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ORIGINAL ARTICLE

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

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Background: Palbociclib, ribociclib, and abemaciclib are approved for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (aBC), in combination with aromatase inhibitors or fulvestrant. However, there is no standard care following progression on cyclin-dependent kinase 4/6 inhibitors (CDK4/6i).

Materials and methods: This study aimed to evaluate treatment patterns and effectiveness following the failure of CDK4/6i therapy. The analysis included 407 patients who received CDK4/6i in first- or second-line treatment across three cancer centers. Primary endpoints included time to next treatment (TTNT) and real-world progression-free survival.

Results: The results demonstrated a median TTNT (mTTNT) of 26 months [95% confidence interval (CI) 21-31 months] for patients receiving CDK4/6i as first-line treatment. Subsequent therapies, including chemotherapy (CT), endocrine therapy (ET) with or without everolimus, and CDK4/6i-based regimens, were evaluated. The mTTNT for second-line treatments was 13 months (95% CI 9-16 months), with CT showing the longest duration [24 months (95% CI 17-30 months) versus 15 months (95% CI 11-18 months)] for CDK4/6-based regimens versus 9.6 months for everolimus with or without ET (95% CI 6-11 months). Multivariate analysis identified the number of disease sites as a significant predictor of longer TTNT in the first-line setting. Safety data revealed that CDK4/6i dose reductions due to toxicity occurred in 47% of patients, with neutropenia being the most common adverse event.

Conclusions: These findings emphasize the variability in treatment efficacy following CDK4/6i therapy and underscore the importance of personalized treatment strategies. Further research is needed to optimize therapeutic sequences and improve patient outcomes in this setting.

Key words: subsequent treatments, cyclin 4/6 inhibitors, breast cancer, palbociclib, ribociclib, abemaciclib

INTRODUCTION

Palbociclib, ribociclib, and abemaciclib have been approved by the European Medicines Agency for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (aBC). These cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are approved for use in combination with aromatase inhibitors (AIs) and/or fulvestrant for patients who are either endocrine sensitive or endocrine resistant. Additionally, CDK4/6i are approved for premenopausal patients when combined with a luteinizing hormone-releasing hormone analog. The approval of these inhibitors is based on phase III studies, including PALOMA-2, PALOMA-3, MONARCH-2, MONARCH-3, MONALEESA-2, and MONALEESA-3 trials.[1-9]

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After disease progression on CDK4/6i therapy, no standard of care exists for the next line of systemic therapy. Available options include the following therapeutic options: endocrine therapy (ET), chemotherapy (CT), exemestane with everolimus, and for patients with germline *BRCA* mutations the poly(ADP-ribose) polymerase inhibitors (talazoparib and olaparib). Emerging therapies include alpelisib with fulvestrant for patients with somatic *PIK3CA* mutations, capivasertib for patients with somatic *AKT/PTEN/PIK3CA* alterations, and elacestrant for patients with estrogen receptor 1 (*ESR1*) mutations. Moreover, the DESTINY-Breast06 trial confirmed the superiority of trastuzumab deruxtecan over standard of care after failure of ET, making it a promising new treatment option.[10-12]

Collecting clinical data after CDK4/6i could provide insights into clinicians' treatment choices. Novel treatments are often implemented in clinical practice without evidence on optimal sequencing. Real-world studies may help bridge this knowledge gap. The primary objective of this study is to describe the pattern and effectiveness of the therapeutic sequence following the failure of CDK4/6i-based therapies in first- or second-line treatment. Clinical outcomes, including time to next treatment (TTNT) and real-world progression-free survival (rwPFS), were evaluated.

MATERIALS AND METHODS

Study design

In this retrospective and prospective observational study, we evaluated the use of CDK4/6i in real-world clinical practice and the impact of subsequent treatments. The primary endpoints were TTNT[13,14] and rwPFS with CDK4/6i plus ET and in the post-CDK4/6i setting.

The secondary endpoints were real-world overall survival (rwOS) with CDK4/6i plus ET and in the post-CDK4/6i setting, occurrence of hematologic adverse events, and drug dose modification. The study continued until patient dropout (due to loss to follow-up or withdrawal of consent) or death from any cause. Subsequent lines of therapy were determined at the discretion of the investigators.

Study population

Patients meeting the following criteria from three national oncology centers were included in this study: age >18 years; HR-positive, HER2-negative aBC not amenable to surgery or curative radiotherapy; and receipt of CDK4/6i in combination with AIs or fulvestrant as first-line treatment or after failure of first-line hormone therapy. Written informed consent was also required. Exclusion criteria included: patients deemed unsuitable for treatment at the investigator discretion, patients unable to understand the purpose of the study, lack of informed written consent, and lack of prior treatment with CDK4/6i.

Data on disease and patient characteristics were collected from clinical charts and recorded in an electronic case report form (eCRF). Patients were followed for up to 5 years after their inclusion in the study, with a 3-year interim analysis already conducted. The clinical data were entered into a data capture system, and remote monitoring was carried out on the information reported in the electronic database.

Demographic and clinicopathological characteristics of the study population were extracted from patients' computerized medical records and entered into an anonymized database to ensure patient privacy. Side-effects and toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Ethical considerations

The 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 local ethical committee (EC) (reference number 754/2022). Although the study was observational, informed consent was obtained from patients who were alive and able to understand and sign a written statement of consent. This included consent to participate in drug-free clinical trials, the use of biological material for scientific purposes, and the processing of personal data, in compliance with the Privacy Law (Italian Legislative Decree No. 196/2003).

For patients who were deceased 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 (published in the Official Italian Gazette No. 72, 26 March 2012). Additionally, the study received approval from the local EC (Comitato Etico Area Vasta Emilia Nord, reference number 001282/20, dated 15 January 2020).

Statistical analysis

Patients' characteristics were presented using descriptive statistics including frequencies for categorical variables and median and range for continuous variables. Categorical variables were evaluated by chi-square test or Fisher's exact test when appropriate. Outcomes of interest were TTNT defined as the time between the date of first line of treatment and the date of subsequent treatment initiation, or the date of death, whichever occurred first,[13,14] rwPFS defined as the time between the initiation of second-line therapy until clinician-recorded progression (or death), and rwOS defined as the time from diagnosis to death/last follow-up. Patients who did not progress or die were considered censored at their last clinic visit. TTNT, rwPFS, and rwOS were estimated using the Kaplan—Meier method. Survival curves were compared using the log-rank test. Median duration of follow-up was estimated using the Kaplan—Meier method. All reported tests were two sided, and $P \leq 0.05$ was considered to indicate moderate strength of evidence against the null hypothesis. Statistical analyses were done using IBM SPSS Statistics for Windows Version 29.0 (IBM Corporation, Armonk, NY). All associations between the categorical variables were assessed using

Table 1. Patients' characteristics

Characteristics	*n* (%)
Median age (range)	66 (31-102)
≤65 years	146 (36)
BC histotype	
Ductal	277 (68)
Lobular	91 (22)
Other	32 (8)
NA	7 (2)
Surgery	
No	93 (23)
Yes	314 (77)
Stage at initial diagnosis	
I	59 (14.5)
II	110 (26.5)
III	104 (25)
IV	121 (31)
NA	13 (3)
Tumor grade	
1	9 (2)
2	195 (48)
3	108 (26)
NA	95 (24)
Ki-67	
Range	2-85
<20	188 (46)
≥20	182 (44)
NA	37 (10)
Hormone receptor status	
ER positive	376 (92)
Range	5-100
NA	31 (8)
PgR positive	390 (95)
Range	1-100
<50	136 (33)
≥50	204 (50)
NA	67 (17)
HER2	
0	187 (46)
1+	125 (31)
2+	47 (11)
3+	8 (2)
NA	40 (10)
Prior neo/adjuvant chemotherapy	
Neoadjuvant	35 (12)
Adjuvant	159 (12)
Type of chemotherapy	
Anthracycline + paclitaxel	103 (53.5)
Only anthracycline	30 (15.5)
Only Taxol	20 (10)
No anthracycline no Taxol	41 (21)
Adjuvant endocrine therapy	
Tamoxifen	70 (26)
Anastrozole	71 (27)
Letrozole	56 (23)
Exemestane	19 (7)
Tamoxifen –> AIs	21 (8)
Other	23 (9)
Adjuvant radiotherapy	
No	189 (48)
Yes	199 (52)
Metastatic disease	
De novo metastatic	121 (30)
Endocrine-sensitive relapse	180 (44)
Primary endocrine resistance	77 (19)
Secondary endocrine resistance	115 (28)
Visceral metastases	194 (48)
Sites of visceral metastases	
Liver	109 (56)
Lung	57 (30)
Other	28 (14)
Bone-only metastases	119 (29)
CNS metastases	11 (3)
Number of metastases sites	
1	181 (44)
2	131 (32)
3	69 (17)
>3	26 (7)
Biopsy of metastatic site	195 (48)
ECOG PS at first-line initiation	
0	185 (45)
1	204 (50)
2	17 (4)
3	1 (1)
First-line therapy	
CDK4/6i + ET	269 (66)
ET	99 (24)
CT	39 (10)
Type of therapy	
CDK4/6i + ET	269 (66)
AI	64 (16)
Fulvestrant	22 (5)
Tamoxifen	8 (2)
CT metronomic	4 (1)
Taxanes	19 (5)
Other CT	14 (3)
Capecitabine	2 (1)
Subsequent therapy after PD to first-line CDK4/6i	
CT	69 (67)
CDK4/6i	8 (8)
ET ± everolimus	26 (25)

AI, aromatase inhibitor; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; CNS, central nervous system; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; Ki-67, a marker of cell proliferation; NA, not available; PD, progressive disease; PgR, progesterone receptor.

Pearson's chi-square test or Fisher's exact test. The same Cox model enabled adjusted effect estimates of each predictor to be obtained by multivariate analysis of significant variables in the univariate analysis. The final model was defined according to the forward stepwise technique that involves an initial model in which the variable found to be most significant in univariate was considered; in the subsequent steps, the other predictors were entered each time in order of significance, considering a value of $P \leq 0.05$. The probabilities considered for the stepwise technique were 0.05 for insertion and 0.10 for removal. As for subgroup analysis, the variables investigated were age (<65 versus >65 years), previous adjuvant therapy (yes versus no), Eastern Cooperative Oncology Group (ECOG) performance status (PS 0-1 versus 2), expression of estrogen and progesterone receptor (>50% versus <50%), Ki-67 value (<20% versus >20%), HER2 (0 versus +1 and +2 not amplified), sites of disease (visceral versus other), number of sites of disease (1 versus >2), and type of CDK4/6i. A multivariate logistic regression model was developed using stepwise regression (forward selection, enter limit and remove limit, $P = 0.10$ and $P = 0.15$, respectively) to identify independent predictors. Data have been collected in a dedicated database program by the research team since the start of the CDK4/6i-based therapy. The database is owned by GOIRC. Before the study began, the participating

center and investigators received training on the protocol, the eCRF, study documents, and any potential study concerns. All changes made during the study were forwarded to the investigators to ensure the proper conduct of the study. All queries were investigated and managed in collaboration with the participating centers through the activities of the monitors. Monitoring visits have been made by monitors at the study start and at the end of study.

During on-site visits, verification of informed consent documentation, compliance with institutional review board/EC approval requirements, study correspondence, and the Site Master File was carried out. Furthermore, compliance with patient eligibility criteria, proper maintenance of records, completion of eCRFs, documentation of adverse events, transmission of serious adverse events, and identification of patients lost to follow-up were checked. Archiving of the study documents will be carried out according to GOIRC standard operating procedures.

This observational research was reported according to the European Society for Medical Oncology (ESMO)-Guidance for Reporting Oncology real-World evidence (GROW) guidelines and the checklists are reported in the Supplementary Material, available at https://doi.org/10.1016/j.esmorw.2025.100154.[15,16]

RESULTS

A total of 407 patients with HR-positive, HER2-negative aBC were identified between 13 January 2017 and 19 January 2023 in three participant centers. Two hundred and eighty-nine and 118 patients were enrolled in the retrospective and prospective parts of the study, respectively. Median follow-up was 38 months (range 34-41 months).

Baseline demographic characteristics and disease features of the patients are summarized in Table 1. Median age was 66 years (range 31-102 years), 68% had ductal carcinoma, and 30% had *de novo* aBC. Forty-eight percent of patients with relapsed disease were biopsied to confirm the aBC recurrence. Neoadjuvant and adjuvant therapies were received in 12% and 56% of patients, respectively, whereas ET was received in 91%. Fifty-two percent had received adjuvant radiotherapy.

CDK4/6i plus ET as first-line therapy

Main baseline characteristics of 269 (66%) patients who received CDK4/6i as first-line treatment were as follows: ECOG PS: 0 in 45% and 1 in 50%, 46% had visceral metastases, 32% had *de novo* aBC, 31% were endocrine sensitive, 9% had primary endocrine resistance, and 27% had secondary resistance. A total of 119 patients received palbociclib, 94 ribociclib, and 56 abemaciclib. After a median follow-up of 36 months (32-39 months), 117 patients progressed and 152 were still on CDK4/6i therapy. Median TTNT (mTTNT) in the group of patients receiving any CDK4/6i-based first-line therapy was 26 months [95% confidence interval (CI) 21-31 months] (Figure 1). The median rwPFS was also calculated and resulted superimposable to mTTNT: 26 months (95% CI 21-31 months). Ribociclib was associated

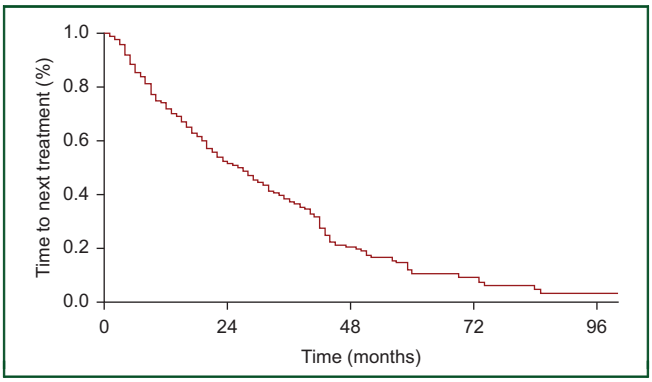

Figure 1. Time to next treatment for patients receiving a CDK4/6 regimen in the first-line cohort.
CDK4/6, cyclin-dependent kinase 4/6.

with higher mTTNT and rwPFS compared with palbociclib (mTTNT 36 versus 22 months, log-rank $P = 0.005$; rwPFS 36 versus 22 months, log-rank $P = 0.009$), and no difference was observed between ribociclib and abemaciclib (mTTNT 36 versus 27 months) (Figure 2). However, no difference was observed in terms of rwOS comparing the three CDK4/6i (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmorw.2025.100154). Treatment patterns according to endocrine sensitivity are shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmorw.2025.100154.

Treatment patterns and effectiveness after failure of first-line CDK4/6i plus ET

One hundred and three patients received second-line treatment, but second-line therapy data were available for 95 patients who received subsequent treatments as follows: 69 patients (67%) received CT, 8 (8%) switched to a different CDK4/6i and ET regimen, and 26 (25%) received ET with or without everolimus (Figure 3). The characteristics of patients according to the second-line type (CT versus CDK4/6i

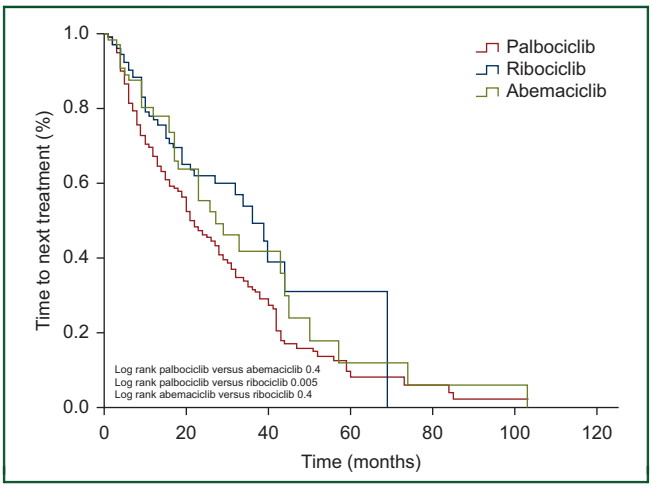

Figure 2. Time to next treatment for patients receiving a CDK4/6 regimen in the first-line cohort, split by type of drug.
CDK4/6, cyclin-dependent kinase 4/6.

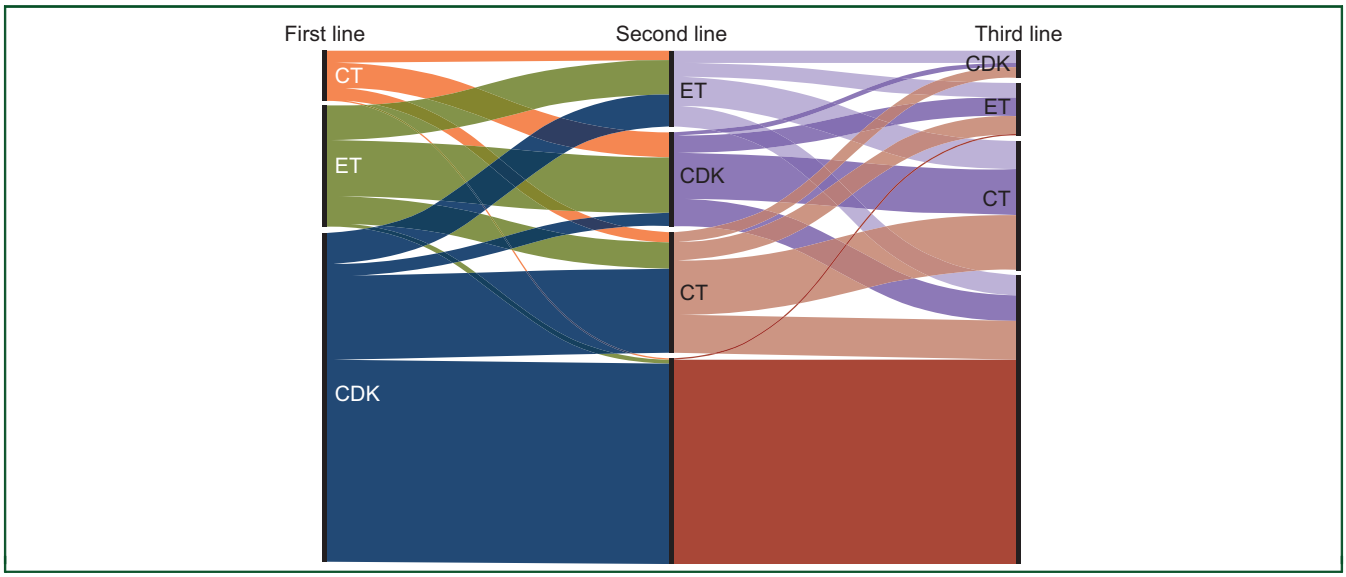

Figure 3. Alluvial plot of subsequent lines after first- or second-line CDK4/6i-based therapy.
CDK4/6, cyclin-dependent kinase 4/6; CT, chemotherapy; ET, endocrine therapy.

versus ET with or without everolimus) are illustrated in Table 2. The characteristics of patients were balanced among the three treatment groups. The overall mTTNT was 13 months (95% CI 9-16 months) (Figure 4): 24 months for CT (95% CI 17-30 months), 9.6 months for ET with or without everolimus (95% CI 6-11 months), and 15 months for CDK4/6-based regimen (95% CI 11-18 months). The most common CT type were taxanes (25/69, 36% of patients), followed by metronomic CT (20/69, 29%), other CT (15/69, 22%), and capecitabine (9/69, 13%). Among ET types, 13 of 26 patients (50%) received fulvestrant, 8 of 26 (31%) received exemestane and everolimus, and the remaining 5 (19%) received an AI or tamoxifen.

In a sub-analysis conducted to evaluate the SONIA trial findings,[17] we did not observe any differences in patients treated with upfront ET or CDK4/6i as first-line treatment in terms of PFS2 (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmorw.2025.100154), while we observed a difference in OS favoring ET ($P < 0.001$) (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmorw.2025.100154).

CDK4/6i plus ET as second-line therapy

Seventy-six patients started a second-line treatment with CDK4/6-based regimen: 52 patients received palbociclib, 9 ribociclib, and 15 abemaciclib. Fifty-five patients progressed and 12 are still ongoing at the time of analysis. Data on third line are available for 52 out of 55 patients.

Main baseline characteristics were as follows: ECOG PS: 0 in 38%, 1 in 57%, 2 in 5%. Visceral metastases were the main site of disease in 46% and bone only in 31%. Sixty-five percent were endocrine sensitive, 13% had primary endocrine resistance, and 20% had secondary resistance. Previous treatments were as follows: 61% received ET, 28% CT, and 11% CDK4/6-based regimen.

Univariate and multivariate analyses

In multivariate analysis, only the number of metastatic sites (>2 versus 1) was independently associated with lower TTNT and PFS in the first setting (HR 1.6, 95% CI 1.2-2.1, $P = 0.001$ and HR 1.4, 95% CI 1.1-1.9, $P = 0.01$), whereas palbociclib was associated with a worse TTNT in the first-line setting (HR 1.5, 95% CI 1.2-1.8, $P = 0.004$). Data are shown in Table 3 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmorw.2025.100154.

Adverse events and compliance to treatment with CDK4/6i treatment

Safety data of CDK4/6i were available for 401 patients. Overall, a first dose reduction of CDK4/6i was observed in 188 patients (47%), whereas a second dose reduction occurred in 54 patients (15%). Neutropenia was the most common toxicity reported, with 44% being grade 3 and 4. Febrile neutropenia occurred in 19 patients (5%). Grade 3 and 4 hepatic toxicities were observed in 8 patients (3%), grade 2 diarrhea in 21 (6%), and grade 3 and 4 in 3 and 2 patients (0.5% each). Grade 3 fatigue was reported in 13% of patients. Toxicities delayed drug recycling in 235 patients (63%). The mean number of cycles before dose reduction was five. Toxicity was the main reason of discontinuation in 9% and 6% of the patients in the first and second lines, respectively.

Table 4 presents the rates of treatment discontinuation and delays due to toxicity, stratified by CDK4/6i type and the principal toxicities observed.

DISCUSSION

The role of subsequent therapies following first- or second-line treatment with CDK4/6i -based therapy remains largely unexplored. Martin et al. reported patterns of systemic

Table 2. Patients' characteristics according to post-CDK4/6 inhibitor treatment

Type of therapy after CDK4/6 + ET	CT $n = 69$	ET ± everolimus $n = 26$	CDK4/6 + ET $n = 8$	*P* value
Median age at diagnosis (range), years	57 (26-82)	55 (36-77)	52 (39-75)	0.7
Histotype, *n* (%)				
Ductal	38 (55)	19 (73)	6 (75)	0.3
Lobular	25 (36)	5 (19)	0	0.2
Other	5 (7)	2 (8)	1 (12.5)	0.8
NA	1 (2)	—	1 (12.5)	
Stage IV *de novo* ($n = 100$), *n* (%)				
Yes	14/67 (21)	11/25 (44)	1/8 (12.5)	0.3
Sensitive endocrine relapse ($n = 98$), *n* (%)				
Yes	24/66 (36)	9/24 (37.5)	5/8 (62.5)	0.4
Primary endocrine resistance ($n = 97$), *n* (%)				
Yes	14/65 (21.5)	7/24 (29)	0	0.8
Secondary endocrine resistance ($n = 98$), *n* (%)				
Yes	24/65 (37)	7/25 (28)	3/8 (37.5)	0.8
Visceral metastases ($n = 98$), *n* (%)				
Yes	36/66 (55)	10/25 (40)	6/8 (75)	0.5
Sites of visceral metastases ($n = 53$), *n* (%)				
Liver	19/36 (53)	3/11 (27)	5/6 (83)	0.5
Lung	11/36 (30)	3/11 (27)	1/6 (17)	0.6
Other	6/36 (17)	5/11 (45)	0	0.2
Bone metastases ($n = 100$), *n* (%)				
Yes	17/68 (25)	7/24 (29)	1/8 (12.5)	0.3
CNS metastases, *n* (%)				
Yes	3/66 (4.5)	0	0	
Number of metastases sites, *n* (%)				
1	21/68 (31)	8/26 (31)	4/8 (50)	0.5
2	29/68 (43)	12/26 (46)	3/8 (37.5)	0.6
3	13/68 (19)	5/26(19)	0	
>3	3/68 (4)	1/26(4)	1/8 (12.5)	0.3
PFS with CDK4/6i plus ET, *n* (%)				
≤6 months	5 (10)	23 (17)	3 (19)	0.6
>6 months	21 (40)	46 (33)	5 (31)	0.8
≤12 months	11 (21)	40 (29)	4 (25)	0.7
>12 months	15 (29)	29 (21)	4 (25)	0.8
ECOG PS at second line starting, *n* (%)				
0	18 (26)	13 (50)	3 (37.5)	0.6
1	42 (61)	9 (35)	5 (62.5)	0.2
2	9 (13)	4 (15)	0	0.6
Type of therapy				
AI	0	3	0	
Fulvestrant	0	8	0	
Tamoxifen	0	2	0	
CT metronomic	20	0	0	
Taxanes	25	0	0	
Everolimus	0	13	0	
Other CT	15	0	0	
CDK4/6i + ET	0	0	8	
Capecitabine	9	0	0	

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; CNS, central nervous system; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; ET ± everolimus, endocrine therapy with or without everolimus; NA, not available/not applicable; PFS, progression-free survival.

therapies used after progression on first-line treatment,[18] while Sawaki et al. reported subsequent therapies after palbociclib in a Japanese real-world setting.[19] In our research, we explored treatment patterns following both first- and second-line CDK4/6i-based therapies. TTNT was used as the primary endpoint in this analysis. TTNT has emerged as a relevant alternative clinical endpoint, reflecting the outcome of a therapeutic decision, as treatment changes typically occur in response to a real change in the patient's status.[13,14,20-22] Our analysis showed comparable TTNT and rwPFS results, confirming the appropriateness of this new statistical endpoint for real-world studies of first-line treatments. The outcomes observed in the subsequent lines of treatment in our study appear longer than those reported by Sawaki et al.,[19] which had a median follow-up of 11 months, compared with 36 months in our study population. Time to treatment failure (TTF) was the endpoint calculated in the Sawaki et al.'s study, reporting 7.5 and 7.4 months, respectively, for patients receiving first and second subsequent therapy after palbociclib-based therapy.[19] In the Sawaki et al.'s study, ∼30% of patients continued palbociclib-based therapy, subsequently transitioning to other ETs as their first subsequent treatment, with a median TTF of 10.9 months. In contrast, the median TTF for ET alone was 4.4 months, and for everolimus-based therapy, it was 6.1 months.[19]

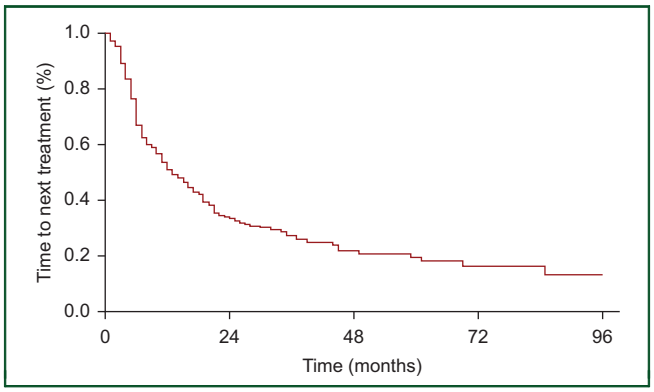

Figure 4. Time to next treatment for patients receiving a second-line therapy after a CDK4/6-based first-line regimen.
CDK4/6, cyclin-dependent kinase 4/6.

Martin et al. observed that 36% of patients treated with a CDK4/6i-based therapy as first-line treatment received a different CDK4/6i as subsequent lines, often in conjunction with ET switching, resulting in an rwPFS of 8.25 months. In contrast, 29% of patients received CT, 10% received ET alone, and 11% received everolimus-based therapy, with rwPFS of 3.74, 3.25, and 3.32 months, respectively. In our study, switching CDK4/6i and the ET companion confirmed the outcomes reported by Martin et al. and Sawaki et al., with an mTTNT of 10 months, supporting the results of the PostMONARCH and MAINTAIN trials.[23,24] Although CDK4/6i treatment beyond progression has demonstrated an advantage in PFS, these trials lack a direct comparison with CT. The outcomes observed for CT in the second-line setting vary significantly and have been minimally explored in real-world settings. In our study, we observed a longer mTTNT of 24 months in patients receiving CT as subsequent treatment in the second-line setting. The observed differences compared with other studies can be attributed to the historical period in which our study began, when CT was the primary salvage treatment after CDK4/6i therapy. Additionally, the smaller number of patients receiving CT in our study (67 compared with 240 in the Martin et al.'s study) and our longer follow-up period may contribute to the discrepancies between the two studies. A recent meta-analysis on the effectiveness of second-line treatments following a CDK4/6i-based regimen confirmed the role of CDK4/6i, including with continued therapy or switching the endocrine companion.[25] Thirty-four percent of the patients included in this analysis received CDK4/6i and ET, with 30% switching to another CDK4/6i. The PFS was longer compared with other treatment choices; however, an *ESR1* or *PIK3CA* mutation status was associated with shorter PFS compared with the wild-type population.[25]

With the availability of brand-new treatments, the landscape of subsequent therapy effectiveness has rapidly changed, and all available guidelines now incorporate treatment options following a CDK4/6i-based regimen.[26,27]

Looking at the other 'older' treatments available, everolimus-based therapy could still represent a reasonable choice for patients lacking targetable mutations.

Conclusions

Exploring subsequent treatments will help us better address a tailored strategy in the management of aBC. Our study explored treatment patterns following CDK4/6i therapy in a time period with a lack of targetable therapies. The findings underscore the variability in subsequent treatment efficacy and highlight the need for personalized strategies. Further research is warranted to optimize therapeutic sequences.

Table 3. Univariate and multivariate analyses for TNTT in the first-line setting

Factor	Status	Univariate TTNT		Multivariate TTNT	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	≤65 years	1.00		1.00	0.3
	>65 years	1.5 (1-2)	0.055	0.8 (0.6-1.1)	
Adjuvant therapy	No	1.00			
	Yes	0.7 (0.4-1.05)	0.07		
Performance status	0	1.00			
	≥1	0.9 (0.6-1.3)	0.73		
Sites of disease	Visceral disease	1.00			
	Bone marrow disease	0.9 (0.5-1.4)	0.72		
ER/PgR	<50%	1.00			
	≥50%	0.7 (0.5-1)	0.11		
Ki-67	<20%	1.00		1.00	
	≥20%	1.3 (1-2)	0.05	1.2 (0.9-1.6)	0.1
HER2	0	1.00			
	+1	0.6 (0.4-1.1)	0.1		
	+2	0.9 (0.7-1.5)	0.09		
Number of disease sites	1	1.00		1.00	
	≥2	1.7 (1-2.8)	0.03	1.6 (1.2-2.1)	0.001
Type of CDK4/6i	Ribociclib	1.00		1.00	
	Palbociclib	1.4 (1.1-1.8)	0.02	1.5 (1.2-1.8)	0.04
	Abemaciclib	1.1 (0.8-1.3)	0.8		

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; TTNT, time to next treatment.

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Table 4. Toxicity-related treatment discontinuation and delay rates, by CDK4/6i type and observed principal toxicities

	Patients	*n* (%)	Palbociclib	Ribociclib	Abemaciclib	*P* value
First dose reduction	401					
Yes		188 (47)	105 (56)	51 (27)	32 (17)	0.001
Delay for toxicity	374					
Yes		235 (63)	138 (59)	67 (28)	30 (13)	0.03
Neutropenia	371					
NR		116 (31)	55 (26)	26 (24)	35 (60)	0.002
G1		10 (2)	6 (3)	3 (2)	1 (2)	0.6
G2		50 (11)	21 (10)	19 (18)	10 (17)	0.02 (P versus A)
G3		151 (34)	92 (44)	47 (44)	12 (21)	0.02 (P versus A)
G4		44 (10)	33 (10)	11 (10)	0	0.3
Febrile neutropenia	374					
Yes		19 (5)	12 (8)	6 (9)	1 (3)	0.008 (P versus A)
Thrombocytopenia	368					
NR		304 (83)	170 (83)	87 (83)	47 (80)	0.3
G1		37 (10)	20 (10)	12 (11)	5 (9)	0.3
G2		16 (4)	7 (3)	5 (5)	4 (7)	0.2
G3		8 (2)	4 (2.5)	1 (1)	3 (5)	0.2
G4		3 (1)	3 (1.5)	0	0	
Diarrhea	361					
NR		283 (78)	169 (82)	67 (68)	47 (81)	0.3
G1		53 (15)	22 (11)	24 (24)	7 (12)	0.1
G2		21 (6)	12 (6)	5 (6)	4 (7)	0.2
G3		3 (0.5)	1 (0.5)	1 (1)	0	0.3
G4		2 (0.5)	1 (0.5)	1 (1)	0	0.3
Hepatic toxicity	368					
NR		310 (84)	175 (85)	85 (81)	50 (86)	0.3
G1		39 (10)	23 (11)	12 (11)	4 (7)	0.2
G2		11 (3)	4 (2.5)	5 (5)	2 (3)	0.2
G3		6 (2)	3 (1.5)	2 (2)	1 (2)	0.2
G4		2 (1)	0	1 (1)	1 (2)	0.2
Fatigue	366					
NR		197 (54)	96 (47)	65 (66)	36 (60)	0.3
G1		118 (32)	80 (39)	22 (22)	16 (27)	0.3
G2		47 (13)	28 (13)	10 (10)	8 (13)	0.3
G3		4 (1)	2 (1)	2 (4)	0	0.3

A, abemaciclib; **G1, G2, G3, G4,** grade 1, 2, 3, 4 (Common Terminology Criteria for Adverse Events toxicity grading); **NR,** not reported; **P,** palbociclib; **R,** ribociclib.

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