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Dexamethasone to prevent everolimus-induced stomatitis (Alliance MIST Trial: A221701)

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ABSTRACT

mTOR inhibitors such as everolimus may cause oral stomatitis, often a dose-limiting toxicity. Prior clinical research has suggested that a dexamethasone mouth rinse might help prevent and/or treat this. Alliance A221701 was a randomized phase III trial of patients initiating 10 mg daily oral everolimus that compared dexamethasone mouthwash taken preventively (initial dexamethasone group) versus therapeutically (initial placebo group) to assess two coprimary endpoints: the incidence of mTOR inhibitor-associated stomatitis (mIAS), and the area under the curve (AUC) of mIAS-associated pain over an 8-week treatment period. A Fisher's exact test was used to compare the incidences while a Wilcoxon rank-sum test was used to compare the AUCs. In addition, we performed an exploratory analysis of the association of everolimus trough concentrations and toxicity using a Mann-Whitney U test. Due to slow accrual, this study closed after 39 patients were randomized (19 to upfront placebo and 20 to upfront dexamethasone). There were no significant differences between groups seen in either of the coprimary endpoints; furthermore, we found no association between whole blood everolimus trough concentrations and toxicity. Although limited by poor enrollment, the results of this study do not suggest that prophylactic dexamethasone mouthwash is superior to therapeutic dexamethasone mouthwash (initiated at the first sign of mouth pain) for reducing the incidence or severity of mIAS from everolimus.

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Background

Mammalian target of rapamycin (mTOR) inhibitors, including everolimus, cause stomatitis, which can significantly impair quality of life in patients with cancer. In the BOLERO-2 study, there was a 59% rate of stomatitis and a 30% rate of grade 2 or 3 stomatitis in patients with breast cancer who received everolimus and exemestane [1]. In a meta-analysis of BOLERO-2, RECORD-2 (for renal cell carcinoma), RADIANT-2 (for carcinoid), RADIANT-3 (for pancreatic neuroendocrine tumors), and EXIST-1 and 2 (for tuberous sclerosis complex), the rate of everolimus-induced stomatitis was 67%, while the rate of grade 3 or 4 stomatitis was 9%. It was noted that 89% of these events occurred within 8 weeks of starting everolimus [2].

Topical corticosteroids were proposed as a means of reducing stomatitis in this setting based on their efficacy for treating recurrent aphthous ulcers and Behcet's syndrome [3–6]. The proposed mechanism for corticosteroids in this setting was a decreased production of lymphocytes and other cytokines involved in an inflam-

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matory response [7]. Given that the underlying pathogenesis of stomatitis due to mTOR inhibitors appears to be inflammatory, like aphthous ulcers, topical corticosteroids were studied as a treatment for mTOR inhibitor-associated stomatitis (mIAS), with non-randomized studies suggesting substantial benefit [8,9].

This My Individualized Stomatitis Treatment (MIST) trial was designed to assess whether a preventative strategy would be superior to a reactive strategy when dexamethasone mouthwash was used during everolimus therapy for cancer.

Methods

This multicenter, randomized, double-blind, placebo-controlled phase III clinical trial enrolled patients who were preparing to start everolimus 10 mg orally daily for cancer, not concurrently on chemotherapy, not suffering from stomatitis/mucositis or mouth ulcers, and not already receiving a corticosteroid or any other agent considered to be a treatment for stomatitis. A history of oral candida infection (thrush) within the last 3 months, hemoglobin A_{1C} greater than 8%, current pregnancy or lactation, non-English literacy, Eastern Cooperative Oncology Group (ECOG) Performance Status >2, and age <18 years were all exclusion criteria. After providing IRB-approved protocol-specific written informed consent, participants were randomized in a 1:1 fashion to one of two treatment arms: (1) dexamethasone mouthwash; (2) placebo mouthwash that consisted of ORA-Sweet, which contains purified water, sucrose, glycerin, and sorbitol, buffered with citric acid and sodium phosphate, and preserved with methylparaben and potassium sorbate. Randomization was done using Pocock-Simon dynamic allocation, stratified by age (<50 *v* 50–65 *v*>65) and cancer type (breast *v* other). Regardless of the arm, participants were instructed to swish 10 mL of their assigned mouthwash for 2 minutes then spit it out, four times per day, for 8 weeks. This schedule was based on what had been used in previous small clinical trials with promising results [10]. Patients were told that if they developed any mouth pain related to mouth sores, they were to fill a prescription for dexamethasone oral solution, stop their study drug, and instead initiate open label swish-and-spit use of dexamethasone four times daily for 2 minutes each time until 8 weeks from the start of treatment.

There were two coprimary endpoints in this study. Patient-reported mouth pain was measured by a simple 11-item response scale [0, 1, 2, …, 10] with zero indicating “no pain” and ten indicating “pain as bad as can be,” obtained at baseline (within 7 days prior to the start of treatment) and then daily for 8 weeks. The first coprimary endpoint was the binary outcome mouth pain (yes; no) defined as a patient reporting at least one serially measured mouth pain score greater than zero during the 8-week study period. The second coprimary endpoint was the area under the curve (AUC) summary measure calculated for each patient based on the patient’s serially measured patient-reported mouth pain scores; the AUC calculated for each patient was scaled according to the number of assessable patient-reported mouth pain scores to obtain a transformed AUC score on a scale of 0–100 with higher scores corresponding to increased pain. We hypothesized that there would be a lower incidence rate of mIAS-associated mouth pain in the dexamethasone arm, and that the average AUC of the mouth pain scores would be less in the dexamethasone arm. The secondary endpoint safety analysis population included all patients who started at least one cycle of treatment (regardless of the availability of postbaseline mouth pain scores).

To achieve the study’s coprimary objectives, the planned sample size was 254 patients or 127 patients per arm. However, due to slow accrual between 2/15/2019 (accrual start date) and 11/1/2020, the study closed to accrual on 11/2/2020 after 39 patients were randomized (19 to upfront placebo and 20 to upfront dexamethasone). The analyses presented herein, therefore, are explorative in nature. For the first coprimary endpoint, we compared the incidence rate of mIAS-associated mouth pain between the two arms using a two-sided Fisher’s exact test [11]. For the second coprimary endpoint, we compared the average AUC of the serially measured mIAS-associated mouth pain scores between the two arms using a two-sided Wilcoxon rank-sum test [12]. The coprimary analyses were based on the full analysis set defined as all randomized patients with at least one postbaseline mIAS-associated mouth pain measurement. In three sensitivity analyses, the coprimary analyses were repeated: (1) excluding the patients with baseline mIAS-associated mouth pain >0; (2) including only those patients who completed at least 50% of their postbaseline pain reports; and (3) including only those patients who completed at least 80% of their pain reports. Everolimus blood trough concentrations at week 4 and week 8 were quantitated by LC-MS/MS with an assay utilizing 20 µL whole blood, [$^{13}C_2D_4$]-everolimus as internal standard, and a protein precipitation with ammonium bicarbonate, zinc sulfate, and acetonitrile; the standard curve was linear over the range of 2–100 ng/mL. Everolimus trough concentrations were corrected for exact sampling time to the 24-hour concentration based on the average everolimus terminal half-life of 30 hours in whole blood as previously described [13,14], and corrected values were compared between patients with or without filling of the dexamethasone prescription, and with or without mouth sores, mouth pain, grade ≥2 mIAS, or any of these events by Mann-Whitney U test (exact significance) [11]. Data were collected by the Alliance Statistics and Data Management Center (SDMC). Statistical analyses were performed by the SDMC using SAS, version 9.4 on a database frozen on January 8, 2021. Data quality was ensured by review of data by the SDMC and by the study chairperson following Alliance policies. Statistical significance was assessed at the nominal 5% significance level for both primary endpoints, with no adjustment for multiple testing.

Results

Thirty-nine patients (19 placebo-Arm A; 20 dexamethasone-Arm B) were randomized. Thirty-three patients were evaluable for the coprimary endpoints: 17 in Arm A (one patient did not start treatment, one patient did not provide any postbaseline pain scores) and 16 in Arm B (three patients did not start treatment, one patient did not provide any postbaseline pain scores).

The number of evaluable patients for toxicity was 18 in Arm A (one patient did not start treatment) and 17 for Arm B (three patients did not start treatment). All grade 3 and above adverse events deemed at least possibly related to treatment were counted. Two patients (11.1%) on the placebo arm reported at least one grade 3 nonhematologic adverse event (lower gastrointestinal hemorrhage, and oral mucositis), and three patients (17.6%) on the dexamethasone arm reported at least one grade 3 nonhematologic adverse event (mucositis, enterocolitis, pneumonitis). No grade 4 or 5 adverse events were reported. The number of evaluable patients for the coprimary endpoints was 17 in Arm A and 16 in Arm B (one patient on each arm was excluded because they did not provide any postbaseline pain scores).

Baseline characteristics were clinically balanced across the two arms in the cohort in whom the coprimary endpoints were assessed (Table 1). More than two-thirds of these participants had breast cancer. The incidence of mouth pain was 52.9% [95% confidence interval: 0.278, 0.770] in the placebo arm and 56.3% [95% confidence interval: 0.299, 0.802] in the dexamethasone arm, *P* value = 0.999. Furthermore, the median AUC was 0.7 in the placebo arm and 5.5 in the dexamethasone arm (*P* value = 0.335). Sensitivity analyses similarly revealed no significant difference between the arms in either coprimary endpoint. Of the patients evaluable

Table 1
Baseline characteristics of patients with at least one postbaseline pain score available.

	Arm		
	A: Placebo ($N=17$)	B: Dexamethasone ($N=16$)	Total ($N=33$)
Age (in years)			
N	17	16	33
Mean	65.3	65.3	65.3
SD	8.46	10.71	9.46
Age group, *n* (%)			
<50	1 (5.9%)	1 (6.3%)	2 (6.1%)
50–65	7 (41.2%)	8 (50.0%)	15 (45.5%)
>65	9 (52.9%)	7 (43.8%)	16 (48.5%)
Cancer type, *n* (%)			
Breast	12 (70.6%)	11 (68.8%)	23 (69.7%)
Other	5 (29.4%)	5 (31.3%)	10 (30.3%)
Sex, *n* (%)			
Female	15 (88.2%)	12 (75.0%)	27 (81.8%)
Male	2 (11.8%)	4 (25.0%)	6 (18.2%)
ECOG performance status, *n* (%)			
0	7 (41.2%)	8 (50.0%)	15 (45.5%)
1	10 (58.8%)	7 (43.8%)	17 (51.5%)
2	0 (0.0%)	1 (6.3%)	1 (3.0%)

ECOG = Eastern Cooperative Oncology Group.

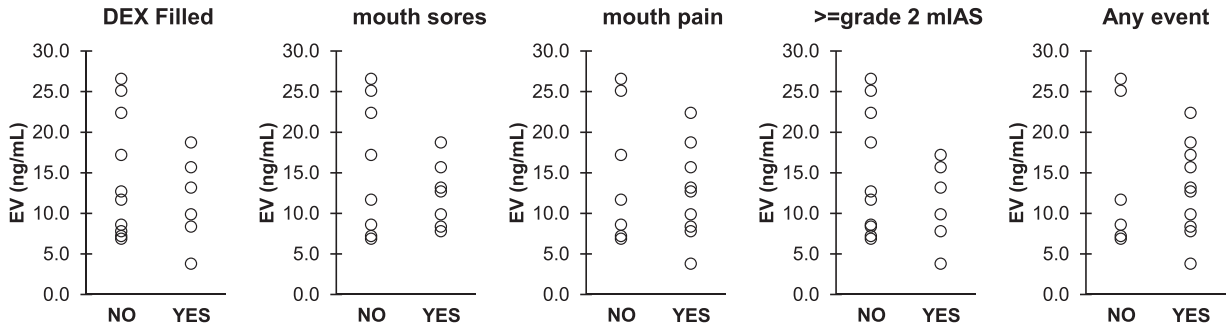

Fig. 1. Whole blood everolimus (EV) trough concentrations in patients with or without EV side effects and who did or did not fill a commercial dexamethasone (DEX) prescription. No statistical significance was detected through Mann-Whitney U test.

for the coprimary endpoints, the percent of patients who filled the prescription dexamethasone script based on weekly phone calls with the nurses was 35.3% in the placebo arm and 31.3% in the dexamethasone arm. Additionally, of those evaluable for the coprimary endpoints, the median number of Numerical Analogue Mouth Pain Scale forms with at least one pain score provided was nine in both arms (Arm A had a lower quartile of 7 and an upper quartile of 9; Arm B had a lower quartile of 5.5 and an upper quartile of 9). No significant difference in everolimus blood levels was detectable between patients with or without side effects or with or without a fill of a dexamethasone script (Fig. 1).

Discussion

We did not observe a significant difference between the two arms in either coprimary endpoint. While these negative results could have been the consequence of our inability to accrue even 20% of the desired 279 total (and 254 evaluable) patients, it is sobering that in our patient population, there was no hint of less stomatitis in the prophylactic dexamethasone arm of this trial (if anything, we might have found less in the placebo arm had we enrolled more patients). This suggests that prophylactic use of dexamethasone mouthwash before initiation of everolimus is not superior to reactive use of dexamethasone mouthwash if mouth pain develops. This trial (MIST) differed from the SWISH trial not only in that it randomized to a reactive versus prophylactic strategy and used a placebo control to blind participants and providers from the treatment, but also in its patient population and primary endpoint. In the SWISH trial, only patients initiating everolimus and exemestane for advanced breast cancer were enrolled [10], and clinician grading of adverse events (using CTCAE version 4.0) was the primary endpoint, with grade 1 stomatitis found in 19% and grade 2 in 2%, totaling 21% ($n=18$, 95% CI 13.06–31.39). Also, SWISH did not evaluate the frequency of mouthwash use or if a delayed start of dexamethasone at the time of development of stomatitis would have been as effective as its use in the preventive setting. It is important to note that very few grade 3 adverse events were observed in the present trial (and all were more likely due to everolimus than to topical corticosteroid therapy), similar to other studies of corticosteroid mouth rinses in this setting [15]. In light of previous studies reporting low rates of severe mucositis when dexamethasone mouthwash is used during everolimus therapy, reactive use of dexamethasone mouthwash (initiated if mouth pain develops) may be beneficial in this setting.

Conflicts of interest

Hope S. Rugo, MD, declares research grant support from Pfizer, Merck, Novartis, Lilly, Roche, Daiichi, Seattle Genetics, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AstraZeneca, Ayala, Astellas and Gilead and honoraria from Puma, Samsung, and NAPO.

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CRediT authorship contribution statement

Kathryn J. Ruddy: Conceptualization, Writing – original draft, Writing – review & editing. **David Zahrieh:** Formal analysis. **Jun He:** Formal analysis. **Blake Waechter:** Formal analysis. **Julianne L. Holleran:** Writing – review & editing. **Lionel D. Lewis:** Writing – review & editing. **Selina Chow:** Project administration. **Jan Beumer:** Investigation, Writing – original draft, Writing – review & editing. **Matthias Weiss:** Writing – review & editing. **Nikolaos Trikalinos:** Writing – review & editing. **Bryan Faller:** Writing – review & editing. **Maryam Lustberg:** Writing – review & editing. **Hope S. Rugo:** Conceptualization, Writing – review & editing. **Charles Loprinzi:** Conceptualization, Writing – review & editing.

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