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RESEARCH

EVERolimus effectiveness after proGREssion on ENdocrine therapy plus CDK4/6 inhibitor for ER-positive/HER2-negative advanced breast cancer: EVERGREEN study

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Abstract

Purpose There is limited evidence supporting the addition of everolimus to endocrine therapy in women with ER-positive/HER2-negative advanced breast cancer disease progression on CDK4/6 inhibitors. We aimed to assess the effectiveness and safety of everolimus in this setting.

Methods EVERGREEN is a multicentre, international, retrospective quasi-experimental study of women with ER-positive/HER2-negative advanced breast cancer who started an immediate next line of endocrine therapy after progression on CDK4/6 inhibitors until 31/12/2022. We compared patients exposed to endocrine therapy plus everolimus in centres where this is the standard-of-care with those treated in centres where endocrine therapy alone is the standard-of-care. The primary endpoint was real-world progression-free survival (rwPFS). Secondary endpoints were time to everolimus failure, time to chemotherapy, and overall survival.

Results We included 207 women (everolimus $n=150$, endocrine therapy alone $n=57$), with a median follow-up of 31.8 months. Baseline characteristics were well balanced, except for a higher number of prior lines of therapy in the everolimus cohort. Median rwPFS was 5.0 for patients exposed to everolimus vs 4.3 months for endocrine therapy alone (adjusted hazard ratio 0.68, 95% confidence interval 0.47–0.99). Time to everolimus failure was 4.2 months. There were no statistically significant differences in time to chemotherapy or overall survival. The safety profile was consistent with previous reports.

Conclusion The addition of everolimus to standard endocrine therapy resulted in a modest clinical benefit for patients with ER-positive/HER2-negative advanced breast cancer candidates for endocrine therapy after CDK4/6 inhibitors. This limited benefit and the toxicity profile warrants careful selection of patients with favourable risk-benefit profile.

Keywords Breast neoplasms · Everolimus · Hormonal antineoplastic agents · Quasi-experimental study · Comparative effectiveness research

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Abbreviations

AKT1	RAC-alpha serine/threonine-protein kinase gene
CDK4/6	Cyclin-dependent kinase 4/6
CI	Confidence interval
CNS	Central nervous system
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
ESR1	Estrogen receptor 1 gene
ET	Endocrine therapy
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IHC	Immunohistochemistry
IPTW	Inverse probability of treatment weighting
ISH	In-situ hybridization
IQR	Interquartile range
mos	Months
mTOR	Mammalian target of rapamycin
NGS	Next-generation sequencing
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene
PTEN	Phosphatase and tensin homolog gene
rwPFS	Real-world progression-free survival
SoC	Standard of care

Introduction

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors represented a substantial breakthrough in the management of patients with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer [1–7]. In February 2015, the U.S. Food and Drug Administration granted palbociclib accelerated approval [8], with subsequent European initial market authorisation later in November 2016 [9]. This breakthrough was followed by ribociclib and abemaciclib [10, 11], redefining the standard-of-care for these patients. For patients who are candidates to continue cytotoxic-free systemic therapy after progression on CDK4/6 inhibitors, the optimal treatment sequence remains uncertain. Clinical practice guidelines recommend genomic biomarker testing and clinical characteristics, such as duration on prior CDK4/6 inhibitors, for defining the next line of systemic therapy [12–16]. Alpelisib for *PIK3CA*-mutated disease (30–40%) [17, 18], capivasertib for patients with tumours harbouring *PIK3CA*/*AKT1*/*PTEN* alterations (≈45%) [19], and elacestrant in the presence of *ESR1*-mutation (commonly acquired after exposure to aromatase inhibitors in up to ≈50%, depending on the timing of testing) [19, 20], have been approved in Europe since July 2020 [21–23], June 2024 [24, 25], and September 2023 [20, 26], respectively. However, these actionable alterations are not detected in nearly half of ER-positive/HER2-negative advanced breast cancer [19]. In their absence, fulvestrant monotherapy is the most studied control arm of prospective clinical trials after progression on CDK4/6 inhibitors [20, 27–30].

Despite limited prospective comparative evidence, the addition of everolimus to endocrine therapy is a recommended treatment option in the post-CDK4/6 inhibitors setting [12, 13, 15, 16]. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor, approved for the treatment of ER-positive/HER2-negative advanced breast cancer since 2012 [31]. BOLERO-2 was the registration trial demonstrating a statistically significant progression-free survival benefit for the addition of everolimus to exemestane after progression on aromatase inhibitor [32]. Although none of the enrolled patients had prior exposure to CDK4/6 inhibitors, non-clinical data suggest PI3K/AKT/mTOR pathway activation after exposure to CDK4/6 inhibitors, supporting the potential role of everolimus to overcome resistance [33, 34]. Several real-world studies assessed the effectiveness of everolimus after CDK4/6 inhibitors, but most are non-comparative [35–41]. Given its toxicity profile and uncertain magnitude of clinical benefit in this setting, the use of everolimus varies across different centres, representing a unique opportunity to leverage the use of real-world data for comparative effectiveness. We aimed to evaluate the effectiveness and safety of adding everolimus to endocrine therapy after progression on CDK4/6 inhibitors.

Methods

Study design and setting

The EVERGREEN study is a multicentre, international, retrospective quasi-experimental study comparing two cohorts of patients with ER-positive/HER2-negative advanced breast cancer treated with endocrine therapy with or without everolimus, after progression on CDK4/6 inhibitors (eFigure 1 in Supplement 1, trial protocol in Supplement 2). The study was conducted in 14 centres from Belgium (four) and Portugal (ten), and the sites were selected according to the local standard use of everolimus in this setting: nine sites where everolimus is routinely added to endocrine therapy (everolimus cohort) vs five sites where endocrine therapy alone is the standard-of-care with no use of everolimus in this setting (endocrine therapy alone cohort) (eTable 1 in Supplement 1). The study was conducted following the ISPOR Guidelines for comparative effectiveness research [42–44] and the manuscript was prepared according to the ESMO Guidance for Reporting Oncology real-World evidence [45].

Participants

We included all the consecutive adult women diagnosed with ER-positive/HER2-negative advanced breast cancer who started the study treatment – immediate next line of therapy after progression on endocrine therapy plus CDK4/6 inhibitors – since the introduction of CDK4/6 inhibitors until December 31, 2022. Patients with visceral crisis and those receiving chemotherapy or alpelisib immediately after progression on CDK4/6 inhibitors were excluded. A total of 515 consecutive patients were screened, and 308 patients were excluded (Fig. 1). Included patients were exposed to endocrine therapy (i.e., exemestane, letrozole, fulvestrant, or tamoxifen) with or without everolimus, dosed at discretion of treating oncologist between 5–10 mg orally once a day, until disease progression or intolerability.

Data sources and independent variables

Participants were screened and identified via institutional databases and clinical data were retrospectively collected and pseudonymised by local investigators from medical records into an electronic case report form specifically designed for this study (Supplement 3). Participant sites were trained before study initiation, and patient summaries were centrally revised for eligibility and data quality check. The following baseline characteristics at the start of the study treatment were extracted: age, menopausal status, weight and height for body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities for Charlson Comorbidity Index [46], and breast cancer characteristics (*de novo* vs recurrent, metastatic sites, histologic subtype, Ki67 index, progesterone receptor status, and HER2 status [47]). Pathology assessments were performed as per local standards and were not centrally reviewed. Whenever available as per local practice, results of somatic genomic testing were collected. Finally, prior treatment for advanced breast cancer (number of prior lines of systemic therapy, prior use of chemotherapy before CDK4/6 inhibitors, CDK4/6 inhibitors used and its duration) and study treatment data (endocrine therapy agent used, initial dose of everolimus, and dose reduction/early discontinuation) were collected. Data were extracted between July 2023 and March 2024, allowing a minimum follow-up period of six months.

Clinical outcomes

Treatment effectiveness was measured by the primary endpoint real-world progression-free survival (rwPFS), defined as time to clinical disease progression (judged by treating oncologist based on clinical, radiological, or laboratorial findings) or death from any cause [48, 49]. Imaging assessments were not centrally reviewed. Secondary endpoints were time to everolimus failure (discontinuation due to any reason or death of any cause), time to chemotherapy

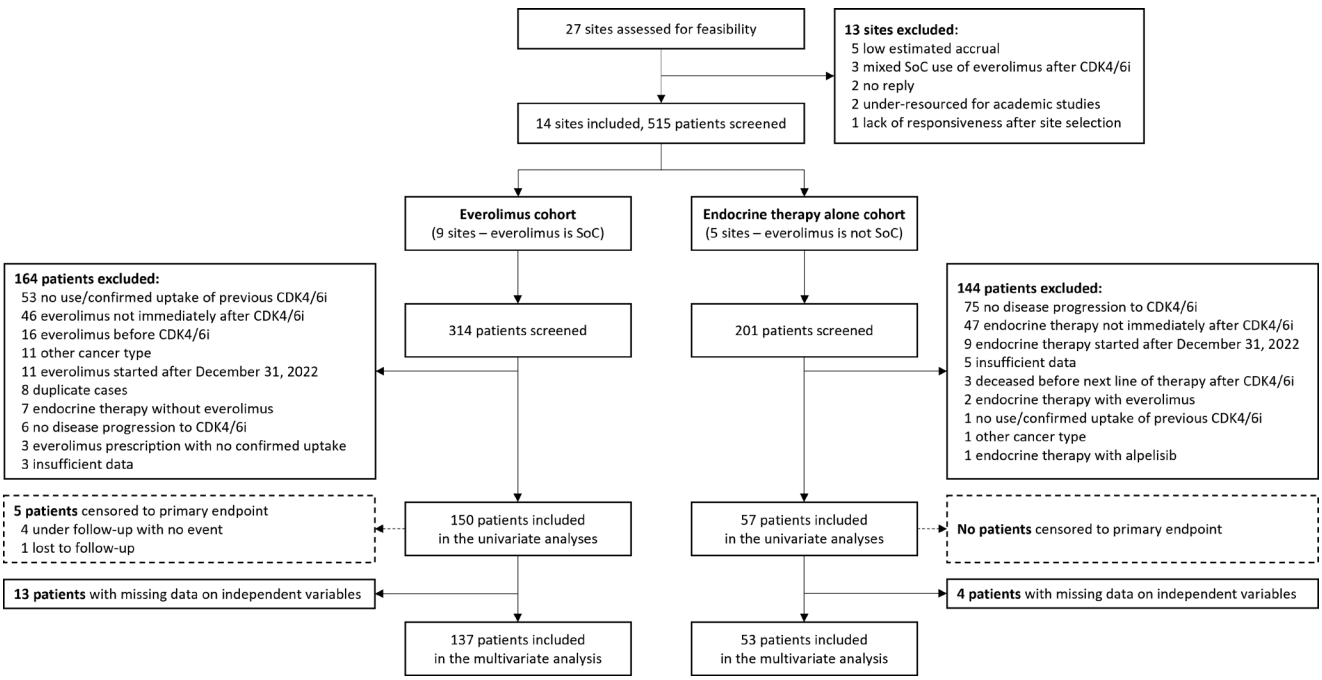


Fig. 1 Flowchart of participant sites and patients per treatment received after disease progression on CDK4/6 inhibitors. Women included in the everolimus cohort were exposed to endocrine therapy plus everolimus, while women included in the endocrine therapy alone cohort were exposed to endocrine therapy without everolimus, as per standard-of-care of the participating sites included in each cohort. Abbreviations: CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitors; ET, endocrine therapy; SoC, standard-of-care

(chemotherapy start date or death of any cause), and overall survival (death of any cause). As exploratory endpoints, we collected the real-world best tumour response to study treatment as previously defined by Patt et al [50] (stable/progressive disease, partial or complete response, as judged by the treating oncologist) and safety data (any adverse event, serious adverse events - defined as adverse events leading to hospitalisation or death, and adverse events leading to treatment discontinuation) as reported in the medical record. Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 5 [51].

Statistical analysis

Despite no statistical sample size calculation, the inclusion of 230 patients was estimated based on the feasibility questionnaires of the selected sites (eFigure 1 in Supplement 1, trial protocol in Supplement 2). A *post-hoc* statistical power calculation was performed for the primary endpoint to estimate the likelihood of type II error. Baseline characteristics, prior treatment for advanced breast cancer, and study treatment data were summarised with descriptive statistics and compared between the two cohorts. All time-to-event endpoints were assessed from start date of study treatment and differences between cohorts were described using Kaplan Meier method and log-rank test. Patients who did not experience the event of interest were censored at the date of last follow-up. For the primary endpoint, we conducted preplanned subgroup analyses for baseline characteristics with interaction testing (random effects *p*-value for heterogeneity), and univariate and multivariate cox regression complete case analyses, adjusting for *a priori* selected clinically relevant potential confounders (age, ECOG performance status, Charlson Comorbidity Index, *de novo* vs recurrent advanced breast cancer, metastatic sites, progesterone receptor status, number of prior lines of systemic therapy, and prior CDK4/6 inhibitor duration). To address the imbalance in the number of prior lines of systemic therapy not mitigated by the study design, we performed a *post-hoc* Inverse Probability of Treatment Weighting (IPTW) sensitivity analysis. A propensity score for the treatment received (endocrine therapy plus everolimus versus endocrine therapy alone) was estimated by logistic regression with the matching factors age, ECOG, Charlson Comorbidity Index, and number of prior lines of systemic therapy. To assess potential informative bias in the measurement of the primary outcome, we surveyed participating sites regarding their standard-of-care schedules for routine clinical and imaging follow-up in this specific disease setting. Real-world best tumour response and safety data were summarised using descriptive statistics. *Post-hoc* exploratory univariate analysis of factors associated with toxic discontinuation was performed. All the statistical estimates were reported with 95% confidence intervals (CI), using SAS version 9.4.

Results

Patient and disease characteristics

We included 207 patients who initiated endocrine therapy with everolimus (everolimus cohort, $n=150$) or without (endocrine therapy alone cohort, $n=57$) following disease progression on CDK4/6 inhibitors between May 2017 and December 2022 (Fig. 1). All clinicodemographic and pathology characteristics were well balanced between the two cohorts (Table 1). Most women included were postmenopausal (87%) with ECOG performance status 0–1 (93%), had no additional comorbidities (77%), and were diagnosed with recurrent advanced breast cancer (71%) with visceral involvement (68%). Tumours were mostly of no special type (69%), highly proliferative (Ki67≥20%, 62%), progesterone receptor-positive (72%), and HER2-low (62%). Results of somatic genomic testing were available for 90 women, with *PIK3CA*/*AKT1*/*PTEN* alterations being the most frequently detected (22%). Regarding prior treatment for advanced breast cancer, most women received palbociclib (77%) and only a small proportion was exposed to chemotherapy before CDK4/6 inhibitors (11%). Only the number of prior lines of systemic therapy was significantly higher among the cohort of patients exposed to endocrine therapy plus everolimus (>1, 43% vs 21%, $p=0.004$), with a trend for longer duration of prior CDK4/6 inhibitor (>12 months, 62% vs 47%, $p=0.057$; Table 1).

Study treatment

The endocrine therapy agent used was significantly different between cohorts, being mostly exemestane in the everolimus cohort (77%) and fulvestrant in the endocrine therapy alone cohort (61%) ($p<0.001$, Table 1). Among women included in the everolimus cohort, 114 were exposed to initial dose of 10 mg (76%), 37 (25%) experienced dose reduction, and 29 (19%) discontinued everolimus before disease progression (Table 1).

Real-world progression-free survival

With a median follow-up of 31.8 months (95% CI, 25.7–36.6), the median rwPFS was 5.0 for women exposed to endocrine therapy plus everolimus vs 4.3 months for those who received endocrine therapy alone (hazard ratio [HR] 0.75, 0.55–1.02, $N=207$). The rwPFS rate was 71% vs 60% at 3-months, 43% vs 35% at 6-months, and 24% vs 18% at

Table 1 Baseline characteristics, prior treatment for advanced breast cancer, and study treatment

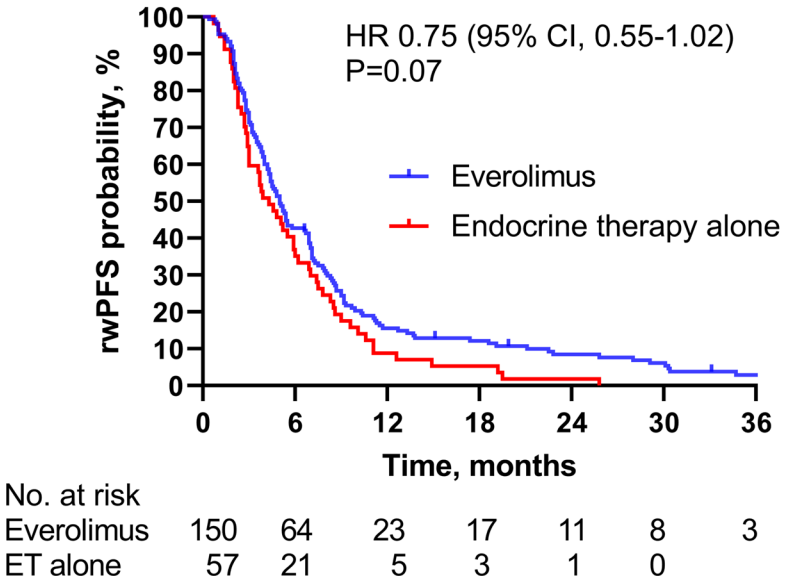
Characteristic	**Endocrine therapy plus everolimus** ($n=150$)	**Endocrine therapy alone** ($n=57$)	*p*-value
Clinicodemographic			
Age, years – median (IQR)	61 (53–71)	63 (50–72)	0.610[a]
Age category, years – No. (%)			
<50	25 (17)	13 (23)	0.824[b]
50–69	86 (57)	27 (47)	
≥70	39 (26)	17 (30)	
Menopausal status – No. (%)[c]			
Pre/perimenopausal	17 (11)	10 (17)	0.243[d]
Postmenopausal	132 (89)	47 (83)	
Body mass index, kg/m^2 – median (IQR)	26 (22–30)	27 (22–31)	0.549[a]
Body mass index category, kg/m^2 – No. (%)			
Underweight (<18.5)	7 (5)	8 (14)	0.769[b]
Normal (18.5–24.9)	64 (42)	18 (32)	
Overweight (25–29.9)	42 (28)	15 (26)	
Obese (≥30)	37 (25)	16 (28)	
ECOG performance status – No. (%)[e]			
0	54 (38)	20 (35)	0.685[b]
1	78 (55)	33 (58)	
2	9 (6)	3 (5)	
3	1 (1)	1 (2)	
Charlson Comorbidity Index – No. (%)			
6	116 (77)	43 (75)	0.676[b]
7	23 (15)	13 (23)	
≥8	11 (7)	1 (2)	
Type of advanced breast cancer – No. (%)			
De novo	42 (28)	19 (33)	0.452[d]
Recurrent	108 (72)	38 (67)	
Metastatic sites – No. (%)			
Visceral (including CNS)[f]	97 (65)	43 (76)	0.155[d]
Bone only	52 (35)	14 (25)	
Pathology[g]			
Histologic subtype – No. (%)[h]			
No special type	99 (66)	43 (77)	0.295[i]
Lobular	29 (20)	6 (11)	
Mixed/other	21 (14)	7 (13)	
Ki67, % – No. (%)[j]			
<20	55 (40)	14 (33)	0.408[d]
≥20	84 (60)	29 (67)	
Progesterone receptor – No. (%)[k,l]			
Positive	107 (73)	36 (67)	0.357[d]
Negative	39 (27)	18 (33)	
HER2 status – No. (%)[m,n]			
HER2-0	55 (38)	17 (38)	0.990[d]
HER2-low	91 (62)	28 (62)	
Genomic[o,p]			
PIK3CA/*AKT1*/*PTEN* alterations – No. (%)	15 (21)	5 (29)	0.518[i]
PIK3CA	12 (16)	5 (29)	0.300[i]
AKT1	2 (3)	0 (0)	-
PTEN	1 (1)	0 (0)	-
ESR1 mutation – No. (%)	3 (4)	0 (0)	-

Table 1 (continued)

Characteristic	**Endocrine therapy plus everolimus** ($n=150$)	**Endocrine therapy alone** ($n=57$)	*p*-value
Prior treatment for advanced breast cancer			
Prior lines of systemic therapy – No. (%)			
1	86 (57)	45 (79)	*0.004*[d]
>1[q]	64 (43)	12 (21)	
Chemotherapy – No. (%)	15 (10)	7 (12)	0.621[i]
CDK4/6 inhibitor – No. (%)[r]			
Palbociclib	118 (78)	37 (73)	0.569[i]
Ribociclib	28 (18)	13 (25)	
Abemaciclib	6 (4)	1 (2)	
CDK4/6 inhibitor, months – median (IQR)	16 (9–25)	12 (9–24)	0.272[a]
CDK4/6 inhibitor, months – No. (%)			
≤12	57 (38)	30 (53)	0.057[d]
>12	93 (62)	27 (47)	
Study treatment			
Endocrine therapy agent used[s] – No. (%)			
Exemestane/letrozole[t]	117 (78)	14 (25)	*<0.001*[i]
Fulvestrant	29 (19)	35 (61)	
Tamoxifen	4 (3)	8 (14)	
Everolimus initial dose, mg[u] – No. (%)			
10	114 (76)	-	-
7.5	1 (1)	-	-
5	34 (23)	-	-
Everolimus dose reduction – No. (%)	37 (25)	-	-
Everolimus early discontinuation[v] – No. (%)	29 (19)	-	-

Statistical test applied: (a) Wilcoxon rank sum test; (b) Cochran-Armitage trend test; (d) Chi-Square test; (i) Fisher's Exact test. **Cases of unknown/missing data per variable:** (c) 1 for everolimus; (e) 8 for everolimus; (g) 2, 1 for each cohort; (j) 25, 11 for everolimus, 14 for endocrine therapy alone; (k) 7, 4 for everolimus, 3 for endocrine therapy alone; (m) 16, 4 for everolimus and 12 for endocrine therapy alone; (o) 117, 77 for everolimus, 40 for endocrine therapy alone; (r) 6 for endocrine therapy alone; (u) 1 for everolimus. **Notes:** (f) includes exceptional cases of isolated serosal, nodal, and/or cutaneous involvement as well as unresectable local recurrences; (g) from metastatic tumor specimen, or if not available, from primary tumor; (l) Positive if progesterone receptor ≥ 1% or Allred ≥ 3; (n) HER2-0, IHC0; HER2-low, IHC1+ or IHC2+ with ISH-negative [47] - one case of IHC3+ with ISH-negative and luminal-B genomic signature, treated as HER2-negative; (p) *TP53* mutation was detected only in 4 patients, all for everolimus; (q) 3 prior lines: 14 for everolimus, 3 for endocrine therapy alone; 4 prior lines: 8 for everolimus; 5 prior lines: 4 for everolimus; (s) premenopausal women treated with aromatase inhibitor or fulvestrant received ovarian function suppression; (t) 5 women received letrozole, 2 plus everolimus and 3 alone; (v) 27 due to adverse events and 2 due to physician decision. **Abbreviations:***AKT1*, RAC-alpha serine/threonine-protein kinase gene; CDK4/6, cyclin-dependent kinase 4 and 6; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; *ESR1*, estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in-situ hybridization; IQR, interquartile range; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; *PTEN*, phosphatase and tensin homolog gene

9-months, respectively for everolimus and endocrine therapy alone cohorts (Fig. 2). Despite shorter interval between medical visits during the first 6 months for patients receiving everolimus, the standard timing for first imaging follow-up did not differ between cohorts (eTable2 in Supplement 1). In the subgroup analyses, the benefit of adding everolimus was more pronounced in women with body mass index ≥ 25 kg/m^2 (HR 0.64, 0.41–0.98), no special type histology (HR 0.64, 0.44–0.92, $n=142$), or Ki67 ≥ 20% (HR 0.59, 0.38–0.91), but statistically significant interaction was only found when duration of prior CDK4/6 inhibitor > 12 months (HR 0.56, 0.36–0.87), or when the endocrine therapy agent used was an aromatase inhibitor (HR 0.55, 0.31–0.96). The same trend was observed in women with detected *PIK3CA/AKT1/PTEN* alterations (HR 0.57, 0.20–1.62, eFigure 2 in Supplement 1) or more than one prior line of systemic therapy (HR 0.56, 0.30–1.05) (Fig. 3). Baseline characteristics most notably associated with rwPFS on the univariate and multivariate analyses were age (50–69 vs reference: <50 years, HR 0.64, 0.44–0.93, adjusted HR 0.63, 0.42–0.95) and number of prior lines of systemic therapy (>1 vs reference: 1 line, HR 1.36, 1.02–1.82, adjusted HR 1.65, 1.17–2.34) (eTable 3 in Supplement 1, Table 2). When adjusted for these and other clinically relevant baseline characteristics, there was a statistically significant association of everolimus addition with longer rwPFS (adjusted HR 0.68, 0.47–0.99, $n=190$) (Table 2). The IPTW-adjusted HR for rwPFS was 0.71 (0.50–0.99, $n=199$). With 202 events and the treatment allocation of 150 cases of endocrine therapy plus everolimus and 57 cases of endocrine therapy alone, the study had a power of 0.80 (at significance level 0.05) to detect a HR of 0.64. The observed adjusted HR of 0.68 corresponds to a



Cohort	ET plus everolimus	ET alone
Events/Total	145/150	57/57
rwPFS, median (95% CI)	5.0 (4.3-6.9)	4.3 (3.0-6.0)
3-mos rwPFS, % (95% CI)	71 (65-79)	60 (48-74)
6-mos rwPFS, % (95% CI)	43 (35-51)	35 (25-50)
9-mos rwPFS, % (95% CI)	24 (18-32)	18 (10-31)

Fig. 2 Kaplan-meier curves for real-world progression-free survival (N=207, 202 events). Five patients were censored in the everolimus cohort, comprising four with no event at last visit and one lost to follow-up. Abbreviations: CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; mos, months; rwPFS, real-world progression-free survival

0.69 power. The study was reasonable powered (~70%) to detect the effect size observed, and would have a 0.80 power to detect a slightly larger benefit (HR≤0.64).

Secondary and exploratory endpoints

The objective response rate was 25% (95% CI, 19–33%) among women treated with endocrine therapy plus everolimus and 16% (7–28%) with endocrine therapy alone (p=0.143, eTable 4 in Supplement 1). The median time to everolimus failure was 4.2 months (3.8–5.4, eFigure 3 in Supplement 1). There were no statistically significant differences between the two cohorts for time to chemotherapy (HR 1.02, 0.75–1.41; everolimus 5.8 vs endocrine therapy alone 6.3 months, eFigure 4 in Supplement 1) or overall survival (HR 0.81, 0.54–1.20; everolimus 24.2 vs endocrine therapy alone 20.6 months, eFigure 5 in Supplement 1).

Adverse events of any grade were reported in 7 (12%) women treated with endocrine therapy alone and in 131 (87%) exposed to endocrine therapy plus everolimus. The most common adverse events in the everolimus cohort were stomatitis (53%), fatigue (34%), decreased appetite (20%), rash (17%), diarrhoea (16%), pneumonitis (15%), and nausea (15%). Thirty women treated with everolimus experienced a grade 3 adverse event (20%), while grade 4 adverse events were reported only in two women (rash and pneumonitis). Serious adverse events were reported in six (4%) patients treated with everolimus. Adverse events led to everolimus discontinuation in 27 patients (18%), mostly due to pneumonitis (n=11, 7%, eTable 5 in Supplement 1). There was a statistically significant association of everolimus discontinuation due to adverse events with older age (≥70 vs reference: <50 years, odds ratio 5.11, 95% CI, 1.03–25.23, eTable 6 in Supplement 1).

Discussion

Our study suggests that among women with ER-positive/HER2-negative advanced breast cancer who start endocrine therapy as immediate next line of therapy after disease progression on CDK4/6 inhibitors, the addition of everolimus to endocrine therapy is associated with a clinically modest improvement of rwPFS. This finding was statistically significant when adjusting for clinically relevant confounders. The subgroup findings generate the hypothesis that the benefit is more pronounced in women with overweight/obesity, no special type histology and highly proliferative tumours, longer duration of prior CDK4/6 inhibitors, or when the endocrine therapy agent used was an aromatase inhibitor. Everolimus resulted in a numerically higher objective response rate but was associated with increased toxicity, without delaying the need for chemotherapy or providing a statistically significant overall survival benefit.

We estimate a rwPFS gain inferior to 1 month with everolimus, resulting in an adjusted rwPFS risk reduction of 32% compared to endocrine therapy alone. This magnitude of clinical benefit is weaker than the one observed in the registration trial BOLERO-2 trial [32, 52]. The median rwPFS of 5 months in women exposed to everolimus in the EVERGREEN study is numerically inferior than the investigator-assessed PFS in women not previously exposed to CDK4/6

Subgroup	ET plus everolimus (events/total)	ET alone – *reference* (events/total)	Hazard ratio (95% CI)	Interaction (*p*-value)
Age, years				
<50	25/25	13/13	0.98 (0.49-1.93)	0.72
50-69	83/86	27/27	0.70 (0.45-1.08)	
≥70	37/39	17/17	0.74 (0.41-1.34)	
Menopausal status				
Pre/perimenopausal	17/17	10/10	0.68 (0.31-1.51)	0.81
Postmenopausal	127/132	47/47	0.76 (0.54-1.07)	
Body mass index, kg/m²				
<25	70/70	20/20	1.01 (0.61-1.67)	0.17
≥25	74/79	31/31	0.64 (0.41-0.98)	
ECOG performance status				
0-1	128/132	53/53	0.76 (0.55-1.05)	0.90
2-3	9/10	4/4	0.70 (0.21-2.35)	
Charlson Comorbidity Index				
6	111/116	43/43	0.72 (0.50-1.03)	0.20
7	23/23	13/13	1.11 (0.55-2.24)	
≥8	11/11	1/1	0.10 (0.01-1.53)	
Type of advanced breast cancer				
De novo	40/42	19/19	0.85 (0.49-1.48)	0.62
Recurrent	105/108	38/38	0.72 (0.49-1.05)	
Metastatic sites				
Visceral (including CNS)	94/97	43/43	0.72 (0.50-1.04)	0.68
Bone only	50/52	14/14	0.83 (0.46-1.52)	
Histologic subtype				
No special type	96/99	43/43	0.64 (0.44-0.92)	0.40
Lobular	28/29	6/6	0.88 (0.36-2.17)	
Mixed/other	20/21	7/7	1.19 (0.49-2.86)	
Ki67, %				
<20	53/55	14/14	1.20 (0.66-2.19)	0.06
≥20	82/84	29/29	0.59 (0.38-0.91)	
Progesterone receptor status				
Positive	102/107	36/36	0.72 (0.49-1.05)	0.72
Negative	39/39	18/18	0.81 (0.46-1.44)	
HER2 status				
HER2-0	54/55	17/17	0.65 (0.37-1.14)	0.97
HER2-low	87/91	28/28	0.66 (0.43-1.01)	
***PIK3CA/AKT1/PTEN* alterations**				
Not detected	56/58	12/12	0.86 (0.46-1.61)	0.51
Detected	15/15	5/5	0.57 (0.20-1.62)	
Prior lines of systemic therapy				
1	82/86	45/45	0.71 (0.49-1.03)	0.53
>1	63/64	12/12	0.56 (0.30-1.05)	
Prior CDK4/6 inhibitor, months				
≤12	54/57	30/30	1.09 (0.70-1.72)	*0.04*
>12	91/93	27/27	0.56 (0.36-0.87)	
Endocrine therapy agent used				
Exemestane/Letrozole	113/117	14/14	0.55 (0.31-0.96)	*0.02*
Fulvestrant	28/29	35/35	1.62 (0.95-2.74)	
Tamoxifen	4/4	8/8	1.07 (0.30-3.82)	

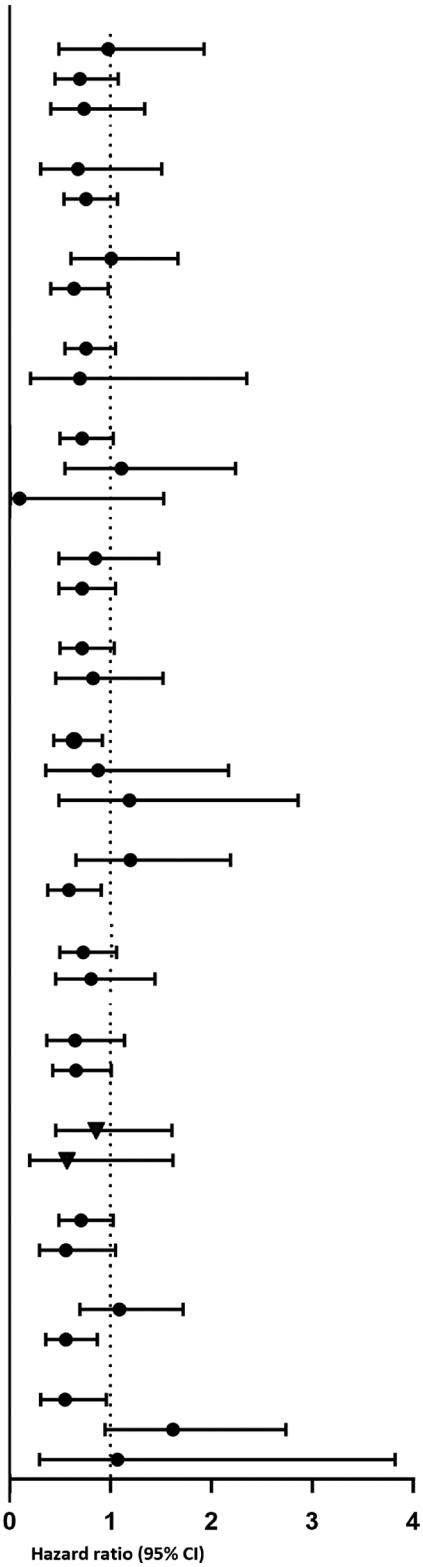


Fig. 3 Subgroup analyses for real-world progression-free survival. Abbreviations: *AKT1*, RAC-alpha serine/threonine-protein kinase gene; CDK4/6, cyclin-dependent kinase 4 and 6; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; *PTEN*, phosphatase and tensin homolog gene

Table 2 Multivariable analysis of real-world progression-free survival ($n = 190$, 185 events)[a]

Variable	Events/total	aHR (95% CI)
Study treatment cohort		
ET alone	53/53	*Reference*
ET plus everolimus	132/137	*0.68 (0.47–0.99)*
Age category, years		
<50	37/37	*Reference*
50–69	101/104	*0.63 (0.42–0.95)*
≥70	47/49	0.65 (0.40–1.04)
ECOG performance status		
0–1	173/177	*Reference*
2–3	12/13	1.12 (0.57–2.19)
Charlson Comorbidity Index		
6	141/146	*Reference*
7	32/32	1.02 (0.67–1.57)
≥8	12/12	0.88 (0.48–1.62)
Type of advanced breast cancer		
De novo	55/57	*Reference*
Recurrent	130/133	0.86 (0.61–1.22)
Metastatic sites		
Bone only	59/61	*Reference*
Visceral (including CNS)	126/129	1.16 (0.83–1.62)
Histologic subtype		
No special type	129/132	*Reference*
Lobular	29/30	1.20 (0.78–1.86)
Mixed/other	27/28	0.65 (0.42–1.01)
Progesterone receptor		
Negative	56/56	*Reference*
Positive	129/134	0.91 (0.65–1.28)
Prior lines of systemic therapy		
1	121/125	*Reference*
>1	64/65	*1.65 (1.17–2.34)*
Prior CDK4/6 inhibitor, months		
≤12	81/84	*Reference*
>12	104/106	0.83 (0.60–1.15)

Abbreviations: aHR, hazard ratio; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy. **Note:** (a) Multivariate cox regression complete case analyses, adjusting the treatment effect estimate for *a priori* selected clinically relevant potential confounders (age, ECOG performance status, Charlson Comorbidity Index, *de novo* vs recurrent advanced breast cancer, metastatic sites, progesterone receptor status, number of prior lines of systemic therapy, and prior CDK4/6 inhibitor duration)

inhibitors included in BOLERO-2 (7.8 months) [53] and BOLERO-6 (8.4 months) [54] trials. Although there was no independent central review of rwPFS in EVERGREEN, the good concordance between local and central review was previously demonstrated for advanced breast cancer trials [55]. However, the rwPFS in the everolimus cohort of EVERGREEN was similar or slightly higher than in smaller USA cohorts in the same setting (3.6 to 4.9 months) [35–39]. More recently, Sánchez-Bayona et al. reported a retrospective cohort study assessing the non-comparative effectiveness of endocrine therapy plus everolimus after disease progression on CDK4/6 inhibitors in 161 patients from four Spanish centres during an identical period up to December 2022 [41]. With a shorter follow-up of 15 months, the rwPFS was 6.0 months, similarly higher in patients with longer exposure to CDK4/6 inhibitors [41]. The biologically plausible association between longer prior exposure to CDK4/6 inhibitors and greater benefit from everolimus requires prospective validation before being used to guide treatment selection in routine clinical practice. Importantly, the estimated median rwPFS of 4.3 months among women included in the endocrine therapy alone cohort of our study aligns with best estimates from clinical trials (1.9 to 5.5 months) [20, 27–30], and large multicentric real-world evidence (3.3 to 4.4 months) [56, 57]. We believe this is strongly warranted by the quasi-experimental design of our study, which mitigates the common confounding by indication bias observed in most real-world evidence of treatment patterns. By including in the endocrine therapy alone cohort only sites in which everolimus is not standard-of-care in this setting, we avoided the selection of patients to this cohort who would not be considered fit enough for the addition of everolimus, increasing the internal validity of our study findings. As a result, all clinicodemographic and pathology characteristics were well balanced, except for a higher number of prior lines in the everolimus cohort, which may have narrowed the rwPFS gain in the crude analysis. The multivariate regression model controlled for this and other potential confounders, and the robustness of this finding is consistently supported by the *post-hoc* IPTW sensitivity analysis. The difference between cohorts of the endocrine therapy agent used as study treatment is explained by the preference for fulvestrant after progression on aromatase inhibitor (endocrine therapy alone cohort) [15, 16], while the label of everolimus is in combination with exemestane (everolimus cohort) [58]. This treatment pattern is consistent with contemporary metastatic breast cancer guidelines [15, 16], and the observed imbalance should be interpreted as reflecting real-world treatment strategies rather than a conventional confounding variable. The use of fulvestrant in combination with everolimus is supported by a small, randomised phase II trial including patients unexposed to CDK4/6 inhibitors [59]. The positive results of this trial were not replicated in our study among the subgroup of patients receiving fulvestrant. Nevertheless, the pre-planned subgroup findings according to endocrine therapy agent used should be interpreted cautiously because the study was not powered to determine whether the treatment effect truly differs according to the endocrine backbone.

Although everolimus was associated with longer rwPFS, no statistically significant differences were observed in overall survival or time to chemotherapy. These endpoints

are less susceptible to assessment bias and may better reflect long-term benefit. However, in ER-positive/HER2-negative advanced breast cancer, the effect of individual therapies is commonly diluted by the multitude of subsequent treatment options. Consequently, the modest rwPFS benefit observed in our study should be interpreted in the context of the absence of demonstrated improvement in these downstream clinical outcomes, while recognising rwPFS as a clinically meaningful endpoint.

During the last years, consecutive targeted therapies were approved for second-line ER-positive/HER2-negative advanced breast cancer, demanding wider genomic testing to guide post-CDK4/6 inhibitors treatment sequencing for patients who are candidates to continue cytotoxic-free systemic therapy [12, 13, 17]. During the accrual period of our study only alpelisib was approved in Europe [21], but its availability and accessibility was limited in the two participating countries [60]. Acknowledging that fewer than half of the study population was tested and that the assays and the origin/timing of sampling used were heterogeneous as by local practice, *PIK3CA* mutation (19%) was the most frequent alteration among the patients with somatic genomic testing, lower than previously reported [17, 18]. Interestingly, we observed a trend towards higher rwPFS benefit of adding everolimus in cases with *PIK3CA*/*AKT1*/*PTEN* alterations. However, this subgroup analysis should be interpreted with caution due to small numbers and the limited availability of genomic testing. Our findings should reinforce that the benefit of adding everolimus seems to be independent of PI3K-pathway alterations [61]. The recent approvals of inavolisib with fulvestrant and palbociclib [62], and capivasertib plus fulvestrant [25] increase the importance of testing PI3K-pathway alterations. The fact that elacestrant was only approved in Europe in September 2023 [26] might partly explain the low *ESR1* mutation detection rate in our study. Due to the lack of clinical actionability during the study period, this gene might not have been included in most assays performed or large panels might have been performed in archival tissue unexposed to aromatase inhibitor. Currently, with access to elacestrant and soon imlunestrant [63], combined with the high performance for tumour next-generation sequencing (NGS) in detecting germline *BRCA1/2* mutations, the range of clinically actionable alterations is expanding, and NGS is now recommended for patients with advanced breast cancer [17]. The limited use and occasional availability of large NGS panels in both countries during the study period [64] limits the precision of biomarker-driven subgroup analyses in our study and might explain also the small number of detected *TP53* mutations, a biomarker of poor prognosis in patients with ER-positive advanced breast cancer [65].

Still, no actionable alterations are detected in nearly half of the cases of ER-positive/HER-negative advanced breast cancer [19]. Fulvestrant with a CDK4/6 inhibitor switch (ribociclib or abemaciclib) beyond progression outperforms fulvestrant monotherapy [28, 30]. Two large multicentric, nationwide real-world studies in the USA and Japan report that, despite the growing use of this strategy in up to one-third of patients after progression on CDK4/6 inhibitors, endocrine therapy with or without everolimus remains the option in around one-fourth of the cases [56, 57]. The efficacy of imlunestrant with abemaciclib in EMBER-3 trial irrespective of *ESR1* status [63], and the results from ongoing trials with novel selective estrogen receptor degraders combined with everolimus (NCT06382948, NCT05306340, NCT05563220) [66–68] might soon bring to clinical practice more effective options in the post-CDK4/6 inhibitors setting. The generalisability of EVERGREEN should be interpreted in the context of the study period and the availability of novel agents and genomic sequencing in the participating countries. While these novel strategies are not widely accessible, our study suggests the benefit of adding everolimus to endocrine therapy and supports optimal patient selection by identifying subgroups with better risk-benefit profile.

Our study has limitations inherent to its retrospective nature, for which we implemented several mitigation strategies. Regarding real-world data source and risk of missing data, the structured data collection from the medical records into a standardised electronic case report form, with central medical revision of critical variables, warranted missing data below 10% in the multivariate model for the primary endpoint. When it comes to the measurement of the primary endpoint and patient's follow-up, all patients had a minimum follow-up of six months and only one case was censored for rwPFS due to loss to follow-up. We did not censor for everolimus discontinuation, mitigating the risk of informative censoring. However, rwPFS measuring has limitations, including potential outcome measurement bias from heterogeneous follow-up schedules. To estimate this bias, we surveyed the participating sites on their standard-of-care schedule for clinical and imaging assessment of patients in this specific disease setting. This bias is likely to be residual towards underestimation of the clinical benefit of adding everolimus, as clinical disease progression in the endocrine therapy alone cohort may have been detected later due to less frequent clinical assessments in the first six months. Although the timing of the first imaging assessment did not differ between cohorts, physician-level differences may still exist. The used rwPFS definition acknowledges the retrospective nature of outcome ascertainment and its methodological differences from protocol-defined PFS used in prospective clinical trials [48, 49]. The lack of a

prospectively standardised assessment of tumour response and safety limits interpretation of these exploratory outcomes. Safety outcomes should be interpreted cautiously because adverse events were retrospectively collected without a standardised prospective assessment schedule. The very low adverse-event rate in the endocrine therapy alone cohort may reflect under-ascertainment, limiting direct comparison of safety frequencies between groups. On the other hand, the incidence of stomatitis (53%) was numerically higher than reported in prospective studies such as evERA trial (47.3%) [66]. One possible explanation is the heterogeneous implementation of prophylactic steroid mouthwash across participating centres during the study period, particularly in Portugal, where routine use was not universal. Despite similar distribution of types of hospitals between the two cohorts (eTable 1), as treatment was assigned at site-level, residual site-level confounding cannot be fully excluded since unmeasured institutional differences in patient management, multidisciplinary care, or treatment culture may have influenced outcomes independently of everolimus exposure.

Finally, external validity was maximised by the international and multicentric design of EVERGREEN, including cancer centres, academic, and peripheral hospitals, with representation of both private and public management, across two distinct European healthcare systems.

Conclusion

The addition of everolimus to standard endocrine therapy resulted in a modest clinical benefit for patients with ER-positive/HER2-negative advanced breast cancer progressing on CDK4/6 inhibitors. This limited improvement in clinical outcomes and the toxicity profile highlight the need for careful selection of patients with more favourable risk-benefit profile. Everolimus-based endocrine therapy may be considered as a control arm for clinical trials in this setting.

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Author contributions DMB: Conceptualisation, Methodology, Software, Investigation, Resources, Writing - Original Draft, Visualisation, Project administration. SLM: Investigation, Resources, Data Curation, Writing - Review & Editing, Project administration. PA: Investigation, Validation, Writing - Review & Editing, Funding acquisition. GNM: Conceptualisation, Investigation, Writing - Review & Editing, Visualisation. MM: Software, Resources, Writing - Review & Editing. MP: Methodology, Validation, Writing - Review & Editing. LA: Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualisation. EdA: Conceptualisation, Methodology, Validation, Writing - Review & Editing, Supervision. Investigation, Writing - Review & Editing: BP, LVdM, LF, EC, DT, FPD, PS, ARG, VP, CC, DAC, JP, CS, FS, TGP, DS, DB, BS, MB, AG.

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Data availability The participating sites agreed to transfer the individual patient data for use exclusively limited to the context of this study protocol. A data extraction dictionary is provided in Supplement 2 and 3. Other supporting documentation may be available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate and for publication The study protocol (Supplement 2) was centrally approved by the ethics committee of the study sponsor - Institut Jules Bordet (CE3499) - and by local independent review boards, with exemption of informed consent due to the retrospective and non-interventional nature of the study. Patients with medical records denoting opt-out of personal data use for research purposes were not considered. The study was performed in accordance with the Declaration of Helsinki.

Competing interests DMB: reports employment from the European Society for Medical Oncology since September 1, 2023; participation as medical research fellow in research studies institutionally funded by Eli Lilly, F. Hoffmann-La Roche Ltd, and Novartis to Institut Jules Bordet (2021–2023); and non-financial interests as past member of the Board of Directors for the Associação de Investigação e Cuidados de Suporte em Oncologia (2022–2024) and member of American Society of Clinical Oncology, Associação Portuguesa de Cuidados Paliativos, Multinational Association of Supportive Care in Cancer, and Sociedade Portuguesa de Oncologia. SLM: reports honoraria and/or advisory board from AstraZeneca, BMS, Gilead Sciences MSD, Novartis, Pfizer, and Roche; travel support for attending medical conferences from Amgen, AstraZeneca, BMS, DaiichiSankyo, Gilead Sciences, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, Roche, and Sanofi; participation as medical research fellow in research studies institutionally funded by AstraZeneca, F. Hoffmann-La Roche Ltd, and Novartis to Institut Jules Bordet. PA: reports consultancy fees from Amcure, Boehringer Ingelheim, Daiichi Sankyo, Deloitte, G1 Therapeutics, Macrogenics, Novartis, Radius, Roche, and Servier; honoraria from Amgen, Gilead, Lilly, Menarini, Novartis, and Synthon; travel support for attending medical conferences from Amgen, Daiichi Sankyo, MSD, Pfizer, and Roche; research funding to institution from Roche. LVdM: reports speaker/consultancy fees from AstraZeneca, Daiichi Sankyo, Lilly, Novartis, Pfizer, and Roche; travel support for attending medical conferences from Lilly, Novartis, Pfizer, and Roche. LF: reports honoraria and/or advisory board from Gilead, MSD, Novartis and Pfizer; travel support for attending medical conferences/preceptorships from AstraZeneca/Daiichi Sankyo, Gilead, MSD, Novartis, Pierre Fabre,

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References

1. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N et al (2016) Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. The Lancet Oncol [Internet]. 17(4):425–439. Available from: https://pubmed.ncbi.nlm.nih.gov/26947331/. 2025 Feb 2
2. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ (2016) Palbociclib and letrozole in advanced breast cancer. N Engl J Med [Internet]. 375(20):1925–1936. Available from: https://doi.org/10.1056/NEJMoa1607303. 2025 Feb 2
3. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, Nusch A, Sonke GS, De la Cruz-Merino L, Beck JT, Pivot X, Vidam G, Wang Y, Rodriguez Lorenc K, Miller M, Taran T, Jerusalem G (2018) Phase III Randomized study of Ribociclib and fulvestrant in hormone receptor–positive, human Epidermal Growth Factor receptor 2–negative advanced breast cancer: MONALEESA-3. JCO [Internet]. 36(24):2465–2472. Available from: https://doi.org/10.1200/JCO.2018.78.9909.
4. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Petrakova K, Blackwell KL, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Mondal S, Su F, Miller M, Elmeliegy M, Germa C, O'Shaughnessy J (2018) Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol [Internet]. 29(7):1541–1547. Available from: https://doi.org/10.1093/annonc/mdy155. 2025 Feb 2
5. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, Hurvitz SA, Chow L, Sohn J, Lee KS, Campos-Gomez S, Villanueva Vazquez R, Jung KH, Babu KG, Wheatley-Price P, De Laurentiis M, Im Y-H, Kuemmel S, El-Saghir N, Liu M-C, Carlson G, Hughes G, Diaz-Padilla I, Germa C, Hirawat S, Lu Y-S (2018 Jul 1) Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. The Lancet Oncol [Internet]. 19(7):904–915. Available from: https://doi.org/10.1016/S1470-2045(18)30292-4. 2025 Feb 2
6. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke E-M, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart-Cussac A (2017 Sep 1) MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. JCO [Internet]. 35(25):2875–2884. Available from: https://doi.org/10.1200/JCO.2017.73.7585. 2025 Feb 2
7. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Trédan O, Chen S-C, Manso L, Freedman OC, Garnica Jaliffe G, Forrester T, Frenzel M, Barriga S, Smith IC, Bourayou N, Di Leo A (2017 Nov 10) MONARCH 3: abemaciclib as Initial therapy for advanced breast cancer. JCO [Internet]. 35(32):3638–3646. Available from: https://doi.org/10.1200/JCO.2017.75.6155. 2025 Feb 2
8. Palbociclib (IBRANCE) | FDA [Internet]. https://www.fda.gov/drugs/resources-information-approved-drugs/palbociclib-ibrance. 2025 Feb 22]
9. Ibrance | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/ibrance. 2025 Feb 2]
10. Kisqali | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/kisqali. 2025 Feb 2]
11. Verzenios | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/verzenios. 2025 Feb 2]
12. ESMO Metastatic Breast Cancer Living Guidelines, 1.2 April 2025 [Internet]. [cited 2025 May 23]. Available from: https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-breast-cancer
13. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, Dent R, Fenlon D, Gligorov J, Hurvitz SA, Im S-A, Krug D, Kunz WG, Loi S, Penault-Llorca F, Ricke J, Robson M, Rugo HS, Saura C, Schmid P, Singer CF, Spanic T, Tolaney SM, Turner NC, Curigliano G, Loibl S, Paluch-Shimon S, Harbeck N (2021 Dec 1) ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer ☆. Ann Oncol [Internet]. 32(12):1475–1495. Available from: https://doi.org/10.1016/j.annonc.2021.09.019. 2025 Feb 2

14. Bardia A, Cortés J, Bidard FC, Neven P, Garcia-Sáenz J, Aftimos P, O'Shaughnessy J, Lu J, Tonini G, Scartoni S, Paoli A, Binaschi M, Wasserman T, Kaklamani V (2024 Oct 1) Elacestrant in ER+, HER2− metastatic breast cancer with ESR1 -mutated tumors: subgroup analyses from the phase III EMERALD trial by prior duration of endocrine therapy plus CDK4/6 inhibitor and in clinical subgroups. Clin Cancer Res [Internet]. 30(19):4299–4309. Available from: https://doi.org/10.1158/1078-0432.CCR-24-1073. 2025 Feb 22
15. Trapani D, Martins-Branco D, Curigliano G, Gennari A, Pentheroudakis G, Harbeck N (2025 Nov 1) Updated treatment recommendations for systemic treatment: from the ESMO metastatic breast cancer living guideline. Ann Oncol [Internet]. 36(11):1414–1418. Available from: https://doi.org/10.1016/j.annonc.2025.07.017. 2026 Jun 5
16. de Azambuja E, Barrios CH, Bartsch R, Curigliano G, Dent R, Gennari A, Loi S, Paluch-Shimon S, Pistilli B, Saura C, Schmid P, Spanic T, Toi M, Tolaney SM, Harbeck N (2026 May) Metastatic breast cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up†. Ann Oncol [Internet]. Available from: https://doi.org/10.1016/j.annonc.2026.05.707. 2026 Jun 5
17. Mosele MF, Westphalen CB, Stenzinger A, Barlesi F, Bayle A, Bièche I, Bonastre J, Castro E, Dienstmann R, Krämer A, Czarnecka AM, Meric-Bernstam F, Michiels S, Miller R, Normanno N, Reis-Filho J, Remon J, Robson M, Rouleau E, Scarpa A, Serrano C, Mateo J, André F (2024) Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO precision medicine working group. Ann Oncol [Internet]. 35(7):588–606. Available from: https://doi.org/10.1016/j.annonc.2024.04.005. 2024 Jul 10
18. Aftimos P, Oliveira M, Irrthum A, Fumagalli D, Sotiriou C, Gal-Yam EN, Robson ME, Ndozeng J, Di Leo A, Ciruelos EM, de Azambuja E, Viale G, Scheepers ED, Curigliano G, Bliss JM, Reis-Filho JS, Colleoni M, Balic M, Cardoso F, Albanell J, Duhem C, Marreaud S, Romagnoli D, Rojas B, Gombos A, Wildiers H, Guerrero-Zotano A, Hall P, Bonetti A, Larsson KF, Degiorgis M, Khodaverdi S, Greil R, Sverrisdóttir Á, Paoli M, Seyll E, Loibl S, Linderholm B, Zoppoli G, Davidson NE et al. (2021 Nov 1) Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the breast international group (BIG) molecular screening initiative. Cancer DiscovCancer Discov [Internet]. 11(11):2796–2811. Available from: https://doi.org/10.1158/2159-8290.CD-20-1647. 2025 Feb 2
19. Bhave MA, Quintanilha JCF, Tukachinsky H, Li G, Scott T, Ross JS, Pasquina L, Huang RSP, McArthur H, Levy MA, Graf RP, Kalinsky K (2024 Oct 1) Comprehensive genomic profiling of ESR1, PIK3CA, AKT1, and PTEN in HR(+)HER2(−) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. Breast Cancer Res Treat [Internet]. 207(3):599. Available from: https://doi.org/10.1007/s10549-024-07376-w. 2025 Feb 2
20. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, Mouret-Reynier M-A, Sohn JH, Taylor D, Harnden KK, Khong H, Kocsis J, Dalenc F, Dillon PM, Babu S, Waters S, Deleu I, García Sáenz JA, Bria E, Cazzaniga M, Lu J, Aftimos P, Cortés J, Liu S, Tonini G, Laurent D, Habboubi N, Conlan MG, Bardia A (2022 May 1) 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. JCO [Internet]. 40(28). Available from: 3246–3256. https://doi.org/10.1200/JCO.22.00338. 2025 Feb 2
21. Piqray | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/piqray. 2025 Feb 2].
22. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu Y-S, Inoue K, Takahashi M, Pápai Z, Longin A-S, Mills D, Wilke C, Hirawat S, Juric D (2019 May 16) Alpelisib for PIK3CA -Mutated, hormone receptor–positive advanced breast cancer. N Engl J Med [Internet]. 380(20):1929–1940. Available from: https://doi.org/10.1056/NEJMoa1813904. 2025 Feb 2
23. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, Park YH, Prat A, Bachelot T, Juric D, Turner N, Sophos N, Zarate JP, Arce C, Shen Y-M, Turner S, Kanakamedala H, Hsu W-C, Chia S (2021 Apr 1) 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. The Lancet Oncol [Internet]. 22(4):489–498. Available from: https://doi.org/10.1016/S1470-2045(21)00034-6. 2025 Feb 2
24. Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, Hu X, Jhaveri K, Krivorotko P, Loibl S, Morales Murillo S, Okera M, Park YH, Sohn J, Toi M, Tokunaga E, Yousef S, Zhukova L, de Bruin EC, Grinsted L, Schiavon G, Foxley A, Rugo HS (2023 Jun 1) Capivasertib in hormone receptor–positive advanced breast cancer. N Engl J Med [Internet]. 388(22):2058–2070. Available from: https://doi.org/10.1056/NEJMoa2214131. 2025 Feb 2
25. Truqap | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/truqap. 2025 Feb 2].
26. Orserdu | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/orserdu. 2025 Feb 2].
27. Lindeman GJ, Fernando TM, Bowen R, Jerzak KJ, Song X, Decker T, Boyle F, McCune S, Armstrong A, Shannon C, Bertelli G, Chang C-W, Desai R, Gupta K, Wilson TR, Flechais A, Bardia A (2022 Aug 1) VERONICA: randomized phase II study of fulvestrant and venetoclax in ER-Positive metastatic breast cancer post-CDK4/6 inhibitors – efficacy, safety, and biomarker results. Clin Cancer Res [Internet]. 28(15):3256–3267. Available from: https://doi.org/10.1158/1078-0432.CCR-21-3811. 2025 Feb 2
28. Kalinsky K, Accordino MK, Chiuzan C, Mundi PS, Sakach E, Sathe C, Ahn H, Trivedi MS, Novik Y, Tiersten A, Raptis G, Baer LN, Oh SY, Zelnak AB, Wisinski KB, Andreopoulou E, Gradishar WJ, Stringer-Reasor E, Reid SA, O'Dea A, O'Regan R, Crew KD, Hershman DL (2023 Aug 20) Randomized phase II trial of endocrine therapy with or without ribociclib after progression on Cyclin-dependent kinase 4/6 Inhibition in hormone receptor–positive, human Epidermal Growth Factor receptor 2–negative metastatic breast cancer: MAINTAIN trial. JCO [Internet]. 41(24):4004–4013. Available from: https://doi.org/10.1200/JCO.22.02392. 2025 Feb 2
29. Mayer EL, Ren Y, Wagle N, Mahtani R, Ma C, Demichele A et al. (2024 Jun 10) PACE: a Randomized phase II study of fulvestrant, palbociclib, and avelumab after progression on Cyclin-dependent kinase 4/6 inhibitor and aromatase inhibitor for hormone receptor-Positive/Human Epidermal Growth Factor receptor-negative metastatic breast cancer. J Clin Oncol [Internet]. 42(17):2050–2060. Available from: https://pubmed.ncbi.nlm.nih.gov/38513188/. 2025 Feb 2
30. Kalinsky K, Bianchini G, Hamilton E, Graff SL, Park KH, Jeselsohn R et al. (2024 Dec 18 [cited 2025 Feb 2];JCO2402086. Available from: Abemaciclib plus fulvestrant in advanced breast cancer after progression on CDK4/6 Inhibition: results from the phase III postMONARCH trial. J Clin Oncol [Internet]. https://pubmed.ncbi.nlm.nih.gov/39693591/
31. Afinitor | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/afinitor. 2025 Feb 2].

32. Baselga J, Campone M, Piccart M, Burris HAI, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN (2012 Feb 9) Everolimus in postmenopausal hormone-Receptor–Positive advanced breast cancer. N Engl J Med [Internet]. 366(6):520–529. Available from: https://doi.org/10.1056/NEJMoa1109653. 2025 Feb 2
33. O'Brien NA, McDermott MSJ, Conklin D, Luo T, Ayala R, Salgar S, Chau K, DiTomaso E, Babbar N, Su F, Gaither A, Hurvitz SA, Linnartz R, Rose K, Hirawat S, Slamon DJ (2020 Aug 14) Targeting activated PI3K/mTOR signaling overcomes acquired resistance to CDK4/6-based therapies in preclinical models of hormone receptor-positive breast cancer. Breast Cancer Res [Internet]. 22(1). Available from: https://doi.org/10.1186/s13058-020-01320-8. 2025 Feb 2
34. Iida M, Toyosawa D, Nakamura M, Tsuboi K, Tokuda E, Niwa T, Ishida T, Hayashi S-I (2020 Sep 1) Decreased ER dependency after acquired resistance to CDK4/6 inhibitors. Breast Cancer [Internet]. 27(5):963–972. Available from: https://doi.org/10.1007/s12282-020-01090-3. 2025 Feb 2
35. Rozenblit M, Mun S, Soulos P, Adelson K, Pusztai L, Mougalian S (2021 Dec 1) Patterns of treatment with everolimus exemestane in hormone receptor-positive HER2-negative metastatic breast cancer in the era of targeted therapy. Breast Cancer Res [Internet]. 23(1). Available from: https://doi.org/10.1186/s13058-021-01394-y. 2025 Feb 2
36. Cook MM, Al Rabadi L, Kaempf AJ, Saraceni MM, Savin MA, Mitri ZI (2021 Feb 1) Everolimus plus exemestane treatment in patients with metastatic hormone receptor-positive breast cancer Previously treated with CDK4/6 inhibitor therapy. Oncologist [Internet]. 26(2):101–106. Available from: https://doi.org/10.1002/onco.13609. 2025 Feb 2
37. Mo H, Renna CE, Moore HCF, Abraham J, Kruse ML, Montero AJ, LeGrand SB, Wang L, Budd GT (2022 Feb 1) Real-world outcomes of everolimus and exemestane for the treatment of metastatic hormone receptor-positive breast cancer in patients Previously treated with CDK4/6 inhibitors. Clin Breast Cancer [Internet]. 22(2):143–148. Available from: https://doi.org/10.1016/j.clbc.2021.10.002. 2025 Feb 2
38. Xi J, Oza A, Thomas S, Ademuyiwa F, Weilbaecher K, Suresh R, Bose R, Cherian M, Hernandez-Aya L, Frith A, Peterson L, Luo J, Krishnamurthy J, Ma CX (2019 Feb) Retrospective analysis of treatment patterns and effectiveness of palbociclib and subsequent regimens in metastatic breast cancer. J Natl Compr Cancer Network 17(2):141–147. https://doi.org/10.6004/jnccn.2018.7094
39. Dhakal A, Antony Thomas R, Levine EG, Brufsky A, Takabe K, Hanna MG et al. (2020;. 14 [cited 2025 Feb 2] Available from: Outcome of everolimus-based therapy in hormone-receptor-positive metastatic breast cancer patients after progression on palbociclib. Breast cancer (auckl) [Internet]. https://pubmed.ncbi.nlm.nih.gov/32753876/
40. Vasseur A, Cabel L, Hego C, Takka W, Trabelsi Grati O, Renouf B, Lerebours F, Loirat D, Brain E, Cottu P, Sablin M-P, Pierga J-Y, Callens C, Renault S, Bidard F-C (2024 Apr 12) Fulvestrant and everolimus efficacy after CDK4/6 inhibitor: a prospective study with circulating tumor DNA analysis. Oncogene [Internet]. 43(16):1214–1222. Available from: https://doi.org/10.1038/s41388-024-02986-6. 2025 Feb 2
41. Sánchez-Bayona R, Lopez de Sa A, Jerez Gilarranz Y, Sanchez de Torre A, Alva M, Echavarria I, Moreno F, Tolosa P, Herrero Lopez B, de Luna A, Lema L, Gamez Casado S, Madariaga A, López-Tarruella S, Manso L, Bueno-Muiño C, Garcia-Saenz JA, Ciruelos E, Martin M (2024 Aug 1) Everolimus plus endocrine therapy beyond CDK4/6 inhibitors progression for HR+ /HER2− advanced breast cancer: a real-world evidence cohort. Breast Cancer Res Treat [Internet]. 206(3):551–559. Available from: https://doi.org/10.1007/s10549-024-07324-8. 2025 Feb 2
42. Berger ML, Mamdani M, Atkins D, Johnson ML (2009) Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good research practices for retrospective Database analysis Task Force report-Part I. Value Health [Internet]. 12(8):1044–1052. Available from: https://pubmed.ncbi.nlm.nih.gov/19793072/. 2025 Feb 2
43. Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML (2009 Nov 1) Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: the international Society for Pharmacoeconomics and outcomes research Good research practices for retrospective Database analysis Task Force report-Part II. Value Heal 12(8):1053–1061
44. Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U (2009) Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good research practices for retrospective Database analysis Task Force report-Part III. Value Health [Internet]. 12(8):1062–1073. Available from: https://pubmed.ncbi.nlm.nih.gov/19793071/. 2025 Feb 2
45. Castelo-Branco L, Pellat A, Martins-Branco D, Valachis A, Derksen JWG, Suijkerbuijk KPM, Dafni U, Dellaporta T, Vogel A, Prelaj A, Groenwold RHH, Martins H, Stahel R, Bliss J, Kather J, Ribelles N, Perrone F, Hall PS, Dienstmann R, Booth CM, Pentheroudakis G, Delaloge S, Koopman M (2023 Dec 1) ESMO Guidance for reporting Oncology real-world evidence (GROW). Ann Oncol [Internet]. 34(12):1097–1112. Available from: https://doi.org/10.1016/j.annonc.2023.10.001. 2025 Feb 2
46. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis [Internet]. 40(5):373–383. Available from: https://doi.org/10.1016/0021-9681(87)90171-8. 2025 Feb 2
47. Tarantino P, Viale G, Press MF, Hu X, Penault-Llorca F, Bardia A, Batistatou A, Burstein HJ, Carey LA, Cortes J, Denkert C, Diéras V, Jacot W, Koutras AK, Lebeau A, Loibl S, Modi S, Mosele MF, Provenzano E, Pruneri G, Reis-Filho JS, Rojo F, Salgado R, Schmid P, Schnitt SJ, Tolaney SM, Trapani D, Vincent-Salomon A, Wolff AC, Pentheroudakis G, André F, Curigliano G (2023 Aug 1) ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer. Ann Oncol [Internet]. 34(8):645–659. Available from: https://doi.org/10.1016/j.annonc.2023.05.008. 2025 Feb 2
48. Rivera DR, Henk HJ, Garrett-Mayer E, Christian JB, Belli AJ, Bruinooge SS, Espirito JL, Sweetnam C, Izano MA, Natanzon Y, Robert NJ, Walker MS, Cohen AB, Boyd M, Enewold L, Hansen E, Honnold R, Kushi L, Mishra Kalyani PS, Pe Benito R, Sakoda LC, Sharon E, Tymejczyk O, Valice E, Wagner J, Lasiter L, Allen JD (2022 Jan 1) The friends of cancer research real-world data collaboration pilot 2.0: methodological Recommendations from Oncology case studies. Clin Pharma Ther [Internet]. 111(1):283. Available from: https://doi.org/10.1002/cpt.2453. 2026 Jun 5
49. Vissers PAJ, Elferink MAG, Bijlsma MJ, van der Geest LG, Koopman M, van Laarhoven HWM, Nieuwenhuijzen GAP, van Rossum PSN, Sijtsma FPC, Vink GR, de Vos-Geelen J, Wilmink HW, de Wilt JHW, Verhoeven RHA, van Erning FN (2025 Dec 1) Recommendations and definitions for time-to-event endpoints using real-world data in oncology. ESMO Real World Data Digit Oncol [Internet]. 10:100649. Available from: https://doi.org/10.1016/j.esmorw.2025.100649:. 2026 Jun 5

50. Patt D, Liu X, Li B, McRoy L, Layman RM, Brufsky A (2022 Aug 1) Real-world treatment patterns and outcomes of palbociclib plus an aromatase inhibitor for metastatic breast cancer: flatiron Database analysis. Clin Breast Cancer [Internet]. 22(6):601–610. Available from: https://doi.org/10.1016/j.clbc.2022.05.002. 2025 Mar 23
51. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (2017) Common Terminology Criteria for adverse events (CTCAE) version 5.0. Internet. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. 2022 May 9].
52. ESMO-MCBS scorecards - everolimus [Internet]. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-12-1. 2025 Feb 2].
53. Yardley DA, Noguchi S, Pritchard KI, Burris HA, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, Piccart M, Melichar B, Petrakova K, Arena FP, Erdkamp F, Harb WA, Feng W, Cahana A, Taran T, Lebwohl D, Rugo HS (2013 Oct 25) Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther [Internet]. 30(10):870–884. Available from: https://doi.org/10.1007/s12325-013-0060-1. 2025 Feb 2
54. Jerusalem G, De Boer RH, Hurvitz S, Yardley DA, Kovalenko E, Ejlertsen B, Blau S, Özgüroglu M, Landherr L, Ewertz M, Taran T, Fan J, Noel-Baron F, Louveau A-L, Burris H (2018 Oct 1) Everolimus plus exemestane vs everolimus or capecitabine monotherapy for estrogen receptor–positive, HER2-negative advanced breast cancer. JAMA Oncol [Internet]. 4(10):1367–1374. Available from: https://doi.org/10.1001/jamaoncol.2018.2262. 2025 Feb 2
55. Jacobs F, Molinelli C, Martins-Branco D, Marta GN, Salmon M, Ameye L et al. (2024 Jan 1;. 197 [cited 2024 Jul 10] Available from: Progression-free survival assessment by local investigators versus blinded independent central review in randomized clinical trials in metastatic breast cancer: a systematic review and meta-analysis. Eur J cancer [Internet]. https://pubmed.ncbi.nlm.nih.gov/38103328/
56. Martin JM, Handorf EA, Montero AJ, Goldstein LJ (2022 Jun 1) Systemic therapies following progression on first-line CDK4/6-inhibitor treatment: analysis of real-world data. Oncologist [Internet]. 27(6):441–446. Available from: https://doi.org/10.1093/oncolo/oyac075. 2025 Feb 2
57. Sawaki M, Muramatsu Y, Togo K, Iwata H (2023 Aug 1) Real-world treatment patterns of subsequent therapy after palbociclib in patients with advanced breast cancer in Japan. Breast [Internet]. 70:1–7. Available from: https://doi.org/10.1016/j.breast.2023.05.006. 2025 Feb 2
58. Afinitor | European Medicines Agency (EMA) [Internet]. [https://www.ema.europa.eu/en/medicines/human/EPAR/afinitor. 2026 Jun 5].
59. Kornblum N, Zhao F, Manola J, Klein P, Ramaswamy B, Brufsky A et al. (2018 Jun 1) Randomized phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor-positive, human Epidermal Growth Factor receptor 2-negative metastatic breast cancer resistant to aromatase inhibitor therapy: results of PrE0102. J Clin Oncol [Internet]. 36(16):1556–1563. Available from: https://pubmed.ncbi.nlm.nih.gov/29664714/. 2025 Mar 23
60. Cherny NI, Trapani D, Galotti M, Saar M, Bricalli G, Roitberg F et al. (2025 Jan) ESMO global consortium study on the availability, out-of-pocket costs, and accessibility of cancer medicines: 2023 update. Ann Oncol [Internet]. Available from: http://www.annalsofoncology.org/article/S0923753424049809/fulltext. 2025 Feb 2
61. Vernieri C, Corti F, Nichetti F, Ligorio F, Manglaviti S, Zattarin E, Rea CG, Capri G, Bianchi GV, de Braud F (2020 Apr 6) Everolimus versus alpelisib in advanced hormone receptor-positive HER2-negative breast cancer: targeting different nodes of the PI3K/AKT/mTORC1 pathway with different clinical implications. Breast Cancer Res [Internet]. 22(1). Available from: https://doi.org/10.1186/s13058-020-01271-0. 2025 Feb 2
62. FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer | FDA [Internet]. [https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive. 2025 Feb 2].
63. Jhaveri KL, Neven P, Casalnuovo ML, Kim SB, Tokunaga E, Aftimos P et al. (2024 Dec 11) Imlunestrant with or without abemaciclib in advanced breast cancer. N Engl J Med [Internet]. http://www.ncbi.nlm.nih.gov/pubmed/39660834. 2025 Feb 2]
64. Bayle A, Bonastre J, Chaltiel D, Latino N, Rouleau E, Peters S, Galotti M, Bricalli G, Besse B, Giuliani R (2023 Oct 1) ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. Ann Oncol 34(10):934–945. https://doi.org/10.1016/j.annonc.2023.06.011
65. Meric-Bernstam F, Zheng X, Shariati M, Damodaran S, Wathoo C, Brusco L, Demirhan ME, Tapia C, Eterovic AK, Basho RK, Ueno NT, Janku F, Sahin A, Rodon J, Broaddus R, Kim T-B, Mendelsohn J, Mills Shaw KR, Tripathy D, Mills GB, Chen K (2018 Nov) Survival outcomes by TP53 mutation status in metastatic breast cancer. JCO Precis Oncol [Internet]. 2(2):1–15. Available from: https://doi.org/10.1200/PO.17.00245. 2025 Feb 2
66. Mayer E, Tolaney S, Martin M, Vidal G, Moscetti L, Jhaveri K et al. (2025 Sep 1) LBA16 giredestrant (GIRE), an oral selective oestrogen receptor (ER) antagonist and degrader, + everolimus (E) in patients (pts) with ER-positive, HER2-negative advanced breast cancer (ER+, HER2- aBC) previously treated with a CDK4/6 inhibitor (i): prima …. Ann Oncol [Internet]. 36:S1561–2. Available from: https://www.annalsofoncology.org/action/showFullText?pii=S0923753425047969. 2026 Jun 5
67. Llombart-Cussac A, Pérez-García JM, Lopez-Miranda E, Saavedra C, Carañana V, Blancas I et al. (2026 Feb 15 [cited 2026 Jun 5];Abstract PS1-11-02. The ADELA study: a double-blind, placebo-controlled, randomized phase 3 trial of elacestrant + everolimus versus elacestrant + placebo in ER+/HER2- advanced breast cancer (ABC) patients with ESR1-mutated tumors progressing on endocrin …. Clin Cancer Res [Internet]. 32(4_Supplement):PS1–11–02. Available from: https://www.clincancerres/article/32/4_Supplement/PS1-11-02/772875/Abstract-PS1-11-02-The-ADELA-study-a-double-blind
68. Rugo H, Tolaney SM, Chan N, Borges G, Yerushalmi R, Sharifi M, McHayleh W, Beck T, Vidula N, Hamilton E, Rinn KJ, O'Shaughnessy J, Curigliano G, Cortés J, Romero P, Tonini G, Paoli A, Binaschi M, Cheng L, Crozier J, Wasserman T, Kaklamani V (2026 Feb 15) Abstract RF7-01: elacestrant in combination with everolimus or abemaciclib in patients with ER+/HER2- locally advanced or metastatic breast cancer (mBC): phase 2 results from ELEVATE, an open-label, umbrella study. Clin Cancer Res [Internet]. 32(4_Supplement):RF7–01. [cited 2026 Jun 5] Available from: https://doi.org/10.1158/1557-3265.SABCS25-RF7-01

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