

Real-world patterns of post-progression treatment and outcomes in patients with HR+/HER2– advanced breast cancer treated with CDK4/6 inhibitors

Rosalba Torrisi^{1,*}, Federica Giugliano^{2,3}, Laura Giordano¹, Giuseppe Saltalamacchia¹, Flavia Jacobs¹, Ambra Carnevale Schianca^{2,3}, Monica Milano⁴, Nadia Bianco⁴, Claudia Anna Sangalli⁵, Rita De Sanctis^{1,6}, Giovanna Masci¹, Giuseppe Curigliano^{2,3}, Armando Santoro^{1,6}, Elisabetta Munzone⁴

¹Medical Oncology and Hematology Unit, Humanitas Research Hospital IRCCS, Rozzano, MI 20089, Italy

²Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, 20141 Milan, Italy

³Department of Oncology and Hemato-Oncology, University of Milan, Milan 20122, Italy

⁴Division of Medical Senology, European Institute of Oncology, IRCCS, Milan 20141, Italy

⁵Scientific Direction, European Institute of Oncology, IRCCS, Milan 20141, Italy

⁶Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, MI 20072, Italy

*Corresponding author: Rosalba Torrisi, MD, Medical Oncology and Hematology Unit, Humanitas Research Hospital IRCCS, viale Manzoni 56, Rozzano, MI 20089, Italy (rosalba.torrisi@gmail.com).

Abstract

Patients and methods: we retrospectively collected data of patients with HR+/HER2– advanced breast cancer (ABC) treated with endocrine therapy (ET) and a CDK4/6 inhibitor (CDK4/6i) aiming to describe the patterns of post-progression outcomes.

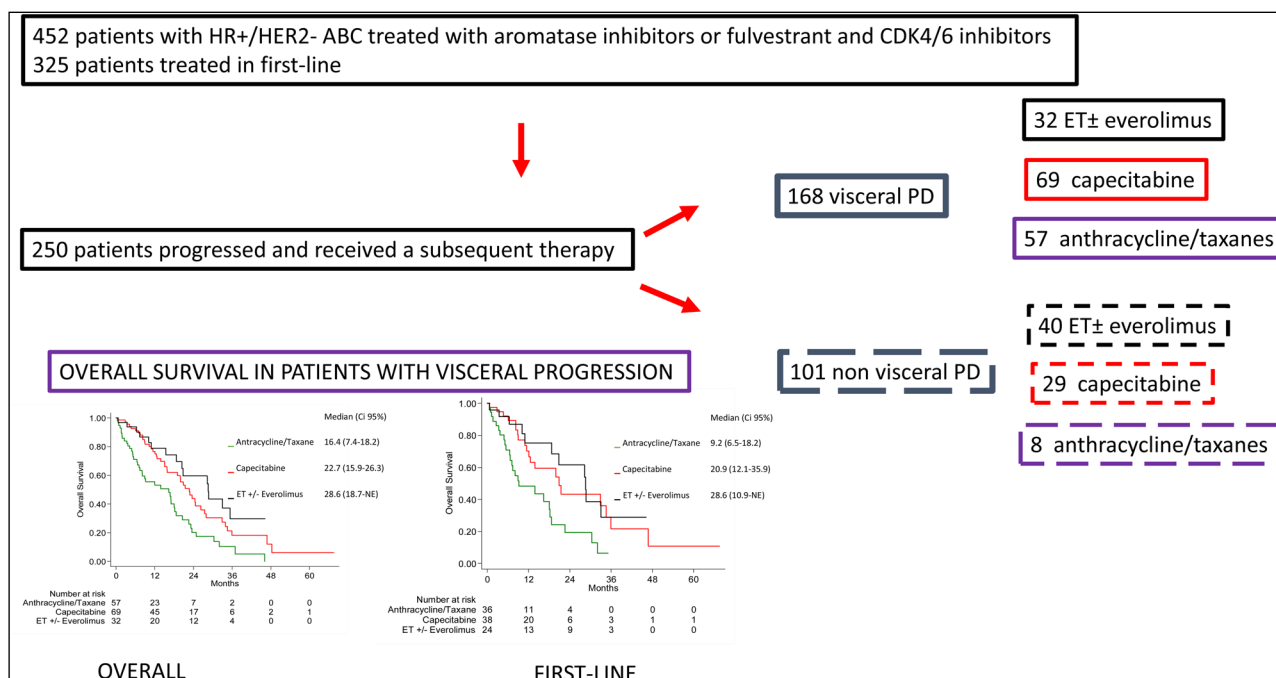
Results: Among 452 evaluable patients 325 were treated in the first-line setting. Median progression-free survival (mPFS) was 22.8 months overall and 29.7 months in patients treated in first-line setting. Factors associated with outcomes in multivariate analysis were the line of CDK4/6i therapy, *de novo* vs recurrent disease, visceral vs bone-only metastases, and primary endocrine resistance.

A total of 300 patients progressed and 250 overall and 156 in the first-line cohort received a subsequent treatment. Visceral progression and CDK4/6i duration <12 months were associated with a higher likelihood of receiving anthracycline or taxanes (AT) as compared to ET ± everolimus (EET). Post-progression PFS (PPFS) and post-progression OS (PPOS) were statistically significantly better with EET and capecitabine (C) over AT overall and in patients with visceral progression. Multivariate analysis confirmed a significant advantage for EET and C, while visceral progression retained a significant impact only on PPOS. After progression to the first post-CDK4/6i treatment C obtained a significant better PPOS as compared to other treatments.

Conclusion: We showed in a large real-world series that most patients with HR+/HER2– ABC failing CDK4/6i and ET unselected for the occurrence of molecular mutations retain endocrine sensitivity and may benefit of a subsequent ET ± a targeted therapy delaying the need for chemotherapy regardless of site of progression and prior CDK4/6i therapy duration.

Key words: HR+/HER2 negative advanced breast cancer; CDK4/6 inhibitors; post-CDK4/6 inhibitors treatment; post-progression outcomes.

Graphical abstract



Implications for Practice

No definite recommendations for treatment of HR+/HER2- advanced breast cancer after endocrine therapy (ET) plus CDK4/6 inhibitors (CDK4/6i) in absence of actionable mutations exist.

Our results show in a real-world series that most patients with HR+/HER2- ABC failing therapy with CDK4/6i and ET unselected for the occurrence of molecular mutations retain endocrine sensitivity and derive a meaningful clinical benefit from a subsequent endocrine manipulation ± everolimus delaying the need for chemotherapy regardless of site of progression and CDK4/6i therapy duration. These findings support a beneficial role for extending endocrine therapies in routine clinical practice when actionable mutations are not detected or not evaluable.

Introduction

Approximately 80% of breast cancers are hormone receptor positive HER2 negative (HR+/HER2-).¹ The combination of endocrine therapy (ET) and CDK4/6 inhibitors (CDK4/6i) is the cornerstone of treatment for HR+/HER2- advanced breast cancer (ABC),^{2,3} having consistently doubled progression free survival (PFS) and prolonged overall survival (OS) in some settings.⁴⁻⁹

On the other hand, no definite recommendations on post-progression treatments exist since multiple mechanisms of resistance to CDK4/6i have been proposed and results with single treatments after CDK4/6i failure are lacking.⁴⁻¹¹

Randomized clinical trials (RCTs) have shown that in patients with actionable molecular alterations further endocrine manipulations as oral Selective Estrogen Degraders (SERDs) like elacestrant and camizestrant for patients with *ESR1* mutations^{12,13} or *PI3KCA/AKT/mTOR* inhibitors as capivasertib, inavolisib, alpelisib for patients with mutations of that pathway are highly active.¹⁴⁻¹⁷

In the present retrospective study we collected patterns of progression and post-progression outcomes in terms of post-progression PFS (PPFS or PFS2) and post-progression OS (PPOS) in patients treated with CDK4/6i in routine clinical

practice at two large-volume Institutions in order to describe treatment choice after progression and clinical features driving clinician's choice and affecting outcomes.

Patients and methods

A retrospective series of patients with HR+/HER2- ABC who received the combination of ET and CDK4/6i as part of their routine treatment at two Italian institutions from January 2016 to March 2023 was included (data cut off: September 30, 2024).

Eligible patients had received treatment with ET and CDK4/6i for at least 1-yr or had progressed before completing 1-yr of treatment; patients treated beyond the third-line were excluded in order to comply with current treatment guidelines and regulatory approvals of drugs.

All patients included in the study had advanced breast cancer at treatment initiation, defined as locally advanced disease not amenable to curative treatment and/or distant metastases. Approximately one-third of patients presented with *de novo* metastatic disease. Thereafter, any subsequent change in disease status was classified as progression, which was further categorized—for clinical purposes—as visceral or non-visceral progression.

Timelines of drug reimbursement by the Italian National Health System, evidence from randomized clinical trials available at the time of treatment start for specific features as menopausal and endocrine resistance status and expected tolerability according to comorbidities were the main determinants guiding the choice of CDK4/6i.

Patients were monitored at about 3-month intervals or less when progressive disease was suspected. CT scans, 18-FDG PET or MRI were used for monitoring disease according to the baseline modality used. Clinical examination was performed alternatively in case of skin involvement.

The objectives of the study were to describe in a real-world setting the patterns of progression and the post-progression outcomes (PPFS or PFS2 and PPOS) and whether clinical and pathological features as site of progression and duration of therapy with CDK4/6i affected treatment choice and outcomes.

Since this was a retrospective study response according to RECIST 1.1 criteria was not feasible in all patients, but CT scans and other imaging were reviewed in order to comply with RECIST 1.1 criteria whenever possible. Information on age at diagnosis, menopausal status at time of initiation of CDK4/6i, previous adjuvant therapies, number and response to previous therapies for metastatic disease, pathological features of primary and metastatic tumor when available, endocrine resistance, sites of metastatic disease at time of CDK 4/6i initiation, best response with ET+ CDK4/6i, site of disease progression if occurred, treatments and outcomes after progression and last follow-up visit were collected.

Endocrine resistance was defined according to the classical criteria¹⁸; we further distinguished patients who had never received ET as endocrine-naïve from endocrine-sensitive to investigate differences in outcomes according to some literature evidence which suggested better outcomes in patients diagnosed with *de novo* MBC reviewed in Torrisi et al.¹⁹

This study was approved by the institutional ethical committee of the coordinating center (Humanitas Research Hospital) and of the other participating Institution (European Institute of Oncology). All patients signed an informed consent. The study was conducted in compliance with Helsinki Declaration. The ESMO GROW criteria were followed in reporting the results of this study.²⁰

Statistical considerations

The study was planned as a retrospective evaluation of post-progression treatments of patients who had progressed on the combination of ET and CDK4/6i in a consecutive series of HR+/HER2- ABC patients.

Progression-free survival was defined as the time from the first day of treatment with ER and CDK4/6i to disease progression. Post Progression-Free Survival (PPFS or PFS2) was defined as the time from the first day of post-CDK 4/6i treatment until disease progression, as shown by radiological or clinical examination, or death from any cause. Patients without any evidence of progressive disease were censored at the date of their last follow-up. Post-progression curves were also analyzed by pattern of progression (visceral vs not visceral), type of therapy (ET or ET+ targeted therapy vs chemotherapy) CDK4/6i, and CDK4/6i treatment duration.

Progression after PFS2 (ie, after the first post-CDK 4/6i treatment) was defined as second progression or Post progression free survival 2(PPFS2). Patients without any evidence of

progressive disease were censored at the date of their last follow-up. Post-progression curves were also analyzed by pattern of progression (visceral vs not visceral), type of therapy (ET or ET+ targeted therapy vs chemotherapy) CDK4/6i, and CDK4/6i treatment duration.

Survival curves were estimated using the Kaplan–Meier method. The impact of potential confounding factors, such as the pattern of progression (visceral vs. non-visceral), type of therapy (ET or ET + targeted therapy vs. chemotherapy), and the specific CDK4/6 inhibitor administered, was assessed. If a statistically significant effect was observed, these factors were included in the multivariable model. Differences between subgroups were analyzed using the log-rank test or the Cox proportional hazards model. Statistical significance was set at 0.050. Data were analyzed using SAS software version 9.4.

Results

A total of 452 consecutive patients were evaluable for analysis. Table 1 summarizes baseline patient characteristics.

154 (34.1%) patients had *de novo* metastatic disease and 298 (65.9%) had recurrent disease with a median disease-free interval of 72 months (range 3-375). 328 patients were post-menopausal at diagnosis, 121 were pre-perimenopausal and 3 patients were male. 219 (48.5%) patients had HER2=0 and 176 (38.9%) had HER2-low (e.g. immunohistochemical score of 1+ and 2+ without gene amplification) tumors assessed in primary tumors. 239 (52.9%) patients had visceral metastases and 117 (25.9%) had bone-only disease. 325 patients (71.9%) received ET + CDK4/6i as first-line line treatment, 85 and 42 as second- and third- line (mostly palbociclib). More than half of patients (54.7%) received palbociclib, 28.3% ribociclib and 17% abemaciclib. Palbociclib was the preferred CDK4/6i also among patients treated in first-line (43.1%) vs ribociclib (35.7%) and abemaciclib (21.2%), probably reflecting the timing of drug approvals. Aromatase inhibitors and fulvestrant were the endocrine agents in 53.1% and 46.9% of patients, respectively. Most patients had an ECOG PS = 0.

In the first-line cohort ribociclib was prescribed more frequently to patients with *de novo* as compared to those with recurrent disease (49.6 vs 28.10%) and to patients with endocrine-sensitive tumors (48% in endocrine-naïve vs 13.2% in primary endocrine resistant tumors), oppositely to abemaciclib which was more commonly prescribed to patients with endocrine-resistant tumors (39.5% in primary endocrine resistant vs 13% in endocrine naïve tumors, respectively). Regarding the association with endocrine partner, ribociclib was used almost exclusively combined with aromatase inhibitors differently from abemaciclib and palbociclib. No significant association between choice of CDK4/6i and disease status at diagnosis (bone-only vs visceral disease) was observed.

Outcomes with CDK4/6i and ET

Outcomes with CDK4/6i and ET are summarized in Table S1 (see online supplementary material). Median follow-up was 43.6 months (1.5-88.3).

mPFS was 22.8 months overall and 29.7 months in patients treated in first-line line. PFS was significantly longer in *de novo* metastatic as compared with recurrent disease either overall (31.5 vs 18.8 months, $P > .0001$) and patients treated in first-line (34.4 vs 25.1 months, $P = .004$). Similarly, patients with bone-only disease had a significantly longer PFS as

Table 1. Patient and tumor characteristics.

	Overall	First-line treated
	N (%)	N (%)
N patients	452	325
Age years mean (range)	58 (20-91)	59 (20-91)
MBC		
De novo	154 (34.1)	115 (35.4)
Recurrent	298 (65.9)	210 (64.6)
Menopausal status		
Pre-perimenopausal	121 (26.8)	92 (28.3)
Postmenopausal	328 (72.6)	232 (71.4)
Not applicable (male patients)	3 (0.7)	1 (0.30)
HER2 status		
HER2 0	219 (48.5)	157 (48.3)
HER2 low	176 (38.9)	133 (40.9)
Missing	57 (12.6)	35 (10.7)
Previous chemotherapy for MBC	54 (12)	/
Previous endocrine therapy		
Adjuvant	275 (60.8)	194 (59.7%)
MBC	103 (22.8)	/
Missing		32 (9.9)
Visceral disease	239 (52.9)	155 (47.7%)
Bone-only disease	117 (25.9)	92 (28.3%)
Biopsy	363	267
Breast	90 (24.8%)	77 (25.1)
Metastatic sites	273 (75.2)	190 (71.2)
Endocrine resistance		
Naïve	131 (29)	123 (37.9)
Hormone sensitive	100 (22.1)	89 (27.4)
Primary resistance	53 (11.7)	38 (11.7)
Secondary resistance	151 (33.4)	74 (22.8)
Missing	17 (3.8)	1 (0.30)
CDK 4/6i line of therapy		
1st	325 (71.9)	/
2nd	85 (18.8)	/
3rd	42 (9.3)	/
CDK 4/6 i		
Abemaciclib	77 (17)	69 (21.2)
Palbociclib	247 (54.7)	140 (43.1)
Ribociclib	128 (28.3)	116 (35.7)
Endocrine agent		
Aromatase inhibitors	240 (53.1)	220 (67.7)
Fulvestrant	212 (46.9)	105 (32.3)
ECOG PS		
0	328 (72.6)	236 (72.6)
≥1	124 (27.4)	89 (27.4)
Treatment at PD		
Everolimus + Exemestane	50 (20)	31 (19.9)
Endocrine therapy	22 (8.8)	22 (14.1)
Capecitabine	97 (38.8)	54 (34.6)
Taxanes	50 (20)	42 (26.9)
Anthracycline	15 (6)	5 (3.2)
Other therapies	10 (2.5)	3 (1.9)
Protocols	6 (2.4)	5 (3.2)

MBC, metastatic breast cancer; CDK4/6i cyclin-dependent kinase 4/6 inhibitors; PS, performance status; PD, progressive disease.

compared to those with visceral involvement (32.2 vs 16.1 months, $P = .0002$ overall and 34.4 vs 20.3 months, $P = .0009$ in patients treated in first-line). PFS was doubled with aromatase inhibitors vs fulvestrant, either overall and in patients treated upfront (33.3 vs 15.7 months, and 33.3 vs 17.5 months, respectively, $P < .0001$ in both cases). This finding

could be biased since the majority of patients receiving fulvestrant had endocrine-resistant disease as compared to those receiving aromatase inhibitors (10.5% vs 91.8% of patients with endocrine-naïve and -sensitive tumors in the fulvestrant vs the aromatase inhibitors cohort, respectively).

In patients treated in first-line a statistically significant difference was observed across the three CDK4/6i. Head-to-head comparisons showed only a trend for statistically longer PFS favoring ribociclib vs palbociclib ($P = .06$), while OS did not differ either overall and in head-to-head comparisons with palbociclib obtaining a numerically longer OS (Table S1 and Figure S1—see online supplementary material).

No statistically significant difference in PFS was observed in patients with HER2=0 vs HER2-low tumors either overall (median 23.2 vs 20.9 months) and in patients treated in first-line (median 29.8 vs 29.7 months).

Overall survival (OS) results showed a statistically significant difference favouring patients with bone-only disease and non-endocrine resistant disease in both cohorts (Table S1—see online supplementary material). Patients with secondary endocrine-resistant tumors performed significantly better than those with primary endocrine-resistant tumors ($P = .011$ and $P < .0001$ overall and in patients treated in first-line, respectively). No difference among CDK4/6i either overall and in head-to-head comparisons was observed with palbociclib obtaining a numerically longer OS than abemaciclib and ribociclib (Table S1—see online supplementary material). HER2 expression (0 vs low) was not associated with OS (data not shown).

Multivariable analysis of PFS showed a significant effect only for the line of therapy of CDK4/6i (later lines vs first line) (hazard ratio (HR) = 1.35 95% confidence intervals (CI) 1.08-1.68, $P = .009$), for *de novo* vs recurrent metastatic disease (HR= 0.62, 95% CI 0.41-0.923, $P = .019$) and for visceral vs bone-only disease at baseline (HR=1.64, 95% CI 1.23-2.18, $P < .001$) (Table S2—see online supplementary material).

In multivariable analysis of OS only the presence of visceral vs bone-only metastases (HR=2.38, 95% CI 1.60-3.51, $P < .001$) and of primary endocrine resistance (HR=2.79, 95% CI 1.72-4.53, $P < .001$) vs no previous ET maintained a significant effect, while the line of CDK4/6i therapy had only a borderline effect (HR=1.29, 95% CI 1.0-1.65, $P = .050$) (Table S2—see online supplementary material).

In patients treated in first-line significant prognostic factors of PFS included visceral vs bone-only disease (HR=1.76, 95% CI 1.26-2.47, $P = .001$) and both primary (HR=2.21, 95% CI 0.41-3.47, $P \leq .001$) and secondary endocrine resistance (HR=2.26, 95% CI 1.56-3.27, $P < .001$) vs no prior ET. In multivariate analysis of OS only visceral metastases (HR=1.70, 95% CI 1.08-2.67, $P = .022$) and primary endocrine resistance (HR=3.04, 95% CI 1.76-5.24, $P < .001$) maintained a significant prognostic effect (Table S2—see online supplementary material).

Outcomes after progression to ET and CDK4/6i

Table 2 summarizes results after progression to CDK4/6i and ET.

Among 300 patients with progressive disease (PD) 250 patients (156 patients treated in first-line) received a treatment after PD. 40 patients were not deemed candidate for further systemic therapies, and no further information was available for 10 patients. PD was mostly visceral (168 overall and 101 in patients treated in first-line) vs non visceral (79 and 54, in the 2 groups, respectively).

The most common post-CDK4/6i treatment was capecitabine either alone or in combination with vinorelbine and cyclophosphamide in standard or metronomic schedule (38.8% and 34.6% overall and in patients treated in first-line, respectively), followed by taxanes (20% and 26.9% in the 2 cohorts), the combination of exemestane and everolimus (20% and 9.5%), endocrine single agent (mostly fulvestrant) (7.7% and 6.7%) and anthracycline-based regimen (6% and 1.5%) (Table 1). In addition, 10 patients received miscellaneous drugs (other cytotoxic agents, trastuzumab-deruxtecan and PARP inhibitors) and 6 patients were treated within experimental protocols.

Median PPFS (PFS2) with the first post-CDK4/6i therapy was 5.7 months (95% CI 5.1-6.9) overall and 5.7 months (95% CI 4.3-8.1) in patients receiving CDK4/6i in first-line. Post-progression treatment (excluding the 16 patients treated with miscellaneous and experimental drugs) was the only factor associated with longer PPFS ($P < .001$ overall and $P < .05$ in patients treated in first-line). Importantly, no difference was observed also in patients progressing at visceral sites vs not, while post-progression overall survival (PPOS) was significantly shorter in patients with visceral progression either overall and in patients receiving CDK4/6i upfront (median 20 vs 29.2 months $P \leq .001$ and median 19.9 vs 28 months $P < .02$, respectively) (Table 2).

CDK4/6i treatment duration either as continuous and a categorized variable ($\geq$ and < 12 months), was statistically significantly associated only with PPOS (HR = 0.98, 95% CI 0.97-1.00 $P = .042$). Median PPOS was 19.9 months (15-23.6) and 27.9 (20.4-31.6) in patients who had been treated with CDK4/6i < 12 and ≥ 12 months ($P = .018$).

When all post-CDK4/6i treatments, excluding the 16 patients treated with miscellaneous and experimental drugs, were considered a significant difference in PPFS was observed either overall and in patients treated in first-line ($P < .001$ and $P < .05$, respectively). PPOS too was statistically significantly different among treatments either overall and in the cohort of patients treated upfront ($P < .001$ for both comparisons) (Table 2, Figure S2—see online supplementary material for a color version of this figure).

Outcomes according to first post-CDK4/6i treatments

In order to obtain information on the outcomes for different first post-CDK4/6i treatments we increased the size of each treatment group by combining patients receiving similar therapies namely exemestane and everolimus and ET (EET $n = 72$) and those receiving anthracyclines and/or taxanes (AT) ($n = 65$) to be compared with the group of patients treated with capecitabine-based regimens (C) ($n = 97$).

Treatments according to type of progression (visceral vs not visceral) and treatment duration with CDK4/6i and ET (< 12 months vs ≥ 12 months) are reported in Figures S3 and S4 (see online supplementary material for a color version of these figures). Patients treated with AT were more likely to have experienced visceral progression and a CDK4/6i treatment duration < 12 months, oppositely to those in the EET group, while in the C group the two features were similarly distributed.

mPPFS (mPFS2) was 5.6 months (95% CI 4.3-6.9) in the EET group, 7.5 months (95% CI 5.5-8.5) in the C group and 4.3 (95% CI 2.9-5.5) in the AT group. While no difference was observed between EET and C groups both showed a statistically significantly prolonged PPFS as compared to the AT group ($P < .003$ and $P < .0001$, respectively) (Table 3, Figure 1A).

mPPOS was 32.5 months (95% CI 27.9-NE) in the EET and 24.5 months (95% CI 19-28) in the C group with a trend for a significant difference favoring the EET group ($P = .064$), while it was significantly shorter in the AT group (16.4 months 95% CI 8.1-18.7) as compared to the former groups ($P < .001$ for both comparisons) (Table 3 and Figure 1A).

Comparable results were observed in the cohort of patients treated in first-line (Table 3 and Figure 1B).

Since the choice of subsequent treatments was affected by the site of progression (Figure S3—see online supplementary material for a color version of this figure), we performed the same analyses separately in patients with visceral progression. mPPFS (mPFS2) was 5.4 months (95% CI 3.6-9) in the EET, 7.6 months (95% CI 5.6-9) in the C and 4.3 months (95% CI 2.8-5.5) in AT groups, respectively confirming the statistically significant inferiority of the latter group as compared with EET and C ($P = .037$ and $P < .001$, respectively) while no difference was observed between EET and C (Table 3 and Figure 2A).

mPPOS was 28.6 months (95% CI 18.7-NE) in the EET group and 22.7 (95% CI 15.9-26.13) in the C group both statistically significantly longer than the 16.4 months (95% CI 7.4-18.2) of the AT group ($P < .001$ and $P = .002$, respectively) (Table 3 and Figure 2A).

In the cohort of patients with visceral progression treated in first-line only C resulted in a statistically significantly better PPFS than AT ($P = .007$), while a not significant trend favoured EET over AT ($P = .058$). No difference between EET and C was shown (Table 4 and Figure 2B). On the other hand, an improved PPOS for either EET and C over AT ($P = .006$ and $P = .008$, respectively) with no difference between the two former groups was shown (Table 3 and Figure 2B).

CDK4/6i treatment duration did not significantly differ in the 3 post-CDK4/6i treatment groups (EET = 23.6 months, 95% CI 20-27; C = 15.1 months, 95% CI 12.7-17.1; AT = 13 months, 95% CI 10.1-15.9, $P = 0.53$).

Results of multivariable analysis of PPFS and PPOS are reported in Table 4. Only post-progression treatment showed a significant effect on all outcomes, while the occurrence of visceral progression maintained a significant independent prognostic effect only on overall PPOS. CDK4/6i treatment duration was not significantly associated with both outcomes regardless it was considered as a continuous or a categorized variable. In the group of patients who had been on treatment with CDK4/6i < 12 months EET and C still performed statistically significantly better than AT for both PPFS (median 6.8, 7.3 and 3.8 months, respectively, $P < .001$) and PPOS (median 42, 23.7 and 12 months, respectively, $P < .001$).

Outcomes after progression to the first post-CDK 4/6i treatment

A total of 179 patients experienced a progression after the first post-CDK4/6i treatment and 172 received a subsequent systemic treatment. Chemotherapy was the preferred treatment: AT in 36.6% of patients followed by C regimens 33.1% while 8.7% of patients received endocrine± targeted therapies. Remaining patients (about 21%) received miscellaneous treatments.

Median post progression free-survival 2 (mPPFS2) was 5.2 months (95% CI 4.4-5.7). No difference among the 3 groups of treatment was observed either overall and in patients treated upfront: 5.8 months (95% CI 4.1-8.1) and 5.8 months (95% CI 4.1-11.2) for C; 4.4 months (95% CI 2.4-8.3) and 4.1

Table 2. Results after progression on CDK 4/6 inhibitors.

	Overall	P-Value	Patients treated in first-line	P-Value
	Median (95% CI)		Median (95% CI)	
N patients (% of total)	250 (55.3%)		156 (48%)	
Site of PD				
Not visceral	79 (31.6%)		54/34.6%)	
Visceral	168 (67.2%)		101 (64.7%)	
Missing	3		1	
PPFS (months)	5.7 (5.1-6.9)		5.7 (5-6.9)	
PPFS Recurrent MBC	6 (5.2-7.2)		6.0 (5.1-7.4)	
<i>De novo</i> MBC	4.7 (3.9-6.9)	ns	5.4 (3.9-7.6)	ns
PPFS Visceral baseline	5.6 (4.8-7.2)		6.4 (5.3-7.5)	
Bone-only baseline	5.3 (3.7-6.9)	ns	4.3 (2.8-5.7)	ns
PPFS by site of PD				
not visceral	5.7 (4.7-6.9)	ns	5.8 (4.3-8.1)	ns
visceral	5.7 (4.7-7.4)		5.6 (4.5-7.4)	
PPFS by CDK 4/6 i				
Abemaciclib	6 (3.8-6.9)	ns	4.3 (2.8-6.7)	ns
Palbociclib	6 (5-7.6)		6.6 (4.8- 8.3)	
Ribociclib	5.5 (4.2-6.9)		5.5 (4.4-7.6)	
PPFS by Endocrine partner				
Fulvestrant	5.6 (4.8-7.4)	ns	5.6 (4.3-7.5)	ns
Aromatase inhibitors	5.7 (4.4-6.9)		5.8 (4.5-7.4)	
PPOS after PD	22.9 (19.9-25.8)		24.3 (18.7-28.7)	
PPOS Recurrent MBC	21.4 (18.2-26.3)	ns	20.9 (16.9-28.7)	ns
<i>De novo</i> MBC	24.3 (18.7-28.6)		27.9 (18.7-33)	
PPOS Visceral baseline	20.8 (17.1-24.5)		22.6 (16.4-28.6)	
Bone-only disease baseline	32.9 (18.2-46.8)	.023	28 (16.9-33)	ns
PPOS by CDK 4/6 i				
Abemaciclib	28.6 (11.4-NE)		28.6 (11.4-NE)	
Palbociclib	23.2 (19-26.3)	ns	25.8 (15.2-32.9)	ns
Ribociclib	22.6 (18.2-30.4)		22.6 (18.2-30.4)	
PPOS by ET				
Fulvestrant	20.4 (16.9-24.6)	ns	18 (12.1-30.4)	ns
Aromatase inhibitors	27.9 (20.6-32)		27.9 (20.1-32.5)	
PPOS by site of PD				
visceral	20 (16.8-22.9)	<.001	18.7 (13.8-28.3)	.007
not visceral	29.2 (25.4-41.7)		28 (24.3-NE))	
PPFS by treatment at PD				
Everolimus + Exemestane	5.4 (4.3-9)	<.001	6.7 (4.3-9.9)	0.049
Endocrine therapy	5.8 (3.4-8.3)		5.8 (3.4-8.3)	
Capecitabine	7.5 (5.5-8.5)		7 (4.7-8.5)	
Taxanes	4.3 (2.8-6)		4.2 (2.8-6.4)	
Anthracycline	4.5 (1.6-6.9)		5.4 (0.7-10.4)	
PPOS by treatment after PD				
Everolimus + Exemestane	33 (20.8-NE)	<.001	33 (20.8-NE)	<.001
Endocrine therapy	28.3 (20.1-NE)		28.3 (20.1-NE)	
Capecitabine	24.5 (19-28)		20.9 (12.8-34.5)	
Taxanes	13.9 (7.2-18)		9.2 (6.6-18.2)	
Anthracycline	18.7 (5.3-30.4)		18.7 (0.9-30.4)	

CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; 95% CI, 95% confidence intervals; PD, progressive disease; PPFS, post progression-free survival; MBC, metastatic breast cancer; PPOS, post progression-free survival; NE, not estimated; NR, not reached.

(95% CI 1.7-8.3) for EET and 5.6 months (95% CI 4.4-6.4) and 5.7 months (95% CI 2.9-6.4) for AT groups.

Median post progression overall survival 2 (mPPOS2) was 16.1 months (95% CI 13.7-19.8), 21 months (95% CI 15.4-30) for C, Not Reached for EET (95% CI 5.3-NE) and 15.9 (95% CI 8.9-21.9) for AT with no significant difference among groups (Figure S5—see online supplementary material for a color version of this figure). However, after excluding the 15

patients treated with EET, C achieved a significantly longer PPOS2 compared to AT both overall and in patients treated in first-line ($P=0.037$ and $P=0.018$).

Discussion

Despite the increasing knowledge of molecular pathways involved in endocrine resistance has made available new

endocrine-based targeted therapies as oral SERDs and PI3KCA/AKT/mTOR inhibitors,^{12–17} which may be useful for more than one half of the patients progressing to first line treatment,²¹ the issue of the optimal treatment after progression remains crucial for a substantial proportion of patients who do not harbor targetable mutations or do not have access to molecular analyses.

In this real-world study we retrospectively analyzed a large cohort of consecutive patients with HR+/HER2– ABC more than two-thirds of whom receiving a first-line therapy, treated in routine practice in two large-volume research hospitals. Patient characteristics were similar to those of pivotal trials: about one-third were metastatic *de novo*, about 50% and 25% had visceral and bone-only disease, respectively. Our OS results with abemaciclib and ribociclib plus ET are slightly different from those of pivotal trials but the smaller size of the 2 groups may account for these differences. Aware of the limitations of non-randomized comparisons, we observed a not statistically significant trend for worse PFS but a numerically longer OS with palbociclib in patients treated in first-line.

As expected, treatment choice following progression was affected by the site of progression with most patients receiving taxane- and anthracycline-based chemotherapy after visceral progression (87.6%), whereas patients with bone progression received mostly endocrine-based therapy or capecitabine. Despite this expected imbalance in treatment choice, ET ±

everolimus resulted in better outcomes either overall and in patients with visceral progression. Moreover, the observed trend for improved OS for endocrine therapies over capecitabine, suggests the persistence of endocrine-sensitivity beyond failure of CDK4/6i and, importantly, that delaying the administration of chemotherapy rather than being detrimental allows the availability of a further line of treatment at the onset of endocrine resistance. The effectiveness of capecitabine-based regimens as salvage chemotherapy after occurrence of endocrine resistance is also supported by the improved PPOS2 after the second progression in patients treated in first-line.

Our results also confirm the role of capecitabine-based regimens as preferable chemotherapy option after CDK/6i failure formerly proposed by the METEORA-II trial which showed an improved PFS and time-to-treatment failure for the VEX regimen (metronomic capecitabine, vinorelbine and cyclophosphamide) as compared with paclitaxel.²²

As expected, duration of benefit with CDK4/6i as a proxy for endocrine sensitiveness, was associated with treatment decision since patients progressing within 12 months were more likely to receive chemotherapy, but unexpectedly it was associated with post-progression outcomes only in univariate analysis of OS and more importantly, it lost its effect in multivariate analysis when considering treatment and visceral progression. In addition, even among patients progressing after <12 months,

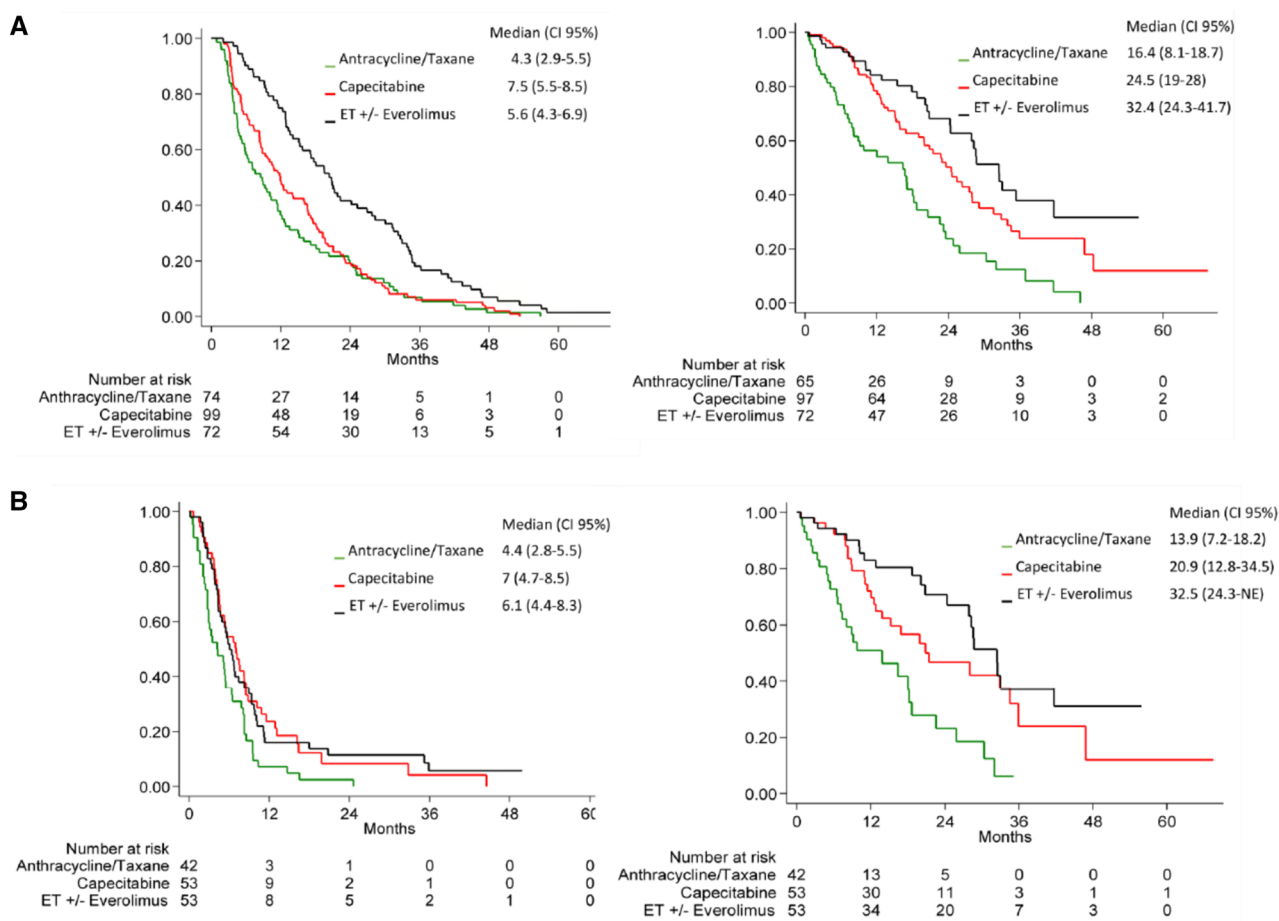


Figure 1. Post-progression free survival (PPFS) and post-progression overall survival (PPOS) according to combined treatment groups A) overall and B) in patients treated in first-line, ET: endocrine therapy.

Table 3. Comparisons of post progression-free survival and post progression-free overall survival according to treatment groups.

Variable	Overall	P-Value	Patients treated in first-line	P-Value
	Median (95% CI)		Median (95% CI)	
PPFS by treatment		<.001		.008
Endocrine Therapy ±everolimus	5.6 (4.3-6.9)	ns ^a	6.1 (4.4-8.3)	ns ^a
Capecitabine regimens	7.5 (5.5-8.5)	.003 ^b	7.0 (4.7-8.5)	.009 ^b
Anthracyclines/taxanes	4.3 (2.9-5.5)	<.001 ^c	4.3 (2.8-5.5)	.007 ^c
PPFS by treatment visceral PD		<.001		.016
Endocrine therapy±everolimus	5.4 (3.6-9)	ns ^a	6.1 (3.8-9.9)	ns ^a
Capecitabine regimens	7.6 (5.6-9)	.037 ^b	7.2 (4.7-8.5)	ns ^b
Anthracyclines/taxanes	4.3 (2.8-5.5)	<.001	3.9 (2.6-5.6)	.007
PPOS by treatment		<.001		<.001
Endocrine Therapy±everolimus	32.5 (24.3-41.7)	ns ^a	32.5 (24.3-NE)	ns ^a
Capecitabine regimens	24.5 (19-28)	<.001 ^b	20.9 (12.8-34.5)	<.001 ^b
Anthracyclines/taxanes	16.4 (8.1-18.7))	.001 ^c	13.9 (7.2-18.2)	.003 ^c
PPOS treatment visceral PD		.001		.004
Endocrine Therapy ±everolimus	28.6 (18.7-NE)	ns ^a	28.6 (10.9-NE)	ns ^a
Capecitabine regimens	22.7 (15.9-26.3)	<.001 ^b	20.9 (12.1-35.9)	.0057 ^b
Anthracyclines/taxanes	16.4 (7.4-18.2)	.002 ^c	9.2 (6.5-18.2)	.0078 ^c

95% CI, 95% confidence intervals; PPFS, post progression-free survival; PD, progressive disease; PPOS, post progression overall survival; NE, not estimated.

^aEndocrine therapy ± everolimus vs capecitabine regimens.

^bEndocrine therapy± everolimus vs anthracycline/taxanes.

^cCapecitabine regimens vs anthracycline/taxanes.

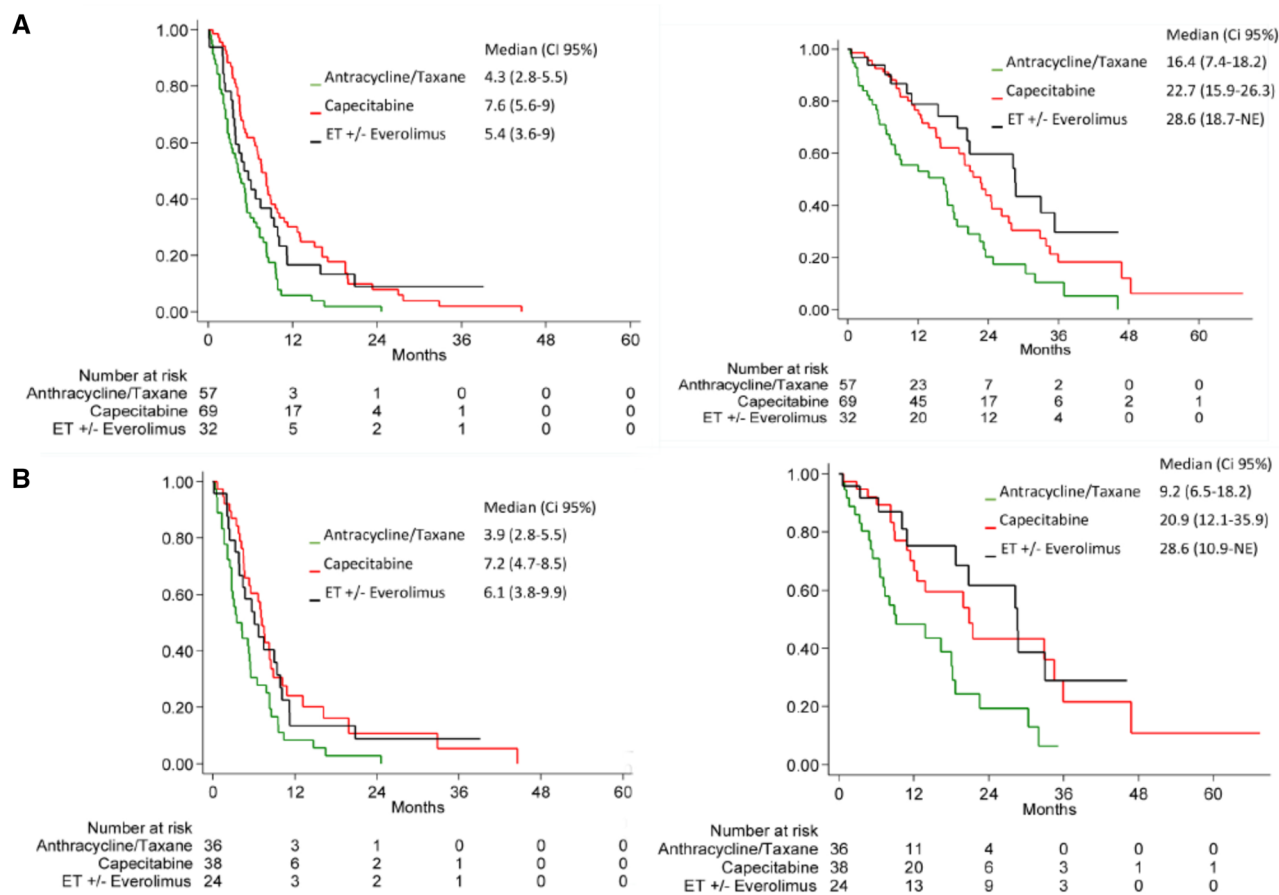
**Figure 2.** Post-progression free survival (PPFS) and post-progression overall survival (PPOS) according to combined treatment groups in patients progressing at visceral sites (A) overall and (B) in patients treated in first-line ET: endocrine therapy.

Table 4. Multivariate analysis for progression-free survival and overall survival at progression overall and in patients treated in first-line.

Variable	PFS			OS		
	Hazard ratio	95% CI	P-Value	Hazard ratio	95% CI	P-Value
Therapy with capecitabine regimens ^a	0.52	0.37-0.73	0.001	0.53	0.35-0.79	<0.002
Therapy with ET ± everolimus ^a	0.57	0.39-0.84	<0.005	0.37	0.23-0.62	<0.001
PD visceral ^b	1.03	0.75-1.43	0.851	1.63	1.05-2.54	0.030
First-line						
	PFS			OS		
Therapy with capecitabine regimens ^a	0.56	0.37-0.86	0.008	0.44	0.25-0.75	0.003
Therapy with ET ± everolimus ^a	0.56	0.37-0.86	0.008	0.27	0.15-0.49	<0.001

PFS, progression-free survival; OS, overall survival; PD, progressive disease; 95% CI, 95% Confidence Interval; ET, endocrine therapy; AT, anthracycline taxane.

^avs AT.

^bvs not visceral PD.

endocrine ± targeted therapies and capecitabine performed better than anthracyclines and/or taxanes.

In our study, both single agent ET and the combination with everolimus in a HR+/HER2– population unselected for driver mutations as *ESR1*, *PI3KCA/AKT* favourably compared with results obtained with targeted agents in cohorts selected for specific mutations [12-16]. Moreover, single agent ET (mostly fulvestrant) performed better than reported in control arms of RCTs. Despite being a real-world series our population mirrors those patients treated within second line RCTs with about 75% of patients having received only one prior ET and < 15% of patients pretreated with chemotherapy for advanced disease [12-16]. On the other hand, we cannot rule out that more stringent intervals in disease restaging reported in clinical studies than routine clinical practice can explain the different results of PFS although OS should not be affected by this bias. In addition, a proportion of patients might have carried unknown mutations of the *PI3KCA/mTOR* pathway and may have benefited of a specific treatment as everolimus.

A number of real-world studies with variable sample size have reported outcomes with post-CDK4/6i treatments but comparisons of the effectiveness of the different therapies were not always included.

The largest report derived from the Flatiron Health database, a longitudinal real-world registry comprising de-identified structured and unstructured data from 280 sites across the United States. This analysis included 1210 patients, of whom 839 received a documented second-line therapy after progression on CDK4/6i plus ET in first line.²³ Differently from our study about 36% of patients continued a CDK4/6i, mostly switching only the endocrine partner, while chemotherapy was administered to 29.7% of patients and endocrine therapy (mostly fulvestrant) was prescribed in 12.4% and everolimus in 11.7%. A marginal proportion of patients received other therapies (2.4%) or were enrolled in clinical trials (about 6%). The better outcomes were obtained maintaining CDK4/6i therapy (PFS= 8.25 months and OS= 35.7 months) while a similar rwPFS for chemotherapy, fulvestrant and everolimus was observed (3.71, 3.25 and 3.32 months, respectively). OS favoured everolimus but not fulvestrant monotherapy as compared to chemotherapy.²³ Differently from our study and due to the inherent limitations of data collection type, no

information about outcomes according to the site of progression or other clinical and pathological characteristics were available.

The cooperative GIM (Gruppo Italiano Mammella) reported the results of the retrospective/prospective GIM14 study evaluating treatment patterns and outcomes in patients with metastatic breast cancer treated at 26 Italian centres.²⁴ Among 701 patients receiving CDK4/6i in first-line 239 received treatment after progression, 45.5% of whom ET ± everolimus, and 40% capecitabine and taxane-based regimens. Consistently with our series patients with shorter CDK4/6i treatment duration received more frequently chemotherapy. No difference in PPFS (PFS2) was observed among treatments. No data on outcomes according to site of progression was reported.²⁴

A systematic review including 18 studies of post-CDK 4/6i treatment reported median real-world PFS of 3.9 months (3.3-6.0 months) for single-agent ET, 3.6 months (2.5-4.9 months) for mTORinhibitors ± ET, 3.7 months for a mix of ET and/or mTORinhibitors (3.0-4.0 months), and 6.1 months (3.7-9.7 months) for chemotherapy. Median real-world OS was not calculated since only 3 studies reported this outcome. No information on treatment after the second progression was reported as well.²⁵

Our study shares the inherent limitations of real-world studies. Firstly, the lack of standardized timing and methods of disease evaluation might affect the calculation of outcome measures. Another limitation is represented by the increasingly smaller sample size for each treatment group along subsequent treatment lines, which might weaken statistical significance of post-progression outcome comparisons among these groups. On the other hand, key strength of our study is the inclusion of only two large-volume centers which reduces the variability in patient management. To our knowledge this is the first real-world post-CDK4/6i study which reports the impact of site of progression on all the second-line treatment outcomes and shows that PPFS and PPOS were not affected by factors associated with CDK4/6i failure. Finally, we report for the first time outcomes after the progression after the first post-CDK4/6i treatment.

In conclusion, our results show in a large real-world series that most patients with HR+/HER2– ABC failing therapy with CDK4/6i and ET who were not selected for the occurrence of

molecular mutations retain endocrine sensitivity and may derive a meaningful clinical benefit from a subsequent endocrine manipulation $\pm$ a targeted therapy delaying the need for chemotherapy regardless of site of progression and duration of prior CDK4/6i therapy. Our findings support a beneficial role for extending endocrine therapies in routine clinical practice when actionable mutations are not detected or not evaluable.

Author contributions

Concept and design: Rosalba Torrisi and Elisabetta Munzone. Acquisition, analysis, or interpretation of data: Rosalba Torrisi, Federica Giugliano, Laura Giordano, Flavia Jacobs, Giuseppe Saltalamacchia, Ambra Carnevale Schianca, and Claudia Anna Sangalli. Drafting of the manuscript: Rosalba Torrisi, Laura Giordano, Federica Giugliano, and Elisabetta Munzone. Funding acquisition: Rosalba Torrisi. Critical review of the manuscript for important intellectual content: Flavia Jacobs, Rita De Sanctis, Monica Milano, Nadia Bianco, Giovanna Masci, Armando Santoro, Giuseppe Curigliano, and Elisabetta Munzone. Rosalba Torrisi and Laura Giordano had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

Rosalba Torrisi (Conceptualization, Data curation, Funding acquisition, Investigation, Writing—original draft, Writing—review & editing), Federica Giugliano (Data curation, Resources, Writing—original draft, Writing—review & editing), Laura Giordano (Data curation, Formal analysis, Writing—original draft, Writing—review & editing), Giuseppe Saltalamacchia (Data curation, Resources, Writing—review & editing), Flavia Jacobs (Data curation, Investigation, Writing—review & editing), Ambra Carnevale Schianca (Data curation, Investigation, Writing—review & editing), Monica Milano (Data curation, Investigation, Writing—review & editing), Nadia Bianco (Data curation, Investigation, Writing—review & editing), Claudia Anna Sangalli (Data curation, Investigation, Writing—review & editing), Rita De Sanctis (Data curation, Writing—original draft), Giovanna Masci (Data curation, Writing—original draft), Giuseppe Curigliano (Supervision, Writing—review & editing), Armando Santoro (Supervision, Writing—review & editing), Elisabetta Munzone (Conceptualization, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *The Oncologist* online.

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Conflicts of interest

R.T., F.G., L.G., F.J., A.C.S., M.M., N.B., C.A.S., and G.M. declare no financial or non-financial competing interests. G.S.: honoraria from Lilly, Daiichi Sankyo, Pfizer, Novartis (all outside the submitted work). R.D.S.: honoraria or served in advisory roles for Daiichi Sankyo, Novartis, Istituto Clinico Gentili,

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Data availability

The datasets generated and analyzed during the current study are available on the repository Zenodo: <https://zenodo.org/records/>

References

- Howlander N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J. Natl. Cancer Inst.* 2014;106:dju055.
- Gennari A, André F, Barrios CH, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol.* 2021;32:1475-1495.
- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Breast Cancer. Accessed July 4, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
- Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with Ribociclib plus Letrozole in advanced breast cancer. *N Engl J Med.* 2022;386:942-950.
- Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. *Ann Oncol.* 2021;32:1015-1024.
- Lu Y-S, Im S-A, Colleoni M, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR $\pm$ /HER2 $\pm$ advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. *Clin Cancer Res.* 2022;28:851-859.
- Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat.* 2019;174:719-729.
- Slamon DJ, Diéras V, Rugo HS, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol.* 2024;42:994-1000.
- Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5:5-8.
- Munzone E, Pagan E, Bagnardi V, et al. Systematic review and meta-analysis of post-progression outcomes in ER+/HER2- metastatic breast cancer after CDK4/6 inhibitors within randomized clinical trials. *ESMO Open.* 2021;6:100332.
- Mittal A, Molto Valiente C, Tamimi F, et al. Filling the gap after CDK4/6 inhibitors: novel endocrine and biologic treatment options for metastatic hormone receptor positive breast cancer. *Cancers (Basel).* 2023;15:2015. <https://doi.org/10.339>
- 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;40:3246-3256. Erratum in: *J Clin Oncol*. 2023 Aug 10; 41(23):3962.
13. Oliveira M, Pominchuk D, Nowecki Z, et al. Camizestrant, a next-generation oral SERD, versus fulvestrant in post-menopausal women with oestrogen receptor-positive, HER2-negative advanced breast cancer (SERENA-2): a multi-dose, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2024;25:1424-1439.
 14. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2023;388:2058-2070.
 15. Turner NC, Im S-A, Saura C, et al. Inavolisib-based therapy in *PIK3CA*-mutated advanced breast cancer. *N Engl J Med*. 2024;391:1584-1596.
 16. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol*. 2021;22:489-498. Erratum in: *Lancet Oncol*. 2021 May; 22(5):e184. PMID: 33794206. [https://doi.org/10.1016/S1470-2045\(21\)00034-6](https://doi.org/10.1016/S1470-2045(21)00034-6)
 17. Burstein HJ, DeMichele A, Fallowfield L, et al. Endocrine and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer—capivasertib-fulvestrant: ASCO Rapid Recommendation Update. *J Clin Oncol*. 2024;42:1450-1453.
 18. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann. Oncol*. 2020;31:623-649. <https://doi.org/10.1016/j.annonc.2020.09.010>
 19. Torrisi R, Jacobs F, Miggiano C, et al. A HR+/HER2- de novo metastatic breast cancer: a true peculiar entity? *Drugs Context*. 2023;12:2022-12-2. <https://doi.org/10.7573/dic.2022-12-2> (eCollection 2023).
 20. Castelo-Branco L, Pellat A, Martins-Branco D, et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW). *Ann Oncol*. 2023;34:1097-1112.
 21. Lloyd MR, Jhaveri K, Kalinsky K, Bardia A, Wander SA. Precision therapeutics and emerging strategies for HR-positive metastatic breast cancer. *Nat Rev Clin Oncol*. 2024;21:743-761. <https://doi.org/10.1038/s41571-024-00935-6>
 22. Munzone E, Regan MM, Cinieri S, et al. Efficacy of metronomic oral vinorelbine, cyclophosphamide, and capecitabine vs weekly intravenous paclitaxel in patients with estrogen receptor-positive, ERBB2-Negative metastatic breast cancer: final results from the phase 2 METEORA-II randomized clinical trial. *JAMA Oncol*. 2023;9:1267-1272.
 23. 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;27:441-446.
 24. Molinelli C, Bruzzzone 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.
 25. 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;24:631.