CLINICAL STUDY REPORT

A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer

(DESIREE)

Eudract No: 2014-005126-35

Investigational Products:	Everolimus
Indication:	Dose escalation of everolimus in patients with metastatic breast cancer
Study Protocol:	GBG 86 (Version 2)
Phase:	
Report Version:	V1.0
First Patient Enrolled:	June 9,2015
Last Patient Completed:	January 19, 2021
Coordinating Investigator:	Prof. Dr. med. Sibylle Loibl GBG Forschungs GmbH Martin-Behaim-Straße 12 63263 Neu-Isenburg
Sponsor:	GBG Forschungs GmbH Martin-Behaim-Straße 12 63263 Neu-Isenburg
Date of this report:	January 17, 2022
Date of any previous reports:	n.a.

1 SYNOPSIS

Name of Sponsor: GBG Forschungs GmbH, Neu-Isenburg	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of finished product: Afinitor®	Volume:	
Name of active ingredient: everolimus	Page:	

Title of Study:

A multicenter randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer (DESIREE)

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Publication (reference):

Loibl S, Schmidt M, Lübbe K, et al. A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer (mBC) (DESIREE). Ann Oncol 2021; Volume 32, Supplement 5, S361-S1344.

Studied Period (years):

Date of the first patient enrolled: June 9, 2015

Date of the last patient completed: January 19, 2021

Phase of Development:

Phase II

Objectives:

Primary Objectives:

The primary objective was to compare the rate of stomatitis episodes of grade ≥2 at 12 weeks after start of treatment using a conventional or a dose escalating administration schema of everolimus in combination with exemestane in patients with metastatic breast cancer (mBC) and progression or relapse after non-steroidal aromatase-inhibitor treatment (NSAI).

Secondary Objectives:

Secondary tolerability objectives were:

- To compare the incidence of stomatitis episodes of grade ≥2 at 24 weeks after treatment start
- To compare the incidence of stomatitis episodes of any grade at 12 weeks after treatment start
- To compare the incidence of stomatitis episodes of any grade at 24 weeks after treatment start

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- To compare the rate of patients on 10 mg daily at 12 weeks after treatment start
- To compare the rate of patients on 10 mg daily at 24 weeks after treatment start
- To compare time to onset of stomatitis grade ≥2 during study treatment

Secondary efficacy objectives:

- To compare the clinical benefit rate (CBR) at 24 weeks after treatment start

Further safety objectives:

- To assess AEs, AE of special interest (AESI), and SAEs between treatment arms

Compliance:

- To assess and compare dose reductions, dose interruptions and premature treatment discontinuations of everolimus.
- To assess and compare dose interruptions and premature treatment discontinuations of exemestane.
- To compare the cumulative dose of everolimus at 4 weeks
- To compare the duration of everolimus treatment
- To compare the relative total dose intensity (RTDI) for everolimus during the planned treatment duration of 24 weeks

Quality of Life (QoL):

- To compare Quality of Life (QoL) between treatment arms

Other exploratory objectives:

- To investigate potential biomarkers predicting safety and compliance in this study setting. These objectives will be analyzed at later time point and are not part of this report.
- To compare post study treatment data between treatment arms

Methodology:

- Multicenter, randomized, double-blind, placebo-controlled phase II study
- Treatment with conventional dosing schedule of everolimus starting with 10 mg at first dose (EVE 10mg) versus dose escalating schema of everolimus over 21 days (EVE esc) in combination with exemestane. Treatment was given for 24 weeks or until disease progression, unacceptable toxicity, or withdrawal of patient's consent.
- Patients with HR-positive, HER2-negative mBC
- Aim of the study was to show a reduction in the rate of stomatitis episodes grade ≥2 within the first 12 weeks after treatment start

Number of patients (planned and analyzed):

Planned: 156, screened: 208, randomized: 160, analyzed: 156

Diagnosis and Main Criteria for Inclusion:

The study included postmenopausal women with locally advanced or mBC not amenable to curative treatment

by surgery or radiotherapy alone and without indication for chemotherapy (e.g. symptomatic visceral metastasis); histologically confirmed HR-positive [estrogen receptor (ER) and/or progesterone receptor (PgR)] defined as >1% stained cells and HER2-negative status defined as either immunohistochemistry 0-1 or 2+ with in situ hybridisation ratio <2.0; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; recurrence during or after adjuvant NSAI treatment or disease progression during or after NSAI treatment for advanced or mBC; adequate hematologic and organ function, glycaemia and blood lipids. Patients had to be available and compliant for treatment and follow-up.

Investigational Products, Dose and Mode of Administration, Batch Number:

- Standard administration schedule of everolimus (Afinitor®)/everolimus-placebo: 10 mg/day (4 tablets of 2.5 mg), orally administrated.
- Escalated dose of everolimus:
  - week 1: 2.5 mg/day (1x verum + 3x placebo)
  - week 2: 5 mg/day (2x verum + 2x placebo)
  - week 3: 7.5 mg/day (3x verum + 1x placebo)
  - week 4-24: 10 mg/day

Batch numbers: S0001 VMLK/2012-4140, S0001 VMLK/2012-4138, S0002 VMLK/2014-2495, S0001 VMLK/2013-0119, S0003 2014952, 1010011066 2016566, SEJ212031838

After a dose escalation period of 3 weeks which was blinded (blinded phase), the interventional part of the study was completed and the patient continued on prescribed everolimus as part of standard of care (open-label phase).

Non-investigational products, Dose and Mode of Administration

- Exemestane: 25 mg/day (1 tablet of 25 mg), orally administrated.

Exemestane was used according to marketed formulation via standard procedures at each site and applied according to recommendations of the manufacturers and treatment guidelines.

Duration of Treatment:

The entire treatment period was 6 months.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Everolimus (Afinitor®), 10 mg/day (4 tablets of 2.5 mg at week 1-3 (blinded phase) and 10 mg/day at week 4-24 (open-label phase).

Criteria for Evaluation:

Primary tolerability endpoint:

- The primary endpoint was the rate of stomatitis episodes grade ≥2 considering stomatitis episodes grade <2 and premature treatment discontinuation due to adverse events (AEs), patient's or investigator's decision within the first 12 weeks of treatment start. Assessment of the stomatitis grade was performed using the WHO's oral toxicity scale (OTS).

Secondary tolerability endpoints:

- Incidence of stomatitis episodes grade ≥2 considering grade <2 and premature treatment discontinuation due to AEs, patient's or investigator's decision within 24 weeks of treatment start.
- Incidence of any grade stomatitis episodes considering premature treatment discontinuation due to AEs, patient's or investigator's decision within 12 weeks of treatment start.
- Incidence of any grade stomatitis episodes considering premature treatment discontinuation due to AEs, patient's or investigator's decision within 24 weeks of treatment start.
- Rate of patients who received everolimus at a dose of 10 mg at week 12.
- Rate of patients in the EVE esc arm who received everolimus at a dose of 10 mg continuously in weeks 4-24 and patients in the EVE 10mg arm who received everolimus at a dose of 10 mg continuously in weeks 1-24.
- Time to onset of stomatitis grade ≥2 defined as the time between randomization and first episode of grade ≥2 stomatitis. Date of first episode of stomatitis grade ≥2 was not explicitly collected, thus week of the visit with stomatitis grade ≥2 was used to calculate the time interval.

Secondary efficacy endpoints

- CBR was defined as CR, PR or SD without any sign of tumor progression assessed at 24 weeks after treatment start. Response assessment was performed at week 12, 24 and at EOT visit (4 weeks after last intake of everolimus). This schema resulted in the following algorithm for derivation of clinical benefit:
  - Complete or partial response in one of the 3 assessments irrespective of the response in the other assessments is considered as clinical benefit
  - SD at week 24, but PD at EOT visit is considered as clinical benefit
  - SD at week 12, but PD at week 24 is considered as no clinical benefit
  - SD at week 12 but no assessment at week 24 is considered as no clinical benefit
  - All three response assessments missing is considered as no clinical benefit.

Further safety endpoints:

Safety was assessed based on any grade (1-4) AE including pneumonitis as AE of special interest (AESI) and SAEs (including AEs of grade 5). Type and severity of all other AEs was documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03. Seriousness and relationship to everolimus/everolimus placebo was documented by the investigator.

Compliance endpoints

- Dose reductions of everolimus: a dose reduction from 10 mg daily to 5 mg daily within week 4-24 of everolimus. Doses which have been reduced for toxicity should not be re-escalated (except for liver function tests if improved to within ranges given).
- Dose interruptions of everolimus and exemestane: an omission of tablet(s) between date of first and date of last known intake.
- Premature treatment discontinuations of everolimus and exemestane: permanent treatment discontinuation of study medication.

- Cumulative dose (mg): a sum of doses applied starting from date of first intake to and including the 4th week as documented by the investigator on the eCRF.
- Duration of everolimus treatment: first intake date subtracted from last intake date.
- RTDI: the total dose intensity within the entire treatment achieved by a patient relative to intended dose intensity based on the planned schedule of the treatment.

QoL Endpoint

QoL was assessed using the FACT-B questionnaire. Based on its items 5 subscales (Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and Additional Concerns), as well as the FACT-B Trial Outcome Index (FACT-B TOI), the FACT-G total score, and the FACT-B total score were derived.

Other exploratory endpoints

- Post study treatment was at the investigator´s discretion but had to be documented in the eCRF until first subsequent chemotherapy or end of study (EOS). Post-study therapy was compared between treatment arms, especially the proportion of patients who continued everolimus beyond EOS.
- Determination of potential biomarkers predicting safety and compliance are not part of this report.

Statistical Methods

Analyses were based on the modified intent-to-treat (mITT) set, the per-protocol analysis set and the evaluable subset for safety (safety analysis set).

Sample size: Sample size calculation was based on the primary endpoint. Overall, 156 patients (78 in each arm) were required to detect a clinically relevant difference of 20% in the rate of mucositis episode grade ≥2 between treatment arms (40% and 20% estimated in the control arm and the treatment arm, respectively) using a two sided continuity-corrected $\chi 2$-test with a significance level of alpha=0.20 and a power of 90%.

Primary and secondary analyses: The main analysis of the primary endpoint was performed on the modified intent-to-treat (mITT) analysis set including all randomized patients who started therapy. The rate of stomatitis episodes of grade≥2 was calculated together with the 80% (due to design α) and additional 95% confidence interval (CI) (Pearson and Clopper 1934) for each treatment arm and overall. Differences in the rates of stomatitis episodes were tested using a continuity-corrected $\chi 2$-test (α=0.20). Additionally, odds ratios (OR) with the 80% and 95% CI were displayed.

The secondary endpoints were also evaluated on the mITT set. The significance level for all secondary analyses was set to a two-sided α=0.05 with 95% CIs, adjustment for multiple testing was not planned. Multivariate logistic regression analysis adjusted for parameters age, ECOG PS, BMI and number of previous therapy lines for mBC was post-hoc conducted for binary outcomes to report odds ratios with 95% CI.

Time to onset of mucositis was analyzed using the Kaplan-Meier method, comparison between treatment arms was performed using a log-rank test. Cumulative incidence of stomatitis grade ≥2 at specific time points was also analyzed by Gray's test (Fine and Gray, 1999). Competing events were defined as discontinuation of study treatment due to AEs, patients' or investigators' decision without mucositis grade ≥2.

The CBR was assessed using a two-sided exact Fisher's test with 95% CI and a continuity-corrected $\chi 2$-test for consistency.

Analyses of further safety concerns: All further safety analyses were conducted in the safety analysis set. Safety analysis set including mITT set, except one patient who was randomized to EVE esc but received the complete dose during the first 3 weeks of treatment. The MedDRA classification system version 24.0 (dated March 1, 2021) was used for AE coding. Unless otherwise specified, AEs were summarized by frequency and percentage of patients within the AE category of interest, by treatment arm and overall. Fisher´s exact test was used to compare frequencies of AEs between treatment arms, p-values were descriptive and no adjustment for α-inflation was performed.

Analyses of compliance: The extent of study treatment exposure and compliance were assessed and summarized based on the safety analysis set. Fisher's exact tests were used to explore differences in the compliance parameter between treatment arms, p-values were descriptive and no adjustment for α-inflation was performed.

QoL analyses: QoL was analyzed in the safety analysis set using repeated-measures mixed-effects models with main effect terms "treatment" and "time", the interaction term "treatment-by-time", and baseline values as covariate.

Post study treatment: Post study treatment was described based on the mITT analysis set. Treatment after completion or discontinuation of study treatment was reported per treatment arm and overall using the categories containing ≥5% of the patients. Fisher's exact tests were used to explore differences in post study treatment between treatment arms, p-values were descriptive and no adjustment for α-inflation was performed.

Post-hoc analyses: Subgroups or covariates of interest

SUMMARY

Tolerability and Efficacy Results (mITT analysis set):

Between June 2015 and October 2020, 208 patients were screened at 29 sites in Germany, 160 were randomized and 156 started therapy (EVE esc: 80 patients, EVE 10mg: 76 patients).

Analysis of tolerability

Within 12 weeks of therapy, the incidence of stomatitis episodes grade ≥2 (primary endpoint) was significantly lower in the EVE esc arm compared to the EVE 10mg arm (28.8% vs 46.1%, p=0.039) (Table 1). Similarly, the rate of mucositis grade ≥2 without considering premature discontinuations was 18.8% in the EVE esc arm versus 35.5% in the EVE 10mg arm. Univariate logistic regression analysis showed that a dose escalation treatment with everolimus significantly predicted for reduced incidence of stomatitis episodes (EVE esc vs EVE 10mg OR=0.47 [95%CI 0.24, 0.92], p=0.026). The reduced rate of stomatitis episodes observed in the escalated dose of everolimus maintained statistical significance in post-hoc multivariate analysis (OR=0.40 [95%CI 0.20-0.81], p=0.011) (Figure 1).

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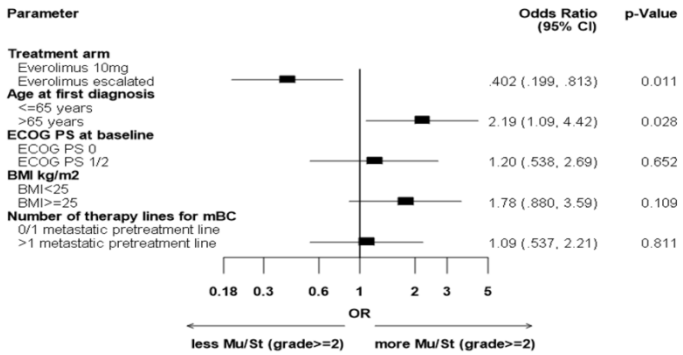
Table 1: Primary endpoint, incidence of stomatitis episodes grade ≥2 within the first 12 weeks

Stomatitis episodes grade ≥2 at 12 wks	EVE esc N=80 N(%)	EVE 10mg N=76 N(%)	Overall N=156 N(%)	p-value
Cumulative rate of stomatitis episodes	**23 (28.8)**	**35 (46.1)**	**58 (37.2)**	**0.039**
- grade ≥2	15 (18.8)	27 (35.5)	42 (26.9)	
- grade <2 and early discontinuation due to AE, patient's or investigator's decision	8 (10.0)	8 (10.5)	16 (10.3)	
80% CI	(22.1%, 36.2%)	(38.2%, 54.0%)		
Difference (80% CI)			-17.3% (-27.1%, -7.5%)	
95% CI	(19.2%, 40.0%)	(34.5%, 57.9%)		
Difference (95% CI)			-17.3% (-32.3%, -2.3%)	

esc, EVE, everolimus escalated; CI, confidence interval; wks, weeks

Figure 1: Multivariate logistic regression on primary endpoint



Mu/St, stomatitis; esc, EVE, everolimus escalated; CI, confidence interval; BMI, Body-Mass-Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mBC, metastatic breast cancer

Within the first 12 week of treatment, there was no significant difference in the incidence of any grade stomatitis between the two arms (62.5% in the EVE esc arm vs 73.7% in the EVE 10mg, p=0.185). The rate of patients receiving full dose of everolimus in the EVE esc arm was 48.8% compared to 56.6% in the EVE 10mg arm (p=0.413). The rate of patients who discontinued everolimus prior to week 12 was 41.3% in the EVE esc arm vs 31.6% in the EVE 10mg arm. The most common reason for everolimus discontinuation was disease progression in the EVE esc arm (27.5% vs 7.9%, respectively) and toxicity in the EVE 10mg arm (6.3% vs 9.2%, respectively).

Within 24 weeks of treatment, the incidence of stomatitis episodes grade ≥2 did not significantly differ between the two arms (37.5% in the EVE esc arm vs 50.0% in the EVE 10mg arm, p=0.158). The incidence of mucositis grade ≥2 without considering premature discontinuations was 23.8% in the EVE esc vs 35.5% in the EVE 10mg (Table 2).

Table 2: Summary of stomatitis episodes grade ≥2 within 24 weeks

Stomatitis episodes grade ≥2 at 24 wks	**EVE esc N=80 N(%)**	**EVE 10mg N=76 N(%)**	**Overall N=156 N(%)**	**p-value**
Cumulative rate of stomatitis episodes	**30 (37.5)**	**38 (50.0)**	**68 (43.6)**	**0.158**
- grade ≥2	19 (23.8)	27 (35.5)	46 (29.5)	
- grade <2 and early discontinuation due to AE, patient's or investigator's decision	11 (13.8)	11 (14.5)	22 (14.1)	
80% CI	(30.2%, 45.2%)	(42.1%, 57.9%)		
Difference, 80% CI			-12.5% (-22.6%, 2.4%)	
95% CI	(26.9%, 49.0%)	(38.3%, 61.7%)		
Difference (95% CI)			-12.5% (-28.0%, 3.0%)	

esc, EVE, everolimus escalated; CI, confidence interval; wks, weeks

Univariate logistic regression analysis showed that dose escalation treatment with everolimus (EVE esc vs EVE 10mg OR=0.60 [95%CI 0.32, 1.14], p=0.117) did not impact the incidence of stomatitis episodes grade ≥2 within 24 weeks. In contrast, the post-hoc multivariate analysis showed that a dose escalation treatment with everolimus significantly predicted for reduced incidence of stomatitis episodes (OR=0.50 [95%CI 0.25, 0.99], p=0.048) (Table 3).

Table 3: Multivariate logistic regression on stomatitis episode grade≥2 at 24 weeks

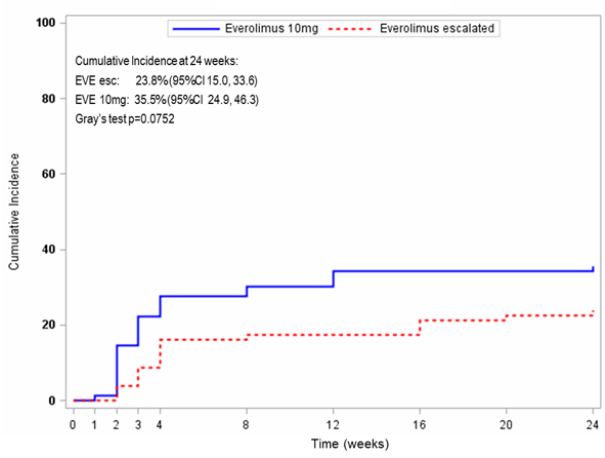
Parameter	**Category**	**OR**	**95% CI**	**p-value**
Treatment arm	EVE 10mg			
	EVE esc	0.50	(0.25, 0.99)	0.048
Age at first diagnosis, years	≤65			
	>65	2.32	(1.17, 4.59)	0.016
ECOG PS	0			
	1-2	1.09	(0.49, 2.41)	0.840
BMI kg/m^2	BMI<25			0.021
	25≤BMI<30	2.82	(1.29, 6.19)	
	BMI≥30	2.35	(0.98, 5.60)	0.055

esc, EVE, everolimus escalated; CI, confidence interval; BMI, Body-Mass-Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status

Within 24 weeks of treatment, there was no significant difference in the incidence of any grade stomatitis between the two arms (67.5% in the EVE esc arm vs 77.6% in the EVE 10mg, p=0.216). The rate of patients maintaining full dose of everolimus in the EVE esc arm was 17.5% compared to 26.3% in the EVE 10mg arm (p=0.255). The rate of patients who discontinued everolimus prior to week 24 was 72.5% in the EVE esc arm vs 65.8% in the EVE 10 mg arm, mainly due to disease progression in both arms (48.8% vs 32.9%, respectively).

The estimated event-free rate of stomatitis grade ≥2 in the EVE esc arm compared to the EVE 10mg arm was 81.4% (95%CI 70.6%, 88.5%) vs 61.8% (95%CI 49.0%, 72.3%) at 12 weeks and 64.9% (95%CI 48.0%, 77.5%) vs 58.7% (95%CI 45.1%, 70.1%) at 24 weeks (HR=0.59 [95%CI 0.32, 1.09], p=0.089). Post-hoc competing risk analysis showed that the cumulative incidence of stomatitis grade ≥2 at 24 weeks was 23.8% (95%CI 15.0, 33.6) in the EVE esc vs 35.5% (95%CI 24.9, 46.3) in the EVE 10mg, p=0.075 (Figure 2).

Figure 2: Stomatitis grade ≥2 free interval within 24 weeks, cumulative incidence considering competing events (post-hoc)



Note, competing events were defined as discontinuation of study treatment due to adverse event, patients' or investigators' decision without stomatitis grade ≥2; esc, EVE, everolimus escalated; CI, confidence interval

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Analysis of efficacy:

CBR at 24 weeks was 23.8% (95%CI 14.9%-34.6%) in the EVE esc arm vs 31.6% (95%CI 21.4%-43.3%) in the EVE 10mg arm (p=0.288) (Table 4).

Table 4: Clinical benefit rate assessed at 24 weeks

Clinical benefit	EVE esc N=80 N(%)	EVE 10mg N=76 N(%)	Overall N=156 N(%)	p-value[b]	p-value[c]
Complete response	1 (1.3)	1 (1.3)	2 (1.3)		
Partial response	8 (10.0)	5 (6.6)	13 (8.3)		
Stable disease	10 (12.5)	18 (23.7)	28 (17.9)		
CBR	19 (23.8)	24 (31.6)	43 (27.6)	0.360	0.288
95% CI for CBR	(14.9%, 34.6%)	(21.4%, 43.3%)			
Difference, 95% CI[a]			-7.8% (-21.8%, 6.2%)		
Progressive disease	47 (58.8)	34 (44.7)	81 (51.9)		
Response not evaluable /missing	14 (17.5)	18 (23.7)	32 (20.5)		

[a] Difference and 95% CI between proportions of clinical benefit rate

[b] Continuity-corrected two-sided $\chi 2$-test, [c] Two-sided exact Fisher's test

CBR, Clinical benefit rate; EVE, everolimus; esc escalated dose; CI, confidence interval

Further Safety Results (safety analysis set)

Analysis of compliance:

Median duration of everolimus exposure through entire study treatment was 12.7 weeks (range 0.1, 24.0) in the EVE esc and 16.0 weeks (range 0.7, 24.0) in the EVE 10mg arm (p=0.592). Median RTDI was 91.1% (range 0.2, 100) in the EVE esc vs 80.0% (range 1.2, 100) in the EVE 10mg arm (p=0.329) (Table 5).

Table 5: Extent of exposure to everolimus

Parameter	Statistic	EVE esc N=79	EVE 10mg N=77	Overall N=156	p-value
Treatment duration within study (weeks)	Mean	14.9	15.3	15.1	0.592
	StD	7.5	8.3	7.9	
	Median	12.7	16.0	14.3	
	Min, Max	0.1, 24.0	0.7, 24.0	0.1, 24.0	
	Missing	0	0	0	
Cumulative dose at 4 weeks	Mean	153.5	225.4	189.0	n.a.
	StD	41.1	68.3	66.6	
	Median	175.0	270.0	175.0	
	Min, Max	2.5, 175.0	20.0, 280.0	2.5, 280.0	

	Missing	0	0	0	
Relative total dose	Mean	77.1	72.0	74.6	n.a.
	StD	30.2	32.1	31.2	
	Median	91.1	80.0	84.6	
	Min, Max	0.2, 100.0	1.2, 100.0	0.2, 100.0	
	Missing	0	0	0	
RTDI	Mean	77.1	72.0	74.6	0.329
	StD	30.2	32.1	31.2	
	Median	91.1	80.0	84.6	
	Min, Max	0.2, 100.0	1.2, 100.0	0.2, 100.0	
	Missing	0	0	0	

*Note, statistical test for parameters "cumulative dose at 4 weeks" and "relative total dose" is not reasonable due to dose-escalation phase within the first 3 weeks of treatment; n.a., not applicable; EVE, everolimus; esc escalated dose; StD, standard deviation; RTDI, relative total dose intensity

During the first 3 weeks of treatment (escalation phase), 6.3% of patients in the EVE esc compared to 15.8% in the EVE 10mg arm discontinued everolimus mainly due to AEs (1.3% vs 6.6%). Discontinuation of everolimus within the 24 weeks of treatment was observed in 72.5% of patients in the EVE esc arm and 65.8% in the EVE 10mg arm (p=0.390) mainly due to disease progression (48.8% vs 32.9%, respectively). Discontinuation of exemestane was seen in 28.8% of patients in the EVE esc arm and 28.9% in the EVE 10mg arm (p=1.000) mainly due to disease progression (47.5% vs 38.2%, respectively) (Table 6).

Table 6: Summary of treatment discontinuations (safety analysis set)

Parameter/reason	EVE esc N=79	EVE 10mg N=77	Overall N=156	p-value
EVE discontinuation during first 3 weeks (escalation phase)	5 (6.3)	12 (15.8)	17 (10.9)	0.073
- Disease progression	1 (1.3)	1 (1.3)	2 (1.3)	
- Death	0 (0.0)	2 (2.6)	2 (1.3)	
- AE	1 (1.3)	5 (6.6)	6 (3.8)	
- Patient's decision	3 (3.8)	2 (2.6)	5 (3.2)	
- Investigator's decision	0 (0.0)	2 (2.6)	2 (1.3)	
EVE discontinuation during first 12 weeks	37 (46.3)	25 (32.9)	62 (39.7)	0.103
- Disease progression	25 (31.3)	7 (9.2)	32 (20.5)	
- Death	0 (0.0)	3 (3.9)	3 (1.9)	
- AE	5 (6.3)	7 (9.2)	12 (7.7)	
- Patient's decision	5 (6.3)	5 (6.6)	10 (6.4)	
- Investigator's decision	2 (2.5)	3 (3.9)	5 (3.2)	
EVE discontinuation during 24 weeks	58 (72.5)	50 (65.8)	108 (69.2)	0.390

- Disease progression	39 (48.8)	25 (32.9)	64 (41.0)	
- Death	1 (1.3)	3 (3.9)	4 (2.6)	
- AE	8 (10.0)	10 (13.2)	18 (11.5)	
- Patient's decision	5 (6.3)	8 (10.5)	13 (8.3)	
- Investigator's decision	5 (6.3)	4 (5.3)	9 (5.8)	
EXE discontinuation	23 (28.8)	22 (28.9)	45 (28.8)	1.000
- Disease progression	38 (47.5)	29 (38.2)	67 (42.9)	
- Death	3 (3.8)	3 (3.9)	6 (3.8)	
- AE	4 (5.0)	2 (2.6)	6 (3.8)	
- Patient's decision	4 (5.0)	3 (3.9)	7 (4.5)	
- Investigator's decision	8 (10.0)	17 (22.4)	25 (16.0)	

EVE, everolimus; esc escalated dose; EXE, exemestane; AE, adverse event

Overall, 31.5% of patients in the EVE esc vs 36.4% in the EVE 10mg arm (p=0.593) required dose reduction of everolimus to 5mg, mainly due to treatment-related non-hematological AEs (20.3% vs 18.2%, respectively, p=0.840).

Dose interruptions for everolimus were required in 59.5% of patients in the EVE esc arm and 55.8% in the EVE 10mg arm (p=0.746) mostly due to treatment related non-hematological AEs (32.9% vs 37.7%, respectively, p=0.616). Treatment with exemestane was interrupted in 19.0% and 15.6% of patients in the EVE esc and EVE 10mg arm, respectively (p=0.674) mainly due to non-hematological toxicity (5.1% vs 6.5%, p=0.744) or other reason (8.9% vs 2.6%, p=0.167).

Analysis of toxicity:

All patients who contributed safety data experienced at least one AE of any grade (91.6% hematological and 100% non-hematological AEs) during treatment in both arms. No significant differences were seen in terms of any AE of high-grade (p=0.747), any grade (p=0.247) and high-grade (p=1.000) hematological and any grade and high-grade (p=0.514) non-hematological AEs. Any grade other AEs (not predefined or free text AEs) did also not differ between treatment arms (p=0.240). A total of 45 (29.0%) patients reported at least one SAE, 29.1% in the EVE esc arm and 28.9% in the EVE 10mg arm (p=1.000). Pneumonitis event of any grade was experienced in 7.6% of patients in the EVE esc arm and in 7.9% in the EVE 10mg arm (p=1.000) (Table 7).

Table 7: Summary of all causality any/high-grade AEs (safety analysis set)

Summary of all causality AEs	EVE esc N=79 N(%)	EVE 10mg N=76 N(%)	Overall N=155 N(%)	p-value
Any AE, any grade	79 (100)	76 (100)	155 (100)	n.a.
Any AE, high-grade	37 (46.8)	33 (43.4)	70 (45.2)	0.747
Hematological AE, any grade	70 (88.6)	72 (94.7)	142 (91.6)	0.247
Hematological AE, high-grade	8 (10.1)	8 (10.5)	16 (10.3)	1.000
Non-hematological AE, any grade	79 (100)	76 (100)	155 (100)	n.a.

Non-hematological AE, high-grade	35 (44.3)	29 (38.2)	64 (41.3)	0.514
Other AEs, any grade	75 (94.9)	68 (89.5)	143 (92.3)	0.240
SAE	23 (29.1)	22 (28.9)	45 (29.0)	1.000
AESI (Pneumonitis)	6 (7.6)	6 (7.9)	12 (7.7)	1.000

EVE, everolimus; esc escalated dose; AE, adverse event; SAE, serious adverse event; AESI, adverse event of special interest

Anemia (74.7% vs 81.6%, p=0.336) and leukopenia (67.1% in both arms) were the most frequently reported any grade hematological AEs. Among grade 3-4 hematological AEs, anemia (3.8% vs 6.6%, p=0.489), leukopenia (3.8% vs 2.6%, p=1.000) and neutropenia (3.8% vs 5.3%, p=0.716) were the most frequent events. The most frequent any grade non-hematologic AEs in the EVE esc vs EVE 10mg arm were HDL cholesterol increased (96.2% vs 93.4%, p=0.489), serum cholesterol increased (77.2% vs 85.5%, p=0.219), ASAT increased (79.7% vs 72.4%, p=0.347), ALAT increased (67.1% vs 53.9%, p=0.103), hypertriglyceridemia (73.4% vs 72.4%, p=1.000), hyperglycemia (57.0% vs 60.5%, p=0.745), fatigue (53.2% vs 52.6%, p=1.000) and LDL cholesterol increased (51.9% vs 72.4%, p=0.013). Across grade 3-4 non-hematological AEs, the most reported AEs in the EVE esc vs EVE 10mg arm were ASAT increased (8.9% vs 2.6%, p=0.168), ALAT increased (5.1% vs 1.3%, p=0.367) and hyperglycemia (5.1% vs 9.2%, p=0.362). With regards to AESI, a total of 12 patients (7.7%) experienced any grade pneumonitis without significant difference between the two arms (7.6% in the EVE esc vs 7.9% in the EVE 10mg, p=1.000). Overall, high-grade pneumonitis was reported in only one patient (0.6%) who received escalated dose of everolimus (1.3%) (Table 8).

Table 8: Predefined all causality hematological and non-hematological AEs any grade (1-4) and high-grade (3-4) with an incidence of ≥ 10% during study treatment (safety analysis set)

Predefined AEs	Grade	EVE esc N=79 N(%)	EVE 10mg N=76 N(%)	Overall N=155 N(%)	p-value
Anaemia	any	59 (74.7)	62 (81.6)	121 (78.1)	0.336
	3-4	3 (3.8)	5 (6.6)	8 (5.2)	0.489
Leukopenia	any	53 (67.1)	51 (67.1)	104 (67.1)	1.000
	3-4	3 (3.8)	2 (2.6)	5 (3.2)	1.000
Thrombocytopenia	any	29 (36.7)	36 (47.4)	65 (41.9)	0.196
	3-4	1 (1.3)	1 (1.3)	2 (1.3)	1.000
Neutropenia	any	33 (41.8)	29 (38.2)	62 (40.0)	0.743
	3-4	3 (3.8)	4 (5.3)	7 (4.5)	0.716
Blood alkaline phosphatase increased	any	41 (51.9)	36 (47.4)	77 (49.7)	0.631
	3-4	2 (2.5)	1 (1.3)	3 (1.9)	1.000
Aspartate aminotransferase increased	any	63 (79.7)	55 (72.4)	118 (76.1)	0.347
	3-4	7 (8.9)	2 (2.6)	9 (5.8)	0.168
Alanine aminotransferase increased	any	53 (67.1)	41 (53.9)	94 (60.6)	0.103
	3-4	4 (5.1)	1 (1.3)	5 (3.2)	0.367
Blood creatinine increased	any	24 (30.4)	31 (40.8)	55 (35.5)	0.184

	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Fatigue	any	42 (53.2)	40 (52.6)	82 (52.9)	1.000
	3-4	2 (2.5)	1 (1.3)	3 (1.9)	1.000
Diarrhoea	any	28 (35.4)	19 (25.0)	47 (30.3)	0.167
	3-4	2 (2.5)	2 (2.6)	4 (2.6)	1.000
Decreased appetite	any	22 (27.8)	16 (21.1)	38 (24.5)	0.355
	3-4	1 (1.3)	2 (2.6)	3 (1.9)	0.615
Nausea	any	23 (29.1)	26 (34.2)	49 (31.6)	0.604
	3-4	1 (1.3)	0 (0.0)	1 (0.6)	1.000
Cough	any	24 (30.4)	21 (27.6)	45 (29.0)	0.727
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Headache	any	24 (30.4)	17 (22.4)	41 (26.5)	0.279
	3-4	0 (0.0)	1 (1.3)	1 (0.6)	0.490
Weight decreased	any	16 (20.3)	22 (28.9)	38 (24.5)	0.263
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Dyspnoea	any	16 (20.3)	23 (30.3)	39 (25.2)	0.195
	3-4	1 (1.3)	2 (2.6)	3 (1.9)	0.615
Arthralgia	any	18 (22.8)	22 (28.9)	40 (25.8)	0.463
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Epistaxis	any	9 (11.4)	6 (7.9)	15 (9.7)	0.589
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Vertigo	any	11 (13.9)	8 (10.5)	19 (12.3)	0.627
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Hypertriglyceridemia	any	58 (73.4)	55 (72.4)	113 (72.9)	1.000
	3-4	1 (1.3)	1 (1.3)	2 (1.3)	1.000
Hypoglycemia	any	16 (20.3)	9 (11.8)	25 (16.1)	0.192
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Hyperglycemia	any	45 (57.0)	46 (60.5)	91 (58.7)	0.745
	3-4	4 (5.1)	7 (9.2)	11 (7.1)	0.362
Serum cholesterol increased	any	61 (77.2)	65 (85.5)	126 (81.3)	0.219
	3-4	1 (1.3)	2 (2.6)	3 (1.9)	0.615
LDL cholesterol increased [a]	any	41 (51.9)	55 (72.4)	96 (61.9)	0.013
HDL cholesterol increased [a]	any	76 (96.2)	71 (93.4)	147 (94.8)	0.489
Pneumonitis [b]	any	6 (7.6)	6 (7.9)	12 (7.7)	1.000
	3-4	1 (1.3)	0 (0.0)	1 (0.6)	1.000

[a] no grading available; [b] adverse event of special interest; Data are N (%).

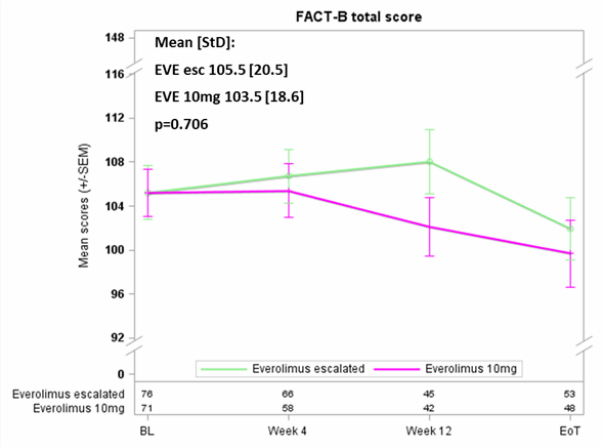
n.a., not applicable; AP, alkaline phosphatase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; EVE, everolimus; esc, escalated; LDL, low-density lipoprotein; HDL, high-density lipoprotein

During the 24 weeks of study treatment 4 patients died (one 1 in the EVE esc and 3 in the EVE 10mg arm) due to disease progression. In total, 60 SAEs were reported. The most frequently reported SOCs were gastrointestinal disorders (12 SAEs), respiratory, thoracic and mediastinal disorders (9 SAEs), infections and infestations (8 SAEs) and general disorders and administration site conditions (8 SAEs).

QoL

The mean FACT-B total score at baseline was high (105.2) in both treatment arms. At the end of treatment, the FACT-B total score remained similar in the EVE esc (102.1) and slightly decreased in the EVE 10mg (99.7) arm compared to the baseline. The overall mean FACT-B total score also did not significantly differ between the EVE esc and EVE 10mg arms (105.5 vs 103.5, p=0.706) (Figure 8).

Figure 8: Summary of the mean FACT-B total score during study treatment



EVE, everolimus; esc, escalated dose; StD, standard deviation

Post Study Treatment

Data on post study treatment was available for 71 patients (EVE esc N=30; EVE 10mg N=41) of whom 57.7% received everolimus and exemestane beyond the study (56.7% in the EVE esc, 58.5 in the EVE 10mg arm), 18.3% other endocrine therapy, 5.6% CDK4/6 inhibitor in combination with endocrine therapy, and 18.3% chemotherapy.

CONCLUSIONS

A dose escalation schema of everolimus over three weeks can be successfully implemented in postmenopausal patients with HR-positive/HER2-negative mBC to reduce the incidence of high-grade stomatitis in the first 12 weeks of treatment. Within 24 weeks of treatment, the incidence of stomatitis episodes grade ≥2 was numerically lower in the EVE esc arm, but there was not significant difference anymore.

Name of Sponsor: GBG Forschungs GmbH, Neu-Isenburg	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of finished product: Afinitor®	Volume:	
Name of active ingredient: everolimus	Page:	
It is important to note that there was a numerical (not statistically significant) difference of -7.8% in the CBR and 14.1% more patients with progressive diseases in the EVE esc arm at 24 weeks, favouring the standard everolimus administration schedule. Differences in the patient characteristics might have influenced this, however we cannot completely rule out if the EVE esc schedule has impaired the efficacy vs the standard administration without dose escalation. Toxicity reported in the DESIREE study was in line with the known safety profile of everolimus and exemestane, without new safety concerns. The use of a dose escalation regimen did not lead to significant differences in dose reductions, interruptions and discontinuations, resulting in a similar median RTDI between arms. QoL was comparable between the two treatment arms. **Date of the Report:** January 17, 2022		