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Outcomes of Everolimus Combined with Exemestane in HR-Positive Metastatic Breast Cancer after CDK4/6 Inhibitor Exposure

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Abstract

Everolimus (EVE) combined with exemestane (EXE) is currently approved for treating patients with metastatic hormone receptor–positive breast cancer (mHRBC) who no longer respond to nonsteroidal aromatase inhibitors (NSAIs). Notably, the BOLERO-2 trial, which supported this approval, did not include patients who had previously received CDK4/6 inhibitors (CDK4/6is), now widely used as first-line therapy for mHRBC. Therefore, the benefits and clinical outcomes of EVE plus EXE in patients with prior CDK4/6i exposure have yet to be established. We conducted a retrospective analysis of adult patients with metastatic hormone receptor–positive breast cancer (mHRBC) at our center who had disease progression following treatment with either a nonsteroidal aromatase inhibitor (NSAI) alone or in combination with a CDK4/6 inhibitor, and who subsequently received at least one cycle of everolimus (EVE) plus exemestane (EXE) between 2012 and 2018. Information collected included patient demographics, prior therapies, adverse events, and treatment outcomes. The study primarily aimed to assess differences in progression-free survival (PFS) and overall survival (OS) between patients with prior NSAI plus CDK4/6 inhibitor therapy and those who received NSAI monotherapy. Of the 43 patients analyzed, 17 had previously received CDK4/6 inhibitors. Apart from differences in the incidence of de novo metastatic disease, the two groups were largely comparable in terms of patient demographics and disease characteristics. Median progression-free survival was 3.6 months for the CDK4/6i-exposed group versus 4.2 months for those without prior exposure, while median overall survival was 15.6 months versus 11.3 months, with no statistically significant differences observed between the cohorts. Previous treatment with CDK4/6 inhibitors did not affect survival outcomes in patients with metastatic hormone receptor-positive breast cancer receiving everolimus combined with exemestane. Nevertheless, a trend toward better overall survival was observed in the CDK4/6 inhibitor-treated group, warranting further assessment in larger patient populations. The combination of CDK4/6 inhibitors with a nonsteroidal aromatase inhibitor has established itself as the standard first-line treatment for metastatic hormone receptor-positive breast cancer. Everolimus combined with exemestane is an approved therapy in subsequent lines; however, the pivotal data supporting this regimen were generated before CDK4/6 inhibitors became available. Consequently, the clinical efficacy of everolimus plus exemestane following prior CDK4/6 inhibitor treatment remained unclear. This retrospective cohort study provides real-world evidence indicating that previous exposure to CDK4/6 inhibitors does not adversely affect survival outcomes with everolimus plus exemestane.

Keywords: Cohort studies, Metastatic hormone receptor-positive breast cancer, CDK4/6 inhibitors, Everolimus plus exemestane

Introduction

Hormone receptor-positive (HR+), HER2-negative (HER2−) breast cancer accounts for the largest proportion of breast cancer cases [1]. Data from the Surveillance, Epidemiology, and End Results Program indicate an age-adjusted incidence of 87 cases per 100,000 women [1]. While localized HR+/HER2− disease carries a 100% 5-year survival rate, this falls sharply to 30.4% when metastases are present [1]. For decades, the primary approach to metastatic HR+ breast cancer (mHRBC) involved sequential endocrine

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monotherapies, with chemotherapy reserved for later palliative use [2]. Recent years have brought significant advances through targeted agents, notably mTOR inhibitors and cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) [3]. As these agents move into earlier lines of therapy, evaluating their effects on subsequent treatments using real-world evidence has become increasingly important.

Adding a CDK4/6 inhibitor to a nonsteroidal aromatase inhibitor (NSAI) has emerged as a major therapeutic advance in mHRBC. This shift is driven by key phase III trials—PALOMA-2, MONALEESA-2, and MONARCH-3—which showed that palbociclib, ribociclib, or abemaciclib combined with an NSAI substantially extended progression-free survival (PFS) versus NSAI monotherapy in the first-line setting [4–6]. Although mature overall survival results are still pending, the substantial PFS gains have established this combination as the preferred frontline standard for mHRBC.

Everolimus (EVE) combined with exemestane (EXE) remains an approved option for later-line treatment in mHRBC. Its regulatory approval rests on the BOLERO-2 study, which reported a clinically meaningful PFS benefit (median 6.9 months with the combination versus 2.8 months with EXE alone) [7]. Overall survival favored the combination arm (31 versus 26.6 months), though without statistical significance [8]. No other mTOR inhibitors have outperformed everolimus in this setting, making it the only one endorsed for clinical use. Importantly, BOLERO-2 recruited patients whose tumors had progressed on prior NSAI therapy (letrozole or anastrozole) but predated the availability of CDK4/6 inhibitors [9]. As a result, the effectiveness of EVE plus EXE after disease progression on an NSAI/CDK4/6i combination had not been established.

Materials and Methods

Patient population

This retrospective cohort study was conducted at the Knight Cancer Institute, Oregon Health & Science University, a comprehensive cancer center serving the Portland metropolitan area through its main hospital and affiliated community oncology clinics. The medical oncology clinics at OHSU evaluate approximately 750–1,000 new breast cancer cases annually.

Departmental databases and electronic pharmacy records were queried to identify patients aged 18 years or older with metastatic hormone receptor–positive breast cancer (mHRBC) who received everolimus between 2012 and 2018. Manual review of electronic medical records confirmed concomitant use of exemestane. Patients were included if their tumors were hormone receptor–positive—defined as progesterone receptor (PR) and/or estrogen receptor (ER) positivity by immunohistochemistry (IHC) per College of American Pathologists (CAP) guidelines—either at initial diagnosis or at metastatic progression. Exclusion criteria included HER2 positivity (by IHC or in situ hybridization per CAP guidelines) or treatment with everolimus plus exemestane for less than 28 days. Patients were subsequently categorized based on prior exposure to CDK4/6 inhibitors: those with previous CDK4/6i therapy and CDK4/6i-naive controls.

Data abstraction was performed by one author (M.C.) and independently verified by two additional authors (Z.M., L.A.) to ensure accuracy, with all reviewers trained in standardized chart review procedures. The study protocol was approved by the institutional review board, with a waiver of informed consent obtained prior to data collection.

Data collection

Information extracted included patient demographics, tumor features, prior treatment history (including chemotherapy, endocrine therapy, and CDK4/6 inhibitors), sites of metastasis, and select adverse events attributed to everolimus. Treatment duration with everolimus plus exemestane, reasons for discontinuation, disease response, progression, and survival outcomes were also captured. Therapy receipt was confirmed through both chart notes and electronic medication records. Disease progression was recorded as the date of the imaging study indicating progression or the clinical visit when progression was documented. Adverse events were collected from clinic visits, hospital admissions, and telephone encounters, covering the treatment period and extending up to 28 days after the final dose. Only adverse events of particular interest—stomatitis, hand-foot syndrome, and pneumonitis—were evaluated. Clinical outcomes were tracked through July 1, 2019.

Statistical analysis

The study's primary endpoints were progression-free survival (PFS) and overall survival (OS) across the two patient cohorts. Secondary endpoints included the duration of everolimus plus exemestane therapy, rates of

everolimus-related adverse events of special interest and dose reductions, and the efficacy of prophylactic steroid mouthwash. Survival analyses were measured from the date of the first everolimus dose. Patient and disease characteristics within each cohort (CDK4/6i-exposed versus control) were summarized using descriptive statistics, with categorical variables compared using Fisher's exact test and continuous variables assessed via the Kruskal–Wallis test. Time-to-event outcomes, including PFS, OS, and time to everolimus plus exemestane treatment failure, were estimated using the Kaplan–Meier method and compared with the log-rank test. The proportional hazards assumption was evaluated through inspection and testing of scaled Schoenfeld residuals, after which Cox regression models were applied to generate unadjusted and covariate-adjusted hazard ratios, with corresponding score or Wald test p-values for treatment group effects. The impact of dexamethasone mouthwash on stomatitis prevention was evaluated using odds ratios and Fisher's exact test. All statistical analyses and figures were performed using R version 3.6.1, and a significance threshold of $p < 0.05$ was applied.

Results and Discussion

A total of 48 patients with metastatic hormone receptor–positive breast cancer (mHRBC) who received everolimus plus exemestane between 2012 and 2018 were initially identified for this retrospective analysis. Five patients were excluded because they received everolimus for less than one cycle (i.e., fewer than 28 days). The final cohort included 43 patients, of whom 17 had prior CDK4/6 inhibitor exposure and 26 were CDK4/6i-naive. Among the 17 patients previously treated with a CDK4/6 inhibitor, 16 received palbociclib and 1 received ribociclib. All patients in this group received therapy after FDA approval, except for one individual who initially participated in a phase III trial of palbociclib before transitioning to standard therapy post-approval. The median interval between the end of CDK4/6i therapy and initiation of everolimus was 12 days. Four patients experienced a gap of more than 30 days between CDK4/6i and everolimus; within this subset, two received intervening treatments, one continued NSAI therapy alone, and one had no additional therapy. Patient characteristics by treatment cohort are summarized in **Table 1**. The only statistically significant difference between cohorts was the proportion of patients with de novo metastatic disease (41.2% in the CDK4/6i group vs. 11.5% in the control group, $p = 0.034$).

Table 1. Clinical characteristics and baseline patient

Patient Characteristic	Control Group (n=26)	Prior CDK4/6 Inhibitor (n=17)	p Value
Newly diagnosed metastatic disease (de novo), n (%)			0.034
No	23 (88.5)	10 (58.8)	
Yes	3 (11.5)	7 (41.2)	
Age at diagnosis, median (range), years	52.5 (29.0–79.0)	55.0 (31.0–78.0)	0.737
Number of prior therapies in the metastatic setting, median (range)	2.0 (0.0–6.0)	1.0 (1.0–8.0)	0.327
Number of prior therapies (categorized), n (%)			0.344
1	9 (34.6)	9 (52.9)	
>1	17 (65.4)	8 (47.1)	
Bone metastases at metastatic diagnosis, n (%)			>0.999
No	5 (19.2)	3 (17.6)	
Yes	21 (80.8)	14 (82.4)	
Brain metastases at metastatic diagnosis, n (%)			>0.999
No	25 (96.2)	16 (94.1)	
Yes	1 (3.8)	1 (5.9)	
Liver metastases at metastatic diagnosis, n (%)			>0.999
No	18 (69.2)	12 (70.6)	
Yes	8 (30.8)	5 (29.4)	
Lung metastases at metastatic diagnosis, n (%)			0.113
No	19 (73.1)	8 (47.1)	

Yes	7 (26.9)	9 (52.9)	
Months from metastatic diagnosis to CDK4/6 inhibitor initiation, median (range)	N/A	3.7 (0.4–105.6)	N/A
Duration of CDK4/6 inhibitor therapy, median (range), months	N/A	10.3 (2.8–33.4)	N/A
Days from CDK4/6 inhibitor discontinuation to everolimus initiation, median (range)	N/A	12.0 (1.0–408.0)	N/A
Months from metastatic diagnosis to everolimus initiation, median (range)	17.2 (0.3–114.3)	32.2 (3.4–111.8)	0.139
Follow-up duration from everolimus initiation, median (range), months	11.3 (2.0–75.4)	13.2 (2.5–36.0)	0.700
Duration of everolimus therapy, median (range), months	4.5 (0.9–16.3)	3.6 (1.0–12.8)	0.535

Abbreviations: Dx, diagnosis; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; N/A, not applicable; EVE, everolimus; Met, metastatic

In this study, the median interval from diagnosis of metastatic disease to initiation of everolimus plus exemestane was 32.2 months in patients previously treated with a CDK4/6 inhibitor and 17.2 months in CDK4/6i-naive patients (p = .139). Among the 17 patients receiving CDK4/6 inhibitors alongside an NSAI, therapy began a median of 3.7 months (mean, 19.3 months) after metastatic diagnosis and continued for a median of 10.3 months. The overall duration of everolimus plus exemestane treatment was similar between cohorts, with medians of 3.6 months (IQR, 2.9–5.9) in the CDK4/6i group and 4.5 months (IQR, 2.2–9.5) in the control group. Six months after starting therapy, 17.6% (95% CI, 6.3%–49.3%) of CDK4/6i-exposed patients remained on treatment compared to 42.3% (95% CI, 27.0%–66.3%) of controls.

Treatment discontinuation due to adverse events occurred in nine patients (20.9%), including four (23.5%) in the CDK4/6i cohort and five (19.2%) among controls. Disease progression prompted discontinuation in 32 patients, affecting 13 patients (76.5%) in the CDK4/6i group and 19 patients (73.1%) in controls. Additional reasons for stopping therapy included transition to hospice care in two control patients and death during treatment in one control patient (cause unspecified). Dose reductions of everolimus were required in nine patients overall (20.9%), with 11.8% in the CDK4/6i cohort and 26.9% in controls (p = .281).

Stomatitis developed in 19 patients (44.2%), most of whom (15/19, 78.9%) did not receive prophylactic dexamethasone mouthwash. Patients who did use the mouthwash prophylactically had a 55% lower odds of developing stomatitis during therapy or within 28 days after treatment (OR, 0.45; 95% CI, 0.08–2.08; p = .324). In the control group, one patient experienced hand-foot syndrome and two developed pneumonitis, whereas no such events occurred in CDK4/6i-exposed patients.

At the time of data cutoff, all patients had either progressed or died, leaving no censored PFS observations. Progression was determined by imaging in all patients except one control patient, whose progression was based on clinical symptoms and a rising cancer antigen 27-29. Median PFS was 3.6 months in the CDK4/6i cohort and 4.2 months in controls (HR, 1.22; 95% CI, 0.65–2.28; p = .538) **(Table 2 and Figure 1).** Adjustment for patient-level factors with univariable Cox models (age, bone metastases, and time from metastatic diagnosis to therapy start; p < .100) minimally altered the hazard ratio or significance **(Table 2).**

Among patients who discontinued therapy due to adverse events, three went on to receive further cancer-directed treatment prior to documented progression: two received alternative endocrine monotherapy and one continued exemestane alone. Consistent baseline and follow-up imaging was not available, so objective disease response rates were not calculated.

Table 2. Progression-free survival and overall survival estimates from Cox models

Covariate in Model	Hazard Ratio (95% CI), CDK4/6i vs. Control	p-value
Overall Survival		
None	0.70 (0.35–1.40)	0.308
De novo metastatic disease	0.98 (0.46–2.10)	0.964
Progression-Free Survival		

None	1.22 (0.65–2.28)	0.538
Age at diagnosis	1.18 (0.63–2.22)	0.603
Presence of bone metastasis	1.16 (0.62–2.19)	0.638
Months from metastatic diagnosis to EVE start	1.11 (0.58–2.11)	0.759

Abbreviations: CI, confidence interval; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EVE, everolimus; Dx, diagnosis; Met, metastatic; HR, hazard ratio.

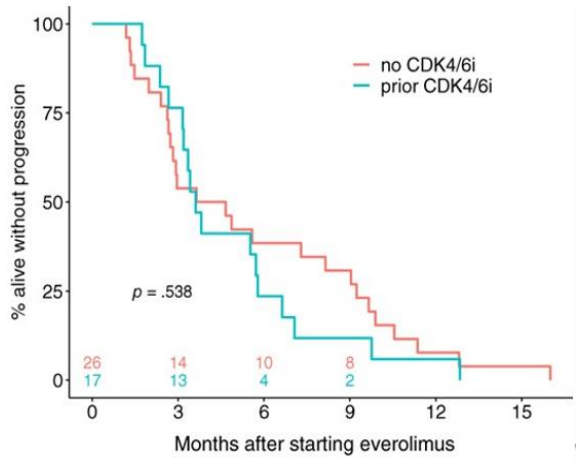

Figure 1. Progression-free survival by 6i/CDK4 exposure.
Abbreviation: CDK4/6 inhibitor, CDK4/6i

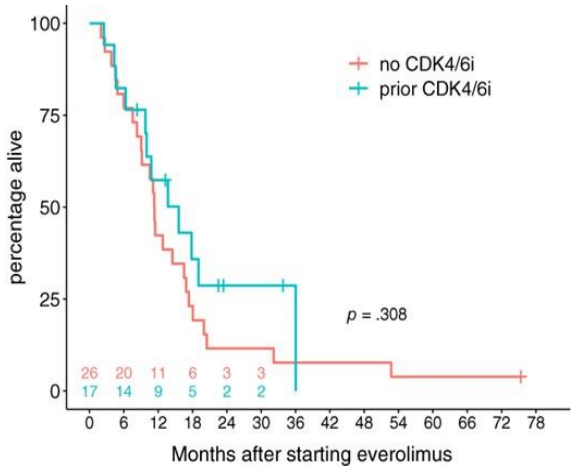

Figure 2. Overall survival by 6i/CDK4 exposure.
Abbreviation: CDK4/6 inhibitor, CDK4/6i

Out of the 43 patients analyzed, 37 had died by the time of data cutoff, with survival times ranging from 2 months to 4.4 years following the first dose of everolimus. Survival data were censored for one patient in the control cohort and five patients in the CDK4/6i group. Although the median overall survival was longer for patients previously treated with CDK4/6 inhibitors (15.6 months) compared to controls (11.3 months), no significant difference in survival was observed during the follow-up period (95% CI, 0.35–1.40; HR, 0.70; p = .308; **(Table 2 and Figure 2).** In multivariable analyses, de novo metastatic disease was associated with a trend toward improved survival (95% CI, 0.16–1.08; HR, 0.41; p = .072), whereas prior CDK4/6i exposure showed no measurable effect on overall survival (95% CI, 0.46–2.10; HR, 0.98; p = .964); **(Table 2).**

Over the past decade, treatment options for metastatic hormone receptor–positive breast cancer (mHRBC) have changed substantially. Between the introduction of tamoxifen in 1977 and 2012, management largely relied on sequential endocrine therapies followed by palliative chemotherapy [2]. Since 2012, targeted agents such as mTOR inhibitors and CDK4/6 inhibitors (CDK4/6is) have become standard-of-care additions to endocrine therapy for mHRBC. Given this evolving landscape, there is a growing need to examine the real-world effectiveness of therapies beyond the initial treatment line evaluated in clinical trials. As new first-line therapies emerge, the subsequent lines of therapy may require reassessment. Everolimus plus exemestane (EVE plus EXE) represents one such second-line therapy originally studied under a different frontline standard; with CDK4/6is now commonly added to NSAIs in first-line therapy, it is important to evaluate whether prior exposure affects the clinical benefit of EVE plus EXE in the second-line setting.

An exploratory analysis of the PALOMA-3 trial, which compared palbociclib plus fulvestrant to fulvestrant alone in mHRBC, examined time on subsequent therapies [10]. Among patients receiving EVE plus EXE after PALOMA-3, median treatment duration was 4.3 months

(95% CI, 2.5–7.6) for the palbociclib plus fulvestrant group and 5.0 months (95% CI, 2.5–9.4) for the placebo plus fulvestrant group [10]. A recent single-center retrospective study similarly found that EVE plus EXE is the most frequently used endocrine therapy after palbociclib progression (n = 12), with a median PFS of 4.9 months [11]. Our findings are consistent with these studies and provide additional real-world insights, specifically evaluating patients previously treated with either CDK4/6i plus NSAI or NSAI alone. Notably, our analysis included patients exposed to any CDK4/6 inhibitor, not limited to palbociclib, reflecting variability in prescribing patterns across practices.

Our results demonstrated that prior CDK4/6i exposure did not significantly affect progression-free survival (PFS) or overall survival (OS) in patients receiving EVE plus EXE. Although the median PFS and OS in our cohort were lower than those reported in the BOLERO-2 trial, our population was more heavily pretreated, which may explain these differences [7]. Retrospective evaluation of PFS in real-world data is limited by variable imaging schedules and absence of standardized RECIST criteria. Median OS was numerically longer in the CDK4/6i cohort (15.6 vs. 11.3 months), though not statistically significant (p = .308) [7]. When adjusted for the presence of de novo metastatic disease, survival differences between cohorts were minimal.

We also assessed adverse events (AEs) related to everolimus. Stomatitis occurred in 44.2% of patients, with 78.9% lacking documentation of prophylactic dexamethasone mouthwash, which was not universally implemented at the time. This rate is slightly lower than the 56% reported in BOLERO-2, where prophylactic mouthwash was not used [7]. These findings support the role of prophylactic steroid mouthwash in reducing stomatitis, as highlighted by the SWISH trial [12]. Other everolimus-related AEs, including hand-foot syndrome and pneumonitis, were observed in 2.3% and 4.7% of patients, respectively. Overall, 20.9% of patients required a dose reduction. Of the nine patients in the included cohort who discontinued everolimus due to AEs, four of the five excluded patients (treated for less than one cycle) also stopped therapy because of an AE. Considering these five patients, 27.1% of patients initiating EVE plus EXE discontinued therapy permanently due to AEs. Importantly, rates of special-interest AEs, dose reductions, and AE-related discontinuations did not differ significantly between patients with or without prior CDK4/6i exposure, indicating that prior CDK4/6i therapy does not preclude safe and effective use of EVE plus EXE.

Limitations of this study include its retrospective design, single-institution setting, and relatively small sample size, which may have limited statistical power and contributed to potential false-negative findings. Therapy lines were not strictly defined; some patients received multiple prior treatments before CDK4/6i or EVE plus EXE, and three patients in the CDK4/6i cohort received additional therapy between CDK4/6i and EVE plus EXE. While narrowing the population to strictly first-line CDK4/6i followed by second-line EVE plus EXE would reduce confounding, we prioritized a broader sample size to provide more real-world data. Despite these limitations, our study supports the use of EVE plus EXE as a safe and effective second-line therapy for mHRBC, even among patients with prior CDK4/6i exposure.

Implications for practice

Using 261 tumor samples from the BOLERO-2 phase III clinical trial, this study shows that a substantial proportion (20%–30%) of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancers do not have a luminal A or B gene expression profile. This group of patients with nonluminal disease has a poor survival outcome regardless of the addition of everolimus to exemestane. This is the second study that confirms the prognostic value of this biomarker. Overall, these findings indicate a necessity to design novel clinical trials targeting nonluminal disease within HR+/HER2-negative breast cancer.

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