Alliance A221701: Phase III Placebo-Controlled Trial to Evaluate Dexamethasone Use for Everolimus-Induced Oral Stomatitis: Prevention Versus Early Treatment Approaches

Kathryn J. Ruddy, MD and Hope S. Rugo, MD

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Rationale

Tyrosine kinase inhibitors (TKIs) are a type of targeted therapy that result in stomatitis, which can significantly reduce the quality of life in patients with cancer. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that is used (sometimes in combination with other drugs) to treat various types of cancer, including metastatic breast cancer. In a metastatic breast cancer study using everolimus and exemestane (BOLERO-2), there was a 59 percent rate of stomatitis and a 30 percent rate of grade 2 or 3 stomatitis. In a meta-analysis of multiple everolimus trials, the rate of everolimus-induced stomatitis was 67 percent. Eighty percent of the stomatitis events occurred within eight weeks of starting everolimus.

In a phase II trial of dexamethasone swish and spit for prevention of everolimus-associated stomatitis in the same patient population as BOLERO-2 showed a 21 percent rate of stomatitis at eight weeks (19 percent grade 1 and 2 percent grade 2). Strong data from this single-arm trial showed excellent tolerability and encouragingly low rates of stomatitis incidence in patients receiving exemestane, everolimus, and dexamethasone swish and spit. These results suggest that this therapy is helpful for preventing mTOR inhibitor-associated stomatitis (mIAS). It has been recommended that this approach be utilized in clinical practice, and many physicians have been using this approach. This sets the stage for a definitive randomized phase III, placebo controlled clinical trial to address whether a steroid mouthwash will prevent mIAS.

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Objective

Primary

- To determine if the initiation of dexamethasone at the start of everolimus treatment prevents mIAS-associated pain, compared to the initiation of placebo.
- To determine if the initiation of dexamethasone at the start of everolimus treatment will be superior compared to the initiation of placebo in terms of the overall severity of mIAS-associated pain.

Secondary

- To utilize the same measurement method that was reported in the SWISH trial: A combination of a patient reported pain scale, data from a normalcy of diet questionnaire, and clinician grading of stomatitis to determine the incidence of greater than grade 2 mIAS.
- To determine if the initiation of dexamethasone at the start of everolimus increases time to development of mouth pain using daily numerical analog scale patient-reported data collection.
- To assess if quality of life is better when dexamethasone mouth rinse use starts at the same time as everolimus use versus at the time when mouth pain begins.
- To investigate if starting dexamethasone mouth rinse concurrent with starting everolimus improves patients' ability to adhere to everolimus therapy.
- To compare dexamethasone prescription fill rates and timing between patients who received placebo versus study drug at the initiation of everolimus.

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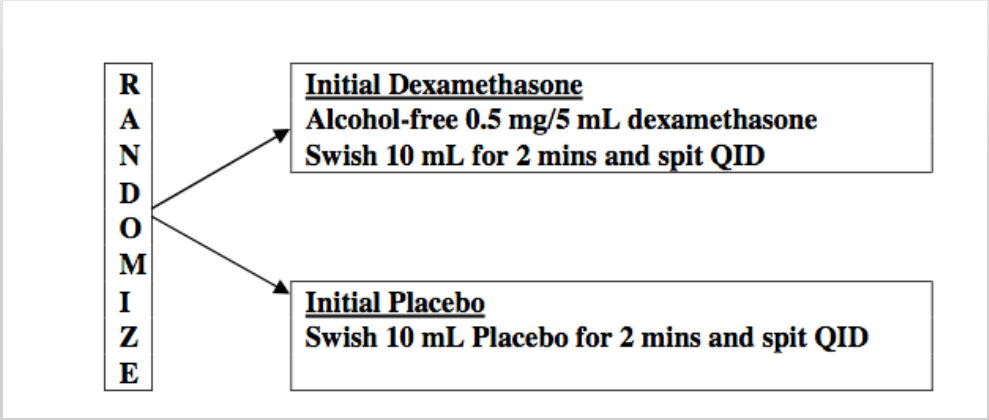
Study Schema



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Duration of treatment is 8 weeks from start of protocol treatment.

A dexamethasone prescription will be provided to all participants when they enroll to the trial. If mouth pain related to stomatitis develops at any time during the 8 week study period, patients may fill the prescription for dexamethasone oral solution from their local pharmacy. Patients will not be unblinded at this time and will continue with all study procedures (such as questionnaires, phone calls and physical exams). They will be instructed to stop taking the initially provided study medication if they start taking the prescription dexamethasone.

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Treatment Plan

- Patients will be randomized into one of two groups.
- Those in Group 1 will receive everolimus orally once daily as standard of care and dexamethasone as mouthwash over two minutes four times per day for eight weeks.
- Those in Group 2 will receive everolimus orally once daily as standard of care and placebo as mouthwash over two minutes four times per day for eight weeks.
- Patients will be provided with a prescription for dexamethasone oral solution when they enroll on the trial. They will be instructed to fill the prescription and stop taking provided study medication if they develop mouth pain related to stomatitis during the eight-week study period. Patients will not be unblinded and will continue study procedures.
- An early change from placebo to a dexamethasone oral solution is incorporated in this protocol so that patients who develop stomatitis are treated early.
- Additionally, there are optional blood studies and quality of life assessments are mandatory.

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Eligibility Criteria

- Current cancer diagnosis about to receive oral 10mg of daily everolimus with or without an endocrine agent
- Not currently receiving chemotherapy
- Not currently suffering from stomatitis/mucositis or mouth ulcers
- No history of candida infection (thrush) within the last 3 months
- Not currently being treated with corticosteroids
- No uncontrolled diabetes mellitus defined by hemoglobin A1C greater than 8%
- Patients should not be receiving any other agent considered treatment for stomatitis at the time of enrollment
- Patients must be able to read and comprehend English
- Not pregnant and not nursing
- ECOG Performance Status 0-2

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