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RESEARCH

Everolimus plus endocrine therapy beyond CDK4/6 inhibitors progression for HR+ /HER2– advanced breast cancer: a real-world evidence cohort

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Abstract

Purpose Everolimus in combination with endocrine therapy (ET) was formerly approved as 2nd-line therapy in HR(+)/HER2(−) advanced breast cancer (aBC) patients (pts) progressing during or after a non-steroidal aromatase inhibitor (NSAI). Since this approval, the treatment landscape of aBC has changed dramatically, particularly with the arrival of CDK 4–6 inhibitors. Endocrine monotherapy after progression to CDK4/6 inhibitors has shown a limited progression-free survival (PFS), below 3 months. Evidence of the efficacy of everolimus plus ET after CDK4/6 inhibitors is scarce.

Methods A retrospective observational study of patients with aBC treated with everolimus and ET beyond CDK4/6-i progression compiled from February 2015 to December 2022 in 4 Spanish hospitals was performed. Clinical and demographic data were collected from medical records. The main objective was to estimate the median progression-free survival (mPFS). Everolimus adverse events (AE) were registered. Quantitative variables were summarized with medians; qualitative variables with proportions and the Kaplan–Meier method were used for survival estimates.

Results One hundred sixty-one patients received everolimus plus ET (exemestane: 96, fulvestrant: 54, tamoxifen: 10, unknown: 1) after progressing on a CDK4/6 inhibitor. The median follow-up time was 15 months (interquartile range: 1–56 months). The median age at diagnosis was 49 years (range: 35–90 years). The estimated mPFS was 6.0 months (95%CI 5.3–7.8 months). PFS was longer in patients with previous CDK4/6 inhibitor therapy lasting for > 18 months (8.7 months, 95%CI 6.6–11.3 months), in patients w/o visceral metastases (8.0 months, 95%CI 5.8–10.5 months), and chemotherapy-naïve in the metastatic setting (7.2 months, 95%CI 5.9–8.4 months).

Conclusion This retrospective analysis cohort of everolimus plus ET in mBC patients previously treated with a CDK4/6 inhibitor suggests a longer estimated mPFS when compared with the mPFS with ET monotherapy obtained from current randomized clinical data. Everolimus plus ET may be considered as a valid control arm in novel clinical trial designs.

Keywords Metastatic breast cancer · Endocrine treatment · Everolimus · Hormone receptor positive

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Introduction

Hormone receptor-positive (HR +), HER2-negative advanced breast cancer (ABC) constitutes around 60–70% of MBC cases, accounting for a substantial burden in clinical practice [1]. It is estimated that 6–10% of breast cancer patients are diagnosed with de novo metastatic disease, while up to 30% of those initially diagnosed with early-stage breast cancer will eventually progress to the metastatic stage [2].

Endocrine therapy (ET) is the cornerstone of the treatment of HR(+)/HER2(−) ABC due to both its efficacy and safety. Delaying the initiation of chemotherapy MBC patients is of paramount importance, especially in cases where endocrine-based therapies or targeted agents remain viable treatment options [3]. Recent clinical evidence has emphasized the significance of prolonging the use of hormone-based therapies, such as selective estrogen receptor modulators (SERMs), aromatase inhibitors, and selective estrogen receptor degraders (SERDs), in HR + ABC. Many pivotal phase III clinical trials with CDK4/6 inhibitors have demonstrated the efficacy of these agents in improving progression-free survival (PFS) and delaying the need for cytotoxic chemotherapy in certain subsets of MBC patients [4–6]. Notably, this approach not only helps to minimize the potential toxicities associated with chemotherapy but also preserves the patient's quality of life, providing them with a longer period of disease management control before the need for more aggressive treatment modalities.

Resistance to endocrine therapies in MBC is a complex and multifaceted phenomenon that presents a significant challenge in the management of HR + breast cancer. Some key points regarding resistance to endocrine therapies in ABC include primary and acquired resistance, alterations in hormone signaling pathways, crosstalk with growth factor signaling pathways, and the emergence of treatment-resistant cell populations [7–9].

The mTOR inhibitor everolimus in combination with ET was shown to restore endocrine sensitiveness in tumors while progressing on or after non-steroidal aromatase inhibitor in HR + /HER2− ABC [10]. The registration randomized BOLERO-2 trial was conducted in the era of pre-CDK 4/6 inhibitors. Other studies have shown the efficacy and safety of everolimus in combination with the SERD fulvestrant as well [11, 12]. Nowadays, CDK4/6 inhibitor-based ET stands as the first-line treatment for HR + /HER2− ABC and pushed everolimus-based combinations to second or later lines, despite data being largely missing in this scenario. Subsequent ET in monotherapy following CDK-i revealed poor disease control in terms of PFS and overall response rates [13–16]. On the other hand, there are limited data on the efficacy and safety of everolimus plus ET beyond CDK-i plus ET [17–21]. While searching new targeted therapies to restore the endocrine sensitiveness after CDK-i everolimus could be a viable consideration in the absence of an accessible clinical trial, offering a potential therapeutic avenue.

In this real-world study, we aimed to assess the efficacy and safety of everolimus + ET after previous CDK 4/6 inhibitor in patients with HR + /HER2− MBC.

Material and methods

Study design

We performed a retrospective observational study of all incident patients with ABC progressing to a CDK4/6-i combo and treated with everolimus between February 2015 and December 2022 from 4 institutions in Madrid, Spain. The selection of patients was obtained from institutional Pharmacy records. The researchers manually gathered information from the electronic health record, which encompassed various patient demographic details, including menopause status, receptor status, de novo metastatic disease, tumor histology, breast cancer phenotype according to immunohistochemistry, primary endocrine resistance, the existence of metastases solely in the lung, liver, or bone, the total count of metastatic sites, previous treatment regimens in the metastatic setting, prior exposure CDK4/6 inhibitor agent, and the ET combined with everolimus (AI, tamoxifen, or fulvestrant). Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET [7]. Patients were considered evaluable if everolimus + ET was administered for at least 30 days.

The main objective was to estimate the median PFS (mPFS). PFS was defined as the difference in time between the start of everolimus + ET and the date of first documented progression, missing of follow-up, or death, whichever occurred first. Gathered information regarding safety, dosing, discontinuation, and the use of prophylactic measures while on treatment with everolimus (as steroid mouthwashes). The type, grade, and relation of the adverse events emerging during the treatment with everolimus were collected according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The study was approved by each institutional Research Ethics Board.

Statistical analysis

For descriptive purposes, quantitative variables were summarized with medians (range), and qualitative variables with proportions. We used the Kaplan–Meier method for survival estimates. Analyses were performed using STATA/SE version 15.0 (StataCorp).

Table 1 Clinical and pathological characteristics of the patients

	Number ($n=161$)
Age, years	49 (28–84)
Number of lines of treatment prior to everolimus	2 (1–8)
Menopausal status at diagnosis, *n* (%)	
Premenopausal	86 (53.4)
Postmenopausal	69 (42.8)
Unknown	6 (3.8)
TNM stage at diagnosis, n (%)	
I–II	56 (35.0)
III	65 (40.6)
IV (de novo)	39 (24.4)
BC phenotype at diagnosis, *n* (%)	
Luminal A	52 (32.9)
Luminal B	99 (62.7)
Non-luminal	7 (4.4)
Hormone resistant, *n* (%)	36 (22.8)
Visceral metastasis, *n* (%)	104 (65%)
Prior chemotherapy in the advanced setting, *n* (%)	48 (30.2)

Results

We identified a total of 161 ABC patients treated with everolimus plus ET. The median follow-up time was 15 months (interquartile range: 1–56 months). Table 1 shows the main clinical and pathological variables of the population included in the study. Median age at diagnosis was 49 years (range: 25–84 years). The median number of prior lines of treatment for advanced disease cohort was 2. 30.2% of patients had received prior chemotherapy for ABC.

The estimated median PFS (Fig. 1) in the overall cohort was 6.0 months (95%CI 5.3–7.8 months). The low number of recorded death events made it impossible to estimate the median overall survival.

Table 2 summarizes the estimated mPFS in subgroups of the post-CDK4/6 inhibitor cohort. When we considered the duration of the prior treatment with CDK4/6 inhibitors, the estimated mPFS was 5.3 months, 95%CI 3.4–8.2 months (CDK4/6 inhibitor for < 6 months, $n=26$ patients); 5.6 months, 95%CI 3.9–7.0 months (CDK4/6 inhibitor for 6–12 months, $n=51$ patients); 5.0 months, 95%CI 3.0–7.7 months (CDK4/6 inhibitor for 12–18 months, $n=34$ patients); and 8.7 months, 95%CI 6.6–11.3 months (CDK4/6 inhibitor for > 18 months, $n=50$ patients).

Regarding the type of prior CDK4/6 inhibitor, we estimated a mPFS of 7.2 months (95%CI 5.3–8.5 months) for patients treated with palbociclib ($n=100$), a mPFS of 5.6 months (95%CI 3.4–7.8 months) for those treated with ribociclib ($n=44$), and a mPFS of 4.8 months (95%CI

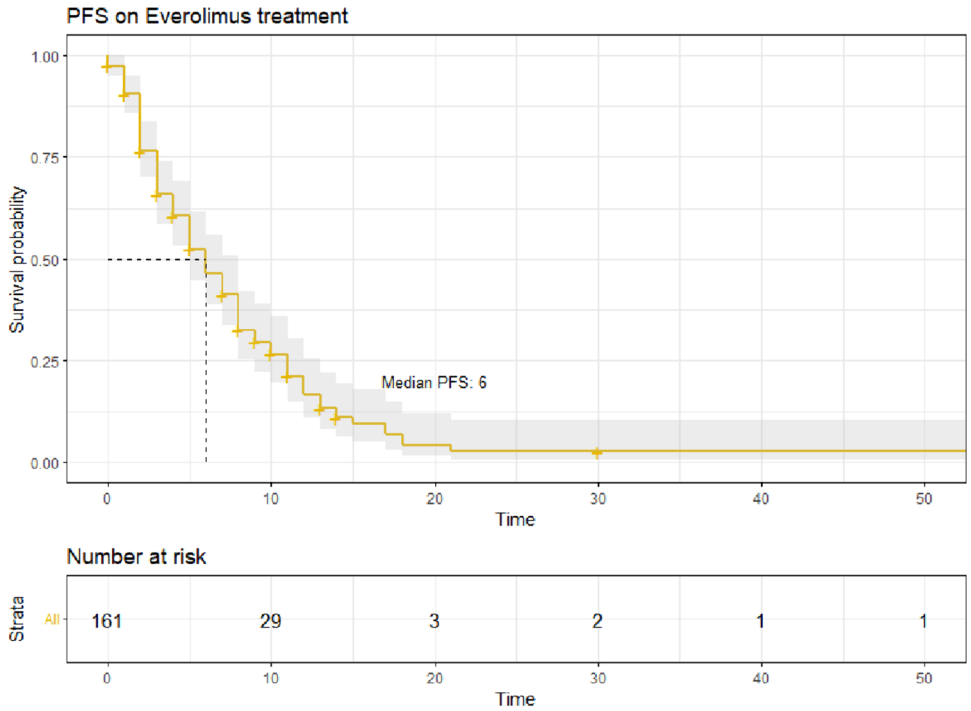

Fig. 1 Kaplan–Meier curve for the estimated progression-free survival in months for the overall cohort of patients with ABC treated with everolimus plus ET

Table 2 Estimated median progression-free survival (PFS) and 95% confidence interval, for the post-CDK4/6 inhibitor cohort, and for subgroups according to duration of prior CDK4/6 inhibitor, type of prior CDK4/6 inhibitor, presence of visceral metastasis, and prior use of chemotherapy for advanced disease

	Number of patients	Median PFS (95% CI), months
Post-CDK4/6 inhibitor	161	6.0 (5.3–7.8)
Duration of prior CDK4/6 inhibitor		
≤6 months	26	5.3 (3.4–8.2)
6–12 months	51	5.6 (3.9–7.0)
12–18 months	34	5.0 (3.0–7.7)
≥18 months	50	8.7 (6.6–11.3)
Type of prior CDK4/6 inhibitor		
Palbociclib	100	7.2 (5.3–8.5)
Ribociclib	44	5.6 (3.4–7.8)
Abemaciclib	17	4.8 (2.9–7.2)
Presence of visceral metastasis		
Yes	105	5.6 (3.9–7.0)
No	56	8.0 (5.7–10.5)
Prior chemotherapy for advanced disease		
Yes	50	4.7 (3.2–6.0)
No	111	7.2 (5.9–8.4)

2.9–7.2 months) for patients who received prior abemaciclib ($n=17$).

According to the endocrine partner combined with everolimus, the estimated mPFS was 5.7 months (95%CI 4.0–7.2 months) with exemestane ($n=96$), 8.2 months (95%CI 1.7–NR) with tamoxifen ($n=10$), and 6.6 months (95%CI 5.3–10.7) with fulvestrant ($n=54$).

Patients without visceral involvement ($n=56$) showed an mPFS of 8.0 months (95%CI 5.8–10.5 months) vs mPFS was 5.6 months (95%CI 3.9–7.0 months) in the presence of visceral metastasis ($n=105$). For patients without prior chemotherapy in the metastatic setting ($n=111$) we estimated an mPFS of 7.2 months (95%CI 5.9–8.4 months), and 4.7 months (95%CI 3.1–6.0 months) for patients with previous chemotherapy ($n=50$).

Everolimus starting doses were 10 mg (85%), 5 mg (14%), and 7.5 mg (1%). The initial dose was reduced in 35% of patients due to adverse events. A total of 50 patients discontinued permanently everolimus due to adverse events (16%). The main reasons for treatment discontinuation were hyperglycemia, skin rash, and pneumonitis. Dexamethasone mouthwash was used as prophylactic measure in 138 patients (46%). Table 3 shows the frequency and grading of the collected adverse events in the entire cohort.

Table 3 Adverse events (incidence > 15%) and grades related to everolimus plus endocrine therapy in the overall cohort ($n=161$)

Adverse event, *n* (%)	Any grade	Grade 1	Grade 2	Grade 3
Mucositis	79 (49)	56 (34.7)	18 (11.1)	5 (3.1)
Anemia	55 (34.1)	50 (31)	4 (2.4)	1 (0.6)
Hyperglycemia	36 (22.3)	30 (18.6)	4 (2.4)	2 (1.2)
Skin rash	42 (26)	30 (18.6)	10 (6.2)	2 (1.2)
Pneumonitis	30 (18.6)	19 (11.8)	10 (6.2)	1 (0.6)
Diarrhea	31 (19.2)	28 (17.3)	3 (1.8)	–

Discussion

In this real-world cohort, the use of ET + everolimus after prior CDK4/6 inhibitor showed a median PFS of 6.0 months. This PFS result appears to be longer when compared to the endocrine monotherapy of the control arms from current RCT [13–16]. The duration of the treatment with the previous CDK4/6 inhibitor can influence the benefit of the subsequent everolimus containing regimen, being those patients with a previous CDK4/6 inhibitor for ≥ 18 months who could do best with everolimus + ET (median PFS 8.7 months). This signal (prior longer exposure to CDK4/6-i correlates to better PFS on subsequent PFS endocrine therapy) was similar to the exploratory analysis observed in other randomized studies [15, 16]. The absence of visceral metastases and chemotherapy-naïve patients also showed longer PFS with everolimus + ET. Therefore, according to these data, treatment strategies with everolimus-based combinations seem to remain effective in selected patients with advanced HR + / HER2− breast cancer after the current standard of care with CDK4/6 inhibitors.

In HR + /HER2− MBC, when disease progression occurs following CDK4/6 inhibitor therapy, the subsequent treatment approach often involves the consideration of various endocrine-based strategies [3]. Current clinical trials exploring the efficacy of new drugs in the second-line setting, after previous CDK4/6 inhibitors, have chosen an endocrine monotherapy as their control arm, usually fulvestrant monotherapy. This treatment shows poor median PFS (2.8–4.8 months among different trials) [15, 22], suggesting that this may not be an optimal comparator in this scenario.

To date, there is no standard treatment recommended as subsequent therapy in patients with advanced HR + / HER2− breast cancer that have progressed under CDK4/6 inhibitors [23]. In this setting of unmet need, several novel drugs are being tested in clinical trials with encouraging results and some FDA/EMA approvals: PIK3CA inhibitors (alpelisib) [24], AKT inhibitors (capivasertib -FDA approved) [22], new oral SERDs such as elacestrant (FDA and EMA approved) [15] or camizestrant [25], and PARP inhibitors (olaparib, talazoparib -approved) [26, 27]. Despite

promising results, the optimal sequence of treatments after progression to CDK4/6 inhibitors in the first line remains challenging, and chemotherapy is still one of the most used therapies even in the absence of visceral crisis. Apart from biomarkers, such as ESR1, PIK3CA, and pathogenic BRCA mutations, the duration of treatment with CDK4/6 inhibitors has been suggested as one of the factors to be considered when selecting the most adequate treatment sequencing. This has been explored in recent clinical trials with new drugs. In the EMERALD trial, the new SERD elacestrant was compared to endocrine monotherapy in patients with HR + /HER2− MBC, all of them pre-treated with a CDK 4/6 inhibitor [15]. The mPFS of elacestrant in patients with tumors harboring ESR1 mutations was 3.8 months. This varied according to the duration of the previous CDK 4/6 inhibitor, with an mPFS of 4.1 months with elacestrant in patients with at least 6 months of CDK 4/6 inhibitor and an mPFS of 8.6 months with elacestrant in patients with at least 12 months of CDK 4/6 inhibitor. This benefit of elacestrant depending on the duration of the CDK 4/6 inhibitor was consistent in both ESR1 mutated and wild-type tumors.

Beyond novel targeted agents, the evidence of the efficacy of older regimens, such as everolimus + ET, is scarce post-CDK4/6 inhibition. We identified 5 studies that explored the efficacy of everolimus in patients with HR + / HER2− MBC who had disease progression after CDK 4/6 inhibitors [18–21]. A real-world study published by Hanjie Mo et al. [18] included 192 patients (79 with previous CDK 4/6 inhibitor and 113 naïve for CDK 4/6 inhibitors). The mPFS of everolimus + ET was 3.8 months and 5.4 months, respectively. Another series by Cook et al. [19] reviewed 43 patients (17 with previous CDK 4/6 inhibitor). The mPFS of everolimus-based combinations were 3.6 months (CDK 4/6 inhibitor pre-treated patients) and 4.2 months (no previous CDK 4/6 inhibitor). One of the biggest series published is the one conducted by Rozenblit et al. [21]. The authors collected information from 622 patients with MBC and estimated the median time to the next treatment (TTNT). Of interest, 54 patients had received everolimus + ET in the second line after CDK 4/6 inhibitor (median TTNT 4.3 months), and 69 patients in the third line after CDK 4/6 inhibitor (median TTNT 4.1 months). One of the most recent articles on this regard is the one published by Cengiz Karacin et al. [20]. The researchers explored the PFS of different treatment patterns in HR + /HER2− MBC after CDK 4/6 inhibitors. The mPFS for everolimus in the second line (36 patients) was 11 months, in the third line (22 patients) was 6.7 months, and fourth and subsequent lines (38 patients) were 6.7 months. The median duration of the CDK 4/6 inhibitor was 19 months in the first line, 13 months in the second line, and 11 months in the third line. This is aligned with our results considering that the longer the duration of the CDK 4/6 inhibitor, the higher the benefit of subsequent treatment with everolimus (especially patients with ≥ 18 months of CDK 4/6 inhibitor).

James M. Martin et al. published a real-world data study from a nationwide de-identified database derived from electronic health records (EHRs), focusing on 1210 patients diagnosed with HR + /Her2 − metastatic breast cancer (MBC) [28]. The authors evaluated subsequent treatment strategies following progression on CDK4/6 inhibitors. They analyzed 839 patients who received documented second-line therapy after first-line CDK4/6 inhibitor treatment failure. A total of 29.7% opted for chemotherapy, with a declining trend observed over time. Additionally, 36.0% of patients continued with CDK4/6 inhibitors as their second-line therapy. Continuing with CDK4/6 inhibitors showed significant associations with improved rwPFS and OS compared to chemotherapy. A total of 99 patients were treated with everolimus after a CDK4/6 inhibitor, with an estimated median rwPFS of 3.3 months. The administration of everolimus did not show statistically significant advantages in terms of rwPFS when compared to chemotherapy. However, in terms of OS, treatment involving everolimus exhibited enhanced OS compared to chemotherapy. In the post-CDK setting, this is relevant because the start of chemotherapy often represents a turning point in terms of quality of life in the journey of patients with metastatic luminal breast cancer.

In clinical research, everolimus has been combined with various endocrine partners. The Pre0102 trial evaluated the addition of everolimus to fulvestrant with an improvement in PFS (10.1 months to 5.3 months) [11]. The phase 2 TAMRAD trial tested the combination of tamoxifen + everolimus vs tamoxifen alone [29]. The estimated median PFS was 8.6 months in the combination arm versus 4.5 months in the tamoxifen monotherapy arm. None of these trials included patients with prior CDK4/6 inhibitor treatment. In our cohort, the estimated median PFS for everolimus + tamoxifen was similar to the TAMRAD trial (8.1 months) although the number of patients in our study with that regimen was very limited (10 patients). Regarding the combination of everolimus and fulvestrant, we estimated a median PFS of 6.6 months. A shorter PFS with everolimus + fulvestrant in our study could be due to many factors such as the previous exposure to CDK 4/6 inhibitor, the common selection of fulvestrant in patients with secondary resistance to ET, and it should also be noted that we lack information regarding the presence of ESR1 mutations.

The biologic mechanisms of resistance to CDK4/6 inhibitors have been described and include increased activity of the CDK4/6 checkpoint kinase, activation of CCNE1/CDK2 leading to phosphorylation of retinoblastoma (RB) protein or RB1 loss of function, c-MET mutations, CDK6 amplification, and activation of the PI3K/AKT/mTOR pathway [30–34]. The activation of compensatory signaling pathways, such as the PI3K/AKT/

mTOR pathway can also facilitate cell cycle progression independently of CDK4/6, contributing to resistance and tumor cell survival. Tough efficacy of everolimus has been observed regardless this pathway activations, the hypothesis that everolimus beyond progression might be more effective when this pathway is activated should be revisited [22, 35].

Further research efforts are ongoing to elucidate additional mechanisms and identify potential biomarkers associated with CDK4/6 inhibitor resistance, facilitating the development of personalized and targeted treatment approaches for breast cancer patients [36]. Maybe it is not the effect of a sole biomarker but a combination of molecular and clinical aspects (such as the performance of the upfront CDK 4/6 inhibitor or the burden of metastatic disease) that should be put into the equation when deciding the treatment sequencing in HR + /HER2− MBC.

Our study has some limitations that need to be considered when interpreting the findings. Firstly, an observational study may be prone to selection bias, where the study population is not representative of the broader population, leading to skewed results [37]. However, all the incident cases along these 4 centers were compiled as well as the multicenter design of our study may control this bias. Second, some confounding variables, such as lifestyle factors, comorbidities, and treatment preferences, can influence outcomes and misunderstand the true effect of the studied exposure, making it challenging to establish causal relationships. Third, it should also be noted that the chance of inaccurate or incomplete data collection, as well as misclassification of exposure or outcome variables, can introduce information bias, compromising the validity and reliability of the study results. Fourth, observational studies may also be susceptible to survivorship bias, where the inclusion of only long-term survivors can skew the results, leading to an overestimation of treatment efficacy. However, this would be more relevant when estimating overall survival effects, and our study focused on progression-free survival as a surrogate. Indeed, the limited number of death events did not allow a formal estimation of median overall survival. We expect this data will become available with a longer follow-up. Fifth, without randomization, observational studies cannot control for all potential confounders, making it difficult to establish a cause-and-effect relationship between exposures and outcomes. While observational studies provide valuable insights into real-world clinical practices and outcomes, they must be interpreted cautiously. Complementary evidence from randomized controlled trials (RCTs) and meta-analyses can help mitigate these limitations and provide a more comprehensive understanding of the complexities of cancer treatment and management. Lastly, our series lacked information concerning molecular markers that are now relevant in the current treatment algorithm, such as ESR1 or PIK3CA mutations.

There are also strengths to this study. Real-world studies often include a diverse patient population and encompass a broad spectrum of patient characteristics. Consequently, they provide a comprehensive representation of the actual patient experience [38]. By observing actual practice patients over extensive periods, these studies provide insights into long-term treatment outcomes and real-world treatment patterns that may not be captured in the relatively controlled setting of clinical trials.

Real-world studies often encompass patients with comorbidities or diverse clinical histories, allowing for a more comprehensive assessment of the treatment's efficacy and safety in daily practice. Thus, these studies provide valuable insights for healthcare providers, aiding in treatment decision-making and the development of tailored treatment strategies, which is of particular importance given the limited access to biomarkers in cancer, particularly in low and middle-income countries [39].

Our study could contribute to a more comprehensive understanding of the real-world effectiveness of everolimus in the treatment algorithm of HR + /HER2− MCB, complementing the findings from RCTs and aiding in evidence-based clinical decision-making and healthcare policy development.

Conclusion

In our cohort, the use of everolimus plus ET in mBC patients previously treated with a CDK4/6 inhibitor showed a clinically significant benefit in terms of PFS, especially in patients with a previous CDK4/6 inhibitor for ≥ 18 months, without visceral metastasis, and no previous chemotherapy for advanced disease. Everolimus plus ET remains an active treatment option after a CDK 4/6 inhibitor and should be considered as a valid comparator in modern clinical trials design.

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Data availability Research data can be provided by the authors per request.

Declarations

Competing interests R.S.B. has received honoraria as speaker: Novartis, AstraZeneca, MSD, Lilly, GSK, Clovis, Seagen, Pfizer, Roche, and Gilead Oncology, Advisory fees: Novartis, Lilly, GSK, Seagen, and Roche, and Non-financial disclosure: ESMO Young Oncologists Committee Member and Scientific Secretary of the Spanish Society of Medical Oncology; A.L.S. has received a speaker honorarium from Pfizer, Novartis, Daiichi-Sankyo, MSD, and Accord; Y.J.G. has received speaker honoraria from Roche, Novartis, Pfizer and Daiichi and travel grants from Roche, Novartis, Pfizer, and Daiichi and Gilead; A.S.T. declares no conflict of interest; M.A. has received a speaker honorarium from Novartis, Pfizer, Lilly, Gilead, and AstraZeneca; I.E.D.G. has received a speaker honorarium from Pfizer, Novartis, Lilly, Gilead, AstraZeneca, and Daiichi-Sankyo; F.M. has received consultancy/speaker fees from Novartis, Roche, Pfizer, Astra Zeneca, Daiichi-Sankyo, Gilead, Exact Sciences, Seagen, and Pierre Fabre and Institution research funding from Pfizer, Travel support from Pfizer, Pierre Fabre, and Gilead; P.T. is a Consultant or played Advisory Role in AstraZeneca, Daiichi-Sankyo, Novartis, Roche, Adamed, and Seagen, Speaker honorarium: Pfizer, MSD, Novartis, Lilly, AstraZeneca, Daiichi-Sankyo, and Seagen, Travel grants: Pfizer, AstraZeneca, Novartis, and GSK, and Research funding: Seagen; B.H.L. has received a speaker honorarium from Roche, Novartis, PharmaMar, Eisai, Pfizer, Teva, Kyowa Kirin, AstraZeneca, GSK, Daiichi-Sankyo, and Gilead as well as travel/educational grants from Roche, Pfizer, Novartis, Merck, Kyowa Kirin, Pierre Fabre, and Lilly; A.L. has received financial support for attending symposia and speaker honorarium from Eli Lilly & Co. and Novartis, which is not relevant to this study; L.L. declares no conflict of interest; S.G.C. declares no conflict of interest; A.M. has received honoraria from AstraZeneca, Clovis, GSK, MSD, and PharmaMar; S.L.T. has not received research grants to disclose nor owns stocks to disclose, speaker honorarium from Lilly, advisory role for AstraZeneca, Daiichi-Sankyo, Gebro Pharma, Gilead, GSK, Lilly, Menarini_Stemline, Novartis, Pfizer, Pierre Fabre, Roche, and Seagen and is a member of board of directors of SEOM and GEICAM; L.M. has received a speaker honorarium from Novartis; C.B. has received speakers' honoraria: Roche, Novartis, Lilly, Daiichi AstraZeneca, and GSK, travel grant: Roche, Novartis, and Pfizer; J.A.G.S. declares consultative and advisory services for Seagen, AstraZeneca, Daiichi-Sankyo, Novartis, Gilead, and Menarini, Consultancy/speaker fees from Celgene, Eli Lilly, EISAI, MSD, Exact Sciences, Tecnofarma, Nolver (Adium), Asofarma, and Roche, Institution and research funding from AstraZeneca, and Travel support from Gilead, AstraZeneca, and Daiichi-Sankyo; E.C. has received research grants from Roche and has received a speaker honorarium and Advisory Board meetings from Astra Zeneca-Daiichi-Sankyo, Roche, Pfizer, Novartis, MSD, Lilly, Gilead, and no owns stock in any company; M.M has received research grants from Roche, PUMA, and Novartis, consulting/advisory fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Taiho Oncology, Daiichi-Sankyo, Menarini/Stemline, and Pfizer and speakers' honoraria from AstraZeneca, Lilly, Amgen, Roche/Genentech, Novartis, and Pfizer.

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