Breast Cancer Treatment With Everolimus and Exemestane for ER+ Women—Results of the 2nd Interim Analysis of the Non-interventional Trial, BRAWO

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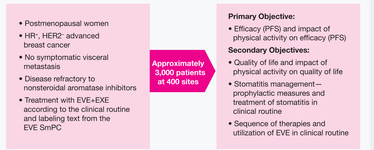
Introduction

- In the pivotal phase 3 BOLERO-2 trial, the combination of everolimus (EVE) with exemestane (EXE) more than doubled median progression-free survival (PFS) versus placebo (PBO)+EXE in postmenopausal women with hormone-receptor-positive (HR^+) advanced breast cancer progressing after a nonsteroidal aromatase inhibitor[1]
  - 7.8 months with EVE+EXE versus 3.2 months with PBO+EXE (hazard ratio [HR]= 0.45; $P < .0001$) by local radiologic assessment
  - Results were confirmed by central radiologic assessment (11.0 months vs 4.1 months, respectively; HR = 0.38; $P < .0001$)
- BRAWO is a large, German, non-interventional study (NIS) with a planned enrollment of 3,000 patients with HR^+ advanced breast cancer receiving EVE+EXE
- Main objectives of the BRAWO study are to extend the knowledge on
  - The efficacy, and the impact of physical activity on efficacy and quality of life, under routine conditions
  - Prophylaxis and management of stomatitis, and
  - The sequence of therapy and drug utilization, when EVE+EXE is used in usual daily care
- In this second preplanned interim analysis, we present, for the first time, efficacy data on EVE+EXE under real-world conditions

Methods

- BRAWO is a large, German, NIS with data collected at ~400 sites (**Figure 1**)
- All patients with HR^+ advanced breast cancer receiving EVE+EXE treated in accordance with EVE labeling text are eligible for inclusion in BRAWO (planned N = 3,000)
  - The BRAWO trial population will be broader than the BOLERO-2 study (eg, previous EXE therapy and more than 1 previous chemotherapy for the palliative setting are allowed)

Figure 1. BRAWO study design and objectives.



Timelines: Start of enrollment, October 2012; End of enrollment, December 2015; End of documentation, December 2016
Abbreviations: EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor 2; HR, hormone receptor-positive; PFS, progression-free survival; SmPC, summary of product characteristics.
Study number: CRAD001JDE53

- The planned individual observation period per patient corresponds to the duration of treatment with EVE+EXE, but ends no later than at the formal study end (1 year after the last patient enters the trial)
- The observation intervals are in line with clinical routine (ie, after approximately 2 weeks, 1 and 3 months, and thereafter at a 3-month interval after the start of treatment with EVE+EXE)
- Quality of life and physical activity are assessed by patient questionnaires:
  - EORTC QLQ-C30/BR23
  - Godin Leisure-Time Exercise Questionnaire
  - Körperliche Aktivitäts-Skalen (Physical Activity Scales, KAS) developed by the Institute of Circulation Research and Sports Medicine at the Sport University Cologne, Germany

Methods (continued)

- According to the methodological features of an observational NIS, all statistical analyses were descriptive and the presented results should be interpreted as such
- Second interim analysis was planned to occur 12 months after inclusion of the 500th patient (data cutoff, 08 July 2014)
  - Data on baseline characteristics, PFS, tumor status, and safety from the first 500 documented patients were analyzed

Results

Study Status and Premature Discontinuation

Study Status

- 1,348 patients had entered study documentation through 19 August 2014
- This second interim analysis includes data of the first 500 patients
- The 500th patient had been included 12 months before the data cutoff on 11 July 2014
  - Data for the first 500 patients were documented at 191 sites

Premature Discontinuation

- Reasons for discontinuation of documentation and EVE+EXE are summarized in **Table 1**

Table 1. Reason for Discontinuation of Documentation and EVE+EXE (N = 500)

Reason for Discontinuation	Patients, n (%) (N = 500)
Discontinuation of Documentation[a]	
Consent withdraw	17 (3.4)
Lost to follow-up	14 (2.8)
Therapy with EVE+EXE discontinued	335 (67.0)
Death	38 (7.6)
Formal study end reached[b]	2 (0.4)
Missing (including ongoing patients)	94 (18.8)
Discontinuation of Therapy With EVE+EXE[a]	
Progression	204 (40.8)
Adverse event	113 (22.6)
Poor compliance	4 (0.8)
Patient's wish	69 (13.8)
Missing (including ongoing patients)	110 (22.0)

[a]The data capture form asks for reason for discontinuation of documentation and reason for discontinuation of therapy as 2 separate questions. Therefore, various combinations of reasons are possible.
[b]For 2 patients formal study end was documented by mistake. Formal study end has not been reached yet.

[{AQ: ARE DATA AVAILABLE TO SEPARATE THE MISSING FROM ONGOING PATIENTS?}]

Baseline Patient and Disease Characteristics

- Median time from primary diagnosis was 7.2 years
  - Includes patients with first diagnosis in advanced setting
- Median time from first diagnosis of recurrence/metastases was 2.7 years
- 53.7% of patients had visceral metastases at baseline
- 43.6% of patients had ECOG performance status 0 at baseline
- 86.7% of patients received 10-mg EVE at the start of therapy
  - 13.3% received an EVE starting dose of 5 mg, which is half of the approved starting dose in this setting
    - No efficacy data are available on the subset of patients who received an EVE starting dose of 5 mg
- Additional baseline demographics and disease characteristics are reported in **Table 2**

Table 2. Baseline Patient and Disease Characteristics[a]

Patient Characteristics	Patients, n (%) (N = 500)
Age, median, y	66
Weight, median, kg	70
Height, median, cm	165
Body mass index, median	25.9
ECOG Performance Status	**Patients, n (%) (n = 420)[b]**
0	183 (43.6)
1	194 (46.2)
2	39 (9.3)
3	3 (0.7)
4	1 (0.2)
Missing	80
Metastasis	**Patients, n (%) (n = 495)[b]**
Visceral (lung, liver, CNS)	266 (53.7)
Visceral and bone	195 (39.4)
Visceral without bone	71 (14.3)
Only bone	130 (26.3)
Bone and other	250 (50.5)
Only other	110 (22.2)
Metastasis Location	**Patients, n (%) (n = 495)[b]**
Lung	136 (27.5)
Bones	380 (76.8)
Liver	175 (35.4)
CNS	12 (2.4)
Skin	23 (4.6)
Lymph nodes	133 (26.9)
Other localization	76 (15.4)
No metastases	5 (1.0)

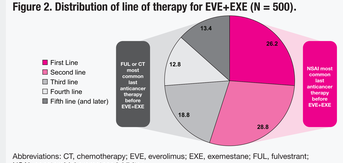
[a]Note that percentages are based on number of patients with available data and numbers of patients are reported in the column headings.
Abbreviation: CNS, central nervous system.

[{AQ: PLEASE CONFIRM THAT NUMBERS FOR "ONLY BONE", "BONE AND OTHER" AND "ONLY OTHER" ARE CORRECT UNDER THE "METASTASIS" CATEGORY ABOVE. THE TOTAL OF THESE 3 CATEGORIES EXCEED 495, THE NUMBER OF PATIENTS WITH AVAILABLE DATA.}]

EVE+EXE Treatment Characteristics

- Most patients received EVE+EXE as first-line (131 patients, 26.2%) or second-line (144 patients, 28.8%) treatment for advanced disease, followed by third-line treatment (94 patients, 18.8%) (**Figure 2**)
  - Most patients (445, 89.0%) switched to EVE+EXE because of disease progression under a previous therapy
- For patients receiving EVE+EXE in the advanced setting as
  - First- or second-line therapy, letrozole and anastrozole, were the most common last prior antineoplastic therapy
  - Third- or later line therapy, fulvestrant or chemotherapy, were increasingly documented as last prior therapy

Figure 2. Distribution of line of therapy for EVE+EXE (N = 500).

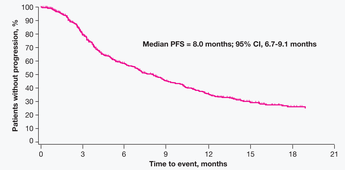


Abbreviations: CT, chemotherapy; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; NSAI, nonsteroidal aromatase inhibitor.

Progression-Free Survival

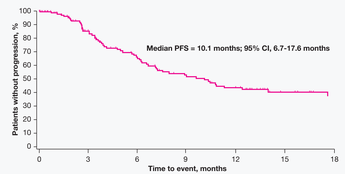
- The median PFS observed with the first 500 patients was 8.0 months (95% CI, 6.7-9.1; **Figure 3**)
- The median PFS observed in the subset of patients who received EVE+EXE as first-line therapy for advanced disease (n = 131) was 10.1 months (95% CI, 6.7-17.6; **Figure 4**)

Figure 3. Progression-free survival (first 500 patients).



Abbreviation: CI, confidence interval; PFS, progression-free survival.

Figure 4. PFS in patients receiving EVE+EXE as first-line therapy for advanced disease (n = 131, subset of first 500 patients).



Abbreviation: CI, confidence interval; PFS, progression-free survival.

Safety

- Adverse events (AEs) observed in BRAWO were consistent with that previously reported with EVE+EXE in patients with advanced breast cancer (**Table 3**)[1]
- The most commonly reported AEs of any grade reported in ≥ 10% of patients were
  - Stomatitis (39.8%)
  - Fatigue (15.6%)
  - Diarrhea (13.2%)
  - Dyspnea (13.0%)
  - Nausea (12.0%)
  - Decreased appetite (10.4%)

Table 3. Adverse Events (First 500 Patients)

AE (Preferred Term)	Patients With Adverse Event by Grade, n (%)[a,b] (N = 500)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis	199 (39.8)	116 (23.2)	85 (17.0)	17 (3.4)	1 (0.2)
Fatigue	78 (15.6)	43 (8.6)	28 (5.6)	11 (2.2)	0
Diarrhea	66 (13.2)	29 (5.8)	40 (8.0)	4 (0.8)	0
Dyspnea	65 (13.0)	24 (4.8)	20 (4.0)	14 (2.8)	3 (0.6)
Nausea	60 (12.0)	26 (5.2)	26 (5.2)	9 (1.8)	1 (0.2)
Decreased appetite	52 (10.4)	22 (4.4)	25 (5.0)	4 (0.8)	0
Peripheral edema	49 (9.8)	28 (5.6)	16 (3.2)	4 (0.8)	0
Cough	44 (8.8)	22 (4.4)	18 (3.6)	2 (0.4)	0
General physical health deterioration	44 (8.8)	6 (1.2)	17 (3.4)	16 (3.2)	4 (0.8)
Malignant neoplasm progression	43 (8.6)	0	5 (1.0)	9 (1.8)	18 (3.6)
Dysgeusia	38 (7.6)	22 (4.4)	14 (2.8)	2 (0.4)	0
Rash	38 (7.6)	20 (4.0)	20 (4.0)	0	0
Epistaxis	35 (7.0)	27 (5.4)	8 (1.6)	1 (0.2)	0
Weight decreased	34 (6.8)	14 (2.8)	18 (3.6)	2 (0.4)	0
Vomiting	33 (6.6)	13 (2.6)	12 (2.4)	7 (1.4)	0
Arthralgia	31 (6.2)	21 (4.2)	9 (1.8)	2 (0.4)	0
Headache	30 (6.0)	20 (4.0)	10 (2.0)	1 (0.2)	0
Anemia	30 (6.0)	10 (2.0)	18 (3.6)	4 (0.8)	0
Pruritus	28 (5.6)	17 (3.4)	9 (1.8)	1 (0.2)	0
Pain in extremity	26 (5.2)	14 (2.8)	10 (2.0)	3 (0.6)	0
Nasopharyngitis	25 (5.0)	15 (3.0)	11 (2.2)	1 (0.2)	0
Pleural effusion	25 (5.0)	1 (0.2)	12 (2.4)	6 (1.2)	3 (0.6)
Pyrexia	25 (5.0)	10 (2.0)	9 (1.8)	4 (0.8)	0

[a]Adverse events in ≥5% of patients.
[b]Grade 1 = mild; grade 2 = moderate; grade 3 = severe; grade 4 = life-threatening.

Everolimus Dose Modification

- 48.1% of patients required EVE dose reduction during therapy (**Table 4**)
  - Patients starting at 10.0 mg received a median dose intensity of 93.5%, patients starting at 5.0 mg received a considerably lower median dose intensity of 50.0%
- Most treatment interruptions were implemented because of adverse events
  - Median duration of treatment interruptions was 10.0 days

Table 4. Frequency of Everolimus Dose Modifications

EVE Dose Modification	EVE 5-mg Start Dose (n = 66)	EVE 10-mg Start Dose (n = 431)	Total (n = 497)
Median relative dose intensity, %	50.0	93.5	88.1
Treatment interruption, n (%)	5 (7.6)	166 (38.5)	171 (34.4)
Dose reduction (incl. to 0 mg), n (%)	14 (21.2)	225 (52.2)	239 (48.1)
Dose increase, n (%)	24 (36.4)	23 (5.3)[a]	47 (9.5)

[a] The majority of patients received the dose increase after a dose reduction.

Stomatitis Prophylactic Measures (n = 494)

- The majority of the patients (n = 429, 86.8%) received recommendations regarding stomatitis prevention from their physician (**Table 5**)
  - Data on recommended prophylactic measures was missing for 6 patients

Table 5. Stomatitis Prophylactic Measures Recommended to Patients

Type of Recommended Prophylactic Measure	Patients, n (%) (n = 494)[a]
Mild dental hygiene (eg, soft toothbrush)	362 (73.3)
Avoidance of hot, sour, or salty food	344 (69.6)
Rinsing with tea	281 (56.9)
Cooling (eg, sucking ice or frozen pineapple)	263 (53.2)
Avoidance of peroxide-/ alcohol-containing mouthwash solutions	213 (43.1)
Rinsing with mouthwash solution	195 (39.5)
Rinsing with NaCl	57 (11.5)
Other	23 (4.7)

[a] Patients with available information.

Therapeutic Interventions for Stomatitis

- At least one therapeutic measure was documented for 232 (83.2%) of the 279 events with stomatitis (**Table 6**)

Table 6. Stomatitis Therapeutic Interventions (First 500 Patients)

	Stomatitis Events, n (%)			
	Grade 1 (n = 143)	Grade 2 (n = 90)	Grade 3 (n = 17)	Unknown (n = 29)
Action Taken				
None specified	43 (30.1)	3 (3.3)	1 (5.9)	0
≥1 therapeutic measure	100 (63.9)	87 (96.7)	16 (94.1)	29 (100)
Type of action (multiple specifications possible)				
Non-drug mouthwash solution	78 (54.5)	46 (51.1)	7 (41.2)	22 (75.9)
Cooling (eg, sucking ice or frozen pineapple)	26 (18.2)	34 (37.8)	7 (41.2)	15 (51.7)
Drug Intervention	35 (24.5)	42 (46.7)	13 (76.5)	8 (27.6)
Topical drug	10 (7.0)	16 (17.8)	8 (47.1)	4 (13.8)
Systemic drug	26 (18.2)	30 (33.3)	10 (58.8)	5 (17.2)
Temporary everolimus dose adjustment	6 (4.2)	16 (17.8)	3 (17.6)	4 (13.8)
Temporary everolimus dose interruption	12 (8.4)	37 (41.1)	10 (58.8)	2 (6.9)

Discussion

- Compared with BOLERO-2, patients in the BRAWO trial were older (66 vs 62 years, respectively) and a smaller percentage of patients had an ECOG PS of 0 (43.6% vs 60%, respectively)[1]
  - The percentages of patients with visceral metastases were comparable in BRAWO and BOLERO-2 (53.7% vs 58%, respectively)[1]
    - Note: BRAWO does not include pleural and peritoneal involvement, unlike BOLERO 2, which included pleural and peritoneal involvement[2]
- Median PFS in BRAWO was consistent with BOLERO-2 in the overall population (8.0 months and 7.8 months, respectively)[1] and in patients receiving EVE+EXE as first-line therapy in the advanced setting (10.1 months and 11.5 months, respectively)[3]
- The overall safety profile observed in the BRAWO study is comparable to that observed in BOLERO-2[1] and reported with EVE in other cancer indications[4]
- The percentage of patients with any grade stomatitis was lower in BRAWO (39.8%) compared with BOLERO-2 (59%)
  - 86.8% of patients received prophylactic stomatitis treatment in BRAWO

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References

1. Yardley DA, et al. *Adv Ther.* 2013;30:870-884.
2. Campone M, et al. *Eur J Cancer.* 2013;49:2621-2632.
3. Beck T, et al. *Breast Cancer Res Treat.* 2014;143:459-467.
4. Afinitor 2014 Summary of Product Characteristics.

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