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Original article

Efficacy and safety of everolimus plus exemestane in patients with HR+, HER2− advanced breast cancer progressing on/after prior endocrine therapy in routine clinical practice: Primary results from the non-interventional study, STEPAUT

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ABSTRACT

Background: STEPAUT, an Austrian non-interventional study, evaluated the safety and efficacy of everolimus plus exemestane in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) recurring/progressing on/after nonsteroidal aromatase inhibitors (NSAIs) in routine clinical practice.
Methods: Postmenopausal women with HR+, HER2− ABC progressing on/after NSAIs receiving everolimus plus exemestane in accordance with routine practice and the current version of Summary of Product Characteristics were eligible. Planned individual observation period corresponded to the duration of treatment until formal study end.
Results: Overall, 236 patients (median age: 65 years) were enrolled at 17 sites across Austria. The median progression-free survival (mPFS) in the overall population was 9.5 months (95% confidence interval [CI]: 8.6–10.7 months). The mPFS (95% CI) in patients who received everolimus 10 and 5 mg was 9.9 months (7.3–11.5 months) and 8 months (4.7–10.7 months), respectively. The median time to progression was

Abbreviations: AE, Adverse event; CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; HR+, Hormone receptor-positive; HER2−, Human epidermal growth factor 2-negative; mTOR, Mammalian target of rapamycin; NSAI, Nonsteroidal aromatase inhibitor; PI3K, Phosphatidylinositol-3-kinase; PFS, Progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTP, Time to progression.

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Non-interventional study
Real-world setting

numerically longer in patients who had a therapy break (11.9 months, 95% CI: 10.0–14.6 months) versus those who did not have any therapy break (10.7 months, 95% CI: 8.9–12.6 months). Patients experienced grade 1 (53.7%), grade 2 (35.9%), grade 3 (9.9%), grade 4 (0.2%) adverse events (AEs). The most common AEs of any grade were stomatitis, mucositis (53.8%), rash, exanthema (29.7%), loss of appetite, nausea (28.4%).

Conclusions: Real-world safety and efficacy data from STEPAUT were consistent with results from BOLERO-2, supporting everolimus plus exemestane as a suitable treatment option for HR+, HER2− ABC recurring/progressing on/after NSAIs.

1. Background

Breast cancer is the most common cancer amongst women worldwide and its recurrence and mortality rates remain high despite therapeutic advances [1]. According to the latest statistics, approximately 2.09 million cases of breast cancer and 627,000 deaths due to breast cancer were reported worldwide in 2018 [2]. In Europe, breast cancer accounted for 523,000 cancer cases and 138,000 deaths [3].

Among the different subtypes, hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) constitutes 75% of all breast cancer cases [4]. Endocrine therapy remains the mainstay for the treatment of advanced HR+, HER2− breast cancer [4,5]. Despite the effectiveness of endocrine therapy in HR + advanced breast cancer, disease progression eventually occurs in the majority of the patients due to either primary or secondary/acquired endocrine therapy resistance [6]. Thus, there is a need to explore additional treatment options that can overcome endocrine treatment resistance.

The phosphatidylinositol-3-kinase (PI3K/Akt) and the mammalian target of rapamycin (mTOR) signalling pathway plays a critical role in the proliferation, survival, angiogenesis and metabolism of cells [7]. Hyperactivity of the PI3K/Akt/mTOR signalling pathway has been associated with endocrine resistance in breast cancer [8]. Furthermore, it has also been shown that there is a close interaction between the PI3K/Akt/mTOR and the oestrogen receptor signalling pathways [9]. Targeting the PI3K/Akt/mTOR pathway has thus improved the outcomes as shown in various clinical studies such as BOLERO-2, BELLE-2 and SOLAR-1 [10–12].

Results from the international, placebo-controlled, randomised, phase III BOLERO-2 study demonstrated the efficacy and safety of everolimus plus exemestane versus placebo plus exemestane in patients with prior relapse or progression on nonsteroidal aromatase inhibitors (NSAIs) [10]. Everolimus plus exemestane more than doubled the median progression-free survival (PFS) versus placebo plus exemestane (7.8 months vs 3.2 months, respectively [hazard ratio = 0.45; $P < 0.0001$]) [13]. These results led to the approval of everolimus plus exemestane in this patient population [14]. However, the majority of the data on the efficacy and safety of this combination are based on the information available from clinical studies, and the data from routine clinical practice are limited. Although randomised controlled studies provide evidence of efficacy, generalisation of these results to patients in the real-world setting is challenging, as these studies are conducted in a highly selected patient population. An understanding of the effectiveness and safety of approved cancer therapies in routine clinical practice is thus essential to optimise the management of patients and identify treatment and safety gaps that are not evident in controlled clinical studies.

Start of mTOR inhibition with Everolimus after Progression on endocrine therapy in advanced breast cancer in clinical routine practice in AUsTria (STEPAUT) is an Austrian, non-interventional study that was designed to obtain insights into the efficacy and tolerability of everolimus plus exemestane in patients with locally advanced or metastatic HR+, HER2− breast cancer in routine clinical practice.

2. Methods

2.1. Patients

The study included postmenopausal women aged ≥18 years with metastatic or locally advanced HR+, HER2− breast cancer without symptomatic visceral metastasis previously treated with an NSAI. The course of treatment with everolimus plus exemestane, in accordance with routine practice and the respective Summaries of Product Characteristics or authorised indication, was documented prospectively in these patients. Written informed consent was obtained from all patients. The study was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. An independent ethics committee or institutional review board at each site approved the study protocol.

2.2. Study design

STEPAUT was a multicentre, open-label, single-arm, non-interventional study conducted across 17 university and community hospitals in Austria. The study sites were uniformly distributed geographically throughout Austria to avoid potential impact of regional differences on response to treatment.

The planned individual observation period per patient corresponded to the duration of treatment with everolimus plus exemestane, ending no later than the formal study end i.e. 18 months after the enrolment of the last patient. Treatment interruption was documented throughout the duration of the treatment. In case of treatment discontinuation, the date of the last administration of everolimus and the main reason for discontinuation were documented. The follow-up phase was documented for 1.5 years.

2.3. Study objective

The objective of this study was to gain insights from routine care into efficacy and tolerability of everolimus. The primary observational parameter was efficacy, which was assessed by PFS and time to progression (TTP) data, collected based on the judgement of the attending physician. PFS was defined as the period between the first administration of medication, the occurrence of progression per the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria or death of any cause. TTP was defined as the period between the first administration of medication and the occurrence of progression per RECIST 1.1. The secondary observational parameters included response (per RECIST 1.1), safety, duration of treatment and changes in dose, prior therapies and follow-up therapies and treatment modifications/interruptions or discontinuation.

2.4. Statistical analysis

The analysis set included patients with documented administration or prescription of everolimus with at least 1 follow-up during treatment. All variables investigated in this non-interventional study were analysed using descriptive statistical methods. The statistical analysis was conducted using MedCalc Version 17 and Excel 2010. Survival time was analysed using the Kaplan-Meier method.

3. Results

3.1. Patient disposition and demographics

The STEPAUT study was conducted from February 22, 2013 to 4 July 2017. Two hundred and thirty-six patients of the planned 240 patients were enrolled at 17 active sites distributed across Austria. The median time from initial diagnosis to enrolment was 6.7 years and the median time from diagnosis of metastatic disease to enrolment was 1.7 years. The median duration of follow-up was 8.8 months.

The median age of the patients was 65 years (Table 1). The majority of the patients (65.1%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 at baseline. Approximately 10% (9.8%) of the patients had only visceral metastases, whereas approximately 24% (23.7%) had bone-only metastases. The most common previous therapies based on therapy lines were: first line: NSAI (n = 25, 31.3%), second line: antioestrogen (n = 16, 34.0% which included fulvestrant [n = 14, 29.8%], tamoxifen [n = 2, 4.2%]), third line: chemotherapy (n = 8, 38.1%), fourth line: antioestrogen (n = 3, 37.5%) and fifth line and beyond: chemotherapy (n = 13, 68.4%).

One hundred and twenty-seven patients (54.5%) received an everolimus start dose of 10 mg, whereas 150 patients (45.1%) received everolimus 5 mg. The start dose was chosen based on the judgement of the attending physician. Overall, 75 patients (32.5%) in the everolimus 10 mg group and 59 (25.5%) in the everolimus 5 mg group did not have a dose change until the end of study (Fig. 1). The median time to dose escalation from everolimus 5 mg–10 mg was 31 days.

Table 1
Baseline patient and disease characteristic.

Patient characteristics	Patients, *n*
Age, years, median	65 (*N* = 236)
Weight, kg, median	68 (*N* = 222)
Height, cm, median	164 (*N* = 230)
Body mass index, median	25.22 (*N* = 220)
ECOG performance status	**Patients, *n* (%) (*N*=189)**
0	123 (65.1)
1	57 (30.2)
2	9 (4.8)
Metastasis	**Patients, *n* (%) (*N*=236)**
Visceral (lung, liver)	126 (53.4)
Only visceral	23 (9.8)
Only bone	56 (23.7)
Visceral and bone	87 (36.9)
Visceral without bone	39 (16.5)
CNS	5 (2.1)
Metastasis location	**Patients, *n* (%) (*N*=236)**
Lung	58 (24.6)
Bones	165 (69.9)
Liver	95 (40.3)
CNS	5 (2.1)
Skin	11 (4.7)
Lymph nodes	63 (26.7)
Other locations	34 (14.4)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

3.2. Efficacy

The median PFS in the overall population was 9.5 months (95% confidence interval [CI]: 8.6–10.7 months) (Fig. 2).

The median PFS was numerically longer in the subgroup of patients who received everolimus 10 mg (9.9 months [95% CI: 7.3–11.5 months]) throughout the study period versus patients who received everolimus 5 mg (8 months [95% CI: 4.7–10.7 months]) (Fig. 3a); however, the difference was not statistically significant ($P = 0.5533$). For patients who had a dose escalation of everolimus from 5 to 10 mg, the median PFS was 7.8 months (95% CI: 5.7–15.4 months). For patients who had dose de-escalation of everolimus from 10 to 5 mg, the median PFS was 9.5 months (95% CI: 7.7–14.7 months). The median PFS was numerically highest in patients who received everolimus plus exemestane in first line, 14 months (95% CI: 8.7–32 months), compared with other lines (Fig. 3b).

The median PFS in patients with bone only metastases at baseline was 13.5 months (95% CI: 10.7–15.4 months), 8.9 months for visceral only (95% CI: 4.9–11.3 months) and 7.3 months for visceral metastases (95% CI: 5.5–8.7 months) (Fig. 3c).

Patients who were on previous exemestane therapy had a median PFS of 5.9 months (95% CI: 4.5–9.1 months), whereas those who had received no prior exemestane therapy had a median PFS of 10 months (95% CI: 8.7–11.3 months) (Fig. 3d). The median PFS in patients aged <65 years and ≥65 years was 8.9 months (95% CI: 7.3–11.5 months) and 9.5 months (95% CI: 8.7–11 months), respectively.

The median TTP was similar in patients who received everolimus 5 mg (10.9 months, 95% CI: 8.8–14.6 months) and 10 mg (11 months, 95% CI: 9.8–14 months) throughout the study. For patients who had a dose escalation of everolimus from 5 to 10 mg, the median TTP was 8.9 months (95% CI: 7.7–16.1 months). Furthermore, the median TTP was numerically longer in patients who had a therapy break (11.9 months, 95% CI: 10–14.6 months) versus those who did not have any therapy break (10.7 months, 95% CI: 8.9–12.6 months). The overall response rates at 3, 6 and 12 months were 6.4%, 12% and 16.5%, respectively. The best overall response rate during cycles was complete response in 2 patients (0.9%) and partial response in 13 patients (5.5%).

3.3. Safety

The majority of the patients had grade 1 ($n = 720$, 53.7%) to grade 2 AEs ($n = 482$, 35.9%). One hundred and thirty-three patients (9.9%) had grade 3 AEs and 3 patients (0.2%) had life-threatening AEs. Four deaths (0.3%) were reported during the conduct of this study, which were not related to the treatment. The most common AEs of any grade were stomatitis, mucositis (53.8%), rash, exanthema (29.6%), dyspnoea, cough (26.3%) and loss of appetite, nausea (28.4%) (Table 2). Stomatitis, mucositis (4.7%), weight loss, reduced general condition (3%) and loss of appetite and nausea (2.5%) were the most frequent grade 3 AEs.

3.4. Treatment interruption/discontinuation and dose modifications and follow-up therapies

Treatment discontinuation was documented for 165 patients; the most common reasons for discontinuation were disease progression (48.5%) and AEs (20%). Among the 233 patients with documented everolimus treatment, 64 patients (27.5%) required

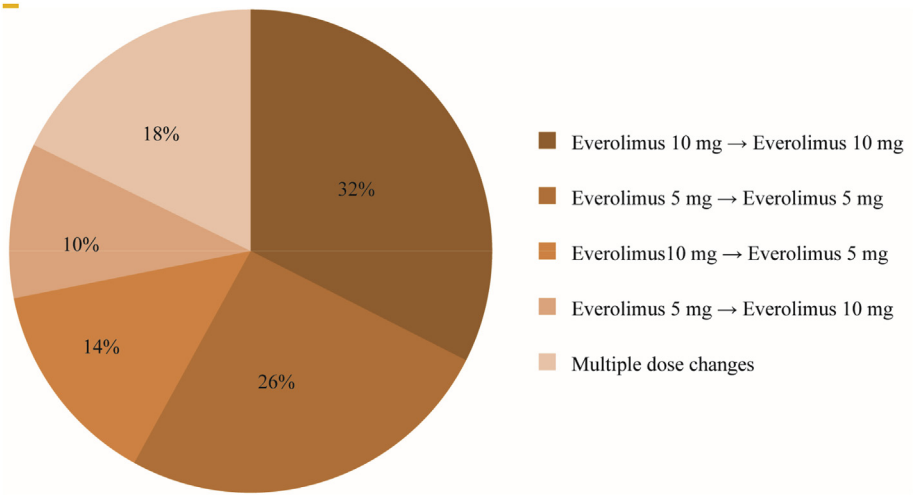


Fig. 1. Distribution of everolimus doses during therapy.

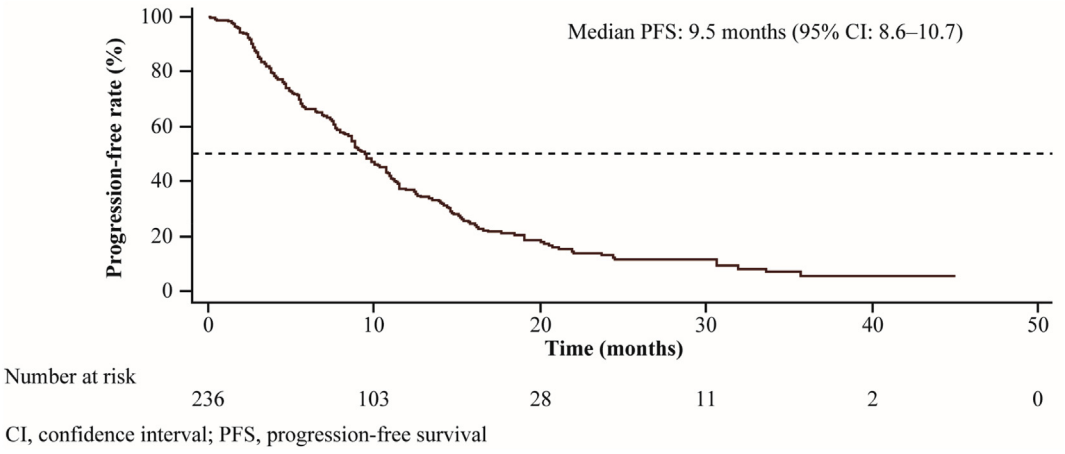


Fig. 2. Progression-free survival (overall population).

treatment interruption. Eleven patients (5%) discontinued therapy due to stomatitis and/or rash. The median time to treatment interruption was 1.2 months, and the median duration of interruption was 12.2 days. The most common restart dose of everolimus after treatment interruption was 5 mg. The median PFS for patients after therapy break was 12 months (95% CI: 9.5–13.3 months) and for patients with no therapy break was 8.8 months (95% CI: 7.5–9.9 months; $P = 0.40$). Follow-up therapy was documented for 181 patients (76.7%). The common subsequent therapies were chemotherapy (47.5%), endocrine therapy (46.6%) and combination therapies or others (28.4%).

4. Discussion

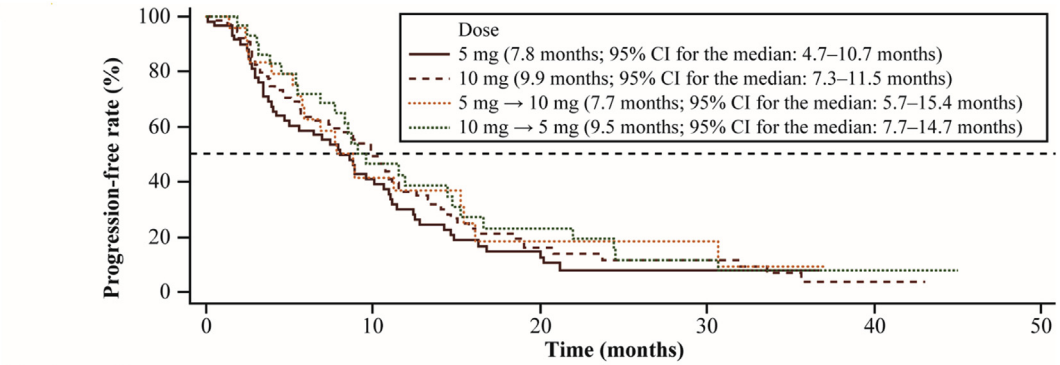
The approval of everolimus plus exemestane was an important milestone as it provided a valuable treatment option for postmenopausal women with HR+, HER2− advanced breast cancer [14]. However, it was important to evaluate the efficacy and safety of this treatment combination in a real-world setting. STEPAUT, an Austrian non-interventional study, evaluated the efficacy and safety in patients treated with everolimus plus exemestane in routine clinical practice.

The study highlighted a few differences in the patient demographics in clinical real-world settings versus clinical studies. For example, patients in the STEPAUT study were older (median age: 65 years) compared with those in BOLERO-2 (age 62 years) [13]. In addition, a higher percentage of patients in this study had an ECOG performance status of 0 (65%) compared with 60% in the BOLERO-2 study. On the other hand, the number of patients with visceral disease was lower in this study (53%) compared with 58% in BOLERO-2 [13].

The overall median PFS in STEPAUT was 9.5 months (95% CI: 8.6–10.7 months), which was numerically longer compared with the results obtained in BOLERO-2 and BRAWO and similar to that observed in EVEREXES [13,15,16]. Various subgroup efficacy analyses were also performed based on the everolimus dosing. It was observed that the median PFS was lower in patients who received everolimus 5 mg compared with 10 mg. This observation could be attributed to poorer prognostic factors in patients receiving the 5 mg starting dose, such as more visceral metastases, worse ECOG performance status and more prior therapies. Another interesting observation was that the median PFS was longer in patients who received everolimus plus exemestane in the first-line setting compared with subsequent settings. Jackisch et al. reported similar results in the BRAWO study when the combination was administered in the first-line setting [15].

The safety profile of everolimus observed in this study was similar to the known safety profile of the drug in both clinical and real-world settings [10,15,16]. Most of the AEs were manageable, with only 10% of the AEs being in the grade 3 category. Stomatitis was the most frequent AE. Of note, only 11 patients (5%) discontinued treatment due to stomatitis and/or rash. Furthermore, for patients who had an everolimus dose escalation from 5 to 10 mg, the median time to the first occurrence of stomatitis was longer than those who started and maintained the everolimus 5 mg or 10 mg dose. The frequency of the AE was higher in the everolimus 10 mg group compared with the everolimus 5 mg group, similar to that reported in the BRAWO study [15]. Treatment interruption was more effective than dose reduction for managing AEs.

While the results of this study provide useful insights into the clinical efficacy and safety of everolimus plus exemestane in routine clinical practice, there are certain limitations that the reader should bear in mind while interpreting these results. STEPAUT was a single-arm study with no formal statistical testing to evaluate differences between the dose groups. Thus, cross-study comparisons should be made with caution. Furthermore, the patient population was exclusively Austrian, and hence, extrapolation

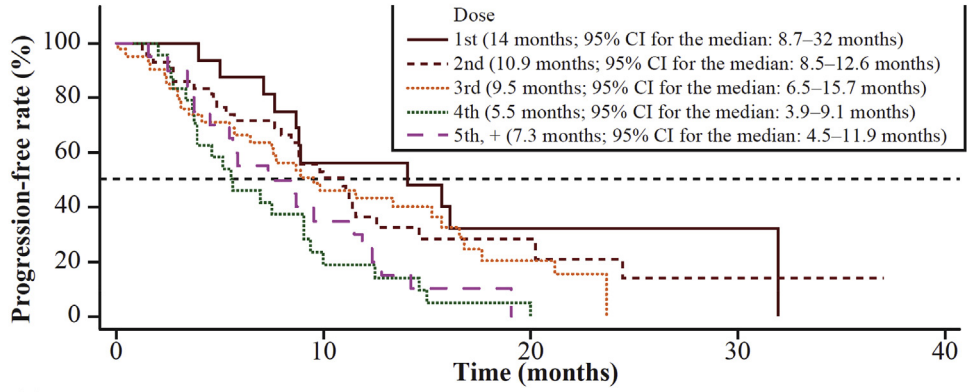


Number at risk

Dose 5 mg	59	23	6	1	0	0
Dose 10 mg	75	35	8	5	1	0
Dose 5 mg →10 mg	24	10	3	2	0	0
Dose 10 mg→5 mg	32	12	6	3	1	0

CI, confidence interval

(a)



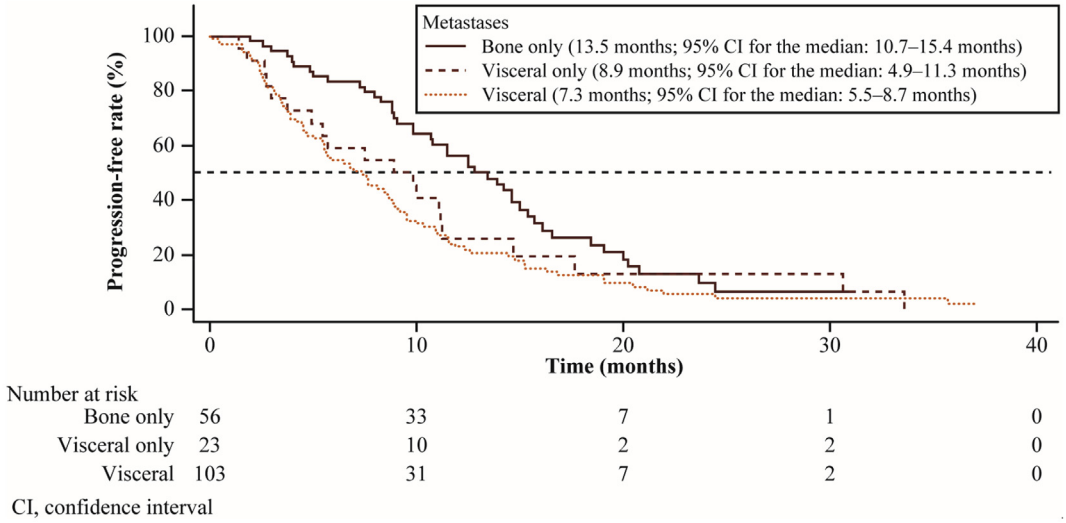
Number at risk

1st	17	9	3	1	0
2nd	45	20	4	1	0
3rd	42	18	4	0	0
4th	25	5	0	0	0
5th, +	20	7	0	0	0

CI, confidence interval

(b)

Fig. 3. Progression-free survival, (a) by everolimus dose. Progression-free survival, (b) by therapy lines. Progression-free survival, (c) by location of metastases. Progression-free survival, (d) by reexposition to exemestane.

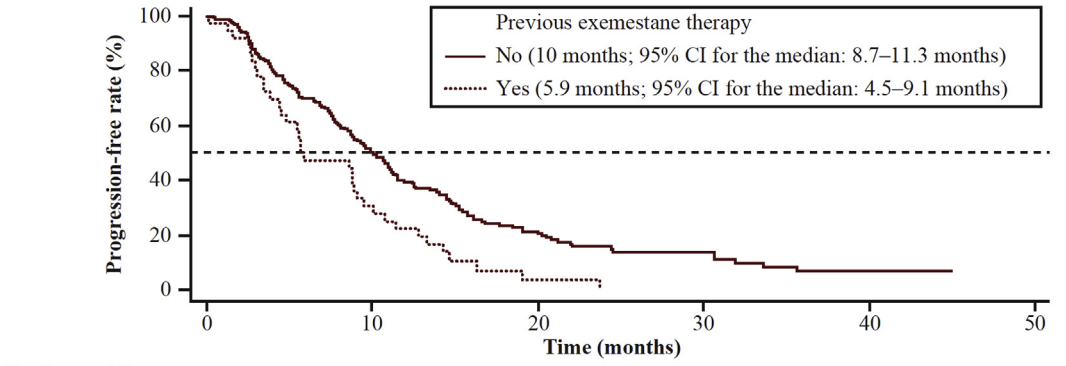


Number at risk

Bone only	56	33	7	1	0
Visceral only	23	10	2	2	0
Visceral	103	31	7	2	0

CI, confidence interval

(c)



Number at risk

No	199	92	27	11	2	0
Yes	37	11	1	0	0	0

CI, confidence interval

(d)

Fig. 3. (*continued*).

Table 2
Number of patients (%) with adverse events.

AE, *n* (%)	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stomatitis, Mucositis	127 (53.8)	87 (36.9)	62 (26.3)	11 (4.7)	0 (0)	0 (0)
Diarrhoea	40 (17)	26 (11)	14 (5.9)	2 (0.9)	1 (0.4)	0 (0)
Exanthema, Rash	70 (29.7)	49 (20.8)	25 (10.6)	1 (0.4)	0 (0)	0 (0)
Fatigue	47 (19.9)	26 (11)	24 (10.2)	1 (0.4)	0 (0)	0 (0)
Pneumonitis	35 (14.8)	10 (4.2)	20 (8.5)	5 (2.1)	0 (0)	0 (0)
Dyspnoea, Cough	62 (26.3)	35 (14.8)	32 (13.6)	5 (2.1)	0 (0)	0 (0)
Hyperglycaemia	21 (8.9)	15 (6.4)	8 (3.4)	0 (0)	0 (0)	0 (0)
Anaemia	19 (8.1)	7 (3)	8 (3.4)	5 (2.1)	1 (0.4)	0 (0)
Oedema	37 (15.7)	26 (11)	17 (7.2)	2 (0.9)	0 (0)	0 (0)
Inappetence, Nausea	67 (28.4)	40 (17)	28 (11.9)	6 (2.5)	1 (0.4)	0 (0)
Weight loss, reduced GC	29 (12.3)	12 (5.1)	15 (6.4)	7 (3)	1 (0.4)	1 (0.4)

AE, adverse event; GC, general condition.

of these results to the overall global population may be misleading. With the introduction of cyclin-dependent kinase inhibitors in the treatment landscape, the optimal initial treatment modality and the best sequential use of targeted agents combined with endocrine therapy becomes crucial. The clinician should weigh in the overall efficacy, tolerability and effect on quality of life while selecting the optimal treatment option for the patients.

5. Conclusions

Overall, results of the STEPAUT study were consistent with those reported in the BOLERO-2 study and confirm the efficacy and safety of everolimus in combination with exemestane in HR+, HER2− advanced breast cancer progressing or recurring on prior NSAIs in routine clinical practice. PFS outcomes support the administration of the approved 10 mg/day dose in the routine clinical setting, despite a non-significant difference in the PFS values with everolimus 5 mg versus everolimus 10 mg. Treatment interruption, instead of dose reduction, is a viable option for effective AE management, based on the median PFS data and a short median duration of interruption.

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Availability of data and material

The data that support the findings of this study are available from Novartis Pharmaceuticals Corporation but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Novartis Pharmaceuticals Corporation.

Authors' contributions

GS, MH, BM were involved in the conception and design of the study. All authors were involved in acquisition, analysis and interpretation of data. All authors were involved in the writing, review, and/or revision of this manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

An independent ethics committee or institutional review board approved the study protocol. All patients signed the informed consent form.

Consent for publication

Not applicable

Declaration of competing interest

GS has received grants and personal fees from Novartis during the conduct of this study; DE has received personal fees and non-financial support from Pfizer and Novartis and personal fees from Roche, Celgene, and Pierre Fabre, outside the submitted work; RB has received grants and personal fees from Novartis during the conduct of the study; personal fees from AstraZeneca, Eli Lilly, Celgene, EISAI, Daiichi, Pfizer, and Roche, outside the submitted work; GP has received honoraria from Novartis, Amgen, Roche, Pfizer, and AstraZeneca, outside the conduct of this study; EP has received honoraria from Novartis during the conduct of the study; RG has received grant and personal fees from Roche, Celgene, Merck, Astra Zeneca, Novartis, Amgen, AbbVie, BMS, MSD, Takeda, Merck, Sandoz, outside the conduct of this study; AL has received grants from Novartis during the conduct of the study; KH, MH, and BM report employment with Novartis Pharma GmbH during the conduct of this study; MG has received grants from AstraZeneca, Novartis, Pfizer, and Roche; and personal fees from Accelsiors, Amgen, AstraZeneca, Celgene, Eli-Lilly, Ipsen, Nano String Technologies, Novartis, Pfizer, and Roche, outside the submitted work. All remaining authors have declared no conflicts of interest.

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