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ORIGINAL ARTICLE

Second-line therapies after CDK4/6 inhibitor failure in HR-positive/HER2-negative metastatic breast cancer patients: real-world data from the HERMIONE-13 study

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) are the standard first-line treatment for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). However, treatment resistance and progression remain significant challenges, and optimal second-line strategies are not well defined.

Materials and methods: HERMIONE-13 is a multicentre, observational study conducted across 18 Italian centres, including both retrospective and prospective cohorts. The study aimed to describe real-world second-line treatment patterns following progression on CDK4/6i and to identify factors influencing therapeutic decisions. Clinical outcomes, including real-world progression-free survival (rwPFS) and overall survival (OS), were also evaluated.

Results: Among 254 assessable patients, 67.3% received chemotherapy (CHT) and 32.7% received ET ± targeted therapy (TT) as second-line treatment. The most common regimens included capecitabine and everolimus plus exemestane. Multivariable analysis showed that younger age, prior fulvestrant use, and shorter CDK4/6i duration were associated with CHT choice. Median rwPFS was 5.8 months for CHT and 5.3 months for ET ± TT. Median OS was longer in the ET ± TT group (3.8 versus 2.3 years). Metronomic CHT showed promising activity with a median rwPFS of 9.7 months.

Conclusions: In the Italian real-world setting, CHT remains the predominant second-line choice after CDK4/6i failure, though ET ± TT may offer comparable or superior outcomes in selected patients. Treatment decisions are influenced by clinical history and patient characteristics. These findings underscore the need for personalized approaches and molecular profiling to guide post-CDK4/6i therapy in HR-positive/HER2-negative MBC.

Key words: CDK4/6 inhibitor failure, rwPFS, chemotherapy, endocrine therapy

INTRODUCTION

Breast cancer is the most common malignancy in women and the leading cause of death from cancer. The most frequent molecular subtype of breast cancer is characterized by the presence of hormone receptors (HRs) and the lack of expression of human epidermal growth factor

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receptor 2 protein (HER2), which accounts for 70% of the total. HR-positive/HER2-negative metastatic breast cancer (MBC) has historically been treated with various sequences of endocrine therapy (ET), until the availability of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), which now represent the first-line standard of care, in association with ET. CDK4/6i have significantly improved progression-free survival (PFS) and overall survival (OS). Despite the excellent results obtained, ∼40% of patients are non-responsive to the treatment and the remaining patients develop disease progression on average after 25-28 months.[1-7] The choice of second-line therapy after CDK4/6i represents a major challenge, as it is still unclear how CDK4/6i alter tumour biology and how subsequent therapies can act in this context. Different options are currently available, including fulvestrant, alone or in combination with alpelisib, in *PIK3CA*-mutated patients, everolimus combined with exemestane, or chemotherapy (CHT). In addition, other new options are in an experimental or clinical setting, like selective degraders (SERD),[8,9] proteolysis targeting chimera, and many others. In the absence of predefined choices of treatment after CDK4/6i failure, except for *ESR1*-mutated tumours and *PIK3CA* ones, identifying which are the most used strategies as second line and the factors influencing such a choice is challenging.

HERMIONE-13 is an observational, retrospective, and prospective study aiming to describe which therapies were given after first-line progression on CDK4/6i and which factors are associated with specific treatment choices. The efficacy of the second-line treatments, in terms of real-world PFS (rwPFS) and OS, is also described.

MATERIALS AND METHODS

Study design

The study was conducted in 18 centres belonging to the HERMIONE Network, an independent platform of academic, secondary, and tertiary hospitals in Italy, dedicated to the conduct of real-world studies.

The primary objective of this study was to describe the second-line treatment choices at CDK4/6i progression. Secondary aims included the evaluation of the clinical benefit rate (CBR), defined as the sum of complete (CR) and partial (PR) responses and stable disease lasting >24 weeks; the overall response rate (ORR), defined as the sum of CR and PR; rwPFS2, defined as the time from the second-line treatment initiation until progression or death, whichever occurred first; OS, defined as the time from second-line treatment start until death; and post-progression survival, defined as the time from second-line treatment progression until death. For all the time-to-event endpoints, patients were censored at the last recorded clinical activity, i.e. last follow-up, if there was no evidence of event. The evaluation of the determinants of choice for second-line treatments was reported as an exploratory objective. The study was closed to enrolment in February 2024 and follow-up was uniformly updated as of December 2024. Raw data were collected from patients' medical records at each participating centre. An electronic, General Data Protection Regulation (GDPR)-compliant platform was set up to collect data.

Study population

Patients meeting the following criteria were included: HR-positive/HER2-negative MBC patients; previous first-line treatment with CDK4/6i in combination with aromatase inhibitors (AIs) or fulvestrant; progression on this treatment; on treatment with a second-line therapy with the availability of at least one radiological disease evaluation; and at least 6 months of observation from second line start. Exclusion criteria included patients deemed unsuitable for treatment at the investigator's discretion or unable to sign the written informed consent.

Ethical considerations

This study was conducted in accordance with the Good Clinical Practice guidelines established by the International Council for Harmonization and the provisions of the Declaration of Helsinki. Approval was granted by the coordinating centre's ethical committee (Comitato Etico Brianza) on 17 June 2021 and subsequently all the others. Informed consent was obtained from all alive patients able to understand and sign a written informed consent, while for those who died, or could not be located, consent was not required, in accordance with the General Authorization to Process Personal Data for Scientific Research Purposes (1 March 2012) issued by the guarantor for the protection of personal data.

Statistical analysis

Demographics, baseline clinical characteristics, and treatment information were summarized descriptively. Results on categorical variables were presented as absolute and relative frequencies, while continuous variables were presented as median (minimum-maximum).

Binary endpoints were described as proportions and reported together with the corresponding 95% confidence intervals (CIs), while for time-to-event endpoints, Kaplan—Meier curves were estimated and results reported at specific time points together with the corresponding 95% CIs.

We evaluated the role of various factors—namely, age at second-line start (years), previous adjuvant ET (yes versus no), presence of visceral metastases before first line (yes versus no), first-line fulvestrant in combination with CDK4/6 (yes versus no), and duration of previous exposure to CDK4/6 (>12 versus <12 months)—on the choice of second-line treatments (ET + TT versus CT). This was done by means of univariate and multivariable logistic regression models, reporting results in terms of odds ratio (OR) and the corresponding 95% CIs.

RESULTS

From January 2016 until December 2023, 257 HR-positive/HER2-negative patients were enrolled in the study, and of

Table 1. Patient and tumour characteristics at diagnosis and at first relapse (i.e. at CDK4/6i start).

Characteristics	$n = 254$	(min-max) or *n* (%)
At diagnosis		
Age (years)	53.1	(28.1-82.2)
Histology ($n = 245$)		
Ductal	182	(74.3)
Lobular	50	(20.4)
Other	13	(5.3)
Hormone receptor status ($n = 253$)		
ER positive	251	(99.2)
PgR positive	219	(86.6)
Ki67 $\geq$ 20	156	(62.2)
(Neo)adjuvant treatment	162	(63.8)
Chemotherapy (only)	11	(6.8)
Endocrine therapy	40	(24.7)
Chemotherapy $\rightarrow$ ET	111	(68.5)
At first relapse		
Age (years)	58.2	(28.3-82.3)
Postmenopause	186	(73.2)
ECOG performance status ($n = 253$)		
0-1	248	(98.0)
2	5	(2.0)
Presence of comorbidities ($n = 252$)	106	(42.1)
Cardiovascular disorders	50	(19.8)
Endocrinologic disorders	41	(16.3)
Haematologic disease	13	(5.2)
Muscle-skeletal disease	11	(4.4)
Pulmonary disorders	5	(2.0)
Neurologic disorders	5	(2.0)
Other comorbidities	47	(18.7)
Relapse during adjuvant ET or within 12 months from the end ($n = 149$)	89	(59.7)
De novo metastatic disease	93	(36.6)
Category of metastatic sites		
Visceral	128	(50.4)
Prevalent sites of metastases		
Bone	167	(65.8)
Liver	80	(31.5)
Lung	62	(24.4)
Soft tissues	69	(27.2)
Number of metastatic sites		
0	2	(0.8)
1	121	(47.6)
2	83	(32.7)
$\geq$3	48	(18.9)
Type of CDK4/6i		
Palbociclib	116	(45.7)
Ribociclib	97	(38.2)
Abemaciclib	38	(15.0)
Switch of CDK4/6i	3	(1.2)

CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; PgR, progesterone receptor.

these, 254 women with data available for the main endpoints were considered for the final analysis. At diagnosis, median age was 53.1 years (min-max 28.1-82.2 years) and 93 (36.6%) patients had *de novo* metastatic disease. Most of the patients received CHT followed by ET (68.5%) as (neo)adjuvant treatment.

At first relapse, 50.4% of patients had visceral metastases, most had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 (98.0%), around half of them (42.1%) had various concomitant diseases, and 186 (73.2%) patients were postmenopausal. Among the 149 patients who received adjuvant ET, 89 patients (59.7%) developed the first relapse during or within the first 12 months after the end of adjuvant ET and should therefore be considered primary endocrine-resistant. Table 1 summarizes the patient and tumour characteristics at baseline and at first relapse.

Ninety-nine patients (39.0%) were retested for molecular characteristics at first relapse. All patients received CDK4/6i + ET as first-line treatment for their metastatic disease; most of them received palbociclib ($n = 116$, 45.6%) or ribociclib ($n = 97$, 38.2%), mainly in combination with AIs ($n = 87$, 34.3%). Eighty-nine out of 149 patients treated with adjuvant ET (59.7%) relapsed during or within 12 months from adjuvant ET; therefore, 61 of them (68.5%) received CDK4/6i in combination with fulvestrant. Median real-world time to progression of previous CDK4/6i was 12.6 months (95% CI 11.3-14.1 months), without any difference according to the time of relapse in endocrine-sensitive and endocrine-resistant patients (12.3 versus 11.3 months, respectively). The main reason for treatment discontinuation was progressive disease (97.6%); 1.6% of the patients interrupted CDK4/6 therapy due to toxicity. The ORR to CDK4/6-based treatment was 35.8% (95% CI 29.9% to 42.1%); at progression, visceral metastases were present in 39.0%.

Median age at second-line treatment start was 62.8 years (min-max 39.4-80.9 years) in patients who received endocrine-based treatments and 57.8 years (min-max 28.8-82.6 years) in those treated with CHT. One hundred and seventy-one (67.3%) patients received CHT and the remaining ($n = 83$, 32.7%) received ET, with or without targeted therapy (TT) as second-line therapy. Among the CHT regimens, the favourite choices were single-agent, standard schedule, capecitabine ($n = 54$, 31.6%), metronomic schedule (mCHT) of oral capecitabine $\pm$ vinorelbine $\pm$ cyclophosphamide ($n = 29$, 17.0%), and paclitaxel ($n = 18$, 10.5%). Among the ET-based treatments, the combinations of everolimus + exemestane ($n = 43$, 51.8%) or fulvestrant alone ($n = 21$, 25.3%) were the preferred choices. Details about the type of second-line treatments are summarized in Table 2.

In the multivariable logistic regression analysis, only fulvestrant + CDK4/6i, a short duration of CDK4/6i (<12 months), and younger age at the beginning of second-line therapy remained associated with the choice of second-line CHT. Conversely, a longer duration of first-line CDK4/6i ($\geq$12 months) and older age were confirmed as factors related to the choice of second-line ET-based treatment (Table 3).

The CBR was 50.9% (95% CI 43.1% to 58.6%) in the CHT-treated group and 38.6% (95% CI 28.1% to 49.9%) in patients treated with ET $\pm$ TT. Median rwPFS of second-line treatment (rwPFS2) was 5.8 months (95% CI 4.9-6.5 months) and 5.3 months (95% CI 4.3-6.8 months) in the CHT and ET $\pm$ TT groups, respectively (Figure 1).

Median duration of previous CDK4/6i therapy was 17.4 months (min-max 2.4-78.1 months) and 10.8 months (min-max 1.8-60.9 months) in second-line ET $\pm$ TT and CHT, respectively. The median rwPFS2 of patients relapsed

Table 2. Type of treatment at progression on CDK4/6i

Treatment	*n*	(%)
CHT	171	(67.3)
Capecitabine (standard schedule)	54	(31.6)
Metronomic CHT	29	(17.0)
Anthracycline-based	26	(15.2)
Paclitaxel	18	(10.5)
Nab-paclitaxel	17	(9.9)
Eribulin	10	(5.9)
Platinum salts	7	(4.1)
Vinorelbine-based	7	(4.1)
Paclitaxel + bevacizumab	3	(1.7)
ET ± TT	83	(32.7)
Everolimus + exemestane	43	(51.8)
Fulvestrant	21	(25.3)
Alpelisib ± ET	9	(10.8)
CDK4/6i + ET	4	(4.8)
SERD/PROTAC (clinical trials)	4	(4.8)
Aromatase inhibitors	1	(1.2)
TT not further specified	1	(1.2)

CHT, chemotherapy; ET, endocrine therapy; PROTAC, proteolysis targeting chimera; TT, targeted therapy.

during or within the first 12 months after the end of adjuvant ET was similar to that of patients relapsed later: 5.9 (95% CI 4.3-6.7) and 6.0 (95% CI 4.3-8.0) months (Figure 2A), while patients with a duration of previous CDK4/6 ≥12 months showed a longer median rwPFS2 as compared with patients with a CDK4/6 duration <12 months (6.5, 95% CI 5.3-8.3 versus 4.5, 95% CI 3.8-5.9, respectively) (Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmorw.2025.100665).

The 3-year real-world OS rate was higher in ET ± TT-treated patients in comparison to CHT-treated patients: 53.6% (95% CI 37.0% to 67.7%) versus 41.6% (95% CI 28.6% to 54.0%). Median OS of second-line treatment was longer in patients treated with ET ± TT than in those treated with CHT [3.8 years, 95% CI 2.6 years-not estimable (NE) versus 2.3 years, 95% CI 1.9 years-NE] (Figure 3).

Median real-world post-progression survival (rwPPS) of second-line therapy in the 201 patients with available follow-up data after progression to second-line treatment was 29.3 months (95% CI 24.4 months-NE) and 19.1 months (95% CI 13.5-24.4 months) in patients receiving ET ± TT and CHT (Figure 4).

In most patients, second-line treatment discontinuation was due to disease progression (222 out of 243 discontinued the second-line treatment, 91.4%). Two hundred and one patients (79.1%) started a third-line treatment: most patients treated in second line with CHT continued with the same type of therapy (108/118, 91.5%), while most of them who had previously received ET ± TT switched to CHT (58/73, 79.5%).

Considering that mCHT was chosen in 29 (17%) patients treated with CHT in the second-line setting, we conducted an exploratory analysis to better characterize this strategy as an option of treatment in HR-positive/HER2-negative MBC patients after progression on CDK4/6i. Patient and disease characteristics of the two groups are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmorw.2025.100665.

Main patient characteristics were very similar between the two groups: median age was ∼55 years and most had an ECOG PS of 0 or 1. Disease characteristics were also very similar, particularly in terms of number and type of metastatic sites.

The CBR in patients treated with mCHT was 61.3% (95% CI 42.2% to 78.2%) versus 48.6% (95% CI 40.0% to 57.2%) in those treated with standard CHT. Median rwPFS2 was 9.7 months (95% CI 4.0-13.7 months) in patients treated with mCHT and 5.4 months (95% CI 4.3-6.3 months) in those who received standard CHT (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmorw.2025.100665).

Similarly, median OS was 2.6 years (95% CI 2.1 years-NE) in the 31 patients treated with mCHT and 2.3 years (95% CI 1.9 years-NE) in the 140 patients who received standard CHT (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmorw.2025.100665).

Median rwPPS was similar in the two groups regardless of the type of CHT (14.1 months, 95% CI 9.4 months-NE versus 21.1 months, 95% CI 13.5 months-NE in mCHT and CHT, respectively).

DISCUSSION

HERMIONE-13 is a real-world study, which enrolled retrospective and prospective HR-positive/HER2-negative MBC patients who failed first-line CDK4/6i + ET, designed to gather information regarding the type of therapy as second-line treatment and its outcomes and to identify potential factors that could have influenced this choice. In Italy, most of the HR-positive/HER2-negative MBC patients

Table 3. Univariate and multivariable logistic regression models for choosing ET ± TT versus CHT as second-line treatment

Characteristic	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Previous adjuvant ET: yes versus no	0.33	0.19-0.57	<0.001	0.62	0.33-1.15	0.130
First-line fulvestrant in combination with CDK4/6: yes versus no	0.22	0.11-0.43	<0.001	0.27	0.13-0.59	0.001
Age at second-line start (years)	1.03	1.01-1.06	0.011	1.04	1.01-1.07	0.010
Presence of visceral metastases before first line: yes versus no	0.57	0.33-0.97	0.004	0.71	0.4-1.27	0.247
Duration of previous exposure to CDK4/6: ≥12 versus <12 months	2.61	1.50-4.54	0.001	2.18	1.21-3.92	0.001

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; ET, endocrine therapy; OR, odds ratio.

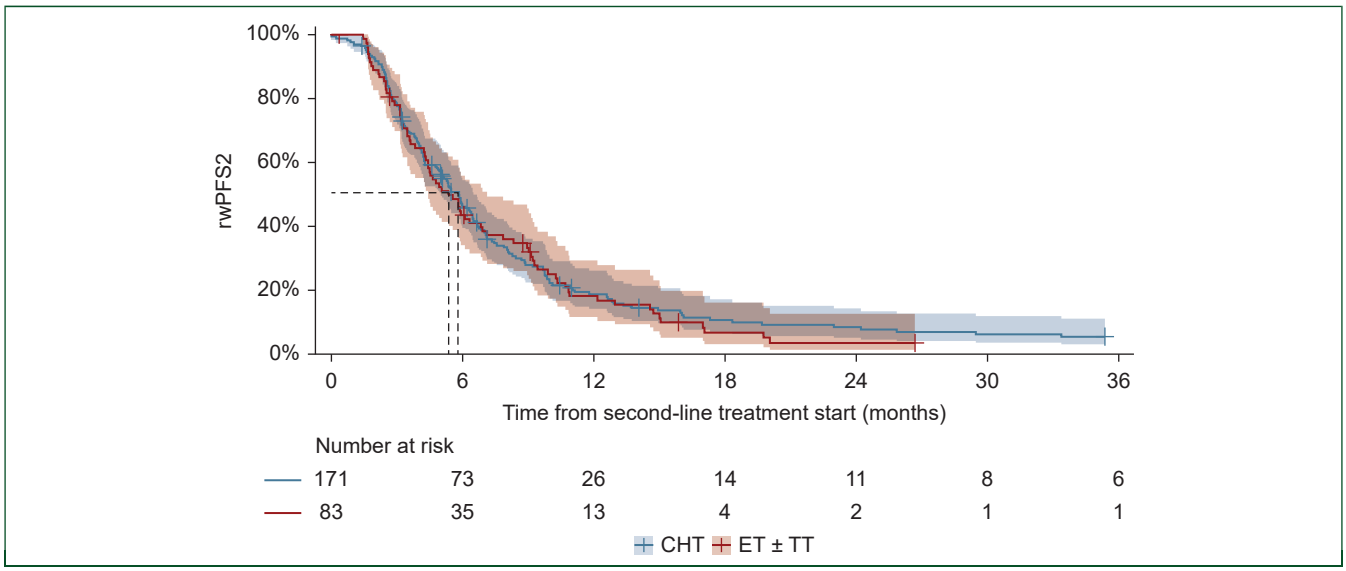

Figure 1. Real-world progression-free survival (rwPFS2) according to the type of treatment.
CHT, chemotherapy; ET, endocrine therapy; TT, targeted therapy.

received CHT (67.3%), similar to what other studies conducted in the era before SERDs have reported. However, second-line choice can vary across countries according to factors such as the type of insurance reimbursement, the attitude of physicians, or the socioeconomic situation.

The multivariable logistic regression analysis identified key factors influencing the choice between second-line CHT and ET ± TT after progression on first-line CDK4/6i. CHT was more likely to be chosen for patients who had received fulvestrant + CDK4/6i as first-line treatment, possibly reflecting a more aggressive disease biology or prior endocrine resistance; those with a short duration of CDK4/6i treatment (<12 months), suggesting early progression and reduced endocrine sensitivity; and younger patients, who may be better candidates for more intensive treatment due to better PS and fewer comorbidities. ET ± TT was more commonly selected for patients with a longer duration of benefit from first-line CDK4/6i (≥12 months), indicating sustained endocrine responsiveness, and older patients, likely due to a preference for less toxic regimens and consideration of comorbidities or frailty. These findings highlight the importance of prior treatment response and patient age in guiding second-line treatment decisions. They suggest that clinicians tailor therapy based not only on disease progression but also on patient characteristics and prior treatment efficacy, favouring CHT in more aggressive or endocrine-resistant cases and reserving ET-based strategies for those with prolonged benefit and greater frailty. The observed differences in OS and post-progression survival according to rescue therapy (CHT versus ET/TT) might be influenced by treatment selection bias, particularly given the tendency to assign less aggressive regimens to patients with more favourable prognostic features. However, as the aim of this study is purely descriptive, with no intention to carry out any comparison, the time-to-event outcomes using Kaplan–Meier curves have been presented, without reporting any *P* values that could imply a comparative analysis.

Martin et al.[10] examined a United States nationwide electronic health record database identifying 1210 patients who were treated with CDK4/6i in the same years as those registered in the HERMIONE-13 study, with the aim of describing what therapies were administered after first-line failure, as in our population, palbociclib was the preferred CDK4/6i used as first-line treatment (88.2%), mainly in association with AIs (68.8%); *de novo* metastatic disease accounted for 29.2% of the patient population, while no data about the site of metastatic disease have been reported. However, CHT was the preferred choice in 29.7% of the patients, while the majority (36%) continued a CDK4/6i, mostly the same used in first line, and 21.7% of the patients with ET ± TT (everolimus or alpelisib). The median rwPFS for those patients who received CHT, fulvestrant monotherapy, or everolimus in combination with exemestane was 3.71, 3.25, and 3.32 months, respectively. These outcome data seem to be quite different from those we reported in our Italian population, where median rwPFS2 was 5.8 months (min-max 4.9-6.5 months) in CHT-treated patients and 5.3 months (4.3-6.8 months) in those treated with ET ± TT. These findings could be related to different factors, mainly an intrinsic difference in the patients enrolled: for example, no data regarding visceral sites or median duration of previous CDK 4/6i treatment have been reported by these authors. West et al.[11] retrospectively reviewed the single-institution database of patients treated with CDK4/6i between 2014 and 2019, reporting a median PFS2 (mPFS2) of 6.1 months (95% CI 4.8-8.0 months) for CHT-treated patients and 5.0 months (95% CI 4.1-11.0 months) for ET-treated patients. The longest mPFS2 was obtained by using a new CDK4/6i (6.9 months, 95% CI 5.1 months-NA).

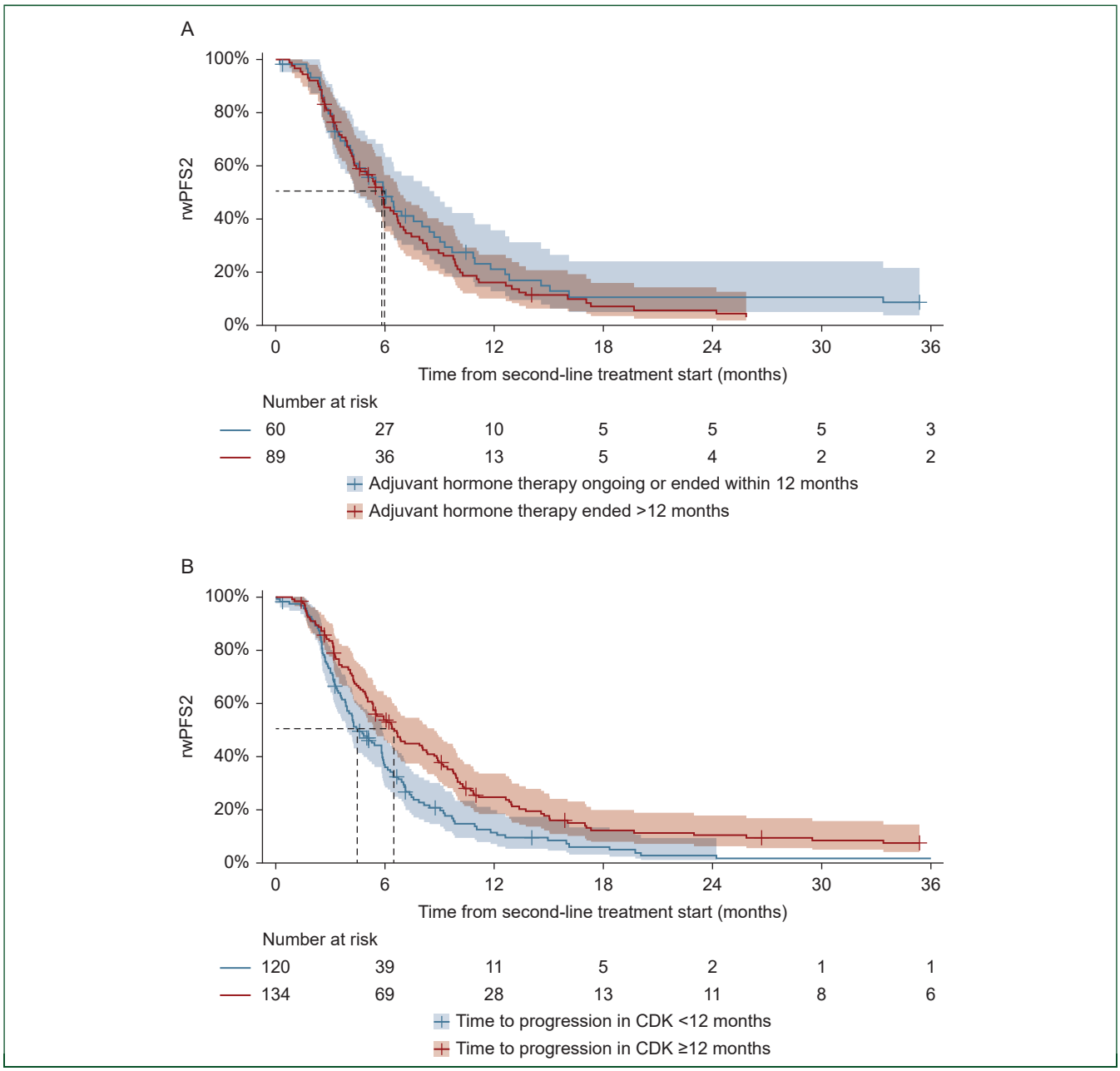

Figure 2. rwPFS2 of second-line treatment. According (A) to the time of first relapse [during or within 12 months from the end of adjuvant ET versus ≥12 months (only patients with adjuvant endocrine therapy, $n = 149$)] and (B) rwPFS2 according to previous CDK4/6i duration (<12 versus ≥12 months). CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; rwPFS2, real-world progression-free survival of second-line treatment.

Different studies have been conducted on the same topic in Europe, where the use of CDK4/6 beyond progression is not allowed in all countries. Molinelli et al.[12] recently reported the data of a real-world analysis of 701 HR-positive/HER2-negative MBC patients enrolled in the Italian GIM14/BIOMETA study, with the primary aim of assessing the effectiveness of CDK4/6i plus ET based on HER2 status and endocrine sensitivity or resistance (primary/secondary) classification. As a secondary objective, these authors also evaluated the effectiveness of different second-line treatments, with second-line time to treatment discontinuation (TTD) as a secondary endpoint. Palbociclib (47%) and ribociclib (42.9%) were the most used first-line CDK4/6i, mainly in combination with AIs (69.6%); 47.6% of the patients had visceral sites at CDK4/6i start, while ∼30% of the patients had *de novo* metastatic disease. Among the 275 patients who had disease progression during first-line CDK4/6i, 40% received CHT, more frequently capecitabine or taxane-based regimens, and 45.5% received endocrine-based treatments, mainly everolimus–exemestane/fulvestrant. Median second-line TTD was 6.11 months for patients treated with capecitabine [interquartile range (IQR) 2.96-11.47 months], 5.06 months (IQR 2.99-9.99 months) for those treated with taxane-based CHT, 5.39 months (IQR 2.53-9.03 months) for the subgroup treated with everolimus plus exemestane, and 6.44 months (IQR 3.38

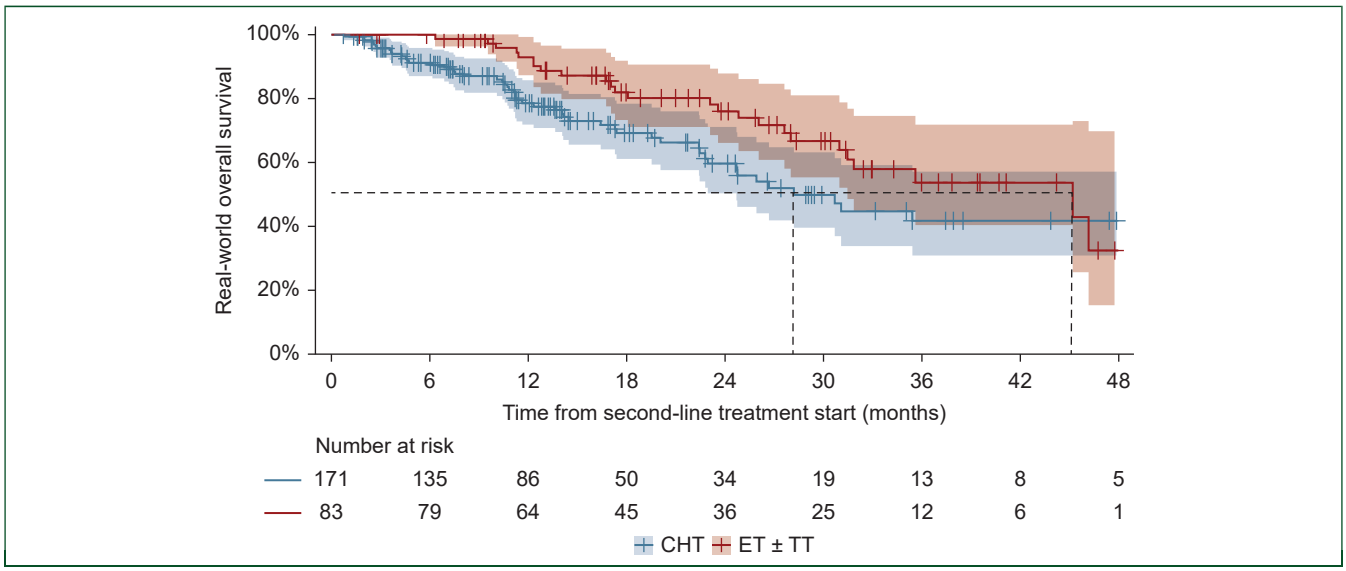

Figure 3. Real-world overall survival of second-line treatment according to the type of therapy.
CHT, chemotherapy; ET, endocrine therapy; TT, targeted therapy.

months-not reached) for patients treated with fulvestrant. In a similar geographical and regulatory context, these results were very close to those reported in our study.

Berton Giachetti et al.[13] evaluated PFS and OS in an Italian cohort of 342 MBC patients between 2015 and 2023 who received ET-based (46.5%) or CHT-based (53.5%) treatment following progression during ET + CDK4/6i. Median age was 61.7 years, most of the patients were treated with palbociclib (60.8%) or ribociclib (28.1%), and the majority (50.6%) had visceral involvement. In this population, the median PFS varied depending on the treatment type, with oral CHT showing a median PFS of 6.89 months, intravenous CHT 5.44 months, everolimus plus exemestane 4.82 months, and ET alone 3.87 months. As in the HERMIONE-13 study, a longer duration of CDK4/6i and an older age were associated with better outcomes.

A systematic literature review of real-world evidence for second-line treatments in HR-positive/HER2-negative MBC after first-line treatment with CDK4/6 has recently been published,[14] highlighting that the weighted rwPFS was 3.9 months for single-agent ET, 3.6 months for ET + everolimus, and 6.1 months for CHT. These findings collectively suggest that despite the fact that CDK4/6i significantly advanced the treatment of MBC, there is still a need for ongoing research and personalized approaches to address resistance and improve patient outcomes. These results strongly suggest that choices made without knowing the gene mutational status do not provide a real outcome

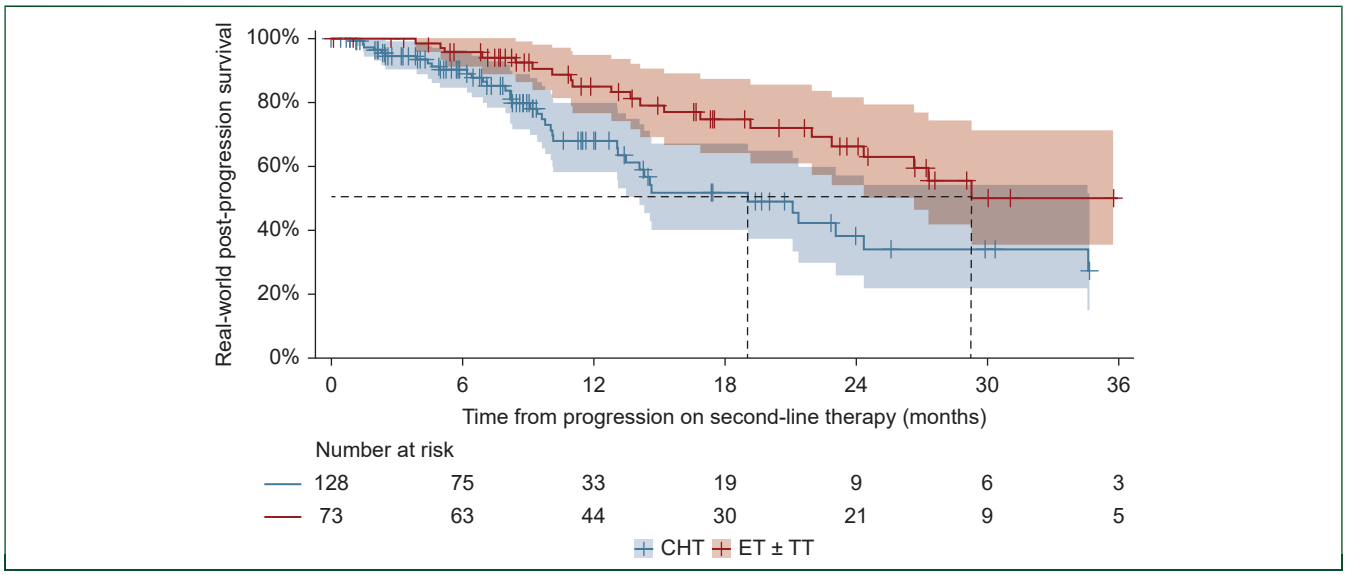

Figure 4. Real-world post-progression survival according to the type of treatment received as second line.
CHT, chemotherapy; ET, endocrine therapy; TT, targeted therapy.

benefit in HR-positive/HER2-negative MBC patients after failure of first-line CDK4/6i.

Another systematic review and meta-analysis[15] recently reported a pooled analysis of Kaplan—Meier-derived individual patient data in terms of PFS and OS. The authors reported that the most common second-line therapy was CDK4/6i plus ET (34.6%), followed by ET monotherapy (30.9%) and CHT (29.4%), after progression on CDK4/6i. They clearly showed that maintaining treatment with a CDK4/6i was associated with longer PFS compared with ET monotherapy (hazard ratio 0.61, 95% CI 0.53-0.70, $P < 0.01$).

Moscetti et al.[16] presented a retrospective and prospective study to describe the pattern and effectiveness of the therapeutic sequence following the failure of CDK4/6i in first- or second-line treatment. Ninety-five out of 103 patients who received a second line were assessable for the purposes of the study: the majority (67%) were treated with CHT, and the remaining patients with CDK4/6 therapy, different from that received in first line (8%), or a combination of ET with or without everolimus (25%). The median time to next treatment was 24 months (95% CI 17-30 months) for CHT, 15 months for CDK4/6-based treatment (95% CI 11-18 months), and 9.6 months (95% CI 6-11 months) for endocrine-based regimens. The differences observed in comparison to our results could be mainly explained by the different sample size, ours being threefold higher than that analyzed by these authors.

Targeting ESR1,[8,9] PI3K,[17] or AKT[18] mutations with specific agents, like elacestrant, imlunestrant, inavolisib, or capivasertib, demonstrated a statistically significant improvement in median PFS across the trials. As the first-line treatment remains CDK4/6i combined with AIs or fulvestrant, according to endocrine sensitivity or resistance, the landscape of second line is deeply changing. While *PIK3CA* mutations can be often present at the very beginning of the metastatic disease as they are early events, *ESR1* mutations are rarely present in primary/untreated HR-positive breast cancer[19,20] and arise after AI exposure and the frequency is up to 25%-40% in the second- to third-line setting. In different studies,[8,9] the percentage of patients harbouring the *ESR1* mutation is ∼35%, PIK3CA 45%, and AKT 40.8%: this means that in all the remaining patients, who constitute the majority, CHT or, more recently, trastuzumab deruxtecan (T-DXd)[21] remain the only available treatment options. A potential role in this setting can be also played by the combination of imlunestrant + abemaciclib,[9] as this combination demonstrated an improvement in PFS over imlunestrant alone in all comers.[14] Altogether, the findings from these studies evaluating the therapeutic choices after CDK4/6i, including the HERMIONE 13 study, have several important implications for the treatment of this MBC population:

1. Need for personalized treatment: The variability in PFS among different treatments highlights the importance of personalized treatment plans. Patients with specific genetic mutations may require tailored therapies to improve outcomes.
2. Importance of genomic testing: The commentary on post-CDK4/6i therapy emphasizes the role of genomic testing in identifying actionable mutations. This can help in selecting the most effective second-line therapies after progression.
3. Challenges in managing resistance: The real-world studies underscore the challenge of managing resistance to CDK4/6i. With a significant portion of patients discontinuing treatment due to disease progression, there is a clear need for novel therapies and further molecular characterization to better understand and combat resistance.
4. Potential for new therapies: The development of new therapies, such as camizestrant, shows promise in improving PFS when combined with CDK4/6i. This highlights the ongoing need for clinical trials and research to find more effective treatment combinations.

The HERMIONE Network continues to collect data regarding second-line choices in a more contemporary landscape (HERMIONE-18 study), to assess how the choice and the effectiveness of second-line strategies have changed after the introduction of new targeted agents and drug-conjugated antibodies, like T-DXd, in the treatment journey of HR-positive/HER2-negative MBC patients.

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REFERENCES

1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936.
2. Slamon DJ, Diéras V, Rugo HS, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol*. 2024;42(9):994-1000.
3. Goetz MP, Toi M, Huober J, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3. *Ann Oncol*. 2024;35(8):718-727.
4. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386(10):942-950.
5. Lu YS, Im SA, Colleoni M, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2- advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. *Clin Cancer Res*. 2022;28(5):851-859.
6. Sledge GW, 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(25):2875-2884.
7. 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(12):1475-1495.
8. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor

2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246-3256.
9. Jhaveri KL, Neven P, Casalnuovo ML, et al. Imlunestrant with or without abemaciclib in advanced breast cancer. *N Engl J Med*. 2025;392(12):1189-1202.
10. Martin JM, Handorf EA, Montero AJ, Goldstein LJ. Systemic therapies following progression on first-line CDK4/6-inhibitor treatment: analysis of real-world data. *Oncologist*. 2022;27(6):441-446.
11. West MT, Goodyear SM, Hobbs EA, et al. Real-world evaluation of disease progression after CDK 4/6 inhibitor therapy in patients with hormone receptor-positive metastatic breast cancer. *Oncologist*. 2023;28(8):682-690.
12. Molinelli C, Bruzzone M, Blondeaux E, et al. The journey of patients affected by metastatic hormone receptor-positive/HER2-negative breast cancer from CDK 4/6 inhibitors to second-line treatment: a real-world analysis of 701 patients enrolled in the GIM14/BIOMETA study. *Eur J Cancer*. 2024;213:115113.
13. Berton Giachetti PPM, Morganti S, Gandini S, et al. Survival following CDK4/6 inhibitor therapy for hormone receptor-positive, ERBB2-negative metastatic breast cancer. *JAMA Netw Open*. 2025;8(2):e2461067.
14. Lambert V, Kane S, Howidi B, et al. Systematic literature review of real-world evidence for treatments in HR+/HER2- second-line LABC/mBC after first-line treatment with CDK4/6i. *BMC Cancer*. 2024;24(1):631.
15. Ravani LV, Calomeni P, Vilbert M, et al. Efficacy of subsequent treatments after disease progression on CDK4/6 inhibitors in patients with hormone receptor-positive advanced breast cancer. *JCO Oncol Pract*. 2025;21(6):832-842.
16. Moscetti L, Barbieri E, Zattarin E, et al. Time to next treatment to evaluate the therapeutic sequence after first- or second-line CDK4/6 inhibitors of hormone receptor-positive, HER2-negative advanced breast cancer in Italy: a retrospective/prospective observational trial GOIRC-04-2019. *ESMO Real World Data Digital Oncol*. 2025;8:100154.
17. Turner NC, Im SA, Saura C, et al. Inavolisib-based therapy in *PIK3CA*-mutated advanced breast cancer. *N Engl J Med*. 2024;391(17):1584-1596.
18. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor—positive advanced breast cancer. *N Engl J Med*. 2023;388(22):2058-2070.
19. Najim O, Seghers S, Sergoynne L, et al. The association between type of endocrine therapy and development of estrogen receptor-1 mutation(s) in patients with hormone-sensitive advanced breast cancer: a systematic review and meta-analysis of randomized and non-randomized trials. *Biochim Biophys Acta Rev Cancer*. 2019;1872(2):188315.
20. Jeselsohn R, Buchwalter G, De Angelis C, Brown M, Schiff R. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. *Nat Rev Clin Oncol*. 2015;12(10):573-583.
21. Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122.