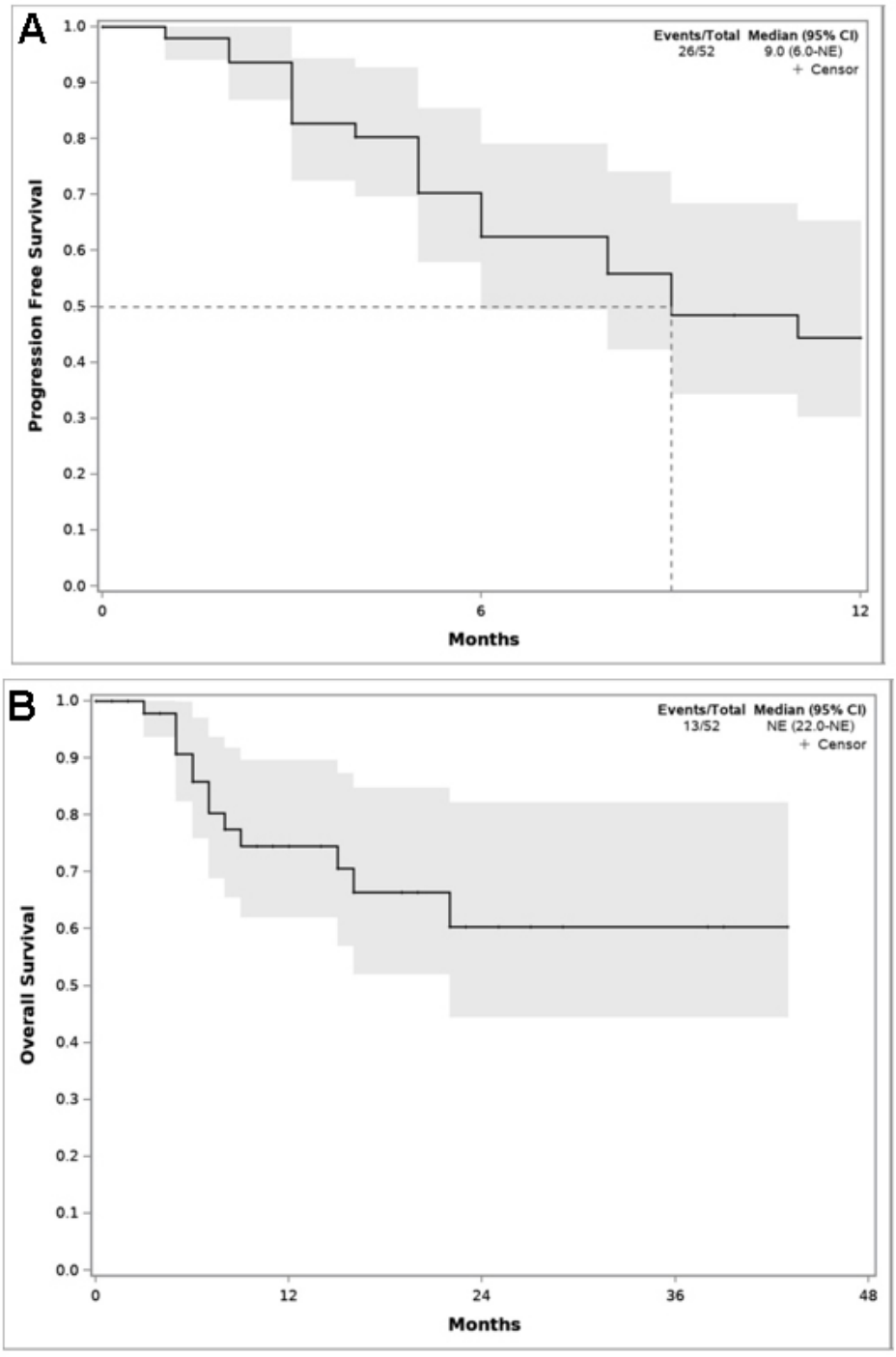

Figure 1. (A) progression-free survival; and (B) overall survival.

while the ECOG score was ≥ 2 in 17.9%, demonstrating the frailty of the population. In addition, 70% had at least one adverse event, including 43.1% with grade 3-4 AEs. The most frequent AE was neutropenia (43.2%), with 32.3% experiencing grade 3-4 neutropenia but only 1.1% experiencing febrile neutropenia. Geriatric data and outcomes have not yet been released[26]. Our results are consistent with those of the previous studies, with 73% and 64% of patients reporting instances of either all-grade or grade 3-4

neutropenia, respectively. Palbociclib-induced neutropenia results from cell cycle arrest as opposed to apoptotic cell death from chemotherapy regimens[27], with subsequently less frequent febrile neutropenia than that seen with traditional cytotoxic chemotherapy agents[28]. Accordingly, we observed only one case of febrile neutropenia in our study. Because of the reversibility of neutropenia, this AE is well manageable in routine practice. Dose delays and dose reductions are the recommended strategies to overcome grade 3-4 hematological toxicities, especially in geriatric populations[17]. Interestingly, dose delays, interruptions, or reductions were not associated with poorer outcomes in either PALOMA-3[29] or real-world retrospective data[30].

In pivotal studies, palbociclib improved survival outcomes compared to ET alone, with reported median PFS of 10.3 and 4.9 months in previously untreated ABC (PALOMA-2)[13] and ABC that progressed after previous ET (PALOMA-3)[14], respectively. Additionally, palbociclib has been proven to improve OS in association with fulvestrant in pretreated ABC (34.9 *vs.* 28.0 months; HR = 0.81), but there is currently no evidence of such an OS benefit in treatment-naive ABC since the data from PALOMA-2 trial have not yet been released[13,16]. However, a signal of potential OS benefit has been reported in real-world retrospective studies[31]. In addition, the CDK4/6i ribociclib demonstrated improved OS in premenopausal and perimenopausal patients (MONALEESA-7) and, more recently, in postmenopausal patients (MONALEESA-2) with ET-naive ABC[32,33]. Considering efficacy according to age subgroups, Clifton *et al.* reported a trend in univariate analysis towards improved PFS in a geriatric population ≥ 70 years old compared to a younger cohort < 70 years old (HR = 0.68; $P = 0.02$)[30]. However, this difference was not observed in multivariate analysis, suggesting probable underlying confounding variables that could include less aggressive tumor characteristics in older patients[34] or earlier use of palbociclib in the course of treatment[30]. Overall, they reported a median PFS of 11 months[30]. Rugo *et al.* reported a median PFS of 27.5 months and not reached in subgroups of 65-74 years old and > 75 years old patients, respectively, with palbociclib plus letrozole, and 16.1 and 13.6 months, respectively, with palbociclib plus fulvestrant[19]. In our study, the median PFS was only nine months. The reduced efficacy may be explained by several hypotheses and many confounding factors. First, our population was heavily pretreated with a median of three (range, 0-9) previous metastatic treatments (chemotherapy or ET). Second, patients in our cohort were unselected and could therefore be frailer, with poorer ECOG status and more comorbidities. However, the frailty in our patient population did not necessarily reflect increased dose reduction (40% *vs.* 51% in Clifton's study) or treatment discontinuation (9% *vs.* 6% in Rugo's pooled analysis)[19,30]. Moreover, older and frailer patients may have reduced compliance with oral treatments, mainly due to forgetfulness or polypharmacy[35]. With the real-life setting of our study, we can hypothesize that compliance may have been poorer than in clinical trials, wherein drug intake is likely to be more closely monitored.

In the FPVD, the analysis of AEs reported from palbociclib treatment is consistent with previous studies based on clinical trial data[36]. When comparing to younger patients, we did not use statistical comparison because of the lack of statistical power, but a trend towards the absence of difference was found concerning the patterns and characteristics of SAEs that occurred in older patients. Neutropenia was the most commonly reported hematological AE. Additionally, while the delay of neutropenia onset (one month) was similar to previous observations, treatment discontinuation occurred more frequently in association with this AE in our study[37].

Since it has been proven to be both effective and well tolerated in all subgroups, palbociclib is recommended regardless of age. Indeed, according to guidelines, ET treatment decisions in geriatric populations should not be based solely on increased age[38-40]. However, it is critical to distinguish between two distinct groups of older patients with cancer[41]; the first group includes fit patients who are more likely to benefit from the

addition of a CDK4/6i with fewer AEs, while the second group includes frail older patient who are more likely to experience AEs and for whom the therapeutic strategy should be more personalized, with quality of life becoming more important than survival in some of these older patients[42]. This cautious strategy is supported by the higher incidence of hematological AEs from CDK4/6i in this population. As our study included unselected older patients, with both greater comorbidities and poorer ECOG status, it may relate more to the second group. Currently, there is no formal recommendation for prescriptions in this particularly older and frailer subgroup. Even though toxicities appear to be manageable, they may become a source of geriatric decompensation in a much older population. For example, neutropenia requires increased monitoring, with more frequent blood tests and unplanned readmissions, which may become a source of anxiety and discomfort. Even grade 1 or 2 diarrhea may have a significant impact on those patients and could likely be responsible for dehydration and renal dysfunction in this frail population. The Young International Society of Geriatric Oncology proposed an algorithm for treating older patients with HR+/HER2- ABC, in which ET alone remains a valid proposition for frail or vulnerable patients with few symptoms and a low tumor burden. The addition of CDK4/6is could still be discussed in cases of disease progression and ET resistance. Nonetheless, palbociclib and other CDK4/6is should always be considered in the fit subgroup, regardless of age, and in patients with threatening metastasis for whom a rapid improved response is crucial.

One of the study's strengths is the inclusion of every patient who received palbociclib in our center. This population was older, with a median age of 80 years, and less fit than patients included in clinical trials. Because of these characteristics, our results may be more generalizable to the real-world population.

The current study, however, has several limitations. First, the retrospective design might have permitted selection or information biases. Only large studies with prospective geriatric assessments can more precisely define the efficacy and safety of CDK4/6is in older and frailer patients. Second, the lack of geriatric data prevented us from providing more accurate geriatric descriptions and could explain the absence of differences in survival regarding geriatric characteristics. Only 63% and 54% of our cohort reported a G8 score and complete CGA, respectively. This underlines the fact that in routine practice, physicians often treat older patients without factual and personalized geriatric assessments, whereas the information gathered through CGAs can help the clinician and patient better assess potential treatment benefits and risks[43]. Considering older patients and their geriatric status is a primordial element, as functional age is often more important than chronological age[43]. Third, because of missing data and the small number of patients in our cohort, we did not perform statistical comparisons between subgroups, as they would have lacked statistical power. The absence of a control arm for younger patients is an additional limitation.

Additionally, the evaluation of autonomy and quality of life was missing in the current study. Health-related quality of life assessments are important in routine clinical practice via the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 and EORTC QLQ-ELD14 questionnaires[44,45]. Health-related quality of life evaluations for older patients receiving palbociclib plus ET in clinical trials have demonstrated that quality of life is maintained when compared to patients receiving ET alone, regardless of age category[19]. In the FDA pooled analysis of CDK4/6is, deterioration in the quality of life was seen in patients ≥ 75 years old when compared to younger patients. However, this deterioration was not associated with CDK4/6is addition and was similarly seen in patients who underwent ET alone[20]. This further highlights the frailty of older patients and the need for close monitoring when considering any cancer treatment. Furthermore, populations in these pooled analyses are different from our cohort of older and frailer patients, and the results may be difficult to extrapolate. The deterioration of quality of life may be more important in our population with additional treatments such as palbociclib. Quality of life analyses

and geriatric descriptions in the PALOMAGE study will be able to further characterize geriatric populations. Finally, as our cohort included patients with both treatment-naive ABC and previously treated ABC, the extrapolation of efficacy data may be difficult. Indeed, we reported a range of 0-9 previous metastatic lines before palbociclib initiation, emphasizing once more the heterogeneity of our population.

CONCLUSION

Palbociclib in patients 70 years old or older was well tolerated in our cohort, with neutropenia being the most common AE. Most toxicities were manageable with dose delay or reduction and supportive care. However, due to the frailty of this population, close monitoring is required as it allows both clinicians and patients to find ways to overcome complications. The efficacy of palbociclib in fit geriatric patients is comparable to that in younger patients, and therefore it is indicated for therapy with CDK4/6is when needed, irrespective of age. However, the results in another group of frailer and more vulnerable older patients raise concerns, and standalone ET remains a valid option for this population. To better understand palbociclib in older patients, real-world prospective studies are required with careful geriatric assessments. This is precisely the purpose of the ongoing national French multicenter observational study PALOMAGE, in which geriatric descriptions and efficacy results will be explored.

DECLARATIONS

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Author's contibutions

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This work was performed after approval by our institutional review board (IPC *Comité d'Orientation Stratégique_ PALBO-IPC 2019-008*). All procedures were performed in accordance with the Declaration of Helsinki and French ethical standards. Because this was a retrospective non-interventional study and no patient identifiable data was collected, formal informed consent was not required.

Consent for publication

Not applicable.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-49. DOI PubMed
2. Mela A, Poniatowski ŁA, Drop B, et al. Overview and analysis of the cost of drug programs in poland: public payer expenditures and coverage of cancer and non-neoplastic diseases related drug therapies from 2015-2018 Years. *Front Pharmacol* 2020;11:1123. DOI PubMed PMC
3. Purrahman D, Mahmoudian-Sani MR, Saki N, Wojdasiewicz P, Kurkowska-Jastrzębska I, Poniatowski ŁA. Involvement of progranulin (PGRN) in the pathogenesis and prognosis of breast cancer. *Cytokine* 2022;151:155803. DOI PubMed
4. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World J Clin Oncol* 2014;5:412-24. DOI PubMed PMC
5. Nakagawa T, Hayashi K, Ogawa A, et al. Bone marrow carcinomatosis in a stage IV breast cancer patient treated by letrozole as first-line endocrine therapy. *Case Rep Oncol* 2022;15:436-41. DOI PubMed PMC
6. Feng Y, Spezia M, Huang S, et al. Breast cancer development and progression: risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis* 2018;5:77-106. DOI PubMed PMC
7. Bergen ES, Tichy C, Berghoff AS, et al. Prognostic impact of breast cancer subtypes in elderly patients. *Breast Cancer Res Treat* 2016;157:91-9. DOI PubMed PMC
8. Kartal M, Tezcan S, Canda T. Diagnosis, treatment characteristics, and survival of women with breast cancer aged 65 and above: a hospital-based retrospective study. *BMC Womens Health* 2013;13:34. DOI PubMed PMC
9. Baban CK, Devane L, Geraghty J. Change of paradigm in treating elderly with breast cancer: are we undertreating elderly patients? *Ir J Med Sci* 2019;188:379-88. DOI PubMed
10. Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther* 2004;3:1427-38. PubMed
11. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009;11:R77. DOI PubMed PMC
12. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25-35. DOI PubMed
13. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925-36. DOI PubMed
14. Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373:209-19. DOI PubMed
15. 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): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016;17:425-39. DOI PubMed
16. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. *N Engl J Med* 2018;379:1926-36. DOI PubMed
17. Ibrance - EMEA/H/C/003853 - IB/0032. DOI
18. Singh H, Kanapuru B, Smith C, et al. FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: A 10-year experience by the U.S. Food and Drug Administration. *JCO* 2017;35:10009. DOI
19. Rugo HS, Turner NC, Finn RS, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. *Eur J Cancer* 2018;101:123-33. DOI PubMed
20. Howie LJ, Singh H, Bloomquist E, et al. Outcomes of older women with hormone receptor-positive, human epidermal growth factor receptor-negative metastatic breast cancer treated with a CDK4/6 inhibitor and an aromatase inhibitor: an FDA pooled analysis. *J Clin Oncol* 2019;37:3475-83. DOI PubMed
21. Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One* 2014;9:e115060. DOI PubMed PMC
22. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged the index of adl: a standardized measure of biological and psychosocial function. *JAMA* 1963;185:914-9. DOI PubMed
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179-86. PubMed
24. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-update and clarification: from the RECIST committee. *Eur J Cancer* 2016;62:132-7. DOI PubMed PMC
25. Omarini C, Piacentini F, Sperduti I, et al. Combined endocrine approaches vs endocrine therapy alone as first line treatment in elderly patients with hormone receptor-positive, HER2 negative, advanced breast cancer: to prescribe for the patient or the physician? *BMC Cancer* 2020;20:418. DOI PubMed PMC

26. Caillet P, Pulido M, Brain E, et al. PALOMAGE, a French real-world cohort of elderly women beyond age 70 with advanced breast cancer receiving palbociclib: Baseline characteristics and safety evaluation. *JCO* 2021;39:1012-1012. DOI
27. Hu W, Sung T, Jessen BA, et al. Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation from cytotoxic chemotherapies. *Clin Cancer Res* 2016;22:2000-8. DOI PubMed
28. Sammons SL, Topping DL, Blackwell KL. HR+, HER2- advanced breast cancer and CDK4/6 inhibitors: mode of action, clinical activity, and safety profiles. *Curr Cancer Drug Targets* 2017;17:637-49. DOI PubMed PMC
29. Verma S, Bartlett CH, Schnell P, et al. Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-Negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). *Oncologist* 2016;21:1165-75. DOI PubMed PMC
30. Clifton K, Min Y, Kimmel J, Litton J, Tripathy D, Karuturi M. Progression-free survival (PFS) and toxicities of palbociclib in a geriatric population. *Breast Cancer Res Treat* 2019;175:667-74. DOI PubMed PMC
31. DeMichele A, Cristofanilli M, Brufsky A, et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2- metastatic breast cancer in US real-world clinical practice. *Breast Cancer Res* 2021;23:37. DOI PubMed PMC
32. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* 2019;381:307-16. DOI PubMed
33. Hortobagyi GN, Stemmer SM, Burris HA, et al. LBA17_PR - Overall Survival (OS) results from the Phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (Pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). *Ann Oncol* 2021;32:S1283-46. DOI
34. O'Connor T, Shinde A, Doan C, Katheria V, Hurria A. Managing breast cancer in the older patient. *Clin Adv Hematol Oncol* 2013;11:341-7. PubMed PMC
35. Shruthi R, Jyothi R, Pundarikaksha HP, Nagesh GN, Tushar TJ. A study of medication compliance in geriatric patients with chronic illnesses at a tertiary care hospital. *J Clin Diagn Res* 2016;10:FC40-3. DOI PubMed PMC
36. Diéras V, Rugo HS, Schnell P, et al. Long-term pooled safety analysis of palbociclib in combination with endocrine therapy for HR+/HER2- advanced breast cancer. *J Natl Cancer Inst* 2019;111:419-30. DOI PubMed PMC
37. Varella L, Eziokwu AS, Jia X, et al. Real-world clinical outcomes and toxicity in metastatic breast cancer patients treated with palbociclib and endocrine therapy. *Breast Cancer Res Treat* 2019;176:429-34. DOI PubMed
38. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J Clin Oncol* 2021;39:3959-77. DOI PubMed PMC
39. Gennari A, André F, Barrios CH, et al. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021;32:1475-95. DOI PubMed
40. Biganzoli L, Battisti NML, Wildiers H, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). *Lancet Oncol* 2021;22:e327-40. DOI PubMed
41. Battisti NML, De Glas N, Sedrak MS, et al. Use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in older patients with ER-positive HER2-negative breast cancer: Young International Society of Geriatric Oncology review paper. *Ther Adv Med Oncol* 2018;10:1758835918809610. DOI PubMed PMC
42. Puts MT, Tapscott B, Fitch M, et al. A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. *Cancer Treat Rev* 2015;41:197-215. DOI PubMed
43. Wildiers H, Heeren P, Puts M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595-603. DOI PubMed PMC
44. Hjermstad M, Fayers P, Bjordal K, Kaasa S. Using reference data on quality of life-the importance of adjusting for age and gender, exemplified by the EORTC QLQ-C30 (+3). *Eur J Cancer* 1998;34:1381-9. DOI PubMed
45. Wheelwright S, Darlington AS, Fitzsimmons D, et al. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. *Br J Cancer* 2013;109:852-8. DOI PubMed PMC