Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2025, Volume 5, Issue 1, Page No: 145-156

Available online at: www.galaxypub.co/page/journals

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A Phase II, Multicenter, Randomized, Double-Blind Study to Assess the Tolerability of Escalating Induction Doses of Everolimus in Patients with Metastatic Breast Cancer (DESIREE)

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Received: 12 October 2024; **Revised:** 16 January 2025; **Accepted:** 18 January 2025

ABSTRACT

Stomatitis represents a primary cause for discontinuing everolimus therapy among individuals diagnosed with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer. The DESIREE study explored a gradual dose-increase approach for everolimus (EVE esc) to mitigate mucositis and reduce premature discontinuations or dosage adjustments. This phase II, multicenter, randomized, double-blind, placebo-controlled investigation involved participants with HR+/HER2– advanced breast cancer who experienced disease progression or recurrence following nonsteroidal aromatase inhibitor therapy. Subjects were allocated to either EVE esc (starting at 2.5 mg daily in week 1, increasing to 5 mg in week 2, 7.5 mg in week 3, and 10 mg from weeks 4 to 24) or standard everolimus at 10 mg daily (EVE 10mg), both combined with exemestane over 24 weeks. The main outcome measure was the occurrence of grade ≥2 mucositis events during the initial 12 weeks. Additional outcomes encompassed adverse effects, relative total dose intensity (RTDI), and patient-reported quality of life (QoL). In total, 160 individuals were allocated randomly, with 156 initiating therapy (EVE esc: 80; EVE 10mg: 76). The average patient age was 64 years (ranging from 33 to 85); liver metastases were present in 56.3% of the EVE esc group compared to 42.1% in the EVE 10mg group (P = 0.081), and more than one prior metastatic treatment line was noted in 62.5% versus 51.3% (P = 0.196). Over the first 12 weeks, grade ≥2 mucositis events occurred less frequently in the EVE esc group than in the EVE 10mg group (28.8% vs. 46.1%; odds ratio 0.47, 95% confidence interval 0.24-0.92; P = 0.026). Adverse event profiles aligned with established data, showing no novel concerns. Median RTDI reached 91.1% for EVE esc versus 80.0% for EVE 10mg (P = 0.329). Early discontinuations within the initial three weeks were 6.3% in EVE esc versus 15.8% in EVE 10mg (P = 0.073). Quality of life measures remained similar across groups. Implementing a three-week gradual increase in everolimus dosing effectively lowers the rate of severe mucositis during the early 12 weeks of therapy in HR+/HER2– advanced breast cancer cases.

Keywords: Everolimus, Exemestane, Metastatic breast cancer, Stomatitis

How to Cite This Article: Moore E, Garcia CZ, Ferrari G. A Phase II, Multicenter, Randomized, Double-Blind Study to Assess the Tolerability of Escalating Induction Doses of Everolimus in Patients with Metastatic Breast Cancer (DESIREE). Asian J Curr Res Clin Cancer. 2025;5(1):145-56. https://doi.org/10.51847/VReJL5V3r5

Introduction

Recent advancements have improved outcomes for individuals with advanced breast cancer. Nonetheless, the condition remains incurable [1], necessitating careful consideration of treatment tolerability, disease management, and symptom relief alongside efficacy. Guidelines nationally and internationally recommend endocrine therapy as the preferred initial approach for HR-positive, HER2-negative advanced disease, except where clinical urgency or patient choice indicates otherwise [1-3].

Endocrine resistance eventually emerges in most cases of advanced breast cancer [4]. The PI3K pathway holds particular significance in HR-positive/HER2-negative disease [5]. As a critical component downstream in the PI3K/AKT/mTOR cascade, mTOR contributes substantially to resistance mechanisms [4]. Combining the mTOR

inhibitor everolimus with the steroidal aromatase inhibitor exemestane provides an established treatment following failure of nonsteroidal aromatase inhibitors. In the BOLERO-2 trial, with 18 months of median follow-up, progression-free survival extended to 11 months with the combination versus 4.1 months with exemestane alone (central assessment; hazard ratio 0.38, 95% CI 0.31-0.48; log-rank P < 0.0001) [6].

Stomatitis emerged as the leading grade 3/4 adverse event in BOLERO-2 (8% in the combination arm versus 1% with placebo) [7]. Comparable severe mucositis rates appeared in additional trials of everolimus plus exemestane for HR-positive/HER2-negative advanced disease [8-10]. Real-world evidence mirrored BOLERO-2 findings on safety and effectiveness [11, 12].

Adverse effects from everolimus, particularly mucositis, frequently prompted dose modifications or therapy cessation. A meta-analysis across solid tumors reported everolimus-associated mucositis in 67% of cases [13]. While predominantly mild (grade 1/2), severe events (grade 3/4) affected 9%. Even moderate mucositis can distress patients, impair quality of life, and compromise adherence. However, BOLERO-2 analysis indicated delayed definitive QoL deterioration with the everolimus combination [14].

Preventive measures against everolimus-induced mucositis have been explored. The single-arm phase II SWISH trial demonstrated that prophylactic dexamethasone oral rinse markedly lowered grade ≥2 mucositis to 2% in advanced HR-positive/HER2-negative breast cancer patients [15].

In the randomized phase II DESIREE investigation, an alternative strategy was evaluated to lessen mucositis in advanced breast cancer patients receiving everolimus plus exemestane. Postmenopausal women with HR-positive/HER2-negative advanced disease were assigned randomly to either the standard 10 mg daily everolimus dose (EVE 10mg) plus exemestane or a gradual escalation regimen (EVE esc) plus exemestane.

Materials and Methods

Patients

The DESIREE trial (NCT02387099) was a phase II, multicenter, randomized, double-blind, placebo-controlled study conducted in postmenopausal women with hormone receptor-positive (HR+), HER2-negative advanced or metastatic breast cancer who had experienced disease progression or recurrence following prior nonsteroidal aromatase inhibitor (NSAI) therapy. The primary objective was to evaluate whether a gradual dose-escalation regimen of everolimus combined with exemestane could reduce the occurrence of grade ≥2 mucositis episodes within the first 12 weeks compared to the standard dosing schedule.

Key inclusion criteria included postmenopausal status; locally advanced or metastatic disease not suitable for curative surgery or radiotherapy alone and without immediate need for chemotherapy (e.g., no symptomatic visceral crisis); histologically confirmed HR-positive disease (estrogen and/or progesterone receptor expression >1% of tumor cells) [16] and HER2-negative status (immunohistochemistry score 0-1+ or 2+ with in situ hybridization ratio <2.0) [17]; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; disease relapse or progression on or after NSAI treatment; and adequate bone marrow, organ function, glycemic control, and lipid profile. Patients with life expectancy <3 months or uncontrolled brain metastases were excluded. The protocol received approval from independent ethics committees, institutional review boards, and relevant regulatory authorities. All participants provided written informed consent for study involvement and biological sample collection.

Study design and treatment

Participants were assigned 1:1 through randomization to one of two regimens: gradual everolimus dose escalation (2.5 mg daily in week 1, 5 mg daily in week 2, 7.5 mg daily in week 3, followed by 10 mg daily from weeks 4 to 24) or standard everolimus at 10 mg daily for 24 weeks, both administered alongside exemestane 25 mg daily. Treatment in either arm continued until completion of 24 weeks, documented disease progression, intolerable toxicity, or patient withdrawal of consent. Subsequent therapy after study completion was left to the discretion of the treating physician and was recorded until initiation of first-line chemotherapy or study closure. No formal follow-up phase was included.

Endpoints and assessments

The primary endpoint was the proportion of patients experiencing at least one episode of grade ≥2 mucositis within the first 12 weeks of therapy. Patients who discontinued treatment early (due to adverse events, personal

choice, or investigator decision) without full mucositis assessment during this period were conservatively classified as having experienced a grade ≥2 episode, even if documented mucositis was milder. Mucositis grading followed the World Health Organization (WHO) Oral Toxicity Scale [18].

Secondary endpoints included the incidence of grade ≥2 mucositis within 24 weeks; cumulative incidence of any-grade mucositis at 12 and 24 weeks; clinical benefit rate (CBR); relative total dose intensity (RTDI); time to first grade ≥2 mucositis episode; overall safety profile; and quality of life (QoL).

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

RTDI was calculated as the percentage of actual cumulative dose intensity delivered relative to the protocol-specified intended dose intensity over the full treatment period.

Time to grade ≥2 mucositis onset was measured from the date of randomization to the first documented occurrence of such an episode.

Clinical benefit rate was defined as the proportion of patients achieving complete response, partial response, or stable disease (without progression) per RECIST version 1.1 criteria [19], evaluated at 24 weeks from treatment initiation.

Quality of life was measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire version 4 [20]. Derived scores included subscale domains (Physical, Social/Family, Emotional, and Functional Well-Being, plus Breast Cancer-Specific Additional Concerns), the FACT-B Trial Outcome Index (TOI), the total FACT-G score, and the overall FACT-B total score.

Statistical analysis

The determination of sample size centered on the primary endpoint. A total of 156 participants (78 per group) were deemed necessary to identify a meaningful reduction of 20% in the proportion of patients experiencing grade ≥2 mucositis episodes at 12 weeks (anticipated rates of 40% in the standard everolimus 10 mg group and 20% in the gradual escalation group), applying a two-sided continuity-corrected chi-square test at a significance threshold of $\alpha = 0.20$ with 90% statistical power.

Analyses of the primary and secondary endpoints utilized the modified intention-to-treat (mITT) population, comprising all randomized patients who initiated treatment. Rates of grade ≥2 mucositis episodes were computed along with 80% confidence intervals (aligned with the study design's α of 0.2) and supplementary 95% confidence intervals [21] for individual arms and combined, with inter-arm comparisons conducted via continuity-corrected chi-square test ($\alpha = 0.20$). Univariate logistic regression provided odds ratios with corresponding 80% and 95% confidence intervals.

Secondary endpoints were evaluated at a two-sided $\alpha = 0.05$ level with 95% confidence intervals, without adjustments for multiplicity. A post-hoc multivariate logistic regression for dichotomous outcomes incorporated adjustments for age (≥65 vs. ≤65 years), ECOG performance status (1-2 vs. 0), body mass index (≥25 vs. <25 kg/m²), and prior metastatic therapy lines (>1 vs. 0/1), yielding adjusted odds ratios with 95% confidence intervals.

Cumulative incidence curves illustrated time to grade ≥2 mucositis onset, with inter-arm differences assessed using the Gray test [22]. Competing risks included treatment discontinuation for adverse events, patient or investigator choice, progression, or death absent grade ≥2 mucositis.

Safety and treatment adherence evaluations were performed in the safety population, encompassing all mITT patients except one randomized to escalation who inadvertently received full dosing in the first three weeks (reassigned to the standard arm for analysis). Additionally, one patient in the standard arm was omitted from safety analyses due to incomplete documentation. Non-mucositis adverse events were tabulated by frequency and proportion within categories, per arm and overall. Descriptive P-values for comparisons of adverse event rates and adherence metrics between arms were derived from Fisher's exact test.

Clinical benefit rate was evaluated in the mITT population with 95% confidence intervals, with arm comparisons via two-sided Fisher's exact test.

Quality of life assessments in the safety population employed mixed-effects repeated measures models, incorporating fixed effects for treatment group, time point, and their interaction, with baseline scores as covariates.

All analyses were conducted using SAS version 9.4 with SAS Enterprise Guide Version 7.1 on Microsoft Windows 10 Enterprise. The data cutoff date was 5 July 2021.

Results and Discussion

Patient characteristics

From June 2015 to October 2020, 208 patients underwent screening across 29 German centers; 160 were randomized, and 156 commenced therapy (escalation arm: 80 patients; standard 10 mg arm: 76 patients); **(Figure 1)**. Median age upon enrollment was 64 years (range 33-85), with a notable imbalance in prespecified age categories (P = 0.014). Prior adjuvant therapy was more common in the escalation arm (60.0% vs. 44.7%; P = 0.046), and liver metastases tended to be more frequent in this group (56.3% vs. 42.1%; P = 0.081). Remaining demographic and disease features were well balanced between arms **(Table 1)**. Prior treatments for advanced disease included endocrine agents (100%), targeted agents (81.4%), and chemotherapy (75.6%).

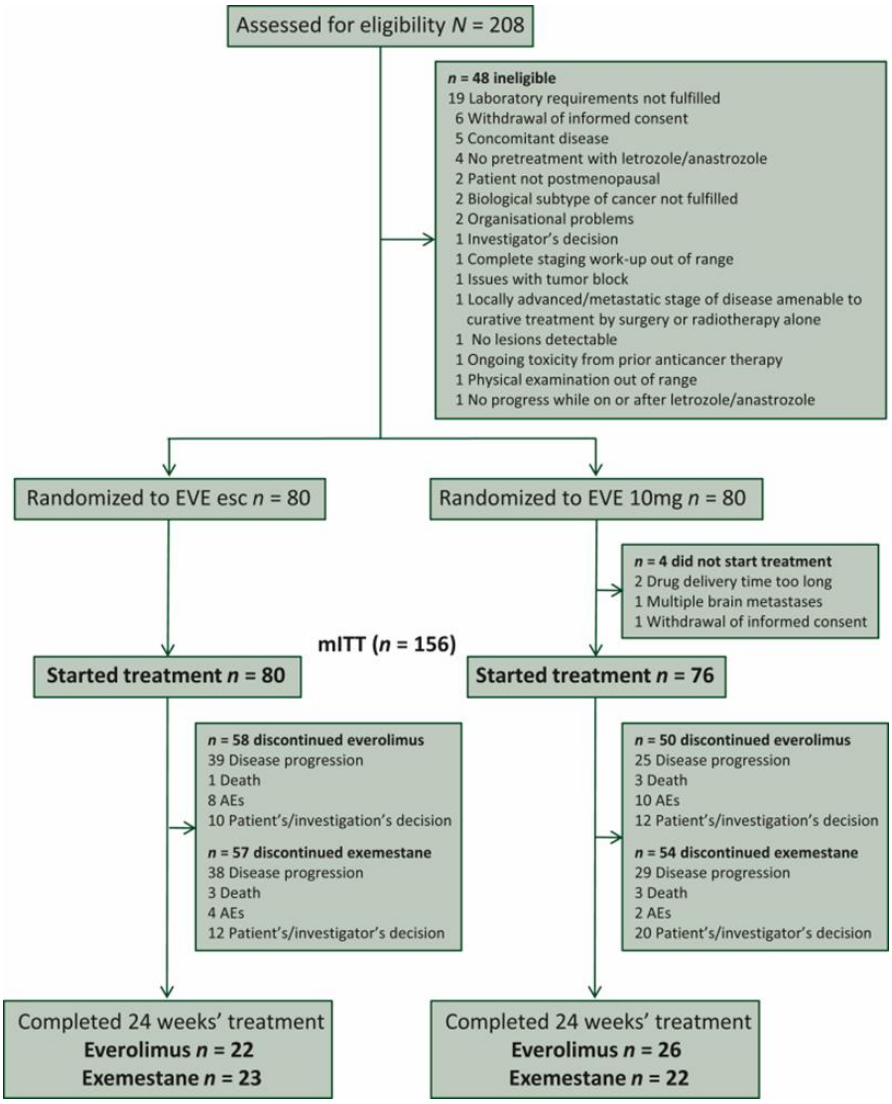


Figure 1. CONSORT diagram.
AE, adverse event; esc, escalated; EVE, everolimus.

Table 1. Patient and Disease Characteristics at Baseline

Parameter	Category	EVE esc (n = 80)	EVE 10mg (n = 76)	Overall (n = 156)	P value
Age, years	Median (range)	64.5 (33.0-85.0)	63.0 (41.0-81.0)	64.0 (33.0-85.0)	0.538
	<40	2 (2.5%)	0 (0.0%)	2 (1.3%)	0.014
	40-<50	11 (13.8%)	2 (2.6%)	13 (8.3%)	
	50-<65	27 (33.8%)	39 (51.3%)	66 (42.3%)	
	≥65	40 (50.0%)	35 (46.1%)	75 (48.1%)	
BMI, kg/m²	<25	35 (43.8%)	39 (51.3%)	74 (47.4%)	0.423

	≥25	45 (56.3%)	37 (48.7%)	82 (52.6%)	
Menopausal status	Pre/perimenopausal[a]	1 (1.3%)	0 (0.0%)	1 (0.6%)	>0.99
	Postmenopausal	79 (98.8%)	76 (100%)	155 (99.4%)	
ECOG performance status	0	57 (71.3%)	63 (82.9%)	120 (76.9%)	0.202
	1	20 (25.0%)	12 (15.8%)	32 (20.5%)	
	2	3 (3.8%)	1 (1.3%)	4 (2.6%)	
Prior stomatitis	No	77 (96.3%)	73 (96.1%)	150 (96.2%)	0.949
	Grade 1	3 (3.8%)	3 (3.9%)	6 (3.8%)	
Histological tumour type	Ductal or ductal-lobular invasive	54 (67.5%)	52 (68.4%)	106 (67.9%)	0.677
	Lobular invasive	19 (23.8%)	20 (26.3%)	39 (25.0%)	
	Other	7 (8.8%)	4 (5.3%)	11 (7.1%)	
Number of metastatic sites	1	22 (27.5%)	28 (36.8%)	50 (32.1%)	0.512
	2	30 (37.5%)	28 (36.8%)	58 (37.2%)	
	3	19 (23.8%)	15 (19.7%)	34 (21.8%)	
	≥4	9 (11.3%)	5 (6.6%)	14 (9.0%)	
Selected metastatic sites[b]	Bone	55 (68.8%)	57 (75.0%)	112 (71.8%)	0.477
	Liver	45 (56.3%)	32 (42.1%)	77 (49.4%)	0.081
	Lung	21 (26.3%)	17 (22.4%)	38 (24.4%)	0.582
	Pleura	12 (15.0%)	7 (9.2%)	19 (12.2%)	0.331
Number of previous metastatic regimens	0	6 (7.5%)	7 (9.2%)	13 (8.3%)	0.849
	1-2	59 (73.8%)	53 (69.7%)	112 (71.8%)	
	>2	15 (18.8%)	16 (21.1%)	31 (19.9%)	
Disease setting at first diagnosis	Neoadjuvant	8 (10.0%)	18 (23.7%)	26 (16.7%)	0.046
	Adjuvant	48 (60.0%)	34 (44.7%)	82 (52.6%)	
	Advanced	24 (30.0%)	24 (31.6%)	48 (30.8%)	
Previous therapy in advanced setting	Chemotherapy[c]	61 (76.3%)	57 (75.0%)	118 (75.6%)	>0.99
	Endocrine therapy[d]	80 (100%)	76 (100%)	156 (100%)	n.a.
	Targeted therapy[e]	66 (82.5%)	61 (80.3%)	127 (81.4%)	0.837

Data are presented as n (%).

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; esc, escalation; EVE, everolimus; n.a., not applicable.

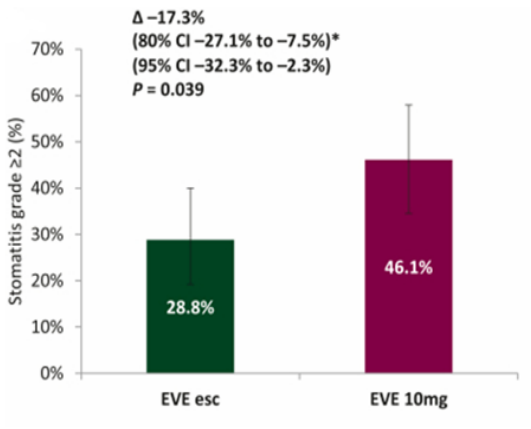
[a]Protocol deviation. [b]Patients could have multiple metastatic sites. [c]Chemotherapy regimens included taxane-anthracycline combinations, non-taxane-anthracycline combinations, anthracycline monotherapy, or taxane monotherapy. [d]Endocrine therapies included anastrozole, letrozole, exemestane, fulvestrant, or tamoxifen. [e]Targeted therapies included palbociclib, ribociclib, bisphosphonates, or denosumab.

Stomatitis

Over the initial 12 weeks of therapy, grade ≥2 mucositis episodes occurred in 28.8% of patients (95% CI 19.2%–40.0%) in the gradual escalation arm versus 46.1% (95% CI 34.5%–57.9%) in the standard 10 mg arm (P = 0.039), corresponding to an odds ratio of 0.47 (95 percent CI 0.24–0.92; P = 0.026); **(Figure 2a).** When excluding patients with premature treatment discontinuation from the analysis, the respective rates of confirmed grade ≥2 mucositis were 18.8% (95% CI 10.9%–29.0%) versus 35.5 percent (95 percent CI 24.9%–47.3%).

A post-hoc multivariate logistic regression adjusting for age, ECOG performance status, body mass index, and number of prior metastatic treatment lines confirmed the reduced risk in the escalation arm (adjusted OR 0.40, 95 percent CI 0.20–0.81; P = 0.011).

No significant difference emerged in the occurrence of any-grade mucositis between the arms (62.5 percent in the escalation arm versus 73.7 percent in the standard arm; P = 0.185).



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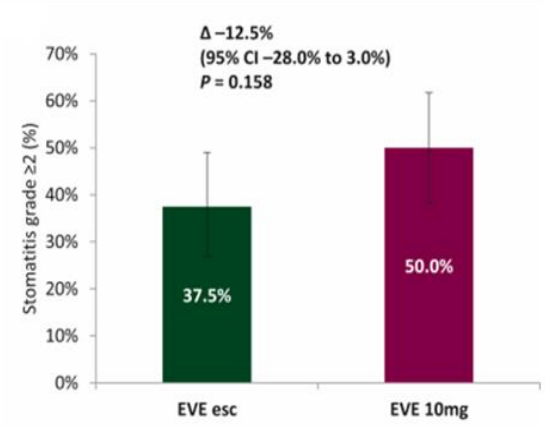

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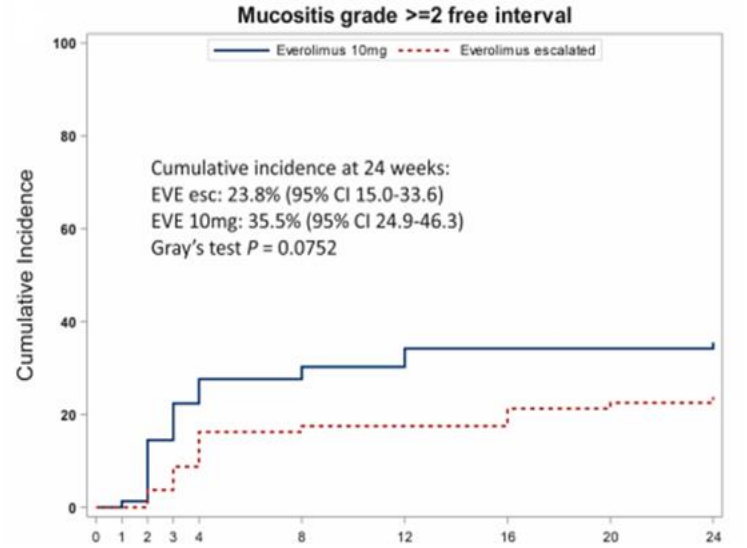

c)

Figure 2. The rates of stomatitis grade ≥2 were assessed at (a) 12 weeks and (b) 24 weeks post-treatment initiation, alongside (c) the duration until onset of grade ≥2 stomatitis across 24 weeks. In the calculations for (a) and (b), instances of stomatitis below grade 2 or early withdrawal from the study (owing to side effects, patient preference, or clinician judgment) were treated as occurrences. The primary endpoint applied a one-sided type I error rate of 20%. The analysis in (c) was conducted after the fact, with competing risks encompassing study drug cessation due to side effects, patient preference, clinician judgment, disease advancement, or death before developing grade ≥2 stomatitis.
CI, confidence interval; esc, escalated; EVE, everolimus; OR, odds ratio.

By the 24-week mark, the rate of grade ≥2 stomatitis occurrences appeared lower in the everolimus dose-escalation group than in the standard 10 mg group, although this did not achieve statistical significance (37.5 percent versus 50.0 percent; OR 0.60, 95 percent CI 0.32-1.14; P = 0.117); **(Figure 2b).** Excluding premature discontinuations from the count, the occurrence of grade ≥2 mucositis stood at 23.8% in the dose-escalation group compared to 35.5% in the standard-dose group. An exploratory multivariable assessment post hoc revealed a notably decreased chance of grade ≥2 stomatitis events among patients on dose escalation (OR 0.49, 95 percent CI 0.25-0.98; P = 0.043). Rates of stomatitis of any grade showed no meaningful distinction between groups (67.5% dose escalation versus 77.6% standard; P = 0.216).

A competing-risk evaluation indicated a cumulative rate of grade ≥2 stomatitis at 24 weeks of 23.8 percent (95 percent CI 15.0 percent to 33.6 percent) for dose escalation versus 35.5 percent (95 percent CI 24.9 percent to 46.3 percent) for the 10 mg regimen (P = 0.075); **(Figure 2c).**

Further safety evaluations

All participants in the safety cohort reported at least one adverse event, with 91.6% involving blood-related issues and 100% involving non-blood-related issues **(Table 2).** Excluding stomatitis, the patterns of side effects were generally comparable between the groups. Prevalent any-grade blood-related events comprised anemia (74.7% escalation versus 81.6% standard; P = 0.336) and leukopenia (67.1 percent in each). Common any-grade events not related to blood included rises in high-density lipoprotein cholesterol (96.2 percent versus 93.4 percent; P = 0.489), elevated serum cholesterol (77.2 percent versus 85.5 percent; P = 0.219), increased aspartate aminotransferase (79.7 percent versus 72.4 percent; P = 0.347), higher alanine aminotransferase (67.1 percent versus 53.9 percent; P = 0.103), elevated triglycerides (73.4 percent versus 72.4 percent; P >0.99), hyperglycemia (57.0 percent versus 60.5 percent; P = 0.745), fatigue (53.2 percent versus 52.6 percent; P >0.99), and increased low-density lipoprotein cholesterol (51.9 percent versus 72.4 percent; P = 0.013). Severe (grade 3-4) blood-related events most commonly included anemia (3.8 percent versus 6.6 percent; P = 0.489), leukopenia (3.8 percent versus 2.6 percent; P >0.99), and neutropenia (3.8 percent versus 5.3 percent; P = 0.716). Prominent severe non-blood-related events involved aspartate aminotransferase increases (8.9 percent versus 2.6 percent; P = 0.168), alanine aminotransferase increases (5.1 percent versus 1.3 percent; P = 0.367), and hyperglycemia (5.1 percent versus 9.2 percent; P = 0.362). No notable differences appeared in pneumonitis rates (an event of particular interest) across groups (any grade: 7.6 percent versus 7.9 percent; grade 3-4: 1.3 percent solely in escalation group); **(Table 2).**

Table 2. Selected adverse events (excluding stomatitis, the primary endpoint) that occurred in at least 10% of patients in either treatment group, irrespective of relationship to study drug. Data are derived from the safety population (total n = 155) after 24 weeks of therapy.

Adverse events	Any grade: EVE 10mg (n = 76), n (%)	Any grade: EVE esc (n = 79), n (%)	P value (any grade)	High-grade (grade 3-4): EVE 10mg (n = 76), n (%)	High-grade (grade 3-4): EVE esc (n = 79), n (%)	P value (high-grade)
Summary of all AEs						
Any AE	76 (100)	79 (100)	n.a.	33 (43.4)	37 (46.8)	0.747
Any haematological AE	72 (94.7)	70 (88.6)	0.247	8 (10.5)	8 (10.1)	>0.99
Any nonhaematological AE	76 (100)	79 (100)	n.a.	29 (38.2)	35 (44.3)	0.514
Other AEs	68 (89.5)	75 (94.9)	0.240	17 (22.4)	25 (31.7)	0.210
At least one SAE	22 (28.9)	23 (29.1)	>0.99	n.a.	n.a.	—
AESI (pneumonitis)	6 (7.9)	6 (7.6)	>0.99	0 (0.0)	1 (1.3)	>0.99
Predefined AEs						
Anaemia	62 (81.6)	59 (74.7)	0.336	5 (6.6)	3 (3.8)	0.489
Leukopenia	51 (67.1)	53 (67.1)	>0.99	2 (2.6)	3 (3.8)	>0.99
Thrombocytopenia	36 (47.4)	29 (36.7)	0.196	1 (1.3)	1 (1.3)	>0.99
Neutropenia	29 (38.2)	33 (41.8)	0.743	4 (5.3)	3 (3.8)	0.716
Blood AP increased	36 (47.4)	41 (51.9)	0.631	1 (1.3)	2 (2.5)	>0.99
ASAT increased	55 (72.4)	63 (79.7)	0.347	2 (2.6)	7 (8.9)	0.168
ALAT increased	41 (53.9)	53 (67.1)	0.103	1 (1.3)	4 (5.1)	0.367
Blood creatinine increased	31 (40.8)	24 (30.4)	0.184	0 (0.0)	0 (0.0)	n.a.
Fatigue	40 (52.6)	42 (53.2)	>0.99	1 (1.3)	2 (2.5)	>0.99
Diarrhoea	19 (25.0)	28 (35.4)	0.167	2 (2.6)	2 (2.5)	>0.99
Decreased appetite	16 (21.1)	22 (27.8)	0.355	2 (2.6)	1 (1.3)	0.615
Nausea	26 (34.2)	23 (29.1)	0.604	0 (0.0)	1 (1.3)	>0.99
Cough	21 (27.6)	24 (30.4)	0.727	0 (0.0)	0 (0.0)	n.a.
Headache	17 (22.4)	24 (30.4)	0.279	1 (1.3)	0 (0.0)	0.490
Weight decreased	22 (28.9)	16 (20.3)	0.263	0 (0.0)	0 (0.0)	n.a.
Dyspnoea	23 (30.3)	16 (20.3)	0.195	2 (2.6)	1 (1.3)	0.615

Arthralgia	22 (28.9)	18 (22.8)	0.463	0 (0.0)	0 (0.0)	n.a.
Epistaxis	6 (7.9)	9 (11.4)	0.589	0 (0.0)	0 (0.0)	n.a.
Vertigo	8 (10.5)	11 (13.9)	0.627	0 (0.0)	0 (0.0)	n.a.
Hypertriglyceridemia	55 (72.4)	58 (73.4)	>0.99	1 (1.3)	1 (1.3)	>0.99
Hypoglycaemia	9 (11.8)	16 (20.3)	0.192	0 (0.0)	0 (0.0)	n.a.
Hyperglycaemia	46 (60.5)	45 (57.0)	0.745	7 (9.2)	4 (5.1)	0.362
Serum cholesterol increased	65 (85.5)	61 (77.2)	0.219	2 (2.6)	1 (1.3)	0.615
LDL cholesterol increased [a]	55 (72.4)	41 (51.9)	0.013	n.a.	n.a.	n.a.
HDL cholesterol increased [a]	71 (93.4)	76 (96.2)	0.489	n.a.	n.a.	n.a.

Adverse events are not mutually exclusive. One participant in the EVE 10mg group was not included due to incomplete safety records (missing information), and one participant assigned to the EVE esc group actually received the full 10 mg dose of everolimus throughout the escalation period, leading to analysis in the EVE 10mg group (resulting in EVE esc: n = 79 and EVE 10mg: n = 76).

AE = adverse event; AESI = adverse event of special interest; ALAT = alanine aminotransferase; AP = alkaline phosphatase; ASAT = aspartate aminotransferase; EVE = everolimus; esc = escalated; HDL = high-density lipoprotein; LDL = low-density lipoprotein; n.a. = not applicable; SAE = serious adverse event.

[a] No grading available.

Beyond the listed predefined adverse events, the most frequently occurring any-grade non-predefined events included nervous system disorders (other than those specified; 26.6% in the dose-escalation group versus 26.3% in the standard 10 mg group; P >0.99), skin rash (22.8 percent versus 11.8 percent; P = 0.091), infections and infestations (other categories; 21.5 percent versus 11.8 percent; P = 0.134), and gastrointestinal disorders (other than predefined; 20.3 percent versus 18.4 percent; P = 0.840).

In total, 45 participants experienced at least one serious adverse event (23 in the everolimus dose-escalation arm and 22 in the 10 mg arm); **(Table 2).** Over the 24-week treatment period, four deaths occurred (one in the escalation arm and three in the standard arm), all attributed to progression of the underlying disease.

Compliance

The median length of exposure to everolimus within the 24-week period was 12.7 weeks (range 0.1–24.0) for the dose-escalation group compared with 16.0 weeks (range 0.7–24.0) for the 10 mg group (P = 0.592). The median relative dose intensity achieved was 91.1% (range 0.2–100) in the escalation arm versus 80.0 percent (range 1.2–100) in the standard arm (P = 0.329).

In the initial 3-week escalation phase, early discontinuation of everolimus affected only 6.3 percent of patients in the escalation arm versus 15.8% in the standard arm (P = 0.073), primarily because of adverse events (1.3% versus 6.6%, respectively). By week 12, discontinuation rates stood at 46.3% in the escalation group compared to 32.9% in the standard group (P = 0.103). The leading causes were disease progression in both groups (31.3% escalation versus 9.2% standard) and adverse events in the standard group (6.3% escalation versus 9.2% standard). By the end of 24 weeks, everolimus had been stopped in 72.5 percent of patients in the escalation arm and 65.8% in the standard arm (P = 0.390), predominantly owing to disease progression (48.8 percent versus 32.9 percent, respectively); **(Table 3).**

Table 3. Overview of treatment discontinuation, dose adjustments, and interruptions during the study period

Status/reason	EVE 10mg (n = 77), n (%)	EVE esc (n = 79), n (%)	Overall (n = 156), n (%)	P value
Discontinued everolimus				
Within the first 3 weeks (escalation phase)	12 (15.8)	5 (6.3)	17 (10.9)	0.073
Disease progression	1 (1.3)	1 (1.3)	2 (1.3)	
Death	2 (2.6)	0 (0.0)	2 (1.3)	
AE	5 (6.6)	1 (1.3)	6 (3.8)	
Patient's or investigator's decision	4 (5.2)	3 (3.8)	7 (4.5)	
Within the first 12 weeks	25 (32.9)	37 (46.3)	62 (39.7)	0.103
Disease progression	7 (9.2)	25 (31.3)	32 (20.5)	
Death	3 (3.9)	0 (0.0)	3 (1.9)	
AE	7 (9.2)	5 (6.3)	12 (7.7)	

Patient's or investigator's decision	8 (10.5)	7 (8.8)	15 (9.6)	
Within 24 weeks	50 (65.8)	58 (72.5)	108 (69.2)	0.390
Disease progression	25 (32.9)	39 (48.8)	64 (41.0)	
Death	3 (3.9)	1 (1.3)	4 (2.6)	
AE	10 (13.2)	8 (10.0)	18 (11.5)	
Patient's or investigator's decision	12 (15.8)	10 (12.6)	22 (14.1)	
Discontinued exemestane	22 (28.9)	23 (28.8)	45 (28.8)	>0.99
Disease progression	29 (38.2)	38 (47.5)	67 (42.9)	
Death	3 (3.9)	3 (3.8)	6 (3.8)	
AE	2 (2.6)	4 (5.0)	6 (3.8)	
Patient's or investigator's decision	20 (26.3)	12 (15.0)	32 (20.5)	
Dose reduction everolimus				
Patients with everolimus reduced to 5 mg	24 (36.4)	23 (31.5)	47 (33.8)	0.593
Haematological AE related to study medication	2 (2.6)	4 (5.1)	6 (3.8)	0.681
Nonhaematological AE related to study medication	14 (18.2)	16 (20.3)	30 (19.2)	0.840
AE not related to study medication	3 (3.9)	0 (0.0)	3 (1.9)	0.118
Other reason	1 (1.3)	1 (1.3)	2 (1.3)	>0.99
Unknown reason	4 (5.2)	3 (3.8)	7 (4.5)	0.718
Interruption everolimus				
Patients with at least one treatment interruption	43 (55.8)	47 (59.5)	90 (57.7)	0.746
Haematological AE related to study medication	6 (7.8)	6 (7.6)	12 (7.7)	>0.99
Nonhaematological AE related to study medication	29 (37.7)	26 (32.9)	55 (35.3)	0.616
AE not related to study medication	14 (18.2)	10 (12.7)	24 (15.4)	0.381
Patient's noncompliance	6 (7.8)	7 (8.9)	13 (8.3)	>0.99
Organisational reason	1 (1.3)	5 (6.3)	6 (3.8)	0.210
Other reason	6 (7.8)	9 (11.4)	15 (9.6)	0.589

Note: One patient randomised to the EVE esc arm received 10 mg everolimus throughout the 3-week escalation phase and was therefore analysed in the EVE 10mg arm.
AE = adverse event; EVE = everolimus; esc = escalated.

Dose adjustments and interruptions for everolimus

A dose reduction to 5 mg was necessary in 31.5 percent of patients in the everolimus dose-escalation arm compared with 36.4% in the standard 10 mg arm (P = 0.593), predominantly driven by non-hematologic adverse events considered related to study treatment (20.3 percent versus 18.2 percent, respectively; P = 0.840). Treatment interruptions of everolimus occurred in 59.5 percent of patients in the escalation arm and 55.8 percent in the standard arm (P = 0.746), again mainly due to treatment-related non-hematologic toxicities **(Table 3).** The median cumulative duration of these interruptions was shorter in the escalation arm at 12 days (range 1–44) than in the standard arm at 15 days (range 1–48; P = 0.009). Interruptions of exemestane were reported in 19.0% of patients in the escalation arm and 15.6% in the standard arm (P = 0.674).

Efficacy outcomes

At 24 weeks, partial response rates were 10.0% in the dose-escalation arm versus 6.6 percent in the 10 mg arm. Progressive disease was observed more frequently in the escalation arm (58.8%) than in the standard arm (44.7%). Clinical benefit rate (CBR) stood at 23.8% in the escalation arm compared with 31.6% in the standard arm (P = 0.288; absolute difference –7.8 percent). A post-hoc multivariable analysis adjusting for baseline liver metastases and number of prior metastatic therapy lines confirmed the absence of a significant difference (OR 0.75; 95 percent CI 0.36–1.55; P = 0.436).

Quality of life

Patient-reported quality of life, prospectively measured with the FACT-B questionnaire, showed no meaningful differences between treatment groups. Mean FACT-B total scores remained high in both arms without statistically

significant or clinically relevant inter-arm variation (105.5 in escalation arm versus 103.5 in standard arm; P = 0.706).

Subsequent therapies

Post-study treatment information was collected for 71 patients (30 in the escalation arm; 41 in the standard arm). Overall, 57.7% continued everolimus plus exemestane beyond the trial, 18.3% received alternative endocrine therapy, 5.6% were treated with a CDK4/6 inhibitor combined with endocrine therapy, and 18.3 percent received chemotherapy.

The DESIREE trial revealed that gradually increasing the everolimus dose when paired with exemestane markedly lowered the occurrence of stomatitis grade ≥2 during the initial 12 weeks compared to the standard 10 mg everolimus plus exemestane regimen (28.8% vs. 46.1%; P = 0.039).

Mouth toxicities like stomatitis represent a typical side effect of mTOR inhibitors, though the precise underlying process is not fully understood [23]. It may involve suppression of proliferative cells in the oral epithelial basal layer. Moreover, due to their immunosuppressive properties, mTOR inhibitors can heighten infection risks if mucosal barriers are compromised. In everyday oncology practice, preventing stomatitis is as crucial as managing it when it occurs. Data from the BOLERO-2 trial indicated that over one-third of grade ≥2 stomatitis cases emerged early in treatment [24]. To tackle this, the DESIREE study examined whether stepwise everolimus dose escalation combined with exemestane could meaningfully decrease grade ≥2 stomatitis rates in the first 12 weeks relative to the usual 10 mg dose plus exemestane.

In BOLERO-2, overall stomatitis and associated oral adverse events (encompassing mouth ulcers, aphthous ulcers, glossodynia, gingival pain, lip ulcers, and glossitis) affected 67% of patients [7]. These were mostly transient, with 98% of grade 2 cases fully resolving in a median of 16 days, yet 24% needed dose interruptions or reductions of everolimus, and 3% stopped the regimen entirely due to such issues. No BOLERO-2 participants had prior exposure to CDK4/6 inhibitors. Nowadays, combining CDK4/6 inhibitors with non-steroidal aromatase inhibitors is the preferred first-line approach for metastatic HR-positive/HER2-negative breast cancer. A retrospective analysis of everolimus plus exemestane outcomes after progression on CDK4/6 inhibitor plus NSAI versus NSAI alone found no influence of prior CDK4/6 therapy on survival [25]. Among 43 patients, 9 (20.9%) needed everolimus dose lowering (11.8% post-CDK4/6 vs. 26.9% in controls; P = 0.281), and 19 (44.2%) experienced stomatitis, with 15 (78.9%) lacking recorded prophylactic dexamethasone rinse (not routine then). Thus, stepwise everolimus dosing could help mitigate stomatitis in this population.

By 24 weeks, grade ≥2 stomatitis events were somewhat fewer in the escalated everolimus group, though without statistical significance. This underscores the value of vigilant oversight in the early phase to proactively address or avert oral complications.

In the first 12 weeks, the escalated arm's 18.8% rate of grade ≥2 stomatitis (excluding early dropouts) aligned with 18% and 12% rates observed using different steroid rinses in a phase II randomized study—an alternative preventive approach for everolimus-induced stomatitis [26]. That trial demonstrated substantial drops in any-grade and grade ≥2 stomatitis over 12 weeks with prophylactic steroid rinses in metastatic breast cancer patients on everolimus plus aromatase inhibitor. The SWISH trial, a single-arm phase II study, showed prophylactic dexamethasone rinse reducing grade ≥2 stomatitis to 2% by 8 weeks, with low oral candidiasis risk (2 cases), in advanced HR-positive/HER2-negative patients on exemestane plus everolimus [15]. Drawing from SWISH, the 5th ESO-ESMO ABC guidelines advocate prophylactic steroid rinse as routine for mTOR inhibitor-related stomatitis prevention [1].

Adverse events in DESIREE matched the established profile of everolimus and exemestane, with no novel risks emerging. The escalation approach yielded no notable differences in dose adjustments, pauses, or terminations, producing comparable median relative dose intensity across groups. In the UNIRAD trial, dose reductions were rarer when starting everolimus at 5 mg versus 10 mg (28.4% vs. 46.8%) [27].

BOLERO-2 found delayed global quality-of-life deterioration with everolimus plus exemestane versus placebo plus exemestane, despite more grade 3/4 toxicities in the combination arm [14]. In DESIREE, FACT-B total scores remained elevated in both groups, without significant or meaningful inter-arm differences.

A non-significant 7.8% lower clinical benefit rate favored the standard everolimus arm, with more progressions at 24 weeks in the escalated group. Baseline imbalances may partly explain this: escalated arm patients more often had ECOG performance status >1, multiple metastatic sites, and liver involvement. While not significant, reduced efficacy in the escalated arm cannot be ruled out. However, the real-world non-interventional BRAWO study of

everolimus plus exemestane in advanced HR-positive/HER2-negative breast cancer showed most starting at 10 mg, with about one-third at 5 mg; starting dose did not affect progression-free survival [9, 28]. This implies clinicians sometimes use escalation in practice to help patients tolerate therapy.

Key strengths include the randomized, double-blind, placebo-controlled design minimizing arm imbalances. To our knowledge, DESIREE is the sole randomized phase II study in postmenopausal advanced HR-positive/HER2-negative patients testing everolimus dose escalation for reducing severe early stomatitis. Limitations involve variable data on prophylactic dexamethasone rinses and prior CDK4/6 exposure, potentially affecting outcomes, plus the fixed 24-week treatment duration prolonging enrollment.

DESIREE achieved its main goal, showing a 3-week everolimus escalation effectively lowers high-grade stomatitis in the initial 12 weeks. This offers another option for mitigating everolimus oral toxicity, given steroid rinses carry a slight candidiasis risk.

Overall, these outcomes could enhance tolerability for everolimus-treated patients. Since stomatitis frequently complicates targeted breast cancer therapies, exploring dose escalation for newer agents may similarly boost patient tolerance.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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