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The efficacy of first-line chemotherapy in endocrine-resistant hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer.

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Abstract

Purpose: Combinations of endocrine therapy (ET) and targeted therapy (CDK4/6 or mTOR inhibitors) are standard of care for HR+/HER2- metastatic breast cancer (MBC). When ET is not effective, chemotherapy is commonly used. However, clinical outcomes of chemotherapy in the endocrine-resistant setting are limited. The purpose of this study was to identify predictive factors and the compare efficacies of chemotherapy agents in endocrine-resistant MBC.

Methods: We conducted a retrospective study of patients with HR+/HER2- MBC who received chemotherapy after progression on ET with or without targeted therapy at MD Anderson Cancer Center from 1999–2017. We collected baseline clinicopathological and all treatment data. Primary endpoint was time to treatment failure (TTF) of first-line chemotherapy for MBC.

Results: For the 1,258 patients analyzed, mean age was 55.3 years (range 21–91). Previous treatment with targeted therapy was recorded for 390 patients (31%): 264 with CDK4/6 inhibitor, 205 with mTOR inhibitor, and 79 treated with both. The most frequent chemotherapy agents were

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Compliance with ethical standards

Ethical approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University of Texas MD Anderson Cancer Center (PA18–1135) approved this study.

Informed consent

For this type of study, formal consent is not required.

Conflict of interest

The authors declare that they have no conflict of interests.

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capecitabine (48.9%) and taxanes (28.6%). After adjustment for all factors in a multivariate model, previous treatment with a CDK4/6 inhibitor had the strongest negative effect on TTF regardless of ET duration (hazard ratio [HR] 1.84; 95% CI 1.49–2.27; $p < 0.001$). Conversely, capecitabine had significantly longer median TTF than taxanes regardless of whether patients had prior exposure to taxanes in primary setting (6.1 vs 4.9 months; HR 0.64; 95% CI 0.55–0.75; $p < 0.001$).

Conclusions: Previous exposure to CDK4/6 inhibitor had a negative predictive effect for the efficacy of chemotherapy. Capecitabine had the best efficacy against endocrine-resistant breast cancer.

Keywords

breast cancer; endocrine resistant; chemotherapy; CDK4/6; mTOR; capecitabine

Introduction

Endocrine therapy (ET) is a standard treatment for metastatic breast cancer with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) status. ET as a single agent or combined with targeted therapy is preferred as initial therapy for patients without visceral crisis [1–3]. Combinations of ET and targeted therapy, such as cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors or mammalian target of rapamycin (mTOR) inhibitors, have been shown by many randomized clinical trials to confer a survival benefit with acceptable toxicities [4–7]. In contrast, chemotherapy is the standard treatment in patients with visceral crisis or concern for endocrine resistance [1–3]. National Comprehensive Cancer Network (NCCN) Guidelines [1] suggest use of chemotherapy after up to 3 sequential ET regimens because of no clinical benefit to further ET (endocrine-resistant breast cancer). Thus, chemotherapy is commonly used in patients for whom available ET has been exhausted or ET options are unavailable.

Various chemotherapy regimens have been used for metastatic breast cancer worldwide. Single-agent anthracycline- and taxane-based regimens have traditionally been considered as first-line treatment for HER2- breast cancer. However, other options are available and effective; these include capecitabine, vinorelbine, and eribulin. The decision should be individualized and considered based on toxicity profiles and patient preferences [2]. However, HR+, HER2- breast cancer is poorly sensitive to neoadjuvant chemotherapy; its rate of complete pathological response is lowest among the breast cancer subtypes [8,9]. In a preclinical model, tamoxifen-resistant breast cancer cell lines (MCF7 and T47D) expressed BARD1 and BRCA1, leading to resistance to some regimens of chemotherapy. These tamoxifen-resistant cells were resistant to doxorubicin and cisplatin but not to paclitaxel [10].

Normally, the first-line chemotherapy regimen should have the greatest benefits and fewest risks of adverse events. However, supporting clinical data on chemotherapy in endocrine-resistant breast cancer are very limited. Moreover, the optimal chemotherapy regimen for endocrine-resistant breast cancer is unclear. Therefore, we aimed to identify predictive factors and to determine the efficacy of first-line chemotherapy in patients with HR+, HER2- metastatic breast cancer who had progressed on ET with or without targeted therapy.

Methods

Study and population

This was a retrospective chart review study in patients with HR+, HER2- breast cancer who received chemotherapy after progression on ET at The University of Texas MD Anderson Cancer Center. The study was approved by the MD Anderson Institutional Review Board (PA18–1135). This study was granted a waiver for informed consent because of its retrospective nature.

We retrospectively reviewed all patients with recurrent or de novo stage IV HR+, HER2- metastatic breast cancer treated between January 1, 1999, and September 30, 2017. HR+ breast cancer was defined as estrogen receptor (ER) and/or progesterone receptor (PR) positivity 10% based on American Society of Clinical Oncology/College of American Pathologists clinical practice guidelines of 2010 [11]. Eligible patients were women aged 18 years with pathologically confirmed invasive breast cancer and ECOG performance status of 0–1 who had been treated with chemotherapy after disease progression during ET (with or without targeted therapy) for metastatic disease. Male patients and patients for whom survival outcomes were not available for analysis were excluded. Patients with discordance between their primary and recurrent breast cancer subtypes or whose subtype changed after diagnosis were excluded.

Data collection

We reviewed the Breast Medical Oncology management system database to identify patients, and then additional data were extracted from their electronic medical records. From the database, we extracted age, race, body mass index (BMI), menopausal status, clinical de novo stage IV vs recurrence status, histological subtype, inflammatory breast cancer (IBC) vs non-IBC status, hormone receptor status, nuclear grade, adjuvant therapies, number and sites of metastases, past history of ET, chemotherapy regimens, treatment stop date, and date of death.

Outcomes

The primary endpoint was time to treatment failure (TTF), defined as the time from first chemotherapy initiation in the metastatic setting until treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death, whichever occurred first. The secondary endpoint was overall survival (OS), defined as the time from chemotherapy initiation until death from any cause. We also evaluated the time from starting ET until stopping chemotherapy and the time from diagnosis of metastasis until death. Date of death and treatment stop date were determined from the medical records.

Statistical analysis

Descriptive statistics were used to summarize all variables collected. For continuous variables, the mean, median, and range were presented as appropriate. For categorical variables, a frequency table was generated. Univariate and multivariate analyses of TTF and OS were performed using the Cox proportional hazard model. Kaplan-Meier methods were used to analyze the endpoints. Results were found to be significant if the p value was < 0.05.

Results

Patients and baseline characteristics

From a total of 2,096 patients with metastatic HR+, HER2- disease who received treatment at MD Anderson Cancer Center from January 1999 through September 2017, we excluded 757 patients who received only ET or received chemotherapy before ET in metastatic setting. Men diagnosed with breast cancer (23 patients) and patients with discordance in breast cancer subtype between their primary and recurrent tumors or a subtype change (58 patients) were excluded. The remaining 1,258 patients were eligible and analyzed in our study. Median follow-up time since chemotherapy initiation was 19 months. The baseline characteristics of the patients are shown in Table 1. The mean age was 55.3 years (range 21–91), and the majority of patients were white (73.8%). Forty-five patients (3.6%) had inflammatory breast cancer (IBC). Single-agent capecitabine was the most common post-ET chemotherapy regimen (48.9%); the second most common was a single taxane (paclitaxel, nab-paclitaxel, or docetaxel) (28.6%). For taxane exposure, 74.4% of adjuvant therapy and 80.1% of neoadjuvant therapy had taxane-based regimens.

For prior ET, 51.1% and 19.8% of patients had received second- and third-line ET regimens, respectively, before starting chemotherapy (Table 2). Combinations of ET and targeted therapy had been received in 390 patients (31.0%): 264 patients had received a CDK4/6 inhibitor, 205 patients had received an mTOR inhibitor, and 79 patients had received both targeted therapies. The most common CDK4/6 inhibitor given was palbociclib (95.1% of cases receiving CDK4/6 inhibitors); the most common mTOR inhibitor was everolimus (99.5%). The most common prior ET was a single-agent aromatase inhibitor (AI) (e.g., letrozole, anastrozole, or exemestane).

Univariate and multivariate analysis

In a univariate analysis, we identified the following factors associated with worse TTF of chemotherapy (Table 3): African-American race, IBC, nuclear grade III, prior exposure to CDK4/6 inhibitor, and treatment with a chemotherapy regimen that did not include a taxane or capecitabine. In contrast, better TTF was associated with adjuvant hormone therapy, more than two regimens of ET, and capecitabine.

After adjustment for all factors in the multivariate analysis model (Table 3), we found that variables significantly associated with shorter TTF were IBC (adjusted hazard ratio 1.39; 95%CI 1.01–1.92; $p=0.048$) and prior exposure to a CDK4/6 inhibitor (adjusted hazard ratio 1.84; 95%CI 1.49–2.27; $p<0.001$). When we stratified patients by duration of all prior ET, we found that prior exposure to CDK4/6 inhibitor had adjusted hazard ratios of 1.78 (95%CI 1.35–2.33; $p<0.001$) among patients with ET duration ≤ 12 months and 1.95 (95%CI 1.48–2.57; $p<0.001$) among patients with ET duration >12 months. In contrast, a multivariate analysis model confirmed significant associations with longer TTF for capecitabine (hazard ratio 0.64; 95%CI 0.55–0.75; $p<0.001$) and adjuvant hormone therapy (hazard ratio 0.77; 95%CI 0.62–0.94; $p=0.010$), although the latter finding may have been confounded by patients who developed recurrent disease during adjuvant chemotherapy (chemotherapy resistance). Bone-only metastasis and visceral metastasis were not associated with

chemotherapy TTF in univariate analysis; however, they were associated with TTF in multivariate analysis.

TTF and OS outcomes

Kaplan-Meier curves for chemotherapy TTF stratified by previous ET and chemotherapy are shown in Figure 1. The median TTFs of chemotherapy in patients previously treated with ET alone, CDK4/6 inhibitor, and mTOR inhibitor were 5.1 months (95%CI 5.0–5.5), 3.4 months (95%CI 3.0–4.0), and 6.1 months (95%CI 5.03–8.13), respectively. Previous treatment with CDK4/6 inhibitor had shorter median TTF than previous treatment with ET alone (adjusted hazard ratio 1.84; 95%CI 1.49–2.27; $p<0.001$). Median TTFs for taxanes, capecitabine, and other chemotherapy were 4.9 months (95%CI 4.4–5.1), 6.1 months (95%CI 5.5–6.6), and 4.4 months (95%CI 4.0–4.9), respectively. The median TTF for capecitabine was significantly longer than that for taxanes (adjusted hazard ratio 0.64; 95%CI 0.55–0.75; $p<0.001$). The increased benefit of capecitabine over taxanes as first-line chemotherapy after ET failure was consistent regardless of whether patients had prior exposure to taxanes (Figure 2). The adjusted hazard ratios were 0.59 (95%CI 0.46–0.75; $p<0.001$) for patients who had received prior taxanes and 0.64 (95%CI 0.53–0.79; $p<0.001$) for those who had not. However, there was no significant difference in median OS stratified by these chemotherapy regimens (Figure S1). The Kaplan-Meier curve for time from starting ET until stopping first-line chemotherapy (Figure S3) showed a longer median survival time in patients previously treated with CDK4/6 inhibitors than in patients without previous CDK4/6 inhibitors (21.5 months [95%CI 19.3–24.1] vs 19.1 months [95%CI 17.9–20.3], respectively).

An exploratory subgroup analysis (Figure 3) evaluating the TTFs between capecitabine and taxanes showed more favorable findings for capecitabine than for taxanes, regardless of whether patients had prior exposure to taxanes. The exceptions were in patients with IBC and in those with prior duration of all ET >12 months and previous treatment with CDK4/6 inhibitor. However, neither hazard ratio was significant owing to small sample size.

Discussion

In this study, we evaluated the survival outcome for first-line chemotherapy after progression on ET in patients with HR+, HER2- advanced breast cancer and found that IBC, prior ET, having received adjuvant hormone therapy, and chemotherapy regimen were associated with chemotherapy TTF. Interestingly, prior exposure to ET plus CDK4/6 inhibitor had the strongest negative effect relative to TTF. In contrast, capecitabine had the strongest positive effect relative to TTF in our study.

In clinical practice, chemotherapy is often used as a subsequent treatment for endocrine-resistant breast cancer as recommended by standard guidelines [1,2]. However, supporting studies are quite limited, and the selection of chemotherapy has been based on individual physician-patient decision making [12]. Our results demonstrate factors that can apply to the chemotherapy selection. Moreover, our results may translate into future directions of clinical trial concepts.

To our knowledge, this is the first cohort study that shows the outcome of chemotherapy for patients with endocrine-resistant breast cancer who had disease progression on ET, including CDK4/6 inhibitors, which were first approved by the U.S. Food and Drug Administration in 2015. Our study found that prior types of ET received were associated with chemotherapy TTF. Patients who were previously treated with CDK4/6 inhibitors had shorter TTFs than patients treated with ET alone, regardless of prior duration of all ET. Median TTFs were 3.4 and 5.1 months in patients previously treated with CDK4/6 inhibitors plus ET and with ET alone, respectively. The adjusted hazard ratio for prior CDK4/6 inhibitor treatment was 1.84 (95% CI 1.49–2.27; $p < 0.001$). PALOMA-3, a randomized phase 3 trial evaluating a CDK4/6 inhibitor (palbociclib) combined with ET (fulvestrant), reported a survival benefit in terms of median PFS for the palbociclib plus fulvestrant group compared with the placebo plus fulvestrant group (9.5 vs 4.6 months, respectively; $p < 0.001$). However, no significant difference in OS (34.9 vs 28.0 months, $p = 0.09$) was found [13,14]. When we looked at subsequent lines of therapy in that trial, more than half of patients received chemotherapy as the first line of treatment after the randomized regimen. Implication, the subsequent chemotherapy had shorter benefit after failed palbociclib plus fulvestrant than after failed placebo plus fulvestrant; therefore, the benefit of PFS did not translate into OS. An important distinction between PALOMA-3 and our study is that the inclusion criteria differed; PALOMA-3 allowed patients with no more than one line of chemotherapy in advanced disease. Thus, careful interpretation is needed.

Recently published OS data from MONARCH-2 [5], a randomized phase 3 trial comparing CDK4/6 inhibitor abemaciclib plus fulvestrant with placebo plus fulvestrant, showed an OS benefit in the abemaciclib group (median OS 46.7 vs 37.3 months, respectively; $p = 0.01$). The exploratory analysis of subsequent treatment reported chemotherapy as the most common first line of subsequent therapy (45.3%), and the median durations of chemotherapy were 4.4 vs 4.6 months in the abemaciclib group and placebo group, respectively. However, these results are not fully parallel to our study in that almost all of our patients treated with a CDK4/6 inhibitor received palbociclib. Our results showed a small absolute difference in median TTF was 1.7 months (5.1 vs 3.4 months), but were statistically significant; however, these results need to be analyzed and confirmed in a larger cohort or prospective trial. Interestingly, if we speculate about the cumulative survival benefits of all treatments since diagnosis of metastasis, the maximum survival benefit of treatments was obtained in patients who had received a CDK4/6 inhibitor. This can translate into longer survival, even though subsequent chemotherapy after CDK4/6 inhibitor was short (Figures S2 and S3).

An ongoing question in treatment of metastatic HR+, HER2- breast cancer is what chemotherapy regimens are suitable. Even though the standard guidelines [1,2] include lists of chemotherapy regimens for this subtype, the optimal type and sequence of chemotherapy regimen have not been established. The many randomized clinical trials in HR+, HER2- breast cancer have showed a variety of chemotherapy regimens after failed ET, and there have been differences regimens in each trial [4,5,13]. However, those trials did not report the optimal regimen. In our study of association of the first line of chemotherapy with survival outcome, capecitabine had the longest TTF compared with taxanes and other regimens (median 6.1 vs 4.9 vs 4.4 months; Figure 1). The absolute benefit was 1.2 months, with a hazard ratio of 0.64 (95% CI 0.55–0.75; $p < 0.001$) compared with taxanes, and this benefit

was consistent regardless of prior exposure to taxane (Figure 2). The efficacy of first-line capecitabine has been evaluated and supported by many randomized clinical trials, with no differences in survival outcomes compared with other types of chemotherapy (paclitaxel, pegylated liposomal doxorubicin) or a combination regimen (cyclophosphamide/methotrexate/fluorouracil) regardless of whether patients were pretreated or naïve with respect to anthracyclines [15–18]. However, none of these trials enrolled only endocrine-resistant patients, as in our study. Capecitabine is a reasonable choice in endocrine-resistant patients, taking into account its favorable safety profile and lack of cumulative toxicity.

For subgroup analysis in patients previously treated with CDK4/6 inhibitor (total duration ET >12 months) and IBC, our results were more favorable for taxanes than capecitabine (Figure 3). These results were inconsistent with those for the other subgroups, which favored capecitabine. Nevertheless, the sample size was too small to interpret; a larger cohort is needed to confirm the results.

TTF was our primary endpoint and has been suggested as a clinical endpoint using real-world evidence. TTF is influenced by factors not related to efficacy alone, such as toxicity and patient preference [19]. TTF is useful in the setting in which toxicity is potentially as serious as tumor progression. Therefore, TTF is appropriate as our endpoint for evaluation in the nonaggressive subtype of HR+, HER2- breast cancer. All patients in our study had familiarity with less toxic treatment (i.e., ET with or without targeted therapy) compared to chemotherapy, so the toxicity of chemotherapy need to be considered.

Some limitations in our study need to be discussed. This was a retrospective review study conducted at a single institution, which could result in bias such as in the variety of chemotherapy regimens. Hence, we organized the regimens into three groups; furthermore, a larger sample size would reduce this bias. As noted earlier, the CDK4/6 inhibitors in our study were largely limited to palbociclib. Additional limitations are that we did not evaluate the dose intensity, patient compliance with each treatment, toxicity, or treatment delays.

Conclusions

The efficacy of chemotherapy in endocrine-resistant breast cancer could be determined based on previously treatment with a CDK4/6 inhibitor and based on chemotherapy regimen. Capecitabine was a suitable chemotherapy regimen for endocrine-resistant breast cancer patients. Our results need further validation in a larger cohort or prospective trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

(ET)	Endocrine therapy
(HR+)	Hormone receptor-positive
(HER2-)	Human epidermal growth factor receptor 2-negative
(CDK4/6)	Cyclin-dependent kinase 4 and 6
(mTOR)	Mammalian target of rapamycin
(ER)	Estrogen receptor
(PR)	Progesterone receptor
(IBC)	Inflammatory breast cancer

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Figure 1. Kaplan-Meier curves for chemotherapy TTF stratified by previous endocrine therapy (A) and chemotherapy regimens (B)

Chemotherapy regimen	Prior exposure to taxanes Adjusted hazard ratio (95%CI)	No prior exposure to taxanes Adjusted hazard ratio (95%CI)
Capecitabine vs taxane	0.59 (0.46-0.75)	0.64 (0.53-0.79)
Other vs taxane	0.96 (0.74-1.26)	1.31 (1.03-1.66)
Capecitabine vs other	0.61 (0.49-0.75)	0.49 (0.38-0.63)

Figure 2.
Kaplan-Meier curves for chemotherapy TTF among patients who had previously received taxanes (A) or had not received taxanes (B), stratified by chemotherapy regimen

Figure 3.
Subgroup analysis of TTF between capecitabine and taxane

Table 1.

Baseline clinical characteristics

Clinical characteristic	No. (N = 1,258)	%
Age at initial chemotherapy, years		
Mean (range)	55.3 (21–91)	
<40	118	9.4
40–60	709	56.4
>60	431	34.3
Race/ethnicity		
White	929	73.8
African-American	123	9.8
Hispanic	61	9.9
Asian	125	4.8
Other	20	1.6
BMI, kg/m ²		
Underweight (<18.5)	18	1.4
Normal (18.5–24.99)	413	32.8
Over weight (25–29.99)	375	29.8
Obese (30 or more)	384	30.5
Unknown	68	5.4
Menopausal status		
Premenopausal	475	37.8
Postmenopausal	578	45.9
Unknown	205	16.3
Metastasis status		
De novo stage IV	336	26.7
Recurrence	916	72.8
Unknown	6	0.5
Histological subtype		
Invasive ductal	958	76.2
Invasive lobular	183	14.5
Other	117	9.3
Inflammatory breast cancer		
IBC	45	3.6
Non-IBC	1213	96.4
Hormone receptor status		
ER+/PR+	981	78.0
ER+/PR-	249	19.8
ER-/PR+	12	1.0

Clinical characteristic	No. (N = 1,258)	%
Unknown ER or PR status	16	1.3
ER+ fraction		
0–9%	13	1.0
10–55%	104	8.3
56–94%	510	40.5
95% or more	367	29.2
Nuclear grade		
Grade I/II	625	49.7
Grade III	482	38.3
Neoadjuvant or adjuvant chemotherapy		
Yes	767	61.0
No	491	39.0
Prior exposure to taxane in neoadjuvant or adjuvant therapy	624	49.6
Neoadjuvant or adjuvant hormone therapy		
Yes	792	63.0
No	466	37.0
No. of organs involved		
1 or 2	1116	88.7
>3	142	11.3
Organ of metastasis		
Lymph node	181	14.4
Bone only	478	38.0
Bone (any)	914	72.7
Visceral organ(s)	466	37.0
Brain	55	4.4
Prior duration of all ET for advanced disease <12 months		
No targeted therapy	503	40.0
CDK4/6 inhibitor	99	7.9
mTOR inhibitor	27	2.1
CDK4/6 and mTOR inhibitors	14	1.1
Prior duration of all ET for advanced disease >12 months		
No targeted therapy	365	29.0
CDK4/6 inhibitor	86	6.8
mTOR inhibitor	99	7.9
CDK4/6 and mTOR inhibitors	65	5.2
No. of ET regimens for advanced disease		
1–2 lines	1009	80.2
At least 3 lines	249	19.8

Clinical characteristic		No. (N = 1,258)	%
First-line chemotherapy after ET failure			
Single agent			
	Capecitabine	615	48.9
	Paclitaxel	215	17.1
	Nab-paclitaxel	88	7.0
	Docetaxel	56	4.5
	Eribulin	37	2.9
	Anthracycline	14	1.1
	Other	55	4.4
Combination			
AC, FAC)	Anthracycline-based combination (e.g.,	73	5.8
	Other combination (e.g., CMF)	105	8.3

Abbreviations: IBC, inflammatory breast cancer; ER, estrogen receptor; PR, progesterone receptor; AC, doxorubicin/cyclophosphamide; FAC, fluorouracil/doxorubicin/cyclophosphamide; CMF, cyclophosphamide/methotrexate/fluorouracil

Table 2.

Prior endocrine therapy

Type of ET	N (%)		
	First line N=1,258	Second line N=643	Third line N=249
Single agent			
Tamoxifen	214 (17.0)	67 (10.4)	27 (10.8)
AI (e.g., letrozole, anastrozole, exemestane)	674 (53.6)	239 (37.2)	43 (17.3)
Fulvestrant	138 (11.0)	136 (21.1)	90 (36.2)
Combination			
Fulvestrant plus other ET	23 (1.8)	10 (1.6)	0
CDK4/6 inhibitor plus ET	167 (13.3)	72 (11.2)	28 (11.2)
mTOR inhibitor plus ET	38 (3.0)	112 (17.4)	47 (18.9)
Other	4 (0.3)	7 (1.1)	14 (5.6)

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy

Table 3.

Univariate and multivariate analysis of TTF for chemotherapy

Variable	Univariate			Multivariate		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age, years						
<40	(reference)			(reference)		
40–60	1.03	(0.84–1.25)	0.803	1.00	(0.81–1.24)	0.983
>60	0.93	(0.76–1.15)	0.506	0.95	(0.74–1.21)	0.664
Race/ethnicity						
White	(reference)			(reference)		
African-American	1.23	(1.02–1.49)	0.033	1.18	(0.97–1.44)	0.106
Asian	1.21	(0.93–1.57)	0.160	1.22	(0.92–1.62)	0.162
Hispanic	1.03	(0.85–1.25)	0.757	1.07	(0.88–1.30)	0.521
Other	0.99	(0.63–1.54)	0.950	1.05	(0.67–1.66)	0.829
Obese vs non-obese	1.00	(0.88–1.13)	0.943	0.99	(0.87–1.12)	0.827
Postmenopausal vs premenopausal	0.96	(0.85–1.09)	0.507	1.07	(0.91–1.25)	0.410
De novo stage IV vs recurrence	0.91	(0.80–1.03)	0.137	1.10	(0.86–1.41)	0.446
Histological subtype						
Invasive ductal	(reference)			(reference)		
Invasive lobular	0.89	(0.76–1.05)	0.158	0.95	(0.80–1.12)	0.525
Other	0.85	(0.70–1.03)	0.095	0.91	(0.74–1.11)	0.349
IBC vs non-IBC	1.52	(1.11–2.06)	0.008	1.39	(1.01–1.92)	0.048
Hormone receptor status						
ER+/PR+	(reference)			(reference)		
ER+/PR-	0.92	(0.80–1.06)	0.244	0.91	(0.78–1.06)	0.222
ER-/PR+	0.90	(0.51–1.60)	0.720	0.75	(0.34–1.67)	0.484
ER fraction						
0–9%	(reference)			(reference)		
10–55%	0.79	(0.44–1.40)	0.415	0.79	(0.36–1.76)	0.564
56–94%	0.74	(0.43–1.29)	0.293	0.73	(0.33–1.59)	0.428
95% or more	0.87	(0.50–1.51)	0.620	0.82	(0.38–1.80)	0.622
Nuclear grade (grade III vs grade I/II)	1.17	(1.03–1.32)	0.012	1.12	(0.99–1.28)	0.082
Neoadjuvant or adjuvant therapy						
Chemotherapy	0.95	(0.84–1.06)	0.341	0.91	(0.71–1.15)	0.418
Hormone therapy	0.85	(0.76–0.95)	0.006	0.77	(0.62–0.94)	0.010
Prior exposure to taxane	1.00	(0.90–1.12)	0.956	1.22	(1.00–1.49)	0.050
No. of organs involved (>3 vs 1–2)	0.88	(0.74–1.06)	0.174	0.92	(0.75–1.14)	0.443
Organs of metastasis						
Lymph node	1.04	(0.88–1.22)	0.655	0.97	(0.80–1.18)	0.753
Bone only	0.97	(0.86–1.09)	0.569	0.82	(0.68–0.99)	0.036
Bone	0.99	(0.87–1.12)	0.832	1.07	(0.92–1.25)	0.362
Visceral	0.97	(0.86–1.09)	0.562	0.82	(0.70–0.97)	0.022

Variable	Univariate			Multivariate		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Brain	0.96	(0.73–1.27)	0.761	0.86	(0.64–1.16)	0.318
Previous ET						
Duration of all ET < 12 months						
No targeted therapy	(reference)			(reference)		
CDK4/6 inhibitor	1.59	(1.27–2.00)	<0.001	1.78	(1.35–2.33)	<0.001
mTOR inhibitor	0.80	(0.54–1.18)	0.252	0.77	(0.51–1.16)	0.210
CDK4/6 and mTOR inhibitors	2.20	(1.26–3.82)	0.005	2.04	(1.15–3.62)	0.015
Duration of all ET > 12 months						
No targeted therapy	(reference)			(reference)		
CDK4/6 inhibitor	1.75	(1.37–2.25)	<0.001	1.95	(1.48–2.57)	<0.001
mTOR inhibitor	0.97	(0.77–1.22)	0.792	1.17	(0.92–1.49)	0.212
CDK4/6 and mTOR inhibitors	1.33	(1.01–1.77)	0.046	1.53	(1.14–2.06)	0.005
Line of ET (at least 3 lines vs 1–2 lines)	0.79	(0.68–0.91)	0.001	0.88	(0.74–1.05)	0.144
Chemotherapy						
Taxane	(reference)			(reference)		
Capecitabine	0.65	(0.57–0.75)	<0.001	0.64	(0.55–0.75)	<0.001
Other	1.20	(1.03–1.41)	0.021	1.15	(0.97–1.36)	0.103

Abbreviations: IBC, inflammatory breast cancer; ER, estrogen receptor; PR, progesterone receptor