Breast Cancer Management

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ibmt20

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To cite this article: Valentina Perrone, Melania Dovizio, Melania Leogrande, Antonella Tamma, Massimo Giovannitti, Carlotta Buzzoni & Luca Degli Esposti (2023) Patients with HR+/HER2- Metastatic Breast Cancer Treated with CDK4/6 Inhibitors: A Real-World Study in Italy, Breast Cancer Management, 12:2, BMT68, DOI: 10.2217/bmt-2023-0020

To link to this article: https://doi.org/10.2217/bmt-2023-0020

Published online: 20 Dec 2023.

Research Article

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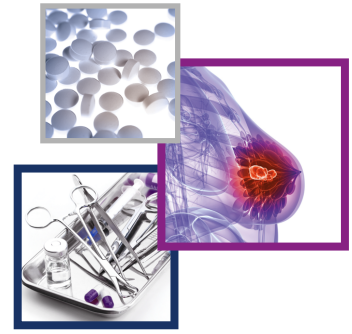

Patients with HR+/HER2- metastatic breast cancer treated with CDK4/6 inhibitors: a real-world study in Italy

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Aim: Italian real-world analysis of CDK4/6 inhibitor (CDK4/6i) treatment in HR+/HER2- metastatic breast cancer aimed at evaluating patients' medical history, treatment duration, treatment patterns (combination with endocrine therapy), line of therapy and drug dose variations. **Materials & methods:** CDK4/6i treatment was analyzed using healthcare administrative databases covering 18% of Italians between January 2017 and June 2022. **Results:** Among CDK4/6i-treated women, palbociclib and abemaciclib (were more frequently combined with fulvestrant, while ribociclib with aromatase inhibitors. CDK4/6i recommended doses were initiated in 72–90% patients and maintained after 3–6 months in respectively 65–57% women. Frontline CDK4/6i use grew over time (reaching 90%). Median time-to-treatment discontinuation was 11.0 months in palbociclib, 15.9 in abemaciclib and 15.4 in ribociclib cohorts. **Conclusion:** CDK4/6i plus endocrine therapy is increasingly utilized as first-line therapy, with low proportions of dose reductions within 6 months and discontinuations at 1 year.

Plain language summary: This study used data from the real clinical practice in Italy to investigate a population of women with metastatic breast cancer (mBC) who received treatment with CDK4/6 inhibitors between January 2017 and June 2022. This is a new class of anticancer drug shown to provide significant survival benefits in combination with endocrine therapy, over endocrine therapy alone, in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) mBC. The results highlighted an increasing use of these combinations as first-line therapy for HR+/HER2- mBC, which was also associated with lower rates of dose reductions of CDK4/6 inhibitors within 6 months after starting therapy and with fewer patients needing to stop the therapy within 1 year.

Tweetable abstract: Combined CDK4/6i plus endocrine therapy is increasingly and successfully utilized as first-line therapy of metastatic breast cancer, with low dose reductions within 6 months and limited discontinuations within 1 year. #MetastaticBreastCancer #CDK4/6Inhibitors #EndocrineTherapy

First draft submitted: 24 July 2023; Accepted for publication: 20 November 2023; Published online: 20 December 2023

Keywords: cyclin-dependent kinase 4/6 inhibitor • CDK4/6i • endocrine therapy • HER2- • hormone receptor-positive • HR+ • human epidermal growth factor receptor 2-negative • metastatic breast cancer • real-world evidence

Breast cancer is the most common neoplasm in women and accounts for more than 1 of 10 new cancer diagnoses every year [1]. In detail, breast cancer represents 41% of all cancers in women aged below 50 years, 35% for those aged between 50 and 69 years, and 22% for those over 70 years [2]. This trend is explained by the fact incidence grows with older aged until menopause, and then gradually decreases or remains stable [3,4].

The Italian Association of Medical Oncology (Associazione Italiana di Oncologia Medica, AIOM) reported a prevalence of 834,200 women living in Italy after breast cancer diagnosis, an estimated incidence of 55,700 new

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breast cancer diagnoses for 2022, with 12,500 deaths in 2021, and a 5-year survival after diagnosis of approximately 88% [5].

As a result of screening campaigns and increased awareness among women, most breast cancers are diagnosed at an early stage when conservative surgical treatment, combined with adjuvant systemic therapy (hormone therapy, polychemotherapy, molecular-targeted therapy), often allows for a significant reduction in risk of recurrence and mortality [6]. However, that in most cases, the metastatic status is detected after a previous diagnosis in a localized stage (distant recurrence), in about 6–7% of cases, breast cancer is already metastatic at diagnosis (*de novo*) [7,8]. The AIOM estimated that approximately 37,000 women in Italy are currently living with metastatic breast cancer (mBC) [5]. Indeed, up to now, there are few updated epidemiological Italian reports on the actual numbers of breast cancer, especially in the metastatic setting [7–9]. A study conducted in Italy applied the 2013 mortality-incidence age-specific ratios for mBC of the US to reckon *de novo* or distantly recurrence diagnoses and deaths in Italian women stratified by age groups. Using this approach, the estimates for Italy during year 2014 were of 12,330 deaths due to breast cancer, 3400 newly diagnosed cases in metastatic stage (7.1% of overall cases) and above 10,000 women with metastasis detection progressed from a localized stage [10].

Nevertheless, diagnostic and therapeutic advances together with the availability of new anticancer drugs and supportive therapies have improved the prognosis and overall survival of patients with mBC [11–19]. In hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) mBC, the combination of a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) with hormone therapy results in significantly increased progression-free survival (PFS) compared with hormone therapy alone in both first-line and second-line treatment strategies [11–19]. The main benefits from the use of these novel agents in combination with hormonal therapy lies in their ability to overcome mechanisms of endocrine resistance, thus reinforcing the role of antiestrogen therapy in estrogen receptor-positive mBC [11]. Thus, the discovery of CDK4/6i that act on cell cycle arrest and apoptosis has revolutionized cancer therapy. The CDK4/6 complex plays as a checkpoint during the cell cycle transition from G1 to S phase, thus its dysregulation or overexpression results in aberrant cell proliferation and cancer growth [20]. CDK4/6is can restore cell cycle by selectively inhibiting cyclin-dependent kinases 4 and 6 and block uncontrolled cell proliferation in several types of malignant cells, including those of breast cancer [20]. The three currently approved CDK4/6is, palbociclib, ribociclib, and abemaciclib, share a similar mechanisms of action, but some differences have emerged in pharmacological, preclinical and clinical studies [21,22].

The present study, conducted in an Italian real-world clinical setting, aimed to describe the characteristics of HR+/HER2- mBC patients treated with the currently available CDK4/6i, namely palbociclib, abemaciclib and ribociclib. Our descriptive evaluation was focused on patients' previous medical history, treatment duration, therapeutic schedules in terms of treatment patterns (combination with endocrine therapy), line of therapy and drug dose variation.

Methods & study design

Study design

Data source

A secondary data retrospective analysis was performed by integrating the administrative databases of a pool of geographically distributed Italian healthcare entities covering approximately 10.9 million health-assisted residents (18% of the Italian population). The following databases were utilized for the analysis: i) demographics database, which includes patients' demographics, sex, age and date of death; ii) pharmaceutical database to collect all the information on drugs reimbursed by the Italian National Healthcare Service (INHS), such as the Anatomical Therapeutic Chemical (ATC) code, number of prescriptions, number of units per package, unit cost per package, dose and prescription date; iii) hospitalization database to extract hospitalization-related data, namely, discharge diagnosis codes classified according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG-related charge (provided by the INHS); iv) outpatient specialist services database that reports information on specialistic visits and diagnostic tests (date and type of delivery, activity description and laboratory test or specialist visit charge); v) exemption database, to gather active exemption codes by which patients are not required to pay for healthcare services/treatments in case of specific disease diagnoses.

In full compliance with European General Data Protection Regulation (GDPR) (2016/679), privacy was ensured by the assignment of an anonymous univocal numeric code to each subject participating in the study.

This patient code also allowed for electronic linkage between the various databases. All results are presented as aggregated summaries and thus were never attributable to a single institution, department, doctor, or individual or to individual prescribing behaviour. The study was approved by the local Ethics Committees of the Healthcare Departments involved.

Identification of study population

Inclusion criteria

From January 2017 to June 2022 (inclusion period), adult (≥18 years) female patients prescribed CDK4/6is were selected, including women with HR+/HER2- advanced or mBC (indication approved in Italy in that timeframe). Namely, the prescribed drugs were palbociclib (ATC: L01XE33/L01EF01), abemaciclib (ATC: L01XE50/L01EF03), and ribociclib (ATC: L01XE42/L01EF02). The patients were then divided into three mutually exclusive cohorts based on the first drug from among the aforementioned CDK4/6is prescribed. The start of inclusion for patients receiving each of the three CDK4/6i was feasibly shifted due to the different time of drug availability in Italy, as palbociclib has been reimbursed for advanced breast cancer since December 2017, ribociclib since September 2018 and abemaciclib since December 2019.

Study timeline

The time of the first CDK4/6i prescription within the inclusion period was considered the index date. The characterization period included the period of data availability from 01 January 2010 onwards. The follow-up period (at least 6 months) comprised all available time after the index date.

Demographic parameters, clinical & past medical history

For each cohort, age at the index date and the distribution of patients by age ranges (18–39, 40–49, 50–59, 60–69, 70–79 and ≥80 years) were collected.

During the 12-month period prior to the index date (characterization period), the comorbidity profile of drug prescriptions and hospitalizations, traditionally used as diagnosis proxies in real-world evidence studies, was assessed [23]. For this analysis, a modified version of the Charlson Comorbidity Index (CCI) [24], not accounting for cancer among the concomitant diseases contributing to the final CCI score [25], applied. Premenopausal status was identified by the presence of at least one prescription for gonadotropin-releasing hormone analogues, namely, leuprorelin (ATC: L02AE02), goserelin (ATC: L02AE03), or triptorelin (ATC: L02AE04).

The patients' clinical history during the characterization period was further examined by searching for previous breast cancer hospitalizations (ICD-9-CM: 174), surgery (procedure codes: 85.2, 85.3, 85.4) or metastases (ICD-9-CM: 197–198).

Treatment schedules

Treatment schedules were evaluated on the basis of the mean daily dose, dose variations, time to treatment discontinuation (TTD), treatment pattern and line of therapy.

The mean daily dosage of CDK4/6i was calculated as the sum of the total dose (mg) prescribed in each prescription divided by the days covered by the prescription. Dose variations were also analyzed in view of the recommendations reported in the summary of product characteristics (SmPC) for each CDK4/6i. Specifically, (i) the palbociclib dose can be lowered from the label-recommended daily dose of 125 mg to 100 mg as the first reduction and to 75 mg as the second reduction; (ii) the abemaciclib recommended daily dose of 300 mg (2 × 150 mg) can be reduced to 200 mg (2 × 100 mg) as the first reduction and to 100 mg (2 × 50 mg) as the second reduction; and (iii) the ribociclib recommended daily dose of 600 mg can be decreased to 400 mg as the first reduction and to 200 mg as the second. For each of the three CDK4/6is, the percentage of patients starting therapy (index-date) with the full label-recommended daily dose was assessed; after 3 months and after 6 months, the proportions of those who were still using the full dose, those with one dose reduction and those with two dose reductions were determined.

TTD is the time interval (in months) from therapy initiation to permanent discontinuation (no other prescription of the specific CDK4/6i during the follow-up period) or the last prescription duration for surviving patients or the date of death plus one day for deceased patients, whichever was first. If a patient was still on treatment at the end of database availability, TTD was censored at the date of database availability.

Table 1. Demographic parameters of the included patients before propensity score matching.

Variables	Palbociclib, n = 2878	Abemaciclib, n = 478	Ribociclib, n = 1083
Age at index date, years, mean ± standard deviation	64.0 ± 11.8	62.5 ± 11.9	61.3 ± 11.8
Age groups, n (%)			
18–39 years	53 (1.8%)	11 (2.3%)	31 (2.9%)
40–49 years	293 (10.2%)	67 (14%)	164 (15.1%)
50–59 years	704 (24.5%)	114 (23.8%)	273 (25.2%)
60–69 years	796 (27.7%)	137 (28.7%)	324 (29.9%)
70–79 years	770 (26.8%)	118 (24.7%)	230 (21.2%)
≥80 years	262 (9.1%)	31 (6.5%)	61 (5.6%)

Continuous variables are given as the mean ± standard deviation, and categorical variables are given as numbers and percentages in brackets.

Concomitant use during therapy with CDK4/6is of the following endocrine drugs was evaluated: fulvestrant (ATC code: L02BA03), aromatase inhibitors (ATC code: L02BG), and tamoxifen (ATC code: L02BA01).

The line of therapy was established by the number of metastatic line treatments. Specifically, for patients with metastases who were in the database before the index date, the number of metastatic lines was searched for the period from metastasis detection to the index date for the following treatments: CDK4/6i, endocrine therapy and chemotherapy (CT), identified by DRG code 410 or by hospital/ambulatory procedures 99.25, 99.28, 99.29 or by ATC code L01. Index treatment was considered the first metastatic line treatment if patients did not have evidence of metastases during the characterization period.

Direct medical costs in Euros (€) derived from resource-use data for drug treatments, hospitalization, and outpatient specialized services were calculated based on the price reimbursed by the INHS at 1-year follow-up (with respect to the index date and only for those patients with at least 1 year of follow-up).

Statistical analysis

Descriptive statistics are presented as the mean ± standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables.

Treatment duration was evaluated with Kaplan–Meier curves, which were used to report the probability of discontinuation and estimate median treatment duration in the three cohorts. Curves are reported overall and stratified by concomitant endocrine therapy (fulvestrant or aromatase inhibitors). To reduce the presence of potential selection bias, propensity score matching (PSM) was applied in survival analysis to balance the three treatment cohorts for the following covariates: age at index date, CCI, previous history of breast cancer-associated hospitalization with mention of surgery and hospitalization for metastasis. Using a 1:1:1 matching algorithm, for each patient treated with abemaciclib, one treated with palbociclib and one treated with ribociclib were sampled. The standardized mean difference (SMD) was used to evaluate balancing of covariates after PSM, and SMD ≤0.2 indicated a good balance [26–28]. For subgroups with ≤3 patients, data were not issuable (N.I.) due to data privacy, as the results might be referrable to single individuals, in compliance with "Codice in materia di protezione dei dati personali [Code for protection of personal data] (D. Lgs. 196/2003)". Descriptive statistics and PSM were performed using STATA SE, version 17.0 (StataCorp LLC, College Station, TX, USA).

Results

Characteristics of the study population

From a catchment area of around 10.9 health-assisted residents which corresponds to above 18% of the Italian population, the analysis included 2,878 women with mBC treated with palbociclib, 478 with abemaciclib and 1,083 with ribociclib, with a mean follow-up of 22.2, 11.5 and 16.2 months, respectively. The baseline characteristics and data on the previous medical history of the patients divided into three cohorts according to the type of CDK4/6i received are provided in Table 1. The mean age at the index date was similar across the groups, specifically 64 years in palbociclib-treated women, 65.5 years in abemaciclib-treated women and 61.3 years in ribociclib-treated women. As Table 2 shows, the comorbidity profile was similar in the three cohorts, with an average CCI of 0.6 and the largest proportion of patients falling into the category of CCI score 0 (53.6% for palbociclib, 59.6% for abemaciclib and 53.6% for ribociclib). Regarding the clinical history preceding the index date, 48.8% of patients in the palbociclib cohort, 44.6% in the abemaciclib cohort and 40.1% in the ribociclib cohort had a past hospitalization for breast

Table 2. Clinical and past medical history of the included patients before propensity score matching.

Variables	Palbociclib, n = 2878	Abemaciclib, n = 478	Ribociclib, n = 1083
Concomitant diseases at baseline, n (%)			
Diabetes	337 (11.7%)	49 (9.6%)	117 (10.8%)
Hypertension	1,611 (56%)	250 (52.3%)	546 (50.4%)
Cardiovascular disease	115 (4%)	14 (2.9%)	31 (2.9%)
COPD	501 (17.4%)	61 (12.8%)	152 (14%)
Arthritis	8 (0.3%)	NI	6 (0.6%)
Osteoporosis	687 (23.9%)	98 (20.5%)	148 (13.7%)
Previous breast cancer-related hospitalizations, n (%)	1405 (48.8%)	213 (44.6%)	434 (40.1%)
Previous surgery, n (%)	1899 (66%)	315 (65.9%)	758 (70%)
Previous metastases reported in the database, n (%)	2000 (69.5%)	376 (78.7%)	846 (78.1%)
Follow-up, months, mean ± standard deviation	22.2 ± 14.6	11.5 ± 8.3	16.2 ± 10.9

Continuous variables are given as the mean ± standard deviation, and categorical variables are given as numbers and percentages in brackets.
COPD: Chronic obstructive pulmonary disease; NI: Not issuable (for data privacy).

Table 3. Distribution of patients, expressed as numbers and percentages, in the three cohorts according to the year of inclusion and by line of treatment.

Year	Palbociclib, n = 2878		Abemaciclib, n = 478		Ribociclib, n = 1083	
	1L	2L+	1L	2L+	1L	2L+
2017	124 (62.3%)	75 (37.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2018	653 (67.8%)	310 (32.2%)	0 (0%)	0 (0%)	22 (64.7%)	12 (35.3%)
2019	595 (75.1%)	197 (24.9%)	25 (71.4%)	10 (28.6%)	289 (83.8%)	56 (16.2%)
2020	423 (75.7%)	136 (24.3%)	169 (79.7%)	43 (20.3%)	285 (81.4%)	65 (18.6%)
2021	301 (83.6%)	59 (16.4%)	180 (87.4%)	26 (12.6%)	297 (87.1%)	44 (12.9%)
2022†	5 (100%)	0 (0%)	21 (84%)	4 (16%)	13 (100%)	0 (0%)

†Referred to the 6-month period January 2022–June 2022 (only a part of the Italian healthcare entities involved in the analysis have data available during 2022).
Percentages computed on the overall number of patients (1L and 2L+) for each year combination of year of inclusion and cohort.
1L: First line; 2L+: Second line or subsequent.

cancer during the characterization period, and approximately two-thirds (from 65.9% to 70%) had previously undergone surgery. During the characterization period, the presence of metastases was observed in 69.5% of the patients treated with palbociclib, 78.7% of those treated with abemaciclib and 78.1% of those treated with ribociclib.

When considering the time of inclusion of the first CDK4/6i received, the patients first treated with abemaciclib were identified beginning in 2019, those with ribociclib beginning in 2018 and those with palbociclib since the start of the study period (2017). The distribution of patients in the three cohorts according to the year of inclusion and by treatment line, described in Table 3, highlights a trend toward increased CDK4/6i use in the first line and a decrease in the second line was observed in the most recent years (from 2020 to 2021).

Analysis of drug utilization

The largest majority of patients with metastatic HR+/HER2- breast cancer included in the analysis had continuous prescriptions of endocrine therapy while on treatment with CDK4/6i, namely, 94.7% in the palbociclib group 91.8% in the abemaciclib group, and 93.4% in the ribociclib group. Specifically, among the 2,878 patients treated with palbociclib, 55.8% received fulvestrant as concomitant endocrine therapy, and 38.7% received aromatase inhibitors (data on tamoxifen are not shown owing to data privacy due to the group number of ≤3 patients). Of 478 patients treated with abemaciclib, fulvestrant comprised concomitant endocrine therapy in 48.5% of cases and aromatase inhibitors in 43.4%; none received tamoxifen. Finally, of the 1,083 women in the ribociclib cohort, 23.6% were cotreated with fulvestrant, 69.4% with aromatase inhibitors and 0.4% with tamoxifen.

The detailed distribution of the type of endocrine drug coadministered in the three cohorts stratified by menopausal status (Table 4) confirmed that in both premenopausal and postmenopausal women, fulvestrant was more frequently combined with palbociclib (58.3% premenopausal and 55.2% postmenopausal) and with abe-

Table 4. Distribution of concomitant endocrine therapy (presented as numbers and percentages) in palbociclib, abemaciclib and ribociclib cohorts stratified by menopausal status.

Variables	Palbociclib, n = 2878	Abemaciclib, n = 478	Ribociclib, n = 1083
Premenopausal status	611 (21.2%)	110 (23%)	297 (27.4%)
Fulvestrant	356 (58.3%)	61 (55.5%)	62 (20.9%)
Aromatase inhibitor	229 (37.5%)	41 (37.3%)	221 (74.4%)
Tamoxifen	NI	0 (0%)	NI
Postmenopausal status	2267 (78.8%)	368 (77%)	786 (72.6%)
Fulvestrant	1251 (55.2%)	171 (46.5%)	194 (24.7%)
Aromatase inhibitor	886 (39.1%)	166 (45.1%)	531 (67.6%)
Tamoxifen	NI	0 (0%)	NI

NI: Not issuable due to privacy (≤3 patients).

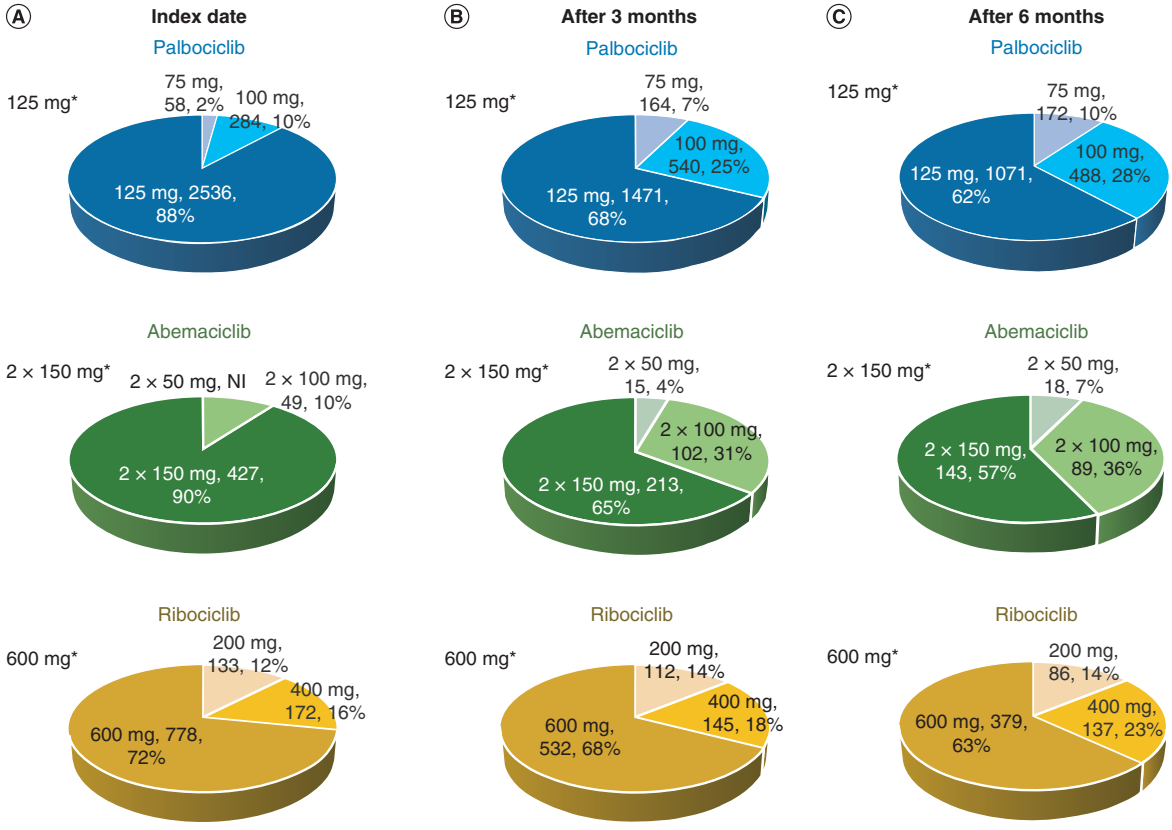


Figure 1. Mean daily dosing of CDK4/6 inhibitors prescribed. CDK4/6 inhibitors prescribed **(A)** at the index date; **(B)** by 3 months among patients with at least 3 months of treatment; **(C)** by 6 months among patients with at least 6 months of treatment.
*Label-recommended daily dose.
NI: Not issuable due to privacy (≤3 patients).

maciclib (55.5% premenopausal and 46.5% postmenopausal). Aromatase inhibitors represented the most common concomitant endocrine therapy in the ribociclib group (74.4% premenopausal and 67.6% postmenopausal).

At the index date, the majority of patients in each group were prescribed the starting dose recommended by the SmPC: 88% in the palbociclib cohort (starting dose of 125 mg), 90% in the abemaciclib cohort (starting dose of 300 mg) and 72% in the ribociclib cohort (starting dose of 600 mg) (Figure 1A). For palbociclib, the proportion of patients treated with the dose of 125 mg decreased to 68% and to 62% after 3 and 6 months from treatment initiation, respectively; for abemaciclib, the proportion of patients treated with the dose of 300 mg decreased to

Table 5. Demographic parameters of the included patients after propensity score matching.

Variables	Palbociclib, n = 478	Abemaciclib, n = 478	Ribociclib, n = 478	Standardized mean difference
Age at index date, years, mean ± standard deviation	62.9 ± 11.3	62.5 ± 11.9	62.1 ± 11.9	0.044
Age groups, n (%)				
18–39 years	5 (1%)	11 (2.3%)	15 (3.1%)	
40–49 years	57 (11.9%)	67 (14%)	64 (13.4%)	
50–59 years	142 (29.7%)	114 (23.8%)	116 (24.3%)	
60–69 years	120 (25.1%)	137 (28.7%)	142 (29.7%)	
70–79 years	122 (25.5%)	118 (24.7%)	108 (22.6%)	
≥80 years	32 (6.7%)	31 (6.5%)	33 (6.9%)	

Continuous variables are given as the mean ± standard deviation, and categorical variables are given as numbers and percentages in brackets.

Table 6. Clinical and past medical history of the included patients after propensity score matching.

Variables	Palbociclib, n = 478	Abemaciclib, n = 478	Ribociclib, n = 478	Standardized mean difference
CCI (mean ± standard deviation)	0.5 ± 0.7	0.5 ± 0.7	0.5 ± 0.7	0.022
0, n (%)	292 (61.1%)	285 (59.6%)	285 (59.6%)	
1, n (%)	147 (30.8%)	154 (32.2%)	161 (33.7%)	
≥2, n (%)	39 (8.2%)	39 (8.2%)	32 (6.7%)	
Previous breast cancer-related hospitalizations, n (%)	225 (47.1%)	213 (44.6%)	226 (47.3%)	0.036
Previous surgery, n (%)	311 (65.1%)	315 (65.9%)	306 (64%)	0.027
Previous metastases reported in the database, n (%)	370 (77.4%)	376 (78.7%)	375 (78.5%)	0.020
Follow-up, months, mean ± standard deviation	22.3 ± 14.9	11.5 ± 8.3	15.7 ± 10.7	0.614

Continuous variables are given as the mean ± standard deviation, and categorical variables are given as numbers and percentages in brackets.
CCI: Charlson comorbidity index.

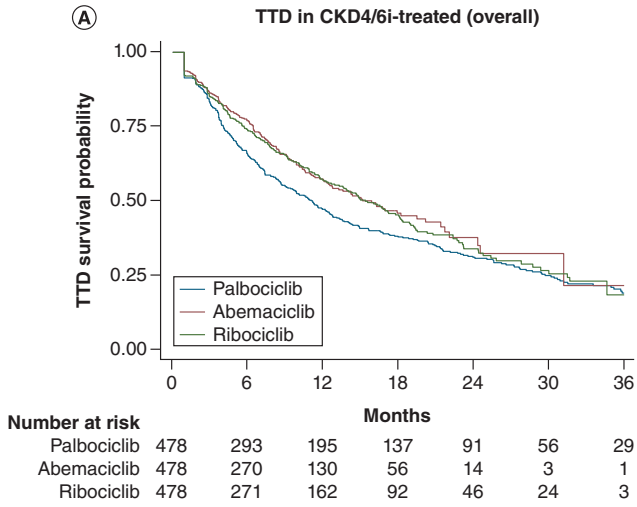
65% and 57% after 3 and 6 months, respectively; for ribociclib, the proportion of patients treated with the dose of 600 mg decreased to 68% and 63% after 3 and 6 months, respectively (Figure 1B & C).

Regarding the number of dose reductions for palbociclib, 25% and 28% of patients experienced only one after 3 months and after 6 months, respectively; a second dose reduction was found in 7% and 10% of cases, respectively, at 3 and 6 months after treatment initiation. For abemaciclib, only one dose reduction occurred in the majority of patients, specifically 31% after 3 months and 36% after 6 months, and a second dose reduction occurred in only 4% and 7%, respectively, at 3 and 6 months after treatment initiation. For ribociclib, 18% and 23% of patients had only one dose reduction after 3 and 6 months, respectively, with a second dose reduction in 14% of patients either at 3 or 6 months after treatment initiation.

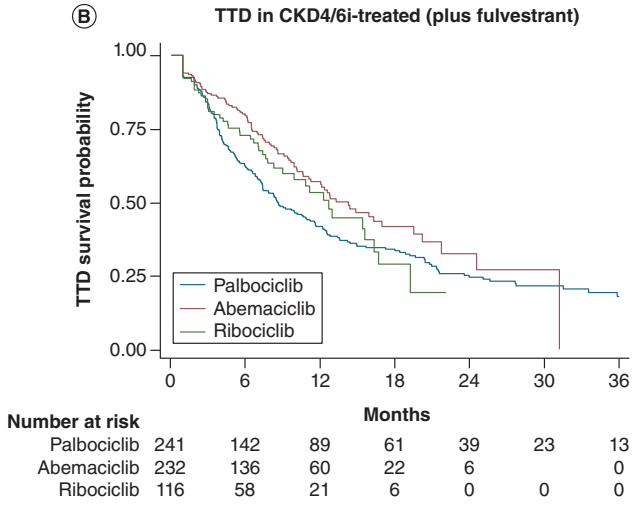
Comparison of variables after PSM

By applying PSM, 478 patients treated with palbociclib, 478 with abemaciclib and 478 with ribociclib were matched. After balancing the groups, baseline variables in terms of age (Table 5), comorbidity profile assessed by the CCI, and clinical history based on previous breast cancer-related hospitalizations, surgery and metastases reported in the database were comparable (Table 6). TTD in patients stratified by the type of CDK4/6i agent combined with endocrine therapy after PSM is illustrated in Figure 2A. The median time to treatment discontinuation was 11.0 months in palbociclib-treated patients, 15.9 months in abemaciclib-treated patients and 15.4 months in ribociclib-treated patients. When analysing the combination of CDK4/6i with fulvestrant, the median TTD was 8.5 months in palbociclib-treated patients, 14.2 months in abemaciclib-treated patients and 12.7 months in ribociclib-treated patients (Figure 2B). For the combination of CDK4/6i with aromatase inhibitors, the median TTD was 15.6 months in palbociclib-treated patients, 21.4 months in abemaciclib-treated patients and 18.0 months in ribociclib-treated patients (Figure 2C).

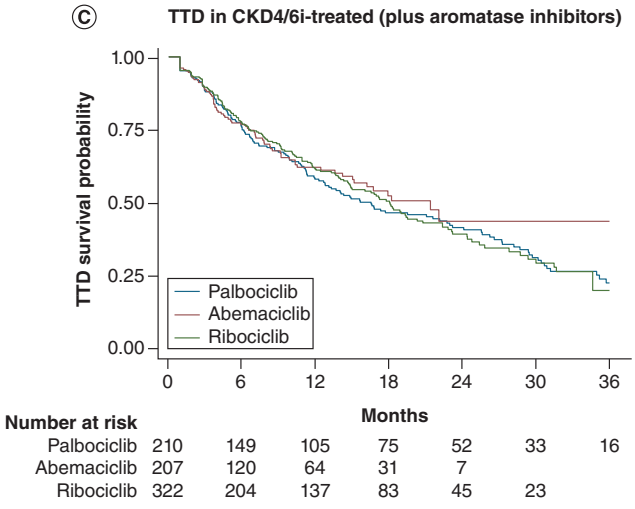
The average annual healthcare costs for the management of patients treated with CDK4/6i, as based on healthcare resource utilization from the index date and 1-year follow-up period, ranged between 30 and 35 k€ after PSM,



TTD, months	n	Median	95% CI	
Palbociclib	478	11.0	9.1	12.6
Abemaciclib	478	15.9	12.4	20.2
Ribociclib	478	15.4	12.9	18.1



TTD, months	n	Median	95% CI	
Palbociclib	241	8.5	7.3	11.1
Abemaciclib	232	14.2	11.0	19.5
Ribociclib	116	12.7	9.0	16.3



TTD, months	n	Median	95% CI	
Palbociclib	210	15.6	12.7	22.7
Abemaciclib	207	21.4	15.0	–
Ribociclib	322	18.0	14.7	20.3

Figure 2. Kaplan–Meier curves for time to treatment discontinuation in patients on treatment at each time point for palbociclib, abemaciclib and ribociclib groups after propensity score matching. (A) Total patients receiving combined therapy with CKD4/6 and endocrine therapy, **(B)** patients receiving combined therapy with CKD4/6 plus fulvestrant; **(C)** patients receiving combined therapy with CKD4/6 plus aromatase inhibitors.
CKD4/6i: CDK4/6 inhibitor; TTD: Time to treatment discontinuation.

with approximately half (13–18 k€) being related to CDK4/6i and the remaining costs associated being with hospitalization, other drugs (mainly chemotherapy) and visits.

Discussion

The introduction of CDK4/6is has redefined the standard of care for HR+/HER2- mBC [10–19,29–36]. The present analysis characterized a population of women with HR+/HER2- mBC on therapy with the CDK4/6i, namely palbociclib, abemaciclib or ribociclib. Across these three cohorts involving different drug treatments, we focused on the patients' previous medical history, treatment schedules in terms of combination with endocrine therapy, line of therapy, duration of treatment and dose variations during follow-up.

By extracting data from administrative databases of a representative sample (over 18%) of the Italian population, the included cohorts involved a robust number of analyzed patients under treatment with palbociclib, abemaciclib and ribociclib. The mean age was comparable between the groups, ranging between 61 and 65.5 years, which is in line with previous reports indicating that CDK4/6is are largely used in older women, consistent with national and international reports [29–31].

The distribution over time of patients starting treatment with CDK4/6i in the metastatic setting exhibited a shift in earlier treatment lines, with a tendency toward increased utilization of these novel agents as first-line treatment and a decrease as second-line treatment, especially in the last few years (from 2020–2021). These data confirm that the era of CDK4/6is is progressively leading toward a shift in treatment approaches for HR+/HER2- mBC [19,20,33,36–40].

Moreover, in the group of women with HR+/HER2- mBC included in this analysis, endocrine therapy was coadministered with CDK4/6is in more than 91% of patients, with a comparable pattern between fulvestrant and aromatase inhibitors, whereas tamoxifen was prescribed in very few cases. There is a large body of evidence to confirm the successful synergistic effects of combinations between endocrine agents and CDK4/6is in both premenopausal and postmenopausal women referring to various clinical end points, including overall survival, PFS, time to chemotherapy, chemotherapy-free survival, and time to second disease progression [41–46].

The present analysis investigated treatment schedules of the three currently approved CDK4/6is, especially focusing on treatment patterns and combination with endocrine therapy, line of therapy and drug dose modification during follow-up. In particular, dose variations were examined. At the index date, the largest majority most of the patients received the initial full dosage with each of the prescribed drugs. Considering patients still on therapy at specific time points, we found that the label-recommended dosage at 3 months after 6 months from therapy initiation was maintained in a high proportion of them (65–68% and 57–63%, respectively). Nevertheless, some differences emerged among the treatment patterns with these drugs. First, for the abemaciclib cohort, there was a higher proportion of patients who experienced only one dose reduction and a lower proportion of those who experienced two dose reductions with respect to the palbociclib and ribociclib treatment groups. Second, although no differences in TTD were noted in the three groups, the palbociclib- and ribociclib-treated patients showed lower point estimates than the abemaciclib-treated patients, regardless of the type of concomitant endocrine therapy. A systematic literature review of real-world evidence studies on CDK4/6is in HR+/HER2- advanced/mBC has reported that among 114 articles identified, dose reductions were analyzed in 11 studies [47]. For palbociclib plus aromatase inhibitors, the percentage of patients with dose reductions ranged from 17.4% [48] to 31.3% [49] in first-line therapy, but a broader range of 10.8% [50] to 72.1% (the highest described incidence for this outcome) [51] was found in all subsequent lines of therapy. For palbociclib plus fulvestrant, dose reduction frequencies were 34.3% in the first-line therapy setting [52] and 33.3% during the second-line and successive line therapy settings [53], with an overall range between 11.1 [50] and 64.6% [51] across all lines of therapy. Concerning the first-line combination ribociclib plus aromatase inhibitor, dose reductions occurred in 55% of patients [54]. The smallest rate of patients with dose reductions was found for abemaciclib plus endocrine therapy in all lines, ranging from 0% to 5.7% [55]. Currently, real-world data on TTD in clinical practice are limited, particularly for the most recently approved CDK4/6i abemaciclib [56]. Hence, this study provides evidence on two related aspects: dose reduction and treatment duration. As demonstrated by the MONARCH trials, patients with dose reduction are more likely to remain on treatment, and those who remain on treatment longer are more likely to have a dose adjustment [57]. Taken together, these reports support our finding with regard to a tendency toward a longer time on treatment in abemaciclib-treated patients, regardless of concurrent endocrine therapy.

Strengths & limits of the analysis

An important strength of the present analysis is related to the large sample size, with known advantages of data generation from real-word evidence analyses, especially the representativeness of a large group of health-assisted patients, which can facilitate generalizability. In the setting of HR+/HER2- mBC, there are to our knowledge no similarly comprehensive studies in Italy investigating all three currently approved CDK4/6is (although without comparative purposes) with respect to treatment duration, drug dose variation, combination with endocrine therapy, lines of therapy and related economic burden. Indeed, there is only limited evidence to date on a single CDK4/6i [58] and a recent cost-effectiveness analysis of CDK4/6is combined with fulvestrant [59].

On the other hand, the current limitations of the present study mainly lie in its retrospective observational design and some flaws related to the use of administrative databases. Although the quality of the data collected in administrative databases has progressively improved, this approach might suffer from potential incompleteness or limited accuracy for some information, such as disease severity, comorbidities, reasons beyond discontinuation (i.e., changing comorbidity status) and other potential confounding factors. Another potential limitation of the analysis might be related to different approval dates of CDK4/6is. Abemaciclib appears to be the agent associated with the lowest discontinuation rate, but at present our data do not allow us to ascertain whether this finding might be due to its more recent introduction into the clinical practice.

Conclusion

The results of this real-world analysis in Italy suggest that combined treatment regimens with CDK4/6is and endocrine therapy are widely implemented in women with HR+/HER2- mBC, and their utilization in the first-line setting has been increasing over time. Only approximately a third of the patients analyzed experienced dose lowering within the 6-month period after the start of CDK4/6i treatment. For currently approved CDK4/6is, the median time to discontinuation was greater than one year. Further comparative analyses between palbociclib, abemaciclib and ribociclib might provide novel interesting insights on the benefits of each of the three agents, also in view of the growing attention given to personalized medicine.

Author contributions

Study conception: V Perrone, M Giovannitti, C Buzzoni, L Degli Esposti. Acquisition/analysis/interpretation of data: V Perrone, M Dovizio, M Leogrande. Medical writing and draft preparation: V Perrone, M Dovizio. Final approval of the publication: all authors.

Acknowledgments

The present manuscript was edited for proper English language, grammar, punctuation, spelling and overall style by A Courey from American Journal Experts (AJE), funded by Eli Lilly upon purchase of the study.

Financial disclosure

Eli Lilly purchased the study report that is the basis for this manuscript. This manuscript was developed with Eli Lilly and CliCon S.R.L. Società Benefit. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

V Perrone and L Degli Esposti report no conflicts of interest related to this work. The agreement signed by CliCon S.R.L. Società Benefit and Eli Lilly does not create any entityship, joint venture or any similar relationship between parties. CliCon S.R.L. Società Benefit is an independent company. Neither CliCon S.R.L. Società Benefit nor any of their representatives are employees of Eli Lilly for any purpose. A Tamma and C Buzzoni are employees of Eli Lilly Italy S.P.A., Italy; M Giovannitti is an employee of Eli Lilly S.P.A. & Company, Roma, Italy. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The analysis has been notified to and approved by the local Ethics Committees of the Healthcare Departments involved in the study.

Data sharing statement

All data used for the current study are available upon reasonable request to CliCon S.R.L.

Summary points

- Although screening campaigns and increased awareness of breast cancer have allowed to intercept the disease at an early stage in most cases, 6–7% of breast cancers are already metastatic at diagnosis. Nevertheless, diagnostic and therapeutic advances have markedly improved the prognosis and life expectancy of women with metastatic breast cancer (mBC).
- The introduction of CDK4/6 inhibitors (CDK4/6is) has redefined the standard of care for mBC: in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) mBC, the combination of CDK4/6i with hormone therapy has proven a significantly better clinical benefit over hormone therapy alone in both first-line and second-line of treatment.
- This analysis was conducted in an Italian real-world clinical setting, to describe the current state-of-art of HR+/HER2- mBC patients treated with the currently approved CDK4/6is, namely palbociclib, abemaciclib and ribociclib. The investigation was especially focused on CDK4/6i utilization in terms of treatment duration, treatment patterns (combination with endocrine therapy), line of therapy, drug dose variations and time to discontinuation.
- The results showed that most of the patients with metastatic HR+/HER2- breast cancer had continuous prescriptions of endocrine therapy while on treatment with CDK4/6is: in particular, palbociclib and abemaciclib were more frequently combined with fulvestrant, while ribociclib with aromatase inhibitors.
- At starting CDK4/6i therapy, the recommended initial dose was administered to 88% of palbociclib-treated, 90% of the abemaciclib-treated and 72% of the ribociclib-treated patients. After 3 and 6 months from therapy initiation, the proportion of women who had one or two dose reductions was generally small, as at least two-thirds of the patients remained with the initial dose with some differences between the single drugs. Median time-to-treatment discontinuation was 11.0 months in palbociclib, 15.9 in abemaciclib and 15.4 in ribociclib cohorts. Taken together, these data suggest that CDK4/6i plus endocrine therapy results in limited dose reductions within 6 months and limited discontinuations within one year.
- Considering that the three available CDK4/6is have been approved for reimbursement in the setting of advanced breast cancer in Italy at different times (palbociclib since December 2017, ribociclib since September 2018 and abemaciclib since December 2019), an analysis was conducted in patients stratified by year of inclusion and by treatment line: a trend toward increased CDK4/6i use in the first line and a decrease in the second line was observed in the latest years (from 2020–2021).

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