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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

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ABSTRACT

Purpose: The aim of this study was to evaluate the effectiveness of CDK 4/6 inhibitors (CDK 4–6i) according to HER2 status (low/zero), and endocrine resistance/sensitivity, as well as the efficacy of second-line treatments, in a large real-world cohort.

Methods: The GIM14/BIOMETA study (NCT02284581) is a retrospective/prospective study of the Gruppo Italiano Mammella evaluating treatment patterns and survival outcomes in patients with metastatic breast cancer (MBC). We retrieved data on patients with hormone receptor-positive/HER2-negative MBC receiving first-line CDK 4/6i.

Results: Among 3832 patients enrolled in the GIM14-BIOMETA study, 701 were eligible. At a median follow-up of 24.80 months, no significant differences were found between HER2-zero and HER2-low subgroups in terms of first-line time to treatment discontinuation (TTD) (26.16 months [IQR 12.84-NR] vs. 27.60 months [IQR 12.12–64.44], $p = 0.972$) or overall survival (OS) (mOS>60 months for both groups, $p = 0.398$). Median TTD was 33.24 months (IQR 16.32-NR) for the endocrine sensitive subgroup, 19.92 months (IQR 8.88–51.24) for the secondary endocrine resistant subgroup and 17.40 months (IQR 7.44–24.72) for the primary endocrine resistant subset, respectively ($p < 0.001$). Among 239 patients receiving second-line treatment, no significant difference ($p = 0.188$) was found in terms of second-line TTD between those treated with capecitabine (6.11 months, IQR

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2.96–11.47), taxane-based chemotherapy (5.06 months, IQR 2.99–9.99), everolimus plus exemestane (5.39 months, IQR 2.53–9.03) or fulvestrant (6.44 months, IQR 3.38-NR).
Conclusions: Endocrine therapy plus CDK 4/6i represents an effective treatment, regardless of HER2 status (low/zero). Second-line agents did not differ significantly in terms of TTD. Endocrine resistant cancers exhibit poor response to CDK 4/6i.

1. Introduction

The combination of CDK 4/6 inhibitors (CDK 4/6i) and endocrine therapy is the standard first-line treatment in patients with hormone receptor-positive/HER2-negative metastatic breast cancer [1–7]. However, there are still some concerns about which patients will benefit the most from this treatment and who will experience early disease progression. Recent trials, such as the SONIA trial, exploring the efficacy of CDK 4/6i in both first- and second-line settings [8], and the INAVO120 trial, which evaluated inavolisib in combination with palbociclib and fulvestrant for PIK3CA-mutated, luminal-like advanced breast cancer [9], offer insights into treatment escalation and de-escalation strategies. Hence, there is a need for finding clinical criteria and biomarkers to tailor the treatment in patients affected by luminal-like metastatic breast cancer. As of now, HER2-low status seems not to have a proper prognostic value in patients affected by HER2-negative breast cancer, whose prognosis is mainly driven by hormone receptor status [10]. Some studies evaluated the prognostic role of HER2-low status in patients treated with CDK 4/6i in first line with conflicting results [11,12]. The efficacy of CDK 4/6i could be influenced by the type of endocrine resistance (primary or secondary) or endocrine sensitivity (with relapse occurring at least one year after completing adjuvant therapy or in patients previously untreated for advanced disease). Primary endocrine resistance is defined as a relapse within the first 2 years of adjuvant endocrine treatment. Conversely, secondary endocrine resistance occurs if relapse happens after the first 2 years of adjuvant treatment or within 12 months of completing it [1]. Median overall survival (OS) is significantly shorter in case of endocrine resistance, and mostly in the primary one, when compared with endocrine sensitive breast cancers. Primary endocrine resistance is also associated with a high probability of developing visceral metastases [13]. Another significant concern is selecting the appropriate second-line treatment after progressing on CDK 4/6i, particularly in those patients who do not harbour any genomic alteration, since no head-to-head comparisons exist between the currently available treatment options in this specific population. The BOLERO-6 trial reported a progression-free survival (PFS) of 8.4 months for subjects treated with everolimus plus exemestane and 9.6 months for those in the capecitabine arm, but these patients were not pretreated with CDK 4/6i. In selected cases, fulvestrant might be a valid second-line agent [14], while the DESTINY-Breast06 trial results suggest that trastuzumab deruxtecan (T-DXd) could be a new option after CDK 4/6i in patients with aggressive disease [15].

The aim of this study was to understand, in a real world setting, the effectiveness of CDK 4/6i plus endocrine treatment according to HER2 status, type of endocrine resistance or sensitivity, and estrogen receptor expression (ER). Moreover, we evaluated the type of treatment administered in second line after CDK 4/6i and its effectiveness.

2. Materials and methods

2.1. Study design and patient population

Our analysis was performed within a retrospective/prospective observational multicentre study of the Gruppo Italiano Mammella (GIM) Study Group (GIM14/BIOMETA study, ClinicalTrials.gov Identifier: NCT02284581). This study aimed at evaluating treatment pattern and survival outcomes of patients affected by metastatic breast cancer. The prospective cohort includes patients diagnosed with metastatic breast cancer after the start of the study at each centre (April 2016 for the coordinating centre) and whose data are collected prospectively, while the retrospective cohort includes patients diagnosed with metastatic disease from January 2000 to the start of the GIM14/BIOMETA study. The reporting of this analysis follows the STROBE statement [16].

For the present analysis, we retrieved retrospective/prospective data on patients treated with first-line CDK 4/6i plus endocrine therapy between May 2014 (when CDK 4/6i became available in Italy within clinical trials) and June 2023 at 26 Italian institutions. Patients were treated according to clinical practice at each participating institution. This study was approved by the ethical committee of each participating institution; written informed consent was required for patients included in the prospective part of the study, according to Italian regulations.

2.2. Data collection

All the data used for the present analysis were retrieved from the GIM14/BIOMETA electronic database. For each patient, we collected information on (neo)adjuvant treatments, distant recurrence, and treatment history for advanced disease. Tumour response was assessed locally according to clinical practice at each participating centre. Hormone receptor status, Ki67, and HER2 expression were determined by the local pathologists on advanced stage biopsy if available and, if not, on primary tumour samples. If both samples were available, the advanced stage biopsy was considered for determining tumour characteristics. Hormone receptors and HER2 status were evaluated according to the American Society of Clinical Oncology/College of American Pathologists guidelines in use at the time of the evaluation [17]. HER2-low status was defined by a score of 1+ or 2+ with ISH not amplified. Those tumours with a HER2 score of 0 were defined as HER2-zero. Primary and secondary endocrine resistance were defined according to the ESO-ESMO international consensus guidelines for advanced breast cancer [1]. Particularly, primary endocrine resistance was defined as relapse during the first 2 years of adjuvant endocrine treatment. Secondary endocrine resistance is defined as relapse during adjuvant endocrine treatment but after the first 2 years, or relapse within 12 months of completing adjuvant endocrine treatment. Endocrine sensitivity is characterized by relapse occurring at least one year after completing adjuvant endocrine therapy or in patients who were previously untreated for advanced disease [1,13].

2.3. Study objectives

The primary objective was to assess the effectiveness of CDK 4/6i plus endocrine treatment based on HER2 status and endocrine sensitivity or resistance (primary/secondary) classification. Primary endpoints were time to treatment discontinuation (TTD) and OS. The secondary objective was to evaluate the effectiveness of different second-line treatments, with second-line TTD as a secondary endpoint.

2.4. Statistical analysis

TTD was defined as the time between the start of first-line treatment and the last treatment administration, or death. OS was defined as the time between the start of first-line treatment and death from any cause. Median follow-up was defined as the time between the start of the first-line regimen and the last contact or death, and it was calculated with the reverse Kaplan-Meier method [18]. Second-line TTD was defined as the

time between the start of second-line treatment and the last treatment administration or death. The Kaplan-Meier method was used to estimate the TTD curves for the prespecified subgroups; the comparison was performed through the log-rank test. Prespecified subgroups were identified according to HER2 status, endocrine resistance/sensitivity classification and ER expression. Hazard ratios (HRs) with 95 % confidence intervals (CIs) were calculated in univariable Cox regression models. All tests were 2-sided and a P value < 0.05 was considered statistically significant. Statistical analyses were performed with Stata, software version 16.1 (StataCorp LLC, College Station, TX, USA).

3. Results

From November 2015 to July 2023, 3832 patients with metastatic breast cancer were enrolled at 26 institutions within the GIM14-BIOMETA study. For the present analysis, 701 patients were considered eligible (Figure 1), of whom 531 patients (75.7 %) were enrolled in the prospective cohort.

3.1. Prognostic value of HER2-low status in patients treated with CDK 4/6 inhibitors

Out of 701 eligible patients, 365 (52 %) had HER2-zero tumours and 336 (48 %) HER2-low tumours. No significant difference in primary tumour characteristics were observed between patients with HER2-zero or HER2-low tumours (Table 1). Overall, 302 patients (43 %) underwent advanced stage biopsy (Supplementary Material Table S1). Median age at cancer diagnosis was 57 years (46−66) in the HER2-zero group and 55 (44−66) in the HER2-low subgroup, with a median age at diagnosis of metastatic disease of 63 and 60 years, respectively. A total of 124 patients (36.9 %) with HER2-low breast cancer were diagnosed with *de novo* metastatic disease compared to 108 (29.6 %) with HER2-zero tumours. The median time from diagnosis of advanced disease to first-line treatment start was 29 days (IQR 16–48).

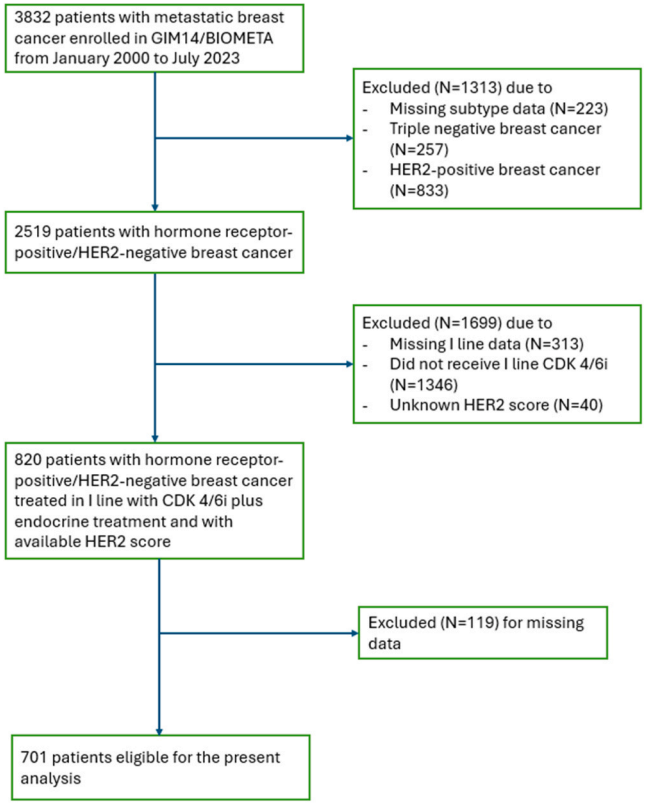

Fig. 1. Patient Flow Chart According to STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) Standards . Abbreviations: CDK 4/6i, CDK 4/6 inhibitors; GIM, Gruppo Italiano Mammella; N, number.

Table 1
Patient and tumour characteristics. *At the advanced stage biopsy the hormone receptor status was positive.

	HER2-zeroN (%) n = 365	HER2-lowN (%) n = 336	*P* value
Age at diagnosis of primary cancer, median (IQR) years	57 (46–66)	55 (44–66)	0.406
Age at diagnosis of metastatic disease, median (IQR) years	63 (52–71)	60 (51–71)	0.059
Age at diagnosis of metastatic disease			0.198
≤ 50 years	80 (21.9)	83 (24.7)	
51 −60 years	79 (21.6)	86 (25.6)	
61 −70 years	114 (31.2)	82 (24.4)	
> 70 years	92 (25.2)	85 (25.3)	
Cohort			0.052
Perspective	265 (72.6)	266 (79.2)	
Retrospective	100 (27.4)	70 (20.8)	
Menopausal status at breast cancer diagnosis			0.249
Pre-menopausal	277 (75.9)	262 (78.0)	
Post-menopausal	77 (21.1)	58 (17.3)	
Missing	11 (3.0)	16 (4.8)	
Histology			0.476
Ductal carcinoma	270 (74.0)	257 (76.5)	
Lobular carcinoma	65 (17.8)	53 (15.8)	
Others/missing	30 (8.2)	26 (7.7)	
Hormone receptor status on primary tumour			0.957
ER-negative/PR-negative*	2 (0.5)	2 (0.6)	
ER-positive/PR-negative	37 (10.1)	34 (10.1)	
ER-negative/PR-positive	1 (0.3)	2 (0.6)	
ER-positive/PR-positive	324 (88.8)	298 (88.7)	
Missing	1 (0.3)	0 (0.0)	
CDK 4/6 inhibitor used			0.686
Palbociclib	175 (47.9)	158 (47.0)	
Ribociclib	160 (43.8)	144 (42.9)	
Abemaciclib	30 (8.2)	34 (10.1)	
Endocrine therapy combined with CDK 4/6 inhibitors			0.553
Tamoxifen → AI	1 (0.3)	1 (0.3)	
Letrozole	218 (59.7)	192 (57.1)	
Anastrozole	7 (1.9)	2 (0.6)	
Exemestane	2 (0.5)	2 (0.6)	
Fulvestrant	94 (25.7)	101 (30.1)	
Aromatase Inhibitors + LhRH anlogue	43 (11.8)	38 (11.3)	
Presentation of metastatic disease			0.092
Non visceral	38 (10.4)	40 (11.9)	
Bone-only	172 (47.1)	133 (39.6)	
Visceral	147 (40.3)	160 (47.6)	
Missing	8 (2.2)	3 (0.9)	
De novo metastatic disease			0.064
No	247 (67.7)	209 (62.2)	
Yes	108 (29.6)	124 (36.9)	
Missing	10 (2.7)	3 (0.9)	

After a median follow-up of 24.80 months, no significant differences were found in terms of TTD (median TTD 26.16 months (IQR 12.84-NR) and 27.60 months (IQR 12.12–64.44) (HR= 1.00, 95 % CI 0.80–1.26, p = 0.972) (Figure 2) or OS (median OS beyond 60 months for both groups) (p = 0.398) (Figure 3) between HER2-zero and HER2-low subgroups. Paired advanced stage and primary tumour biopsies were available for 231 subjects (Supplementary Material Table S2): 65 (43.6 %) out of 149 HER2-zero primary tumours turned into HER2-low at the advanced stage biopsy. Among 82 HER2-low primary breast cancers, 29 (35.4 %) were classified as HER2-zero at the biopsy performed in the metastatic setting.

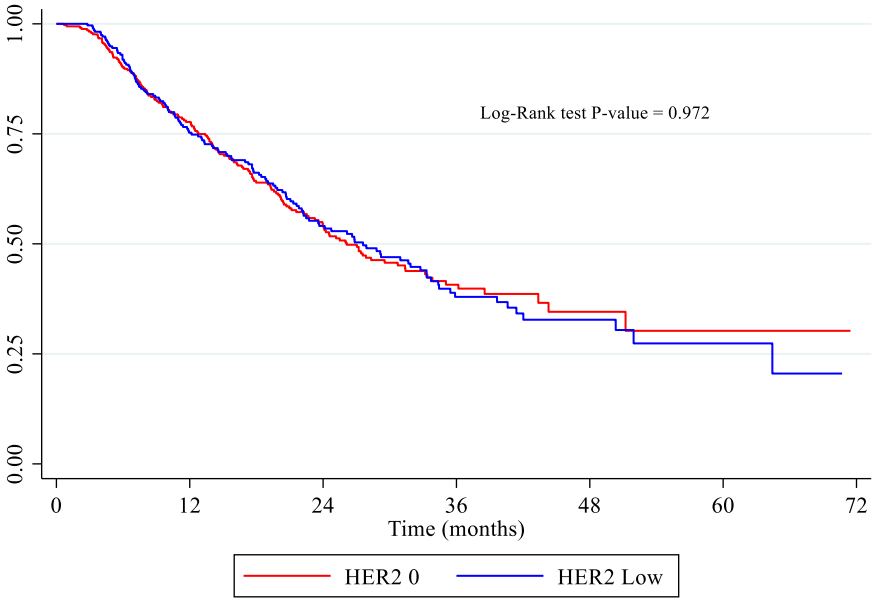

Fig. 2. Time to treatment discontinuation according to HER2 status (HER2-low vs. HER2-zero).

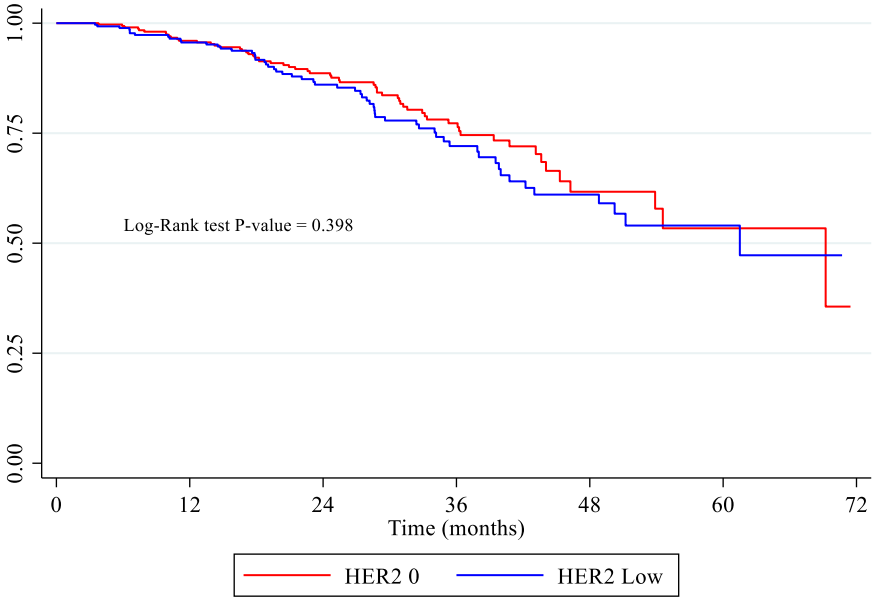

Fig. 3. Overall Survival according to HER2 status (HER2-low vs. HER2-zero).

3.2. Effectiveness of CDK 4/6 inhibitors according to endocrine resistance/sensitivity

Overall, 426 patients (60.8 %) had tumours defined as endocrine-sensitive, with 232 subjects having *de novo* metastatic disease. The disease was considered secondary endocrine-resistant in 142 (20.3 %) patients and primary endocrine-resistant in 54 (7.7 %) patients. Data about the timing of relapse and endocrine resistance/sensitivity were missing in 11.2 % of cases (Table 2). The subgroup with endocrine-sensitive cancers exhibited a median TTD of 33.24 months (IQR 16.32-NR) ($p < 0.001$) (Figure 4). Median TTD was 19.92 months (IQR 8.88–51.24) for the subgroup with secondary endocrine-resistant disease and 17.40 months (IQR 7.44–24.72) for patients with primary endocrine-resistant breast cancer. Median OS was 69.24 months (IQR 42.24-NR) for patients with endocrine-sensitive tumours, NR (IQR 29.28-NR) for patients with secondary endocrine-resistant disease, and 32.64 months (IQR 25.32–43.08) for those with primary endocrine-resistant tumours ($p < 0.001$) (Figure 5).

Table 2
Endocrine resistance/sensitivity classification.

Endocrine resistance/sensitivity classification	N (%) n = 701
De novo metastatic disease	232 (33.1)
Endocrine sensitive	194 (27.7)
Secondary endocrine resistant	142 (20.3)
Primary endocrine resistant	54 (7.7)
Missing	79 (11.2)

3.3. Effectiveness of CDK 4/6i according to Estrogen Receptor expression

All patients (n = 701) were divided into four groups according to ER expression. Overall, 32 subjects (4.6 %) had tumours with ER≤ 50 %,

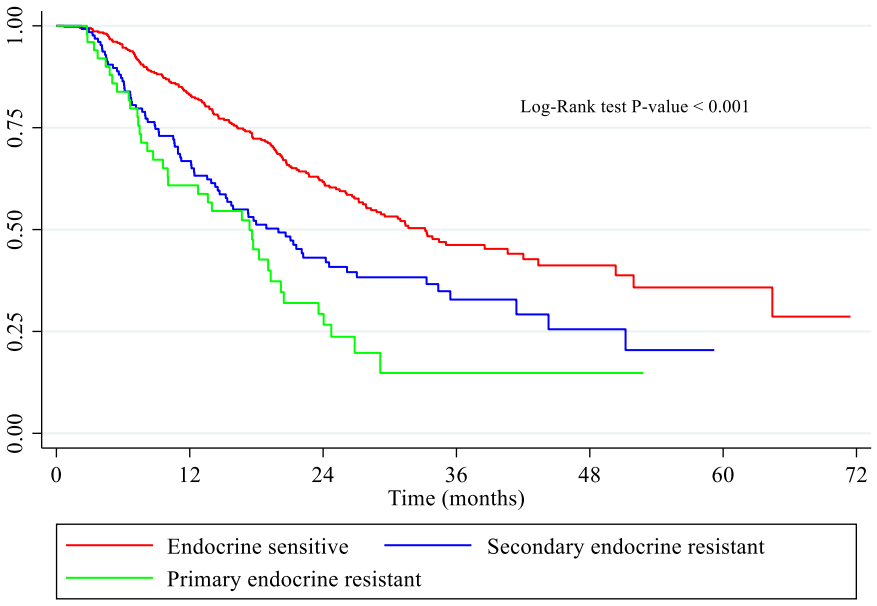

Fig. 4. Time to treatment discontinuation according to Endocrine resistance/sensitivity.

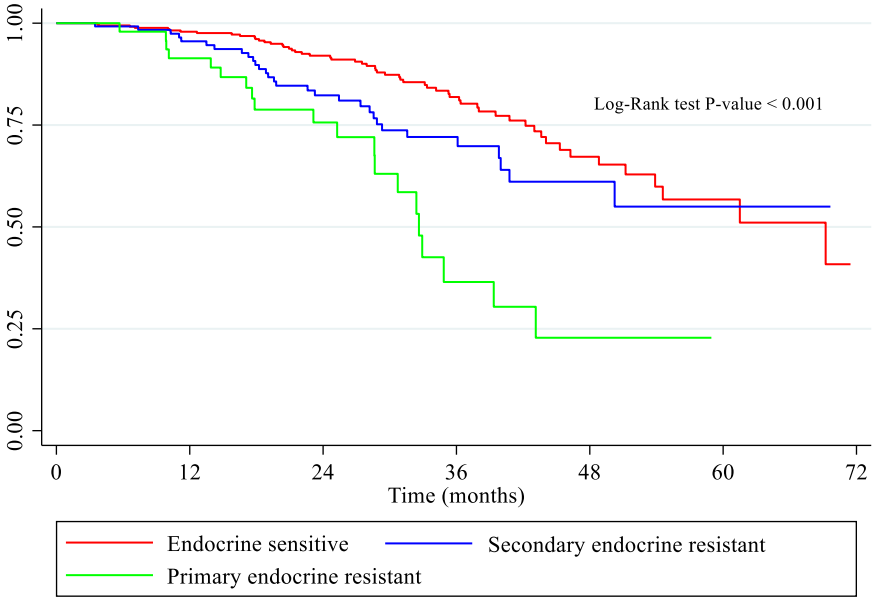

Fig. 5. Overall Survival according to Endocrine resistance/sensitivity.

173 (24.7 %) with ER between 51 % and 80 %, 255 (36.4 %) with ER between 81 % and 90 %, and 241 (34.4 %) had tumours with ER> 90 %. Median TTD was 19.08 months (IQR 8.16–40.56) for those with ER ≤ 50 %, 27.84 months (IQR 12.12-NR) for ER between 51 % and 80 %, 24.00 months (IQR 12.36–51.96) for ER between 81 % and 90 %, and 29.16 months (IQR 13.80-NR) for ER > 90 %. Median OS was 42.96 months (IQR 21.48-NR), NR (IQR 32.88-NR), 61.56 months (IQR 36.24-NR), and 69.24 months (IQR 39.84-NR), respectively. No significant differences were found between these four subgroups in TTD (p = 0.198) (Supplementary Material Figure S1) or OS (p = 0.059) (Supplementary Material Figure S2).

3.4. Second-line treatment

Among patients (n = 275) who experienced disease progression during first-line CDK 4/6i, 40 % (n = 110) received chemotherapy (more frequently capecitabine or taxane-based regimen), 45.5 % (n = 125) received endocrine-based treatment (the majority exemestane+ everolimus or fulvestrant), 0.3 % (n = 1) PARP inhibitors, 1 % (n = 3) received other treatments. In 13.1 % of patients, data were missing (Table 3).

Table 3
Second-line treatment.

Type of second line treatment	N (%) n = 701
Died within 120 days	22 (3.1)
First line ongoing	404 (57.6)
Chemotherapy	110 (15.7)
Endocrine-based treatment	125 (17.8)
PARPi	1 (0.1)
Others	3 (0.4)
Missing	36 (5.1)

A higher rate of *de novo* metastatic disease (47.3 %) was found among patients treated with fulvestrant, compared to the other agents (10.7 % for capecitabine, 16 % for taxane-based chemotherapy, and 26.5 % for everolimus plus exemestane) ($p < 0.001$). Similarly, those tumours treated with second-line fulvestrant, were more frequently classified as endocrine-sensitive (40 %) than those treated with capecitabine (17.9 %), taxane-based chemotherapy (28 %), and everolimus plus exemestane (20.6 %) ($p < 0.001$) (Table 4). The rate of bone-only presentation was similar among patients treated with fulvestrant, capecitabine, and everolimus plus exemestane (50.9 % vs. 48.2 % vs. 50 %, respectively) and lower in those administered a taxane-based regimen (24 %) ($p = 0.344$). The type of second-line treatment was also evaluated according to the duration of first-line TTD: in patients treated with capecitabine, the TTD for CDK 4/6i was 11.16 months (IQR 6.6–17.76), in those administered a taxane 6.00 months (IQR 4.56–11.64), in those treated with everolimus plus exemestane 19.80 months (IQR 13.68–24.00), and in those who received fulvestrant 19.68 months (IQR 11.76–27.60).

Second-line TTD for capecitabine, taxane-based chemotherapy (with or without bevacizumab), everolimus plus exemestane, and fulvestrant was evaluated. No significant differences were found between these four groups ($p = 0.188$): median second-line TTD was 6.11 months for patients treated with capecitabine (IQR 2.96–11.47), 5.06 months (IQR 2.99–9.99) for those treated with taxane-based chemotherapy, 5.39 months (IQR 2.53–9.03) for the subgroup treated with everolimus plus exemestane, and 6.44 months (IQR 3.38-NR) for patients treated with fulvestrant (Figure 6).

4. Discussion

In this analysis of the observational, multicentre, retrospective/prospective GIM14/BIOMETA study, we evaluated possible clinical biomarkers of the effectiveness of CDK 4/6i and compared the effectiveness of the second-line treatment options available at the time of the study.

No significant differences were found between patients with HER2-low and HER2-zero breast cancer in terms of TTD or OS. In contrast, a recent meta-analysis including nine studies and 2705 patients treated with CDK 4/6i, found that patients with HER2-low tumours had shorter PFS (HR: 1.22, 95 % CI 1.10–1.35, $p < 0.001$) and OS (HR: 1.22, 95 % CI 1.04–1.44, $p = 0.010$), compared to those with HER2-zero breast cancers [19]. However, another meta-analysis evaluating patients with hormone receptor-positive metastatic breast cancer found no difference in terms of PFS between patients with HER2-low and HER2-zero tumours [20]. Although some studies showed that HER2-low breast cancer patients exhibit shorter PFS than patients with HER2-zero tumours, all patients with hormone receptor-positive/HER2-negative metastatic breast cancer must be treated with first-line CDK 4/6i plus endocrine treatment, as this combination represents the best treatment option available in this setting.

Based on our findings, CDK 4/6 inhibitors were effective regardless of ER expression. However, endocrine sensitivity and resistance significantly influenced survival outcomes, highlighting their importance in determining treatment benefit. Individuals experiencing primary endocrine resistance exhibited the poorest outcomes when treated with CDK 4/6i. Our data are consistent with the results of CDK 4/6i registration trials, which demonstrated the high efficacy of these agents with similar relative benefits in both endocrine-sensitive and endocrine-resistant tumours. Nevertheless, the absolute benefit in these studies appears to be definitely more relevant in patients with endocrine-sensitive tumours compared to patients with endocrine-resistant disease, and our analysis confirms this trend [2,3,6,7,21,22].

Table 4
Baseline characteristics according to second-line treatment.

	Capecitabine N (%) n = 56	**Taxane N (%) n = 25**	**Exemestane Plus Everolimus N (%) n = 34**	**Fulvestrant N (%) n = 55**	***P* value**
Age at cancer diagnosis, median (IQR) years	56 (45 –66)	54 (48 –59)	54 (42 –60)	59 (46 –70)	0.216
Age at diagnosis of metastatic disease, median (IQR) years	62 (51 –72)	61 (54 –67)	56 (47 –64)	66 (53 –73)	0.042
Age at diagnosis of metastatic disease					0.009
≤ 50 years	14 (25.0)	4 (16.0)	13 (38.2)	9 (16.4)	
51 –60 years	12 (21.4)	8 (32.0)	8 (23.5)	10 (18.2)	
61 –70 years	14 (25.0)	12 (48.0)	11 (32.3)	17 (30.9)	
> 70 years	16 (28.6)	1 (4.0)	2 (5.9)	19 (34.5)	
Cohort					0.011
Perspective	41 (73.2)	16 (64.0)	16 (47.1)	44 (80.0)	
Retrospective	15 (26.8)	9 (36.0)	18 (52.9)	11 (20.0)	
Menopausal status at cancer diagnosis					0.606
Pre-menopausal	40 (71.4)	20 (80.0)	24 (70.6)	43 (78.2)	
Post-menopausal	13 (23.2)	4 (16.0)	8 (23.5)	8 (14.5)	
Missing	3 (5.4)	1 (4.0)	2 (5.9)	4 (7.3)	
CDK 4/6 inhibitor used					0.119
Palbociclib	34 (60.7)	15 (60.0)	23 (67.6)	30 (54.5)	
Ribociclib	15 (26.8)	10 (40.0)	9 (26.5)	24 (43.6)	
Abemaciclib	7 (12.5)	0 (0.0)	2 (5.9)	1 (1.8)	
Presentation of metastatic disease					0.344
Non visceral	5 (8.9)	3 (12.0)	3 (8.8)	4 (7.3)	
Bone-only	27 (48.2)	6 (24.0)	17 (50.0)	28 (50.9)	
Visceral	21 (37.5)	16 (64.0)	14 (41.2)	23 (41.8)	
Missing	3 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	
De novo metastatic disease					< 0.001
No	49 (87.5)	21 (84.0)	25 (73.5)	29 (52.7)	
Yes	6 (10.7)	4 (16.0)	9 (26.5)	26 (47.3)	
Missing	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	
cision Medicine Unit in Senology, Fondazione					< 0.001
Polic					
De novo metastatic disease	6 (10.7)	4 (16.0)	9 (26.5)	26 (47.3)	
Endocrine sensitive	10 (17.9)	7 (28.0)	7 (20.6)	22 (40.0)	
Secondary endocrine resistant	21 (37.5)	9 (36.0)	11 (32.3)	2 (3.6)	
Primary endocrine resistant	10 (17.9)	5 (20.0)	5 (14.7)	1 (1.8)	
Missing	9 (16.1)	0 (0.0)	2 (5.9)	4 (7.3)	

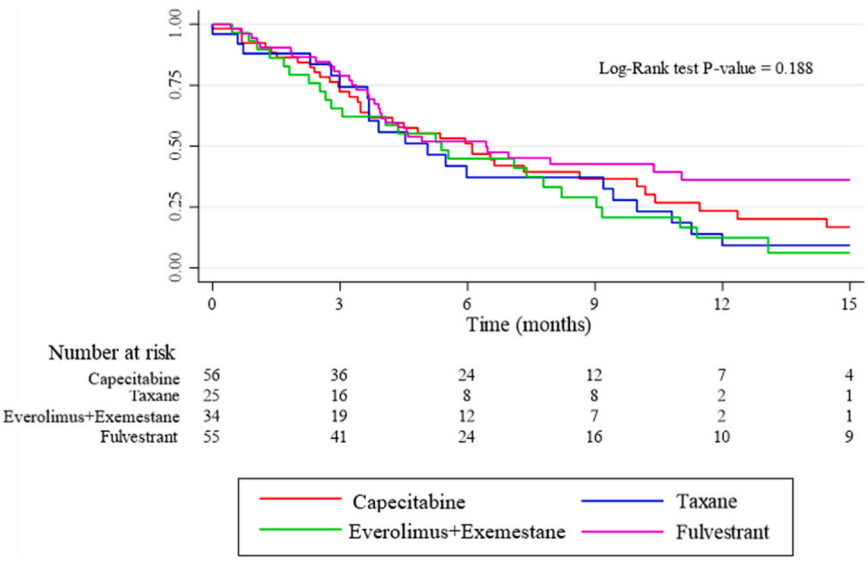

Fig. 6. Second-line time to treatment discontinuation.

No significant differences were found in terms of TTD or OS according to ER expression. Moreover, no significant difference between the different types of second-line treatment was observed, with all subgroups exhibiting a second-line TTD of about 6 months. In the BOLERO-6 trial, patients treated with second-line everolimus plus exemestane exhibited a PFS of 8.4 months, while those administered capecitabine had a PFS of 9.6 months. However, these subjects were pretreated with aromatase inhibitors and not exposed to CDK 4/6i [23]. The second-line TTD of patients treated with taxane-based chemotherapy (5.06 months) is similar to the findings of the RIBBON-2 trial. In this study, those treated with taxane plus bevacizumab exhibited a second-line PFS of 7.2 months, and those treated with only chemotherapy had a second-line PFS of 5.1 months [24]. Comparable results were found in a multicentric study enrolling Asian patients [25]. Our results underline that baseline characteristics influenced the second-line treatment choice: patients who received fulvestrant exhibited a more favourable tumour profile (e.g. *de novo* metastatic disease, bone-only presentation). On the contrary, a monocentric study showed that baseline features did not have any significant impact on the choice of second-line agent. However, their analysis demonstrated that endocrine treatment is a valid second-line option, consistently with our data [14].

In our study, patients receiving chemotherapy as second-line treatment exhibited a shorter TTD during first-line treatment. Conversely, TTD with CDK 4/6i was longer in those who received second-line endocrine treatment. Similarly, in the study involving 609 patients treated with CDK 4/6i, a shorter duration of CDK 4/6i led clinicians to choose chemotherapy more frequently as subsequent treatment rather than endocrine therapy [26]. Analogous results were found in a population-based study involving 525 patients [27]. Although these data are derived from real-world studies, the duration of CDK 4/6i treatment and the aggressiveness of the metastatic disease might be relevant factors to consider when choosing the second-line treatment. Further investigations within randomized clinical trials are certainly needed.

These results are especially relevant following the recent DESTINY-Breast06 trial publication. In this trial, 866 patients with hormone receptor-positive/HER2-low or HER2-ultralow and chemotherapy-naïve in the metastatic setting were randomized to receive T-DXd or physician's choice treatment. The subjects assigned to the T-DXd arm had significantly longer PFS than those in the control arm, both in HER2-low (HR 0.62, 95 % CI 0.51–0.74, $p < 0.0001$) and HER2-ultralow (HR 0.78, 95 % CI 0.50–1.21) subgroups [15]. Oncologists will soon have an additional option after CDK 4/6i. Our data highlight key features clinicians tend to consider for second-line treatment, crucial for optimal sequencing and delaying chemotherapy in less aggressive tumours.

Other new second-line agents now available include alpelisib, elacestrant and capivasertib. In the SOLAR-1 trial, among patients with *PIK3CA* mutations, the addition of alpelisib to fulvestrant led to a significantly longer PFS (11.0 vs. 5.7 months, HR 0.65, 95 % CI 0.50–0.85, $p = 0.00065$) and a prolonged OS, although not statistically significant (HR 0.86, 95 % CI, 0.64–1.15, $p = 0.15$). Alpelisib is approved for luminal-like metastatic breast cancer harbouring *PIK3CA* mutations [28]. In the phase III EMERALD trial, patients treated with elacestrant had longer PFS than those receiving endocrine monotherapy, particularly in those with ESR1 mutation (47.8 %) (HR 0.55, 95 % CI 0.39–0.77, $p = 0.0005$) [29]. This agent is now approved in patients affected by ER-positive/HER2-negative advanced breast cancer with ESR1 mutation [30], and HER2 status (low/zero) seems not to have any impact on its efficacy [31]. Capivasertib is an AKT-inhibitor: in the CAPItello-291 trial it prolonged median PFS from 3.1 months to 7.3 months in the AKT pathway–altered population (HR 0.50; 95 % CI, 0.38 to 0.65, $p < 0.001$) [32], and it is now FDA-approved in patients with luminal-like advanced breast cancer with PIK3CA/AKT1/PTEN-alterations [33]. Although the approval of these drugs is restricted to specific populations, these agents must be considered as second-line options for selected patients. These advancements underscore the importance of personalized treatment and targeting mutations to improve outcomes in metastatic breast cancer.

Our study has some limitations. Data were from a retrospective/prospective registry without centralized tissue sample review or disease evaluation. The observational design and variability in patient characteristics and tumour assessment methods may have impacted our results, and patients could have stopped treatment due to progression but also other reasons. Data on patients' characteristics at the time of progression on CDK 4/6i were not available. Moreover, our data only partially reflect the current landscape of second-line treatment, as novel drugs (e.g., elacestrant, T-DXd) were unavailable for the patients in our analysis. On the other hand, the patients included in this analysis mainly belonged to the prospective registry including several different Italian institutions.

5. Conclusions

CDK 4/6i represent an effective first-line treatments for hormone receptor-positive metastatic breast cancer, regardless of HER2 status. Endocrine-resistant cancers, especially with primary resistance, showed poor TTD compared to endocrine-sensitive ones. In our real-world

analysis, despite varying tumor and metastatic characteristics, approved second-line agents (taxane-based chemotherapy, capecitabine, everolimus plus exemestane, fulvestrant) showed no significant differences in second-line TTD. Endocrine-based second-line treatments were mainly chosen for less aggressive disease.

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CRediT authorship contribution statement

Claudia Bighin: Writing – review & editing, Data curation, Conceptualization. **Matteo Lambertini:** Writing – review & editing, Investigation, Conceptualization. **Stefania Russo:** Writing – review & editing, Investigation. **Lucia Del Mastro:** Writing – review & editing, Project administration, Data curation, Conceptualization. **Ferdinando Riccardi:** Writing – review & editing, Investigation. **Valentina Sini:** Writing – review & editing, Investigation. **Francesco Cognetti:** Writing – review & editing, Investigation. **Grazia Arpino:** Writing – review & editing, Investigation. **Alessandra Fabi:** Writing – review & editing, Investigation. **Chiara Molinelli:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Palma Pugliese:** Writing – review & editing, Investigation. **Marco Bruzzone:** Writing – review & editing, Formal analysis. **Elena Collovà:** Writing – review & editing, Investigation. **Eva Blondeaux:** Writing – review & editing, Methodology, Investigation, Data curation. **Andrea Fontana:** Writing – review & editing, Investigation. **Tommaso Ruelle:** Writing – review & editing, Investigation, Data curation. **Fabio Puglisi:** Writing – review & editing, Investigation. **Chiara Lanzavecchia:** Writing – review & editing, Investigation, Data curation. **Michelino De Laurentiis:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Chiara Molinelli reports honoraria for consultancy and consulting fees from Daiichi Sankyo, travel support to attend conferences from Gilead, Menarini and fees for medical writing from Lilly and Seagen. Eva Blondeaux reports honoraria from Eli Lilly and research funding (to institution) from Gilead. Michelino De Laurentiis reports honoraria or consultation fees for speaker, consultancy or advisory roles from Eli Lilly, Seagen, Therapeutics, GSK, Roche, Novartis, Genetic, Pfizer, Pierre Fabre, MSD, Menarini Stemline, Sophos Biotech, Max Farma, Celltrion Healthcare, Gilead, Daiichi Sankyo; institutional financial interests, financial support for clinical trials or contracted research, from: Novartis, Pierre Fabre, Pfizer, Roche, Stemline Therapeutics. Alessandra Fabi reports consulting fees and honoraria from Roche, Novartis, Lilly, Pfizer, MSD, Gilead, Seagen, Astra Zeneca, Daiichi Sankyo. Support for attending meetings and/or travel from Novartis, Lilly, Pfizer, MSD. Grazia Arpino reports research and medical writing from AstraZeneca; advisory boards, travel grants, activities as a speaker, consultancy from AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Exact Science, Novartis, Roche, Seagen, Viatris. Andrea Fontana reports advisory boards from Roche, Novartis, Eli Lilly, Pfizer, MSD, Pierre Fabre, Eisai, Gilead, Seagen, Astra Zeneca, Exact Sciences; consulting fees from Dompé Farmaceutici S.p.A. D.G. Research funding from Menarini, Seagen, Novartis, AstraZeneca; advisory boards, activities as a speaker, consultancy from Seagen, Novartis, Eli Lilly, Roche, Gilead, Pfizer, Eisai, Exact Sciences. Fabio Puglisi reports advisory role for and receiving speaker honoraria from Amgen, AstraZeneca, Daichii Sankyo, Celgene, Eisai, Eli Lilly, Exact Sciences, Gilead, Ipsen, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Takeda, and Viatris. Travel grants from AstraZeneca, Daichii Sankyo, Novartis, Roche. Research grants (to his institution) from Astrazeneca, Eisai, Roche. Claudia Bighin reports personal fees from Roche, Novartis, Lilly, Gilead, and Daiichi. Matteo Lambertini reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, Menarini; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Menarini, AstraZeneca; travel Grants from Gilead, Daiichi Sankyo, Roche; research funding (to the Institution) from Gilead all outside the submitted work. Lucia Del Mastro reports grants from Eli Lilly, Novartis, Roche, Daiichi Sankyo, Seagen, AstraZeneca, Gilead, and Pierre Fabre; receiving consulting fees from Eli Lilly, Gilead, and Daiichi Sankyo; receiving speaker honoraria from Roche, Novartis, Pfizer, Eli Lilly, AstraZeneca, MSD, Seagen, Gilead, Pierre Fabre, Eisai, Exact Sciences, Ipsen, GSK, and Agendia-Stemline; receiving travel grants from Roche, Pfizer, Eisai, Daiichi Sankyo, and AstraZeneca; and having an advisory role for Novartis, Roche, Eli Lilly, Pfizer, Daiichi Sakyo, Exact Sciences, Gilead, Pierre Fabre, Eisai, AstraZeneca, Agendia, GSK, and Seagen. All the other authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115113.

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