Drugs in Context

drugsincontext.com

ORIGINAL RESEARCH

Efficacy and activity of treatments after progression from palbociclib plus endocrine therapy in patients with HR+/HER2- metastatic breast cancer: a prospective, monocentric study

Raffaella Palumbo[1], Erica Quaquarini[1], Giuseppe Saltalamacchia[1,2], Alberto Malovini[3], Pietro Lapidari[1,2], Barbara Tagliaferri[1], Ludovica Mollica[1,2], Cristina Maria Teragni[1], Chiara Barletta[1,2], Laura Deborah Locati[1,2], Federico Sottotetti[1]

[1]Medical Oncology Unit, ICS Maugeri-IRCCS SpA SB, Pavia, Italy; [2]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; [3]Laboratory of Informatics and Systems Engineering for Clinical Research, ICS Maugeri-IRCCS SpA SB, Pavia, Italy

Abstract

Background: Breast cancer is the most frequent tumour worldwide, and the HR+/HER2- subtype is the most common. For this tumour type, endocrine therapy (ET) is the mainstay of treatment. The association of ET and CDK4/6 inhibitors (CDK4/6i) represents the gold standard for first-line or second-line therapies. However, the optimal therapeutic strategy after CDK4/6i progression is still a matter of debate, with several randomized clinical trials still ongoing.

Patients and methods: This is an observational, prospective, real-world study including women with HR+/HER2- metastatic breast cancer progressing to palbociclib plus ET. Patients received either ET or chemotherapy (CT). The primary objective was the evaluation of efficacy of the different therapeutic strategies after palbociclib in terms of median progression-free survival 2. Secondary objectives were the activity of therapeutic strategies measured with the clinical benefit rate, evaluation of the parameters used for the treatment choice, and progression-free survival 1 related to palbociclib plus ET treatment.

Results: Overall, 48 patients (median age 53, range 33–78 years) were included. The median progression-free survival 2 was of 5 months in the overall cohort (95% CI 4–48 months) with a statistically significant difference between the two therapeutic strategies adopted (ET *versus* CT, 10 months *versus* 5 months, respectively). Regarding secondary objectives, the clinical benefit rate was 55.2% in the CT cohort and 50% in ET. Moreover, women treated with CT had a greater number of visceral metastases and a shorter median progression-free survival 1 than patients who received ET.

Conclusions: ET and CT represent two possible therapeutic alternatives for patients progressing on CDK4/6i plus ET. The choice is based on clinical parameters, with a potential preference for ET.

Keywords: endocrine resistance, metastatic breast cancer, palbociclib, post-progression, therapeutic strategies.

Citation

Palumbo R, Quaquarini E, Saltalamacchia G, Malovini A, Lapidari P, Tagliaferri B, Mollica L, Teragni CM, Barletta C, Locati LD, Sottotetti F. Efficacy and activity of treatments after progression from palbociclib plus endocrine therapy in patients with HR+/HER2- metastatic breast cancer: a prospective, monocentric study. *Drugs Context*. 2024;13:2023-7-5. https://doi.org/10.7573/dic.2023-7-5

Introduction

Female breast cancer is the most common cancer worldwide. In 2021, 2.3 million new cases (11.7% of total tumours) were recorded, ranking in fifth position for death from cancer.[1] The most common phenotype of breast cancer is hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-), which accounts for up to 75% of invasive tumours.[2] During the last decades, endocrine-based therapy (ET) has been convincingly demonstrated to

be the most active and appropriate option for patients with metastatic breast cancer (MBC).[3–5] Despite the activity and effectiveness of ET, a subgroup of patients is primarily resistant to ET, and up to 50% will develop secondary resistance via different molecular mechanisms during treatment, ultimately leading to treatment failure.[6]

Inhibitors of cyclin-dependent kinases 4/6 (CDK4/6i) have an established role as first-line treatment in combination with an aromatase inhibitor (AI) or selective oestrogen down-regulator (SERD), or in the second-line setting after progression to ET alone. Amongst patients receiving CDK4/6i + AI or fulvestrant as first-line treatment, approximately 15% and 30%, respectively, will have early disease progression within 6 months.[7] The population of patients with *de novo* metastatic disease or with progression after at least 12 months of adjuvant ET has been addressed by large prospective clinical trials (PALOMA-2, MONALEESA-2, MONALEESA-7, MONARCH-3), in which CDK4/6i plus AI proved superior to ET alone.[8–12] The combination of CDK4/6i + AI or SERD was superior to ET monotherapy also in the endocrine-resistant population, according to the results of different phase III clinical trials (PALOMA-3, MONALEESA-3 and MONARCH-2).[13–15] Given this evidence as well as their versatility and favourable toxicity profile, CDK4/6i are strongly recommended by ESMO guidelines, which indicate them as preferred first-line treatment for patients with HR^+ MBC without imminent organ failure, for whom systemic chemotherapy (CT) remains the recommended choice.[16] According to the results of a recent metanalysis by Piezzo et al. including eight randomized clinical trials, treatment with CDK4/6i + ET can provide a progression-free survival (PFS) advantage compared with ET alone, also in presence of visceral metastases, and independently from the number of metastatic sites and length of the treatment-free interval.[17] Moreover, the possibility to delay CT is a major advantage of CDK4/6i treatments, thus offering reduced toxicity and improving quality of life.

The literature currently lacks high-quality prospective trials involving patients progressing to an CDK4/6i + ET, and most data derive from retrospective studies.[18–21] In this context, the guidelines suggest a biomarker-driven approach for patients whose disease harbours *PIK3CA* or *BRCA* mutations. Switch to other endocrine-based regimens or CT is recommended for patients with imminent organ failure or in late treatment lines.[16]

The aim of this prospective study is to evaluate the efficacy and activity of the different oncological treatments in patients with HR^+/HER^- MBC progressing to CDK4/6i therapy in a real-world setting.

Patients and methods

Study design

This is a prospective, observational monocentric cohort study conducted from May 2017 to October 2021 at the Unit of Medical Oncology of ICS Maugeri IRCCS located in Pavia, in Northern Italy. In our centre, more than 150 new cases of breast cancer per year are usually treated. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the coordinating Institution (ICS Maugeri-IRCCS Pavia Ethical Committee, approval number 2295). All patients provided written informed consent for the analysis and anonymized publication of clinical data.

Study population

Eligible patients were premenopausal or postmenopausal women with a histologically proven HR^+ MBC who were candidates to receive other ET-based therapy or CT (from the second-line therapy in according to their clinical situation) after progression to palbociclib plus ET. Additional inclusion criteria were $HER2^-$ disease (immunohistochemistry (IHC) 0–1+ or IHC2+, confirmed as fluorescence *in situ* hybridization (FISH) negative), presence of measurable or evaluable lesions, and life expectancy of at least 4 months. The participants were also required to have adequate bone marrow, hepatic and renal function according to clinical practice guidelines for antineoplastic drug administration. The therapeutic strategy was defined following multidisciplinary discussion and physician choice and was based on the analysis of the multifaceted and complex aspects of each patient's clinical conditions, disease extension, response to previous treatment and adverse events profile of the proposed treatment.

The parameters considered, according to current guidelines,[16] were (1) disease site and burden: patients with widespread progression, visceral disease as opposed to bone-only/oligometastatic disease or imminent risk of organ failure were preferably treated with CT; (2) median PFS1 (<4 months *versus* ≥4 months) defined patients with more pronounced benefit from previous endocrine-based treatment and more likely to benefit from subsequent endocrine-based lines; (3) side-effects of the possible therapeutic strategies; and (4) patient preferences (i.e. regarding oral *versus* intravenous therapy, possibility to reach the hospital for medical visits and treatment, personal conditions).

The tumour assessment was performed approximately every 4 months, except in cases of signs of disease progression, according to clinical practice and physician's approach. Treatment efficacy were evaluated according

to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[22] A complete blood count, organ functional test, and medical examination were performed before each treatment cycle; dose reduction, delay or discontinuation of treatments were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0).[23] Data collection started from the first dose of the new therapy after CDK4/6i treatment and included patient performance status, sites and number of metastases, tumour biology and previous therapies received in neoadjuvant, adjuvant and metastatic settings.

Primary and secondary objectives and endpoints

The primary objective of this study was to analyse the efficacy of the different therapies after palbociclib progression, evaluated by mean of median PFS2, defined as the interval from the start of treatment chosen at palbociclib progression and the subsequent documented disease progression.

We also considered secondary objectives, trying to identify the best therapeutic strategies, as follows: (1) to determine the activity of the different treatments adopted, evaluated by clinical benefit rate (CBR), defined as the percentage of patients with a stable disease (SD), partial response (PR), and complete response (CR) according to RECIST criteria;[22] (2) to analyse the clinical parameters considered as determinants of the ultimate treatment choice of CT or ET; (3) to define PFS1, measured as the interval from palbociclib plus ET start and subsequent disease progression (PD); and (4) to define the presence of statistically significant differences in the primary objective according to the following variables of interest: biology of primary breast cancer, including grade (G1–G2 *versus* G3), progesterone receptor status (<20% *versus* ≥20%), Ki-67 percentage (<20% *versus* ≥20%), as expressed by the St Gallen Consensus Conference for the classification of luminal breast cancer;[23] tumour size (T1 *versus* T2–T4) and nodal involvement (N0 *versus* N+); previous CT for early breast cancer (yes *versus* no); the disease-free interval from adjuvant treatment (<12 months *versus* ≥12 months); adjuvant CT (and the type of regimen used), adjuvant ET (and the type of treatment used), endocrine-resistance patterns (de novo metastatic disease, endocrine primary resistance, endocrine secondary resistance), PFS1; visceral progression on palbociclib treatment. Primary endocrine resistance was defined, according to ESMO terminology, as disease progression during the first 6 months of first-line ET-based therapy whilst secondary endocrine resistance was defined as disease progression after more than 6 months of ET in any treatment line.[2] Visceral involvement was defined as the presence of metastasis to visceral organs, including lung, liver, peritoneum and pleura. Finally, an exploratory analysis was performed on three different cohorts (de novo metastatic, primary endocrine-resistance and secondary endocrine-resistance disease) trying to evaluate differences amongst these clinical parameters: treatment types (ET *versus* CT), disease burden before palbociclib start (visceral metastases, bone-only disease, visceral plus bone metastases), activity and efficacy of the treatment at palbociclib progression (mPFS2, CBR).

Statistical methods

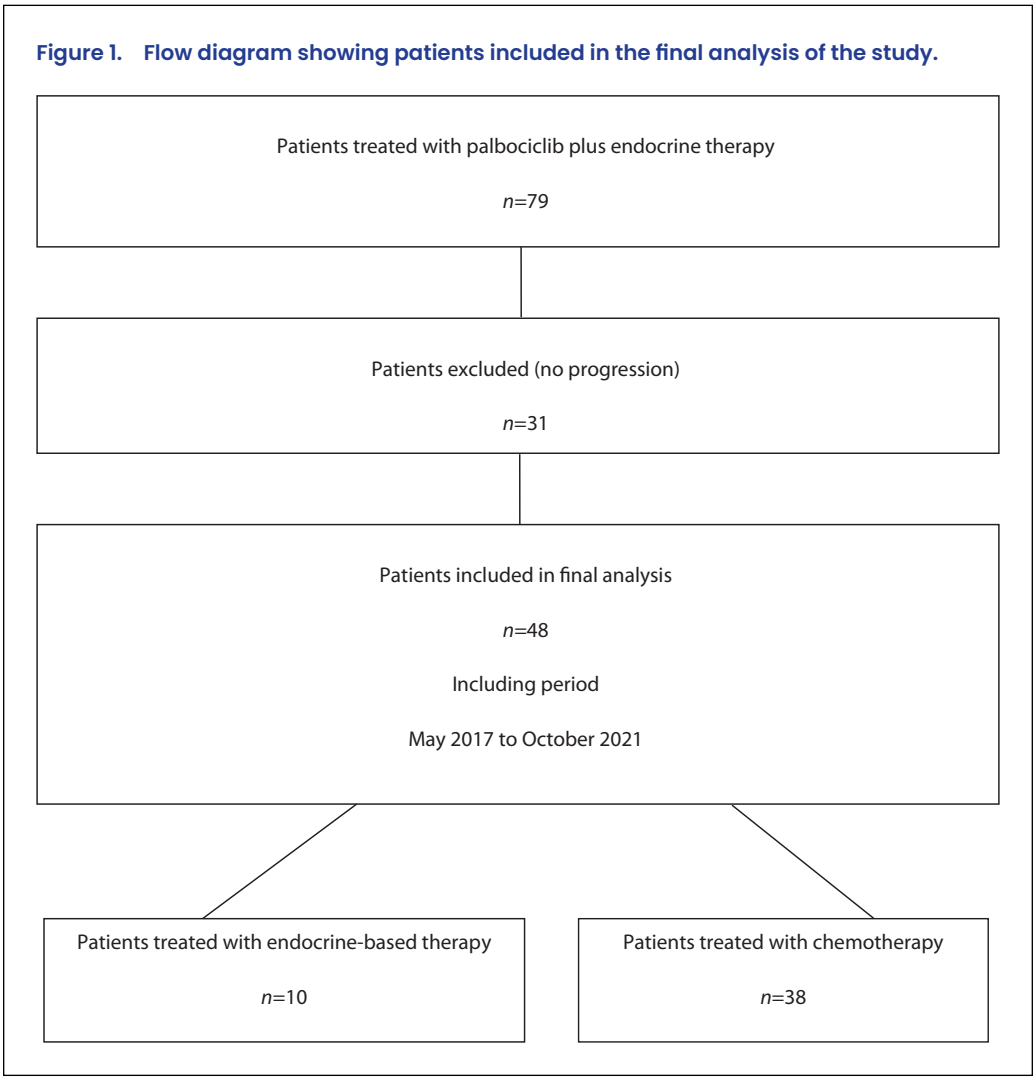
Data were collected in a dedicated database programme by the research team. The distribution of numeric continuous and discrete variables was described in terms of mean ± standard deviation (SD) or median (25th to 75th percentiles, IQR) if the variable's frequency distribution deviated significantly from the normality assumptions (Shapiro test, $p<0.05$). Categorical and ordinal variables distribution was described in terms of absolute and relative (%) frequencies. The log-rank test has been applied to compare survival profiles between strata. Multivariate Cox proportional hazard regression coupled with a backward elimination strategy of uninformative variables aimed at minimizing the Bayesian Information Criterion (BIC) was applied to identify variables informative with respect to the condition of PFS during the second treatment line. Analyses were performed by the R environment for statistical computing version 4.0.5 (www.r-project.org).

Results

Patient characteristics

Over the study period, 79 female patients with $HR^+/HER2^-$ MBC were enrolled and 48 were evaluated and included for the final data analysis. Thirty-one patients were excluded because palbociclib therapy was still ongoing at the time of the last follow-up (Figure 1). Table 1 reports the baseline characteristics of the whole population and Table 2 reports the biological and demographic characteristics related to patients included in the final analyses. The median age in the population analysed was 53 years (range 33–78 years). Most patients presented with progesterone receptor expression ≥20% (77.08%), Ki-67 expression <20% (72.92%), and a low tumour grade (G1–G2; 81.25%). Regarding treatment for early-stage disease, 62.5% of patients received adjuvant CT and 91.67% received adjuvant ET. Anthracycline-based CT was the most common regimen used (90% of cases) and most women received AI (56.82%). About 12.5% had *de novo* MBC whilst 16.67% and 70.83% had primary and secondary endocrine resistance, respectively. Fulvestrant was the most common concomitant drug used

Figure 1. Flow diagram showing patients included in the final analysis of the study.



(79.17%), whilst 20.83% of patients received an AI. Finally, 61.7% developed visceral disease progression to palbociclib. Amongst the 48 patients included in this analysis, 79.17% (38 patients) received CT, whilst 20.83% (10 patients) received ET. In detail, ET strategies were as follows: everolimus 10 mg daily combined with exemestane 25 mg administered orally on a continuous schedule, or fulvestrant at the dose of 500 mg intramuscular on days 1, 14 and 28, then every 4 weeks. CT regimens included eribulin (1.23 mg/m^2 intravenously on days 1 and 8 of a 21-day cycle), capecitabine (1000–1250 mg/m^2 orally twice daily on days 1–14 of a 21-day cycle) in monotherapy or in combination with vinorelbine (25 mg/m^2 intravenously on days 1 and 8 of a 21-day cycle), gemcitabine (800–1200 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle), nab-paclitaxel (260 mg/m^2 intravenously on day 1 of a 21-day cycle), pegylated liposomal doxorubicin (50 mg/m^2 intravenously on day 1 of a 28-day cycle), docetaxel (75 mg/m^2 intravenously on day 1 of a 21-day cycle), paclitaxel (80 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle) in monotherapy or in combination with carboplatin (AUC 1.5 on days 1, 8 and 15 of a 28-day cycle) and bevacizumab (15 mg/kg intravenously on day 1 of a 28-day cycle) plus paclitaxel (80 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle). Treatments were continued until documented PD, unacceptable toxicity or patient refusal and were given in an outpatient setting, according to approved national guidelines.

Primary objective

The mPFS2 was 5 months (95% CI 4–48 months) in the whole population. Moreover, 40/48 patients (83.33%) had PD during follow-up (minimum follow-up period: 1 month; maximum follow-up period: 35 months) (Figure 2).

A statistically significant difference in terms of mPFS2 was observed between the ET and CT cohorts (10 *versus* 5 months, respectively, log-rank p=0.0351) (Figure 3).

Secondary objectives

None of the other clinical-biological variables mentioned above resulted informative with respect to mPFS2 after palbociclib progression (p>0.05). A multivariate stepwise Cox regression with backward elimination of

Table 1. Main baseline characteristics of the whole cohort (*n*=79).

Enrolled/treated	*n* (%)
Median age, years (range)	53 (33–78)
≤65	44 (55.6)
>65	35 (44.3)
ECOG performance status	
0	55 (69.6)
1	21 (26.5)
2	3 (3.7)
Menopausal status	
Pre	34 (43.0)
Post	45 (56.9)
Histology	
Ductal	58 (73.4)
Lobular	21 (26.5)
Receptor status	
ER ≤10	–
ER >10	79 (100)
PgR ≤20	19 (24.1)
PgR >20	60 (75.9)
Ki-67	
<20	55 (69.6)
>20	24 (30.4)
Grade	
G1/G2	65 (82.3)
G3	14 (17.7)
Visceral metastases	
No	41 (51.9)
Yes	38 (48.1)
Adjuvant CT	
No	32 (40.5)
Yes	47 (59.5)
Adjuvant CT regimen	
Anthracyclines	26 (55.3)
Anthracyclines + fluorouracil + taxane	8 (17.0)
Anthracyclines + taxane	8 (17.0)
Cyclophosphamide +methotrexate + fluorouracil	5 (10.7)
Adjuvant ET	
No	7 (8.9)
Yes	72 (91.1)
Adjuvant ET type	
Anastrozole	31 (39.2)
Letrozole	12 (15.2)
Exemestane	2 (2.5)
Tamoxifen	12 (15.2)
Tamoxifen + LH-RH analogue	15 (19.0)
Missing	7 (8.9)
Endocrine resistance	
Primary	11 (13.9)
Secondary	56 (70.9)
De novo metastatic disease	12 (15.2)
Line of palbociclib therapy	
First	22 (27.8)
≥Second	57 (72.2)
Concomitant ET to palbociclib	
Aromatase inhibitors	22 (27.8)
Fulvestrant	57 (72.2)

CT, chemotherapy; ER, oestrogen receptor; ET, endocrine-based therapy; LH-RH, luteinizing hormone-releasing hormone; PgR, progesterone receptor.

Table 2. Characteristics of patients who started therapy after progression disease on palbociclib/ET (*n*=48).

Enrolled/treated	*n* (%)
Median age, years (range)	50.7 (33–75)
≤65	25 (52.0)
>65	23 (47.9)
ECOG performance status	
0	31 (64.5)
1	17 (35.4)
Menopausal status	
Pre	20 (41.6)
Post	28 (58.3)
Histology	
Ductal	32 (66.6)
Lobular	16 (33.3)
Receptor status	
ER ≤10	–
ER >10	48 (100)
PgR ≤20	11 (22.9)
PgR >20	37 (77.1)
Ki-67	
<20	35 (72.9)
>20	13 (27.1)
Grade	
G1/G2	39 (81.3)
G3	9 (18.7)
Adjuvant CT	
No	18 (37.5)
Yes	30 (62.5)
Adjuvant CT regimen	
Anthracyclines	17 (56.6)
Anthracyclines + fluorouracil + taxane	5 (16.7)
Anthracyclines + taxane	5 (16.7)
Cyclophosphamide +methotrexate + fluorouracil	3 (10.0)
Adjuvant ET	
No	4 (8.3)
Yes	44 (91.7)

(*Continued*)

Table 2. (Continued)

Enrolled/treated	*n* (%)
Adjuvant ET type	
Anastrozole	17 (38.6)
Letrozole	8 (18.2)
Exemestane	–
Tamoxifen	8 (18.2)
Tamoxifen + LH-RH analogue	11 (25.0)
Missing	74 (8.3)
Endocrine resistance	
Primary	8 (16.7)
Secondary	34 (70.8)
De novo metastatic disease	6 (12.5)
Line of palbociclib therapy	
First	10 (20.8)
≥Second	38 (70.2)
Metastatic disease site at progression	
Aromatase Inhibitors	22 (27.8)
Fulvestrant	57 (72.2)

CT, chemotherapy; ER, oestrogen receptor; ET, endocrine-based therapy; LH-RH, luteinizing hormone-releasing hormone; PgR, progesterone receptor.

Figure 2. Kaplan–Meier curve describing the progression-free survival profile of patients who started the therapy at PD.

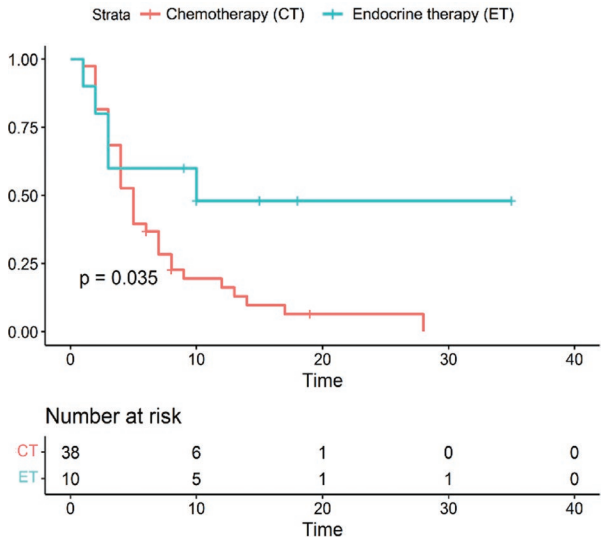
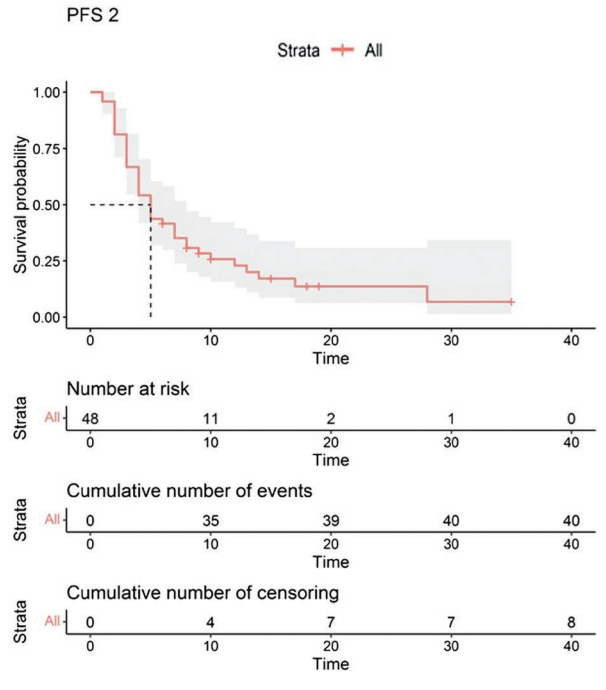


Figure 3. Kaplan–Meier curve describing the progression-free survival profile of the analysed cohort (patients who started the therapy at PD) by type of therapy at PD.

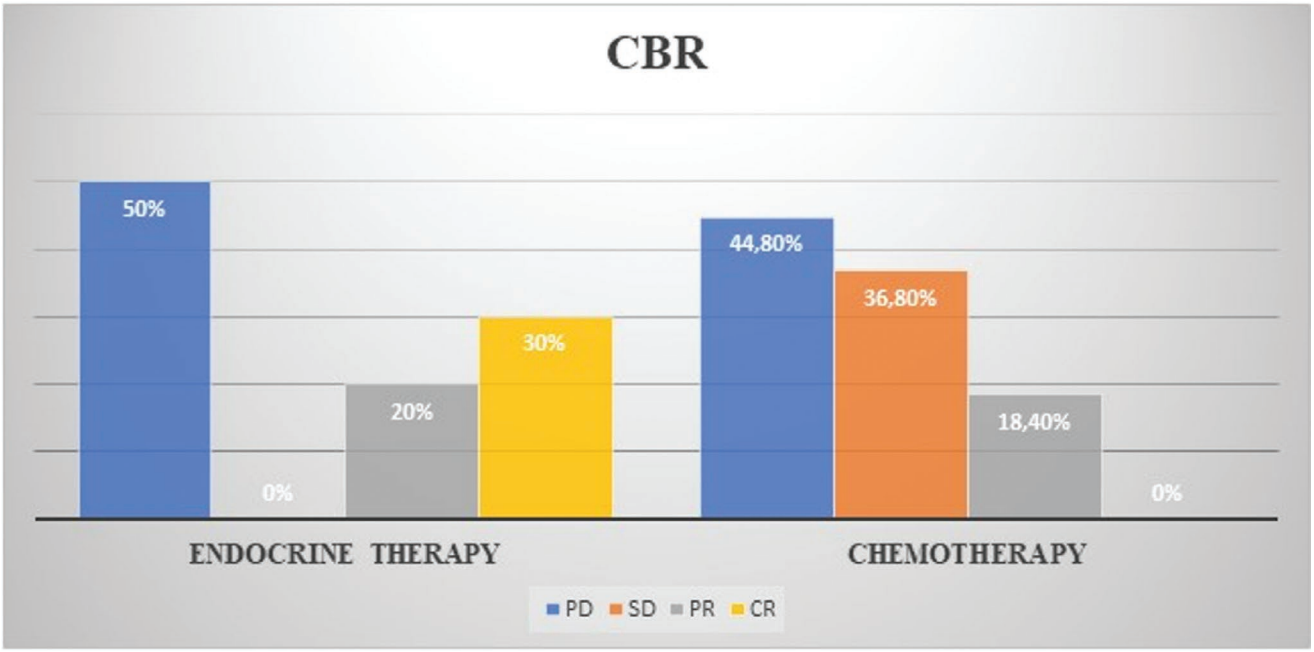


uninformative features confirmed that therapy at PD was the only informative variable with respect to progression (HR for CT 2.64, 95% CI 1.02–6.83; p=0.0451).

Moreover, the ET cohort (10 patients) recorded a CBR of 50% (partial response (PR) 20% and CR 30%; one woman was maintaining CR at the time of the last follow-up). In the CT cohort (38 patients), CBR was 55.2% with 44.8% of cases developing a PD at first instrumental evaluation; in particular, 36.8% recorded SD, 18.4% PR, whilst no patient achieved a CR (Figure 4).

Regarding the disease burden at palbociclib progression, 29 (60.4%) patients developed visceral metastases. The site and disease burden were the first criteria to guide the choice for post-palbociclib treatment. In fact, considering the two cohorts, in the ET group, exemestane plus everolimus was the most used therapy (9/10 patients), whilst only one woman received fulvestrant monotherapy. These patients were characterized by a low disease burden or bone-only disease (60% of patients with bone-only disease, 20% bone and visceral metastases, and 20% visceral disease) and recorded a mPFS1 of 15.7 months (range 4–30 months). Patients included in the CT group received a taxane-based regimen in 44.8% of cases (17 patients), 34.2% (13 patients) received capecitabine, 10.5% (4 patients) received eribulin, and one was treated with liposomal doxorubicin. These patients were characterized by a higher tumour burden (31.6% visceral metastases, 31.6% bone-only disease, 36.8% visceral and bone metastases) and recorded an mPFS1 of 12.1 months (range 3–31 months).

Figure 4. Clinical benefit rate between the two cohorts (ET *versus* CT) based on the type of treatment.



CR, complete response; PD, disease progression; PR, partial response; SD, stable disease.

Another criterion of treatment choice was the presence of inadequately controlled diabetes or metabolic syndrome such that, for these patients, a CT regimen without a steroid premedication was preferred. Moreover, patient preferences were considered before CT prescription; in particular, patients refusing alopecia were treated with ET or with CT associated with low alopecia potential (e.g. capecitabine).

The final exploratory analysis described that, amongst 48 patients included, 6 women presented a de novo metastatic disease (12.5%), 9 patients presented a primary endocrine resistance (18.7%) and 33 patients (68.8%) presented a secondary endocrine resistance. Considering the first group, 4/6 patients presented visceral metastases, 1 patient bone-only disease, and another bone and visceral metastases. In the first group, all patients received CT; 66.7% (4 patients) had PD at first evaluation *versus* 33.3% (2 patients) who had a response to treatment (1 PR, 1 SD). mPFS2 was 4.5 months (range 2–8 months). In the second group, 3/9 had visceral metastases at recurrence, 2/9 visceral and bone disease, and four patients had bone-only metastases; 7/9 received CT and 2/9 ET. At first disease re-evaluation, 4 (44.6%) patients recorded PD, whilst 5 (55.6%) obtained a response to treatment (3 SD, 2 PR). mPFS2 was 5.4 months (range 2–8 months). Finally, in the third group: 6/33 patients presented visceral disease, 13 bone and visceral metastases, 14 bone-only disease; 75.8% (25) received CT *versus* 24.2% (8) receiving ET. At first disease re-evaluation, 15 (45.5%) patients recorded PD and 18 (54.5%) obtained a response to treatment (10 SD, 6 PR, 2 CR). mPFS2 was 7.33 months (range 1–28 months).

Discussion

At present, the optimal therapeutic sequence after progression on CDK4/6i remains a matter of debate. Data about this issue are limited to retrospective studies reporting conflicting results on the benefit of ET *versus* CT following CDK4/6i progression in molecularly unselected patient populations.[18–21,24–27]

Considering the mechanism of resistance to CDK4/6i, two studies evaluated the efficacy of everolimus after CDK4/6i, reporting a median PFS of 6 and 9.1 months, respectively.[28,29]

In another analysis evaluating the efficacy of CDK4/6i continued beyond first PD, the median PFS for the sequential administration of a CDK4/6i was 11.8 months.[30] The strategy of treatment 'beyond progression' after CDK4/6i has been investigated in two recently reported randomized trials. In the Maintain phase II trial, 120 patients affected by $HR^+/HER2^-$ MBC progressed on a CDK4/6i were randomized to receive fulvestrant or exemestane with or without ribociclib: the experimental arm recorded a statistically significant benefit in terms of PFS independently of the hormonal partner used.[31] In

the TREnd trial, 115 patients progressing on 1 or 2 previous ET were randomized to receive palbociclib monotherapy versus palbociclib combined with a previous ET administered: the median time to treatment failure recorded was 3.8 months independently of the drugs used.[32]

A recent real-world study by Basile et al. focusing on first-line and second-line treatment strategies for HR^+ MBC, first-line ET + CDK4/6i followed by CT had worse overall survival compared to first-line ET + CDK4/6i followed by ET.[33]

In the population included in our analysis, patients recorded a mPFS2 of 5 months (95% CI 4–48 months) with a statistically significant difference between patients receiving ET and CT (10 *versus* 5 months, respectively). The efficacy results reported in our study are similar to other data available in the literature; the only difference regards the higher mPFS2 achieved by women treated with ET. Moreover, patients who received CT had mainly a SD (36.8%), whereas patients receiving ET experienced a CR in 30% and a PR in 20% of cases. Based on these results, we can assume a greater benefit of ET over CT following progression on CDK4/6i. However, it must be considered that, since patients receiving CT had a greater disease burden, the visceral site of metastatic disease was more common (68.4% of patients) and mPFS1 was more limited. These variables can explain, at least partially, the worse outcome of CT in this group. Additionally, the presence of a greater number of visceral metastases in the overall population progressing on palbociclib therapy (60.4%) could justify the choice of a CT switch, in agreement with current guidelines.

It is important to underline that, in our exploratory analysis, women affected by *de novo* metastatic disease were characterized by the worst prognosis, with an mPFS2 of 4.5 months, whilst patients with a secondary endocrine resistance recorded the longer mPFS2 of 7.3 months. Moreover, patients with *de novo* metastatic disease had the smallest benefits to therapies, with a progression rate at first instrumental re-evaluation of approximately 66.7% compared with patients with first and secondary endocrine resistance (PD 55.6% and 54.5%, respectively).

For patients progressing on CDK4/6i, different options are currently available according to tumour mutational status, patient clinical conditions and disease burden: alpelisib for patients who present *PIK3CA* mutation; CT for women with high visceral burden disease or visceral crisis; fulvestrant monotherapy for low-burden disease or patients who are pluricomorbid; exemestane plus everolimus for patients with good PS and minimal comorbidity; and PARP inhibitors for patients with a germline *BRCA1–2* mutations.[16] Promising results have been derived from the new class of the antibody–drug conjugate trastuzumab deruxtecan and sacituzumab govitecan.[34,35]

The most important limitations of our analysis consist in the small size of the population included in the final analysis (48 patients), the disproportion in the number of patients treated with ET compared with CT, the monocentric design, and the lack of data regarding the molecular status of PD. It is worth noting that, at the moment of study conduction, rebiopsy or liquid biopsy were not considered as compulsory or strongly recommended diagnostic procedures. Conversely, the value of our analysis resides in the heterogeneity of the population enrolled, which provides a real clinical/demographic description of the population in our clinical practice.

Conclusions

Our real-world study expands the data regarding the outcome of therapeutic strategies following progression on CDK4/6i, helping clinicians' choice, on the basis of the current guidelines and considering the clinical variables of the individual patient.

Contributions: RP, EQ, GS and FS designed the study; AM designed the statistical plan analysis and performed all analyses. RP, EQ, PL, GS, CB, CMT, BT and AM designed the database, collected data, and clinically followed-up the patients. RP, EQ, GS and FS interpreted data and drafted the manuscript. FS and LDL reviewed the manuscript for important intellectual contents. All authors revised and approved the final version of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2023/11/dic.2023-7-5-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Copyright: Copyright © 2024 Palumbo R, Quaquarini E, Saltalamacchia G, Malovini A, Lapidari P, Tagliaferri B, Mollica L, Teragni CM, Barletta C, Locati LD, Sottotetti F. Published by *Drugs in Context* under Creative Commons License Deed CC BY NC ND 4.0, which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

Correct attribution: Copyright © 2024 Palumbo R, Quaquarini E, Saltalamacchia G, Malovini A, Lapidari P, Tagliaferri B, Mollica L, Teragni CM, Barletta C, Locati LD, Sottotetti F. https://doi.org/10.7573/dic.2023-7-5. Published by *Drugs in Context* under Creative Commons License Deed CC BY NC ND 4.0.

Article URL: https://www.drugsincontext.com/efficacy-and-activity-of-treatments-after-progression-from-palbociclib-plus-endocrine-therapy-in-patients-with-hr-her2-metastatic-breast-cancer-a-prospective-monocentric-study

Correspondence: Raffaella Palumbo, Medical Oncology Unit, ICS Maugeri-IRCCS SpA SB, Via Maugeri, 10 27100, Pavia, Italy. Email: raffaella.palumbo@icsmaugeri.it

Provenance: Invited; externally peer reviewed.

Submitted: 28 July 2023; **Accepted:** 6 November 2023; **Published:** 5 February 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights, and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Sung MA, 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;71:209–249. https://doi.org/10.3322/caac.21660
2. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC4). *Ann Oncol.* 2018;29:1634–1657. https://doi.org/10.1093/annonc/mdy192
3. National Comprehensive Cancer Network. NCC clinical practice guidelines in oncology. Breast Cancer, Version 4.2020. https://doi.org/10.6004/jnccn.2020.0016
4. Rugo H, Rumble B, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Cancer Society of Clinical Oncology guideline. *J Clin Oncol.* 2016;34:3069–3103. https://doi.org/10.1200/JCO.2016.67.1487
5. Tryfonidis K, Zardavas D, Katzenellenbogen BS, et al. Endocrine treatment in breast cancer: cure, resistance and beyond. *Cancer Treat Rev.* 2016;50:68–81. https://doi.org/10.1016/j.ctrv.2016.08.008
6. Osborne C, Schiff R. Mechanisms of endocrine resistance in breast cancer. *Ann Rev Med.* 2011;62:233–247. https://doi.org/10.1146/annurev-med-070909-182917
7. Migliaccio I, Bonechi M, McCartney A, et al. CDK4/6 inhibitors: a focus on biomarkers of response and post-treatment therapeutic strategies in hormone receptor-positive HER2-negative breast cancer. *Cancer Treat Rev.* 2021;93:102136. https://doi.org/10.1016/j.ctrv.2020.102136
8. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375:1925–1936. https://doi.org/10.1056/NEJMoa1607303
9. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29:1541–1547. https://doi.org/10.1093/annonc/mdy155

10. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19:904–915. https://doi.org/10.1016/S1470-2045(18)30292-4
11. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol.* 2017;35:3638–3646. https://doi.org/10.1200/JCO.2017.75.6155
12. Sammons S, Shastry M, Dent S, et al. Practical treatment strategies and future directions after progression while receiving CDK4/6 inhibition and endocrine therapy in advanced $HR^+/HER2^-$ breast cancer. *Clin Breast Cancer.* 2020;20:1–11. https://doi.org/10.1016/j.clbc.2019.06.017
13. 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;17:425–439. https://doi.org/10.1016/S1470-2045(15)00613-0
14. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36:2465–2472. https://doi.org/10.1200/JCO.2018.78.9909
15. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with $HR^+/HER2^-$ advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35:2875–2884. https://doi.org/10.1200/JCO.2017.73.7585
16. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32:1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019
17. Piezzo M, Chiodini P, Riemma M, et al. Progression-free survival and overall survival of CDK 4/6 inhibitors plus endocrine therapy in metastatic breast cancer: a systematic review and meta-analysis. *Int J Mol Sci.* 2020;21:6400. https://doi.org/10.3390/ijms21176400
18. Wander SA, Han HS, Zangardi ML, et al. Clinical outcomes with abemaciclib after prior CDK4/6 inhibitor progression in breast cancer: a multicenter experience. *J Natl Compr Canc Netw*. 2021;24:1–8. https://doi.org/10.6004/jnccn.2020.7662
19. Cogliati V, Capici S, Pepe FF, et al. How to Treat HR+/HER2- metastatic breast cancer patients after CDK4/6 inhibitors: an unfinished story. *Life*. 2022;12:378. https://doi.org/10.3390/life12030378
20. Princic N, Aizer A, Tang DH, et al. Predictors of systemic therapy sequences following a CDK 4/6 inhibitor-based regimen in post-menopausal women with hormone receptor positive, HEGFR-2 negative metastatic breast cancer. *Curr Med Res Opin*. 2019;35:73–80. https://doi.org/10.1080/03007995.2018.1519500
21. Munzone E, Pagan E, Bagnardi V, et al. Systematic review and meta-analysis of post-progression outcomes in ER+/HER2- metastatic breast cancer after CDK4/6 inhibitors within randomized clinical trials. *ESMO Open.* 2021;6:100332. https://doi.org/10.1016/j.esmoop.2021.100332
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205–216. https://doi.org/10.1093/jnci/92.3.205
23. National Cancer Institute. *Common Terminology Criteria for Adverse Events Version 5.0*. Bethesda: National Cancer Institute. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed March 10, 2020.
24. Burstein HJ, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol.* 2021;32:1216–1235. https://doi.org/10.1016/j.annonc.2021.06.023
25. Li Y, Li W, Gong C, et al. A multicenter analysis of treatment patterns and clinical outcomes of subsequent therapies after progression on palbociclib in HR+/HER2- metastatic breast cancer. *Ther Adv Med Oncol.* 2021;13:17588359211022890. https://doi.org/10.1177/17588359211022890
26. Xi J, Oza A, Thomas S, et al. Retrospective analysis of treatment patterns and effectiveness of palbociclib and subsequent regimens in metastatic breast cancer. *J Natl Compr Canc Netw.* 2019;17:141–147. https://doi.org/10.6004/jnccn.2018.7094
27. Fabi A, Ciccarese M, Scagnoli S, et al. Post-Progression treatments after palbociclib plus endocrine therapy in HR+/HER2- metastatic breast cancer patients: what is the better choice? *Oncology*. 2021. https://doi.org/10.1159/000521252
28. Jeong H, Jeong JH, Kim JE, et al. Comparison of the effectiveness and clinical outcome of everolimus followed by CDK4/6 inhibitors with the opposite treatment sequence in hormone receptor-positive, HER2-negative metastatic breast cancer. *Cancer Res Treat*. 2022;54:469–477. https://doi.org/10.4143/crt.2021.205

29. Kitano S, Honda A, Itoi N, Lee T. Everolimus for treating hormone receptor-positive metastatic breast cancer previously treated with cyclin-dependent kinase 4/6 inhibitors. *Anticancer Res*. 2022;42:3913–3919. https://doi.org/10.21873/anticanres.15885
30. Samuel Eziokwu A, Varella L, Lynn Kruse M, et al. Real-world outcomes of cyclin-dependent kinase inhibitors continued beyond first disease progression in hormone receptor-positive metastatic breast cancer. *Clin Breast Cancer*. 2021;21:205–209. https://doi.org/10.1016/j.clbc.2020.09.010
31. Kalinsky K, Accordino MK, Chiuzan C, et al. A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN trial. *J Clin Oncol*. 2023;41(24):4004–4013. https://doi.org/10.1200/JCO.22.02392
32. Malorni L, Curigliano G, Minisini AM, et al. Palbociclib as single agent or in combination with the endocrine therapy received before disease progression for estrogen receptor-positive, HER2-negative metastatic breast cancer: TREnd trial. *Ann Oncol*. 2018;29:1748–1754. https://doi.org/10.1093/annonc/mdy214
33. Basile D, Gerratana L, Corvaja C, et al. First- and second-line treatment strategies for hormone-receptor (HR)-positive HER2-negative metastatic breast cancer: a real-world study. *Breast*. 2021;57:104–112. https://doi.org/10.1016/j.breast.2021.02.015
34. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387:9–20. https://doi.org/10.1056/NEJMoa2203690
35. Rugo HS, Bardia A, Tolaney SM, et al. TROPiCS-02: a Phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncol*. 2020;16:705–715. https://doi.org/10.2217/fon-2020-0163