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Prevention of Everolimus/Exemestane Stomatitis in Postmenopausal Women With Hormone Receptor–Positive Metastatic Breast Cancer Using a Dexamethasone-Based Mouthwash: Results of the SWISH Trial

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SWISH
dexamethaSone mouthWash for everolImus-related stomatitiS prevention in HR+ MBC

BACKGROUND

- Stomatitis is a significant complication associated with mammalian target of rapamycin (mTOR) inhibition that can impact adherence and patient quality of life.
- In the BOLERO-2 trial, patients received everolimus (EVE) plus exemestane (EXE) for hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2–) metastatic breast cancer (MBC); incidence of all-grade stomatitis was 67%; 33% of patients had grade ≥2 and 8% had grade 3.[1-2]
  - Median time to grade ≥2 onset was 15.5 days; the incidence of new stomatitis (grade ≥2) plateaued at 6 weeks.[1]
- In a recent meta-analysis of phase 3 trials of solid tumors (breast cancer, renal cell carcinoma, pancreatic neuroendocrine tumors) and tuberous sclerosis complex, 89% of first stomatitis events occurred within 8 weeks of initiating everolimus.[3]
- mTOR inhibitor–associated stomatitis (mIAS) is similar to aphthous stomatitis, but distinct from chemotherapy-induced mucositis.[4,5]
- Use of topical steroids as prophylaxis has been anecdotally reported for treatment of aphthous ulcers; however, there is no clinical evidence to guide prophylactic strategies for prevention of mIAS.[4,6,7]

OBJECTIVE

- The objective of the dexamethaSone mouthWash for everolImus-related stomatitiS prevention in HR+ MBC (SWISH) study was to evaluate an alcohol-free, steroid-based mouthwash to prevent stomatitis (grade ≥2) in patients with HR+, HER2– advanced breast cancer receiving EVE and EXE treatment and to compare with BOLERO-2 historical controls.

METHODS

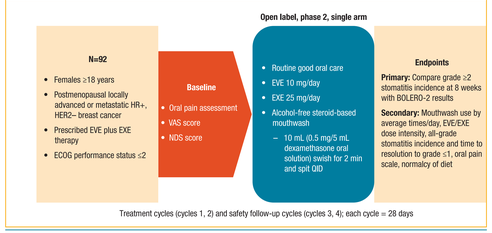
Study Design and Patient Population (Figure 1)

- US-based, multicenter, single-arm, phase 2 prevention trial
- 23 investigational sites
- Enrollment: May 2014 to October 2015
- Key inclusion criteria
  - Postmenopausal women ≥18 years of age
  - Locally advanced or metastatic HR+, HER2– BC
  - Prescribed EVE 10 mg plus EXE 25 mg
  - Initiated EVE and EXE therapy concurrently on cycle 1 day 1 of trial
  - Eastern Cooperative Oncology Group (ECOG) performance status ≤2
  - Adequate renal function: serum creatinine ≤1.5× upper limit of normal
  - Willingness to self-report dietary intake using the Normalcy of Diet Scale (NDS)[8-9] and level of oral pain using the visual analog scale (VAS),[10-12] as required in the patient diary
- Key exclusion criteria
  - Current stomatitis, oral mucositis, or mouth ulcers
  - Receipt of other anticancer therapies (except bisphosphonates, denosumab)
  - Chronic treatment with corticosteroids or other immunosuppressive agents

Study Interventions

- EVE 10 mg plus EXE 25 mg once daily
- 10 mL of alcohol-free dexamethasone 0.5 mg/5 mL oral solution (Roxane Laboratories/West-Ward Pharmaceuticals, Eatontown, NJ) to swish for 2 minutes and spit four times daily (nothing by mouth for 1 hour after mouthwash) for 8 weeks in conjunction with EVE 10 mg and EXE 25 mg
  - All 3 treatments initiated on day 1 of cycle 1.
  - 1 cycle had a duration of 28 days.
  - Patients could continue dexamethasone mouthwash regimen after the first 2 cycles by clinician discretion for a maximum of 4 total cycles.
  - Dose modification/dose interruption of EVE was permitted for the management of adverse events (AEs).
    - EVE was held for grade 2/3 stomatitis until recovery to grade ≤1.
- Patients received instructional materials
  - Information on stomatitis and routine good oral hygiene (ie, brushing teeth with a soft-bristled toothbrush, daily flossing and continuing routine dental care/maintenance with their dentist)
  - Timer to monitor duration of mouthwash treatment
- Patients completed daily logs to document NDS and VAS (for oral pain) scores, and number of doses of mouthwash.
- Patients remained on study until one of the following occurred:
  - Interruption of EVE for ≥4 consecutive weeks or permanent discontinuation of EVE
  - Diagnosis of grade 4 stomatitis
  - Intolerance of or significant AE related to the mouthwash regimen
  - Withdrawal of consent

Figure 1. Study Design



At the completion of cycle 2 (day 56), the treating clinician determined whether to continue the patient's assigned mouthwash regimen. Patients could continue to receive their mouthwash regimen from Novartis for an additional 56 days.

ECOG: Eastern Cooperative Oncology Group; EVE: everolimus; EXE: exemestane; HER2–: human epidermal growth factor receptor 2–negative; HR+: hormone receptor–positive; NDS: Normalcy of Diet Scale; QID: four times a day; VAS: visual analog scale

Study Endpoints and Assessments

- Primary endpoint
  - Incidence of grade ≥2 stomatitis at 8 weeks compared to BOLERO-2 historical controls
    - Grade ≥2 stomatitis by physical exam or telephone interview, based on evidence of changes to patient's oral mucosa that were consistent with stomatitis, and ≥1 of the following criteria also being met (**Table 1**):
      - Patient's oral intake reported at ≤50 using the NDS and/or
      - Patient-reported oral pain using VAS was 7 on 2 consecutive days or a rating of 8, 9, or 10 on any 1 day

Table 1. Stomatitis Diagnosis and Grading

Grade	Description	Stomatitis Diagnosis and Grading		
		Investigator-Assessed		Patient-Reported
		Physical Exam	Normalcy of Diet Scale*	Visual Analog Scale (oral pain)
1	Minimal symptoms, normal diet	Changes to oral mucosa consistent with stomatitis are confirmed by investigator	≥60	<7; or 7 (1 day only) Recovery from grade ≥2 to grade ≤1 means a patient must have VAS score <4 for 2 days without use of analgesics (if analgesics are used, the patient needs to report their maximum pain each day before the analgesics)
2	Symptomatic, but can eat and swallow modified diet		≥60	7 on 2 consecutive days; or 8, 9, or 10 on any 1 day
			50, 40	0–10 on any 1 day
3	Symptomatic and unable to aliment or hydrate orally		30, 20, 10	0–10 on any 1 day
4	Symptoms associated with life-threatening consequences		0	0–10 on any 1 day

*Normalcy of Diet Scale assessed by the investigator or site staff. It was also reported daily by the patient in the patient diary.

- Secondary endpoints
  - Average number/day mouthwash regimen was performed at 8 weeks
  - Dose intensity of EVE/EXE at 8 weeks
  - Incidence of all-grade stomatitis at 8 weeks
  - Time to resolution (number of days) from diagnosis of grade ≥2 stomatitis to resolution to grade ≤1
- Safety assessments including:
  - AEs, serious adverse events (SAEs), AEs leading to study drug discontinuation (by Common Terminology Criteria for Adverse Events v4), and laboratory abnormalities
  - Patient-reported outcomes
    - Recorded in a daily log of oral pain scores and normalcy of diet ratings
- A pre-dose blood sample was collected at cycle 1 (day 28) for pharmacokinetic (PK) assessment of steady-state levels of systemic absorption of EVE and EXE.

Statistical Analyses

- The sample size was based on the incidence rate of 33% for grade ≥2 stomatitis reported in BOLERO-2.
- A test of the incidence rate R was performed with the null hypothesis H0: R=0.33 and alternative hypothesis Ha: R<0.33 with a 1-sided significance level of 0.05.
- For a 1-sided alpha=0.05, 80% power and using a chi-square test, 73 evaluable patients were required.
  - The incidences of all grades and each component grade of stomatitis were summarized by counts, percentages, and 95% confidence intervals (CIs).

RESULTS

Patient Demographic Characteristics (Table 2)

- 92 patients enrolled and 86 were evaluable.
  - 6 patients were unevaluable; receipt of at least 1 dose of dexamethasone mouthwash could not be confirmed.
- Median age was 61 years (range 34-87), the majority of patients (61.6%) were Caucasian, and 93% of the study population was classified with ECOG performance status of 0-1.
- More than 35% of patients received EVE and EXE treatment in ≥2nd-line setting.
- 20 patients received optional antifungal oral prophylaxis against oral thrush.

Table 2. Patient Demographic Characteristics at Baseline

Baseline Demographic	N=86
Age, years, median (range)	61 (34-87)
Race, n (%)	
Caucasian	53 (61.6)
Black	14 (16.3)
Asian	9 (10.5)
Other	10 (11.6)
ECOG performance status, n (%)	
0	57 (66.3)
1	23 (26.7)
2	6 (7.0)
Time since most recent recurrence, months, median (range)	1.15 (0-30)
Number of metastatic sites, n (%)	
1	15 (17.4)
2	13 (15.1)
3-4	25 (29.1)
≥5	33 (38.4)
Select metastatic sites, n (%)	
Lung/pleura	44 (51.2)
Liver	31 (36.0)
Previous antiestrogen therapy, n (%)	
Fulvestrant	14 (16.3)
Tamoxifen	23 (26.7)
Previous aromatase inhibitors, n (%)	
Anastrozole	42 (48.8)
Exemestane	4 (4.7)
Letrozole	33 (38.4)
Previous protein kinase inhibitor, n (%)	
Palbociclib	5 (5.8)
Pazopanib	1 (1.2)

ECOG: Eastern Cooperative Oncology Group

Primary and Secondary Outcomes and PK Assessment

- The incidence of grade ≥2 stomatitis at 8 weeks was 2.4% (n=2, 95% CI 0.29-8.24, *P*<0.001) compared with 33% in BOLERO-2 (**Figure 2**).
- The incidence of all-grade stomatitis at 8 weeks was 21.2% (n=18, 95% CI 13.06-31.39), a markedly reduced incidence rate compared with all-grade stomatitis reported in BOLERO-2 (67%) (**Figure 2**).
  - The rate of grade 1 stomatitis was 18.8% (**Figure 2**).
  - Of the 18 patients who developed stomatitis, 3 used antifungal prophylaxis.
  - Of the 20 patients who used antifungal prophylaxis, 7 developed stomatitis.
- Resolution of grade ≥2 to grade ≤1 in the 2 patients who developed stomatitis occurred after a duration of 11 days for 1 patient and 15 days for the other patient.
- 95% of patients used dexamethasone mouthwash 3-4 times/day (median 3.95 [range 1.9-4]), and 74% of patients remained on all 3 drugs at ≥8 weeks (**Table 3**).
- The median dose intensities of EVE and EXE were 10 mg (range 3-10) and 25 mg (range 8-25), respectively (**Table 3**).
- PK assessment was conducted in a subset of the 86 evaluable patients who had a blood sample for PK analysis, took their EVE and EXE between 20 and 28 hours before the blood sample, had no dose interruptions within the 4 days prior to the blood sample, and did not report vomiting within the first 4 hours after taking the last dose of study drug.
  - 50 patients met the criteria to be included in the PK subset; EVE C_{min} results were available for 42 patients.
  - Mean and median EVE levels were 13.91 ng/mL and 11.10 ng/mL, respectively, which are consistent with a 10 mg daily dose and do not suggest any effect by the dexamethasone mouthwash.

Figure 2. Incidence of Stomatitis

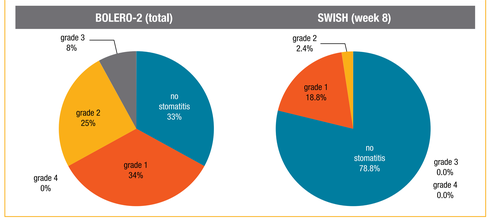


Table 3. Study Drug Dose Intensity

Outcomes	
Number of mouthwash applications/day, median (range)	3.95 (1.9-4.0)
Actual dose intensity, mg, median (range)	
Everolimus	10 (3-10)
Exemestane	25 (8-25)

Safety Outcomes

- The overall incidence of AEs, regardless of causality, was 90.2%.
- The most commonly reported (≥5%) all-grade AEs, regardless of causality, included:
  - Stomatitis (27.2%), fatigue (17.4%), nausea (15.2%), and hyperglycemia (15.2%) (**Table 4**).
- The most commonly reported (≥5%) all-grade AEs, with suspected causality, included:
  - Stomatitis (21.7%), hyperglycemia (13%), and fatigue (9.8%).
- AEs that led to study drug discontinuation occurred in 19.6% of patients, compared with 26.3% of patients in BOLERO-2.[1]
  - 13% of patients discontinued EVE/EXE due to AEs related to treatment.
    - The most common events were stomatitis, rash, and hyperglycemia at 2% each.
    - The remaining AEs occurred at a 1% incidence rate, including pneumonitis.
- The incidence of SAEs regardless of causality was 21.7%.
  - Dyspnea (grade 3 [1.1%]; grade 4 [2.2%]), pneumonia (grade 3 [2.2%]), pyrexia (grades 3 and 4 [1.1% each]), and respiratory failure (grades 3 and 4 [1.1% each]) were the most frequently reported SAEs.
- The incidence of treatment-related SAEs was 6.5%.
- 2 patients developed oral candidiasis; both used antifungal prophylaxis.
- 3 deaths occurred during the study, unrelated to study drugs.
- Among 75 patients with complete ECOG scores, 88% maintained or improved ECOG status.

Table 4. Adverse Events With ≥5% Incidence (Regardless of Causality)

Adverse Event*	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)
Stomatitis	17 (18.5)	7 (7.6)	1 (1.1)	0	25 (27.2)
Fatigue	8 (8.7)	8 (8.7)	0	0	16 (17.4)
Hyperglycemia	2 (2.2)	5 (5.4)	7 (7.6)	0	14 (15.2)
Nausea	11 (12.0)	3 (3.3)	0	0	14 (15.2)
Dyspnea	4 (4.3)	6 (6.5)	1 (1.1)	2 (2.2)	13 (14.1)
Dysgeusia	11 (12.0)	1 (1.1)	0	0	12 (13.0)
Cough	8 (8.7)	2 (2.2)	0	0	10 (10.9)
Diarrhea	5 (5.4)	4 (4.3)	1 (1.1)	0	10 (10.9)
Headache	8 (8.7)	1 (1.1)	1 (1.1)	0	10 (10.9)
Insomnia	6 (6.5)	2 (2.2)	1 (1.1)	0	9 (9.8)
Pyrexia	5 (5.4)	2 (2.2)	1 (1.1)	1 (1.1)	9 (9.8)
Urinary tract infection	2 (2.2)	6 (6.5)	0	0	8 (8.7)
Rash	3 (3.3)	1 (1.1)	4 (4.3)	0	8 (8.7)
Oral pain	5 (5.4)	1 (1.1)	0	0	6 (6.5)
Oropharyngeal pain	5 (5.4)	1 (1.1)	0	0	6 (6.5)
Vomiting	2 (2.2)	4 (4.3)	0	0	6 (6.5)
Anemia	3 (3.3)	1 (1.1)	1 (1.1)	0	5 (5.4)
Back pain	3 (3.3)	1 (1.1)	1 (1.1)	0	5 (5.4)
Hypercholesterolemia	2 (2.2)	2 (2.2)	1 (1.1)	0	5 (5.4)
Hypokalemia	3 (3.3)	2 (2.2)	0	0	5 (5.4)
Peripheral edema	1 (1.1)	4 (4.3)	0	0	5 (5.4)

*A patient with multiple occurrences of an adverse event (AE) was counted only once in the AE category. A patient with multiple AEs within a primary system organ class was counted only once in the total row. A patient with multiple severity ratings for an AE while on treatment was only counted under the maximum rating. Only events occurring from date of first study drug administration until date of last dose +28 days are included.

Patient-Reported Outcomes

- Normal diet was reported in 88% of patients at 8 weeks.
  - 90% experienced no/few diet restrictions throughout the study.
- The mean oral pain score was <1 at all visits (range 0.1-0.6).
- More than 90% of patients reported brushing 1-2 times/day, >93% used a soft-bristled toothbrush, and 70%-75% reported flossing daily.

LIMITATIONS

- This single-arm study lacked a formal control population; the historical control group from BOLERO-2 served as a benchmark for stomatitis incidence rates.

DISCUSSION AND CONCLUSIONS

- **Prophylaxis with dexamethasone mouthwash 3-4 times/day significantly minimized or prevented the incidence of all grades, especially grade ≥2, stomatitis in postmenopausal patients receiving EVE 10 mg/EXE 25 mg for HR+, HER2– advanced or metastatic BC compared to that seen in the BOLERO-2 trial.**
  - **Preventive use of dexamethasone mouthwash resulted in a greater than 10-fold reduction in the incidence of grade ≥2 stomatitis compared with BOLERO-2 patients.**
  - **Patient-reported outcomes monitoring diet and oral pain further supported efficacy of the dexamethasone mouthwash.**
- **Dexamethasone mouthwash was well tolerated with minimal toxicity.**
- **This treatment may have contributed to the favorable dose intensity of EVE/EXE seen in the SWISH study.**
- **No new safety signals were observed; the incidence of AEs was consistent with previous observations of EVE-based therapy, and AEs associated with corticosteroid use (eg, oral thrush or an increase in hyperglycemia) were minimal.**
- **An association between antifungal prophylaxis and stomatitis was not apparent.**
- **Patients were compliant with the treatment regimen and maintained good daily oral care.**
- **Steroid mouthwash as prophylaxis for EVE-related stomatitis is a new standard of care for patients receiving EVE/EXE for treatment of HR+, HER2– advanced or metastatic BC.**

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