ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221701

PHASE III PLACEBO-CONTROLLED TRIAL TO EVALUATE DEXAMETHASONE USE FOR EVEROLIMUS-INDUCED ORAL STOMATITIS: PREVENTION VERSUS EARLY TREATMENT APPROACHES: MIST (MY INDIVIDUALIZED STOMATITIS TREATMENT)

A limited access study

Supplied agent: Dexamethasone; (IND: exempt)

ClinicalTrials.gov Identifier: NCT03839940

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Limited Access Institutions, See Page 2

Participating Organizations:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

Limited access institutions

Altru Cancer Center (ND028)(Alliance)

Cancer Care Center of O'Fallon (IL413) (Alliance, SWOG, ECOG,NRG)
Centralia Oncology Clinic (IL385) (Alliance, SWOG, ECOG,NRG)
Crossroads Cancer Center (IL208) (Alliance, SWOG, ECOG,NRG)
Great Lakes Cancer Management Specialists-Van Elslander Cancer Center (MI202) (Alliance, SWOG, ECOG,NRG)
Illinois CancerCare-Bloomington (IL352)(Alliance, SWOG,ECOG, NRG)
Illinois CancerCare-Canton (IL361)(Alliance, SWOG,ECOG,NRG)
Illinois CancerCare-Carthage (IL362) (Alliance, SWOG, ECOG, NRG)
Illinois CancerCare-Eureka (IL366) (Alliance, SWOG, ECOG, NRG)
Illinois CancerCare-Galesburg (IL188) (Alliance, SWOG, ECOG, NRG)
Illinois CancerCare-Kewanee Clinic (IL344) (Alliance, SWOG, ECOG, NRG)
LSU Health Sciences Center at Shreveport (LA017) (Alliance, SWOG, ECOG, NRG)
Mayo Clinic (MN026) (Alliance, SWOG, ECOG, NRG)
Mayo Clinic Health System - Eau Claire Clinic (WI045) (Alliance, ECOG, NRG)
Mayo Clinic Health System Eau Claire Hospital-Luther Campus (WI036) (Alliance, ECOG, NRG)
Memorial Medical Center (IL097) (Alliance, SWOG, ECOG,NRG)
Missouri Baptist Outpatient Center-Sunset Hills (MO191) (Alliance, SWOG, ECOG,NRG)
Missouri Baptist Sullivan Hospital (MO190) (Alliance, SWOG, ECOG,NRG)
Parkland Health Center – Farmington (MO199) (Alliance, SWOG, ECOG,NRG)
Self Regional Healthcare (SC015) (Alliance, SWOG, NRG)
Siteman Cancer Center at Christian Hospital (MO020)(Alliance, ECOG, NRG)
Siteman Cancer Center at Saint Peters Hospital (MO152)(Alliance, ECOG, NRG)
Siteman Cancer Center at West County Hospital (MO053) (Alliance, ECOG,NRG)
Siteman Cancer Center-South County (MO187)(Alliance, ECOG,NRG)
Washington University School of Medicine (MO011)(Alliance, ECOG,NRG)
Illinois CancerCare-Princeton (IL358)(Alliance, SWOG, ECOG,NRG)
Decatur Memorial Hospital (IL094) (Alliance, SWOG, ECOG,NRG)
Springfield Clinic (IL194) (Alliance, SWOG, ECOG,NRG)
South Illinois University School of Medicine (IL096) (Alliance, SWOG, ECOG,NRG)

IHA Hematology Oncology Consultants-Ann Arbor (MI349) (Alliance, SWOG, ECOG,NRG)

Sanford Thief River Falls Medical Center (MN137) (Alliance, ECOG, NRG)
Sanford Bismarck Medical Center (ND007) (Alliance, ECOG, NRG)
Sanford Roger Maris Cancer Center (ND005) (Alliance, ECOG, NRG)
Sanford Broadway Medical Center (ND003) (Alliance, ECOG, NRG)
Sanford USD Medical Center - Sioux Falls (SD003) (Alliance, ECOG, NRG)
Sanford Cancer Center Oncology Clinic (SD004) (Alliance, ECOG, NRG)
Legacy Salmon Creek Hospital (WA179) (Alliance, SWOG, NRG)
Mayo Clinic Health System –Franciscan Healthcare (WI077) (Alliance, ECOG, NRG)
Sainte Genevieve County Memorial Hospital (MO188) (Alliance, SWOG, ECOG,NRG)
Missouri Baptist Medical Center (MO046) (Alliance, SWOG, ECOG,NRG)
Cancer Care Center of O'Fallon (IL413) (Alliance, SWOG, ECOG,NRG)
SIH Cancer Institute (IL414) (Alliance, SWOG, ECOG,NRG)
Saint Francis Medical Center in Cape Girardeau (MO009) (Alliance, SWOG, ECOG,NRG)
Cancer Care Specialists of Illinois – Decatur (IL185) (Alliance, SWOG, ECOG,NRG)
Eastern Maine Medical Center Cancer Care (ME040)(Alliance)
Illinois CancerCare-Peoria (IL101)(Alliance, SWOG, ECOG, NRG)
Illinois CancerCare-Peru (IL353)(Alliance, SWOG,ECOG, NRG)
Illinois CancerCare-Ottawa Clinic (IL277) (Alliance, SWOG, ECOG,NRG)
Illinois CancerCare-Pekin (IL354) (Alliance, SWOG, ECOG,NRG)
Illinois CancerCare-Macomb (IL355) (Alliance, SWOG, ECOG,NRG)

Study Resources:

Expedited Adverse Event Reporting [redacted]	**Medidata Rave® iMedidata portal** [redacted]
OPEN (Oncology Patient Enrollment Network) [redacted]	**Biospecimen Management System** [redacted]

Protocol Contacts:

A221701 Nursing Contact
[redacted]

A221701 Pharmacy Contact
[redacted]

Alliance Biorepository at Mayo Clinic
[redacted]

Drug Distribution Contact
[redacted]

Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository
Questions regarding drug supply and administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

Institutions will order the following supplies from the CTSU Operations Office: Questionnaire booklets. Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.

For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.

For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email:
CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.

PHASE III PLACEBO-CONTROLLED TRIAL TO EVALUATE DEXAMETHASONE USE FOR EVEROLIMUS-INDUCED ORAL STOMATITIS: PREVENTION VERSUS EARLY TREATMENT APPROACHES

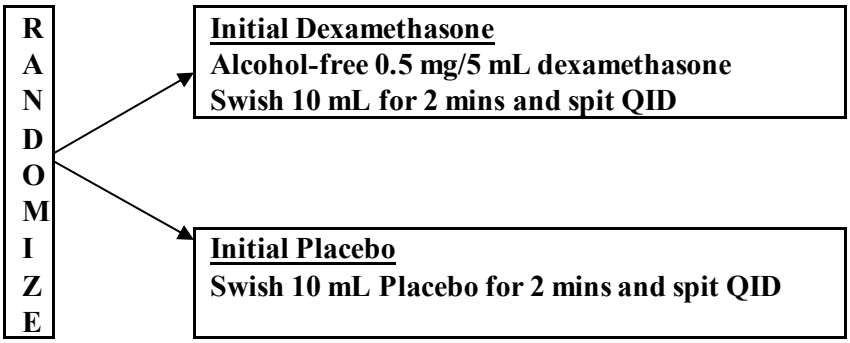
Eligibility Criteria (see Section 3.0)

- Current cancer diagnosis, about to receive everolimus See 3.2.1
- Not currently receiving chemotherapy See 3.2.2
- Not currently suffering from stomatitis/mucositis or mouth ulcers See 3.2.3
- Patients should not receive any other agent considered treatment for stomatitis. See 3.2.4
- No history of candida infection (thrush) within the last 3 months See 3.2.5
- Not currently being treated with corticosteroids See 3.2.6
- No uncontrolled diabetes mellitus defined by hemoglobin A1C greater than 8% See 3.2.7
- Patients must be able to read and comprehend English See 3.2 8
- Not pregnant and not nursing See 3.2.9
- ECOG Performance Status ≤ 2
- Age ≥18 years.

Required Initial Laboratory Values

None

Schema



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.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

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1.0 BACKGROUND

1.1 Introduction

Tyrosine kinase inhibitors (TKIs) result in stomatitis, which can significantly impair quality of life in cancer patients. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that is used (sometimes in combination with other drugs) to treat a variety of cancers including metastatic breast cancer. In the BOLERO-2 study, there was a 59% rate of stomatitis and a 30% rate of grade 2 or 3 stomatitis with everolimus and exemestane therapy in breast cancer patients.[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 also 67%, and the rate of grade 3 or 4 stomatitis was 9%[2]. It was noted that 89% of these events occurred within 8 weeks of starting everolimus.

1.1.1 Topical corticosteroids appear to treat benign aphthous ulcers

For patients with recurrent aphthous ulcers, topical steroids appear to reduce pain and promote healing.[3,4] Oral steroid paste, ointment, or solution has been found to be effective against the symptoms of this condition, which mimics drug-induced stomatitis. In patients with Behcet's syndrome, who are prone to oral ulcers, a randomized trial of triamcinolone vs. phenytoin syrup revealed substantially more improvement in ulcer symptoms in those who received triamcinolone.[5] In some severe cases of aphthous ulcers that are refractory to topical treatments, systemic steroids have been beneficial.[6,7] The proposed mechanism by which corticosteroids are thought to decrease mucosal ulcer pain is via decreased production of lymphocytes and other cytokines involved in the inflammatory response.[8]

1.1.2 Topical corticosteroids appear to treat and/or prevent everolimus-induced stomatitis-early reports

The underlying pathogenesis of stomatitis due to TKIs appears to be inflammatory, like aphthous ulcers. In 2011, a report was published regarding 17 patients with mTOR inhibitor-associated stomatitis (mIAS) who were treated with a topical corticosteroid, including topical oral dexamethasone solution; this was put in the oral cavity and then expectorated. Over 85% of these patients appeared to improve with this therapy.[9] In another trial involving 15 women, 7 of whom (47%) had developed greater than or equal to grade 2 stomatitis, their ulcers, treated with topical dexamethasone, all appeared to resolve over a median of 2 weeks.[10] In addition, an early report suggested that patients treated with a prophylactic hydrocortisone, tetracycline, nystatin, and diphenhydramine mouthwash prevented mIAS in patients who were receiving everolimus.[11]

1.2 Larger phase II trials of corticosteroids for prevention of everolimus-associated stomatitis

In the SWISH study, an alcohol-free, dexamethasone-based mouthwash was investigated as a means to prevent stomatitis in patients with advanced breast cancer receiving everolimus and exemestane.[12] Patients receiving 10 mg of everolimus in combination with exemestane started an alcohol-free dexamethasone solution simultaneously. Patients were asked to swish, hold for 2 minutes, then spit out 10 ml of a 0.5 mg/5 ml dexamethasone solution. In this study, the 8 weeks incidence of CTCAE grade 1 stomatitis was 19% and grade 2 stomatitis was only 2%, resulting in an overall stomatitis incidence rate at 8 weeks of only 21% (n=18, 95% CI 13.06-31.39), significantly lower than that seen in BOLERO-2 historical controls ($p<0.001$). In SWISH, 95% of patients used dexamethasone mouthwash 3-4 times/day (median 3.95 [range 1.9-4]), and more than 70% remained on all 3 drugs for at least 8 weeks. The median dose intensities of everolimus and exemestane were 10 mg and 25 mg, respectively. SWISH did not

evaluate the frequency of mouthwash use, or if delayed start of dexamethasone at the time of development of stomatitis would be as effective as use in the preventive setting.

At the San Antonio Breast Cancer Symposium in 2016, a separate prospective phase 2 randomized trial of 2 steroid-based mouth rinses as oral prophylaxis for patients receiving 10 mg of everolimus combined with exemestane was presented.[13] These two rinses included the following: 1) 320 ml diphenhydramine, 2g tetracycline, 80mg hydrocortisone, 40mg Nystatin, and water; or 2) prednisolone 15mg/ml and 1.8% alcohol. Four times a day, participants were instructed to swish and spit one of these two solutions, and the incidence of stomatitis and all grade related adverse events appeared to be relatively low in both arms of the study (29% and 27.5% in arms 1 and 2, respectively over twelve weeks). The incidence of grade 2 adverse events was 12% and 8% in arms 1 and 2, respectively.

While a variety of topical steroids have shown promise in treatment of recurrent aphthous ulcers, we have selected dexamethasone solution as the intervention to be tested in this trial (as opposed to another corticosteroid medication) because of the strong data from the previous SWISH single-arm study showing excellent tolerability and encouragingly low rates of stomatitis incidence (only 2% ≥grade 2) in patients receiving exemestane, everolimus, and dexamethasone swish and spit.

1.3 Rationale for a randomized phase III trial

The results of these two phase II trials assessing prevention of mIAS with oral corticosteroid medications are quite impressive. They strongly suggest that this therapy is helpful for preventing 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 3, placebo controlled clinical trial to address whether a steroid mouthwash will prevent mIAS.

An early change from placebo to a corticosteroid medication is incorporated in this protocol so that patients that develop mIAS are treated early with dexamethasone, expecting that this will provide benefit and prevent patients from developing the severe mIAS that was seen in the BOLERO-2 trial.

1.4 Study design

We have proposed, as is illustrated in the study schema, to conduct a placebo-controlled trial investigating a dexamethasone preparation for prevention of stomatitis. To address the potential concern that we are holding back medication that looks quite effective for prevention of everolimus-induced stomatitis, we will allow a patient to start getting a corticosteroid preparation at the initiation of any pain associated with mouth sores. Thus, this protocol is designed to test 1) a prevention approach versus 2) an early treatment intervention approach. Instead of having the patient have to come back into the clinic and get such a preparation, we have opted to provide a prescription for all patients who can then quickly get this filled and start on dexamethasone treatment should mouth sores develop. If and when the patient decides to switch to prescription dexamethasone, he/she will be asked to notify a protocol nurse and/or clinician. Weekly phone calls from a study nurse will also collect information about whether the prescription was filled. If the corticosteroid preparation is helpful for preventing the stomatitis, then we would expect the placebo arm patients to be more likely to fill the corticosteroid prescription and to do that earlier in the course, compared with patients who were actually receiving the corticosteroid preparation initially. Whether a patient chooses to go to prescription dexamethasone, and when that happens, will be prominent study endpoints.

The primary reason that a phase III trial is needed is that there really is equipoise as to which of our 2 proposed study arms is best. While some might say that the phase II study data

convincingly show that the use of a corticosteroid QID is beneficial in patients starting everolimus (which is hard to argue, compared to not ever using a corticosteroid), there may be an advantage for the initial placebo arm (understanding that a patient would be instructed to start prescription dexamethasone if they developed any painful mouth sores), in that about a third of patients will likely be spared the hassle and expense and potential toxicities (e.g. thrush) of using a corticosteroid mouthwash, because about a third of patients did not experience any mIAS in the BOLERO trial. It might well be that starting use of dexamethasone at the beginning of any mouth pain will effectively prevent the development of moderate to severe pain. The need to compare a prevention versus treatment strategy is highlighted in the excellent editorial by Spring and Bardia.[14] These authors state, "Because the development of everolimus-induced oral mucositis is usually preceded by a prodrome, treatment with steroid rinses at the earliest indication of stomatitis, rather than attempts at prevention, could be an alternative approach for some patients".

1.5 Potential study populations

We initially considered only studying patients receiving everolimus in combination with endocrine therapy, to mimic the two large phase II trials described above. However, hearing from practicing clinicians that they frequently use everolimus in clinical practice for a more diverse group of patients with a variety of conditions (such as renal cell and islet cell cancer), and that these patients have similar mIAS problems, we opted to be more inclusive in this clinical trial and include any cancer patient being treated with everolimus (10 mg/day). This makes sense as it is the everolimus that causes mIAS, not the antiestrogen therapies.

1.6 Methods and Assessment Procedures

We plan to collect all of the data elements from the SWISH trial (CTCAE delineation of mucositis, pain, normalcy of diet scale), obtained in the same manner, in addition to other data elements.

The endpoint that was developed and used de novo in the SWISH trial used composite criteria, with a clarification that a grade 2 or higher designation needed to be confirmed by 1) an oral pain score of greater than 8/10 on 1 occasion or 7/10 for 2 days, or 2) that patients could only eat soft chewable foods (or less, like liquids alone) as determined by a Normalcy of Diet Scale score less than or equal to 50/100. With this rule, a patient with classic CTCAE determination of grade 2 stomatitis could have been downgraded to grade 1 stomatitis if they did not meet the pain or diet criteria to keep them at grade 2 stomatitis (noting that this only happened for 2 patients in the SWISH trial—unpublished data provided to us). This composite clinician-determined measurement is not well validated psychometrically by itself, or by adding the 2 criteria noted above, so this will be a secondary endpoint for our trial.

For our primary endpoint, we will use a numerical analog scale of patient-reported mouth pain. We have validated these numerical analog scales for symptom collection in numerous trials.[15] PRO measures are believed to be more accurate than clinicians' CTCAE reporting for many toxicities.[16,17] For example, in a prospective study including lung cancer patients, PRO measurements of toxicities better reflected patients' underlying state and functional status than clinicians' evaluations.[18] As in multiple previous Alliance trials,[19,20,21] patient questionnaires will be utilized to obtain outcome data. Daily data collection by patient questionnaires will allow us to more accurately see daily changes on the days before and after patient actually took prescription dexamethasone (which they would have started because they developed mouth pain); we might not be able to collect data at that exact time, if we used the SWISH measurement method.

Further supporting the use of a PRO measure of mouth sore related pain is that the SWISH definition of grade 2 or 3 mucositis is primarily based on pain, as is illustrated in the table below (thus the mouth pain that patients developed would have been the predominant factor to determine their score).

Grade:	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Thus, we propose to use the PRO pain score as our primary measurement tool, while using the SWISH trial method as a secondary endpoint for both concurrent validation of the SWISH approach and comparison of the two results.

These patient-reported study data will be collected by daily patient logs and a more extensive survey weekly. There will also be weekly nurse phone calls (Appendix VI). The daily logs will collect a numerical analog mouth pain score, as shown in the Appendix II. Once a week, patients will also be asked to respond to a single-item overall quality of life (QOL) linear analogue self-assessment (Appendix III), as well as two NCI-developed PRO-CTCAE items regarding mouth sores, two regarding insomnia, and two regarding fatigue (as shown in Appendix IV).[21,22,23,24] A mouthwash use questionnaire (Appendix V) will also be included in the weekly survey.

Patients will be strongly encouraged during each weekly nurse phone call (Appendix VI) to immediately report back by phone if they fill the prescription for dexamethasone mouthwash in between the routine weekly calls. Weekly nurse phone calls will also be used to remind the patients to:

- Fill out the daily mouth pain form (Appendix II)
- Fill out the weekly PRO-CTCAE items [21,22,23,24](Appendix IV),
- and mouthwash use questionnaire (as shown in Appendix V).

The nurses will also collect information on (Appendix VI):

- Everolimus dose (and reasons for any dose reductions)
- Study mouthwash use frequency
- Whether and when the patient obtained the prescription mouthwash
- CTCAEs; and
- Normalcy of Diet Scale data

There are data to support the utility and validity of the above measures. The numerical analog mouth pain scale (Appendix II) was used effectively to assess patient-reported mouth pain in the SWISH study.[2] The single-item overall QOL assessment (Appendix III) is a simple linear analogue scale that has been successfully used in multiple trials including patients with advanced cancer,[25,26,27,28] and is routinely included in most Alliance trials. The three 2-item PRO-CTCAE assessments (Appendix IV) were recently developed and validated for use in cooperative group clinical trials.[21,22,23] PRO-CTCAE is a library of questions asking patients about specific symptomatic adverse events associated with cancer therapy. They are meant to be used in combination with clinician-determined CTCAE, so both PRO-CTCAE and CTCAE

collection will be performed weekly, and all three symptoms that will be collected by PRO-CTCAE (mouth sores, insomnia, and fatigue) will be collected by CTCAE as well. CTCAE assessments will also be performed to assess for other toxicities of dexamethasone for which PRO-CTCAE items are not available (i.e., thrush, hyperglycemia, irritability) weekly during the study period (during the nurse phone calls if a patient is not scheduled to be seen in the clinic that week).

Survey items about frequency of use of study and prescription mouthwashes (Appendix V) were adapted from multiple previous Alliance symptom intervention trials, as was the nurse telephone assessment form (Appendix VI).

2.0 OBJECTIVES

2.1 Co-Primary objectives

2.1.1 To determine if the initiation of dexamethasone at the start of everolimus treatment prevents mIAS-associated pain, compared to the initiation of placebo.

2.1.2 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.

2.2 Secondary objectives

2.2.1 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 ≥ grade 2 mIAS.

2.2.2 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.

2.2.3 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.

2.2.4 To investigate if starting dexamethasone mouth rinse concurrent with starting everolimus improves patients' ability to adhere to everolimus therapy.

2.2.5 To compare dexamethasone prescription fill rates and timing between patients who received placebo versus study drug at the initiation of everolimus.

2.3 Pharmacogenetics objectives (also see Section 14.1.2)

2.3.1 To derive tagSNPs for FBXW7 and together with SNPs reported (Table 1), genotype all patient samples for those SNPs.

2.3.2 To explore the association of the genotypes with severity of everolimus-related stomatitis (mIAS-associated pain) within the patients who initially received placebo at the start of everolimus treatment.

2.3.3 To explore the association of the genotypes with severity of everolimus-related stomatitis (mIAS-associated pain) within the patients who initially received dexamethasone at the start of everolimus treatment.

2.4 Pharmacokinetics objectives (also see Section 14.2.2)

2.4.1 To determine the intrapatient and interpatient variability of everolimus exposure (C0) in cancer patients being treated with everolimus.

2.4.2. To correlate everolimus exposure (C0) with toxicity.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease:**

Current cancer diagnosis, about to receive oral everolimus 10 mg/day with or without an endocrine agent. Patients about to receive everolimus for off label use for any cancer are also eligible.

___ **3.2.2 Prior Treatment**

- Not currently receiving chemotherapy or any other agent known to cause mucositis or stomatitis. Trastuzumab and ovarian function suppression are allowed.
- Any prior chemotherapy or other stomatitis/mucositis-causing therapy must be completed at least 2 weeks prior to registration.

___ **3.2.3 Not currently suffering from stomatitis/mucositis or mouth ulcers.** Patients should not have had any stomatitis or mouth pain for at least 7 days prior to registration.

___ **3.2.4 Patients should not receive any other agent which would be considered treatment for stomatitis or impact the primary endpoint.**

___ **3.2.5 No history of candida infection (thrush) within the last 3 months**

___ **3.2.6 Not currently being treated with corticosteroids**

___ **3.2.7 Comorbid conditions**

No uncontrolled diabetes mellitus, defined by hemoglobin A1C greater than 8%, although A1C is not needed for all patients, HgbA1C <8 is required for everyone with diabetes or suspected diabetes.

___ **3.2.8 Patients must be able to read and comprehend English.** Local translation, including verbal translation of PROs is not permitted.

___ **3.2.9 Not pregnant and not nursing**, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.10 ECOG Performance Status 0, 1 or 2.**

___ **3.2.11 Age ≥ 18 years**

___ **3.2.12 Required Initial Laboratory Values:** ***None***

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted]

4.2 CTSU Site Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;

- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Protocol Specific Requirements for Site Registration

Limited access information

With Update 2 to the protocol, this is a limited access study. Institutions that have previously enrolled participants and have expressed continued interest in participating in this study have been identified and listed on Page 2 of the protocol.

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *[Alliance]*, and protocol number *[A221701]*.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting regulatory documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.5 Checking your site's registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

Informed consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient completed booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221701 CTSU site) and submitting it through the CTSU regulatory portal. Samples of the questionnaires included in the booklets are found in Appendices II-V, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

Protected Health Information: Whole blood samples collected for the pharmacokinetics sub-study A221701-PP1 will be sent directly to the University of Pittsburgh Cancer Center. These samples will be labeled with patient initials, study ID and collection date/time.

4.4 Patient Enrollment (registration/randomization procedures (Step 1))

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer

in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted]. For any additional questions, contact the CTSU Help Desk at [redacted].

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudies described in Section 14.0

There are two substudies within Alliance A221701. These correlative science studies must be offered to all patients enrolled on Alliance A221701 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies) included within Alliance A221701 are:

- Pharmacogenomics and Everolimus induced stomatitis, Alliance A221701-ST1 (Section 14.1)
- Population Pharmacokinetics of Everolimus, Alliance A221701- PP1 (Section 14.2)

If a patient answers "yes" to "My samples and related information may be used for the additional studies described above," Question #2 in the model consent "I agree that my samples and related health information may be used for the laboratory study described above", they have consented to participate in the substudies described in Section 14.0. The patient should be registered to Alliance A221701-ST1 and A221701- PP1 at the same time they are registered to the treatment trial (A221701). Samples should be submitted per Section 6.2.

4.6 Stratification Factors and Treatment Assignments

4.6.1 Stratification factors

a) Age (<50 versus 50-65 versus >65)

b) Cancer type (breast versus other)

4.6.2 Treatment Assignments and Blinding

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the 2 treatment groups using the Pocock-Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups[70].

Patients will be randomized in a 1:1 fashion to receive one of two treatments:

- Intervention Group: Participants will receive Dexamethasone mouthwash for 8 weeks.
- Control Group: Participants will receive placebo for 8 weeks.

After the treatment assignment has been ascertained in the OPEN application, the patient's study medication code number will be displayed on the confirmation of registration screen.

The pharmacist or designated contact person at the treating site will maintain records that indicate the identity of the patient and their corresponding study medication code number.

4.7 Procedures for Double-Blinding the Treatment Assignment

After the treatment assignment has been ascertained by randomization, the Registration Specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be indicated in the OPEN registration system at the time of registration. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the OPEN registration Form as the person completing the form. The OPEN registration form should provide the source of communication, either fax or e-mail, and the appropriate contact information. The Registration Specialist will then communicate the treatment assignment "active or placebo" to designated contact at the patient's institution.

Once the treatment assignment has been communicated, the designated contact should prepare dexamethasone mouthwash or placebo mouthwash for delivery to the patient.

The dose will be prepared and labeled as "dexamethasone/placebo" so that the contents are not discernible to the person administering the treatment.

The pharmacist or designated contact person will maintain records that indicate the identity of the patient and their corresponding treatment assignment. The pharmacist or designated contact person at the treating site will maintain records that indicate the identity of the patient and their corresponding study medication code number.

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals:

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

	Prior to Registration	Baseline*	Weekly, for 8 weeks from start of treatment	4 and 8 weeks after start of treatment
Tests & Observations:				
History and physical, weight, PS	X			
Adverse Event Assessment		X	X (1)	
Serum or Urine HCG	X(2)			
PRO/QOL assessments:				
Numerical Analogue Mouth Pain Scale (Appendix II)		X	A	
Numerical Analogue Self-Assessment (Appendix III)			X	
PRO-CTCAE assessments (Appendix IV)		X	X	
Patient reported Mouthwash use frequency (Appendix V)			X	
Other assessments:				
Nurse Weekly Phone call (Appendix VI)			X (1)	
Normalcy of Diet scale (Appendix VII)			X (1)	
Correlative Studies				
Whole Blood		X		X (3)

* To be completed within 7 days prior to the start of treatment.

A To be completed daily

1 Nurse/Research Coordinator will contact the patient every week to remind patients to complete questionnaires, answer questions, to assess adverse events and ask normalcy of diet scale questions (see Appendices VI and VII).

2 For women of childbearing potential (see Section 3.2). Must be done ≤ 7 days prior to registration

3 For patients who consent to the correlative studies described in Section 14.0. Week 4 sample and questionnaire is not required for patients who are not scheduled to come back to the clinic for a week 4 visit. See Section 6.2.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule:

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted].

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendices II- VII for reference and IRB submission only. They are not to be used for patient completion.

Weekly Booklets: Eight booklets to be completed weekly must be given to patients to complete at home and patients should be instructed to return the booklets by mail weekly or to return the booklets at their regularly scheduled clinic visit. Institutions must provide patients with sufficient self-addressed stamped envelopes for this purpose. Site staff will enter patient responses into Rave upon receipt of the completed booklets.

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.2 Specimen collection and submission

For patients registered to substudies A221701-ST1 and A221701-PP1, all participating institutions must ask patients for their consent to participate in these correlative substudies, although patient participation is optional. Pharmacogenetic (A221701-ST1) and pharmacokinetic (A221701- PP1) studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, blood will be collected at the following time points for these studies:

	Prior to Treatment	**4 weeks (+/-7 days) after start of study medication**	**8 weeks (+/- 7 days) after start of study medication**	**Storage/ Shipping conditions**	**Submit to:**
For patients registered to A221701-ST1 and A221701-PP1, submit the following: (optional)					
Number and volume of tubes to draw					
Whole blood (1) (EDTA/lavender top) (See Section 6.2.2)	1 x 10 mL*			Cool pack/ship overnight	Mayo BAP Freezer
Whole blood (2) (EDTA/lavender top) (see Section 6.2.3)	1 x 5 mL	1 x 5 mL**	1 x 5 mL	Cool pack/ship overnight	University of Pittsburgh

* Can be collected at a subsequent visit if the sample cannot be obtained prior to treatment

** Not required for patients who are not scheduled to come back to the clinic for a week 4 visit

1 Pharmacogenomic analyses described in Section 14.1

2 Pharmacokinetic analyses described in Section 14.2. Patients will be asked to complete a pharmacokinetics questionnaire (Appendix VIII) at the 4 week and 8-week visits (not required at the Baseline visit). The questionnaire can be completed before or after the blood draw. A copy of the questionnaire will be sent by site staff along with the samples to the University of Pittsburgh. Questionnaire responses are to be entered into Rave by site staff.

6.2.1 Specimen Submission Using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the appropriate protocol number (either A221701-ST1 or A221701- PP1), Alliance patient number, patient's initials, date and type of specimen collected (i.e., whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

6.2.2 Blood submission (for pharmacogenomic studies); A221701- ST1

For patients who consent to participate, (model consent question, "I agree to have my specimen collected and I agree that my specimen sample and related information may be used for the laboratory study described above"), whole blood samples will be used for the pharmacogenomic studies described in Section 14.1. This sample should be collected prior to the initiation of protocol treatment.

Collect 10 mL of peripheral venous blood in an EDTA (lavender) tube. The tubes should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository. The samples should be shipped the same day that the blood is drawn per Section 6.2.1.

Label samples with the following identification:

1) Procurement date/time of collection
2) Alliance patient number
3) Patient initials
4) Alliance study number (i.e., A221701- ST1)
5) Specimen type (i.e., whole blood)

The 10 mL of blood can be collected in one 10 mL EDTA tube, or two 5 mL EDTA tubes or three 3 mL EDTA tubes, as long as the final volume is ~10 mL.

Ship specimens on Monday through Friday. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Saturdays.

These specimens should be sent to the following address:

[redacted]

6.2.3 Blood submission (for pharmacokinetic studies); A221701- PP1

For patients who consent to participate, (model consent question, "I agree to have my specimen collected and I agree that my specimen sample and related information may be used for the laboratory study described above"), whole blood samples will be used for the pharmacokinetic studies described in Section 14.2. This sample should be collected prior to the initiation of protocol treatment, at 4 week visit (prior to everolimus dosage), (+/- 7 days) and at 8 weeks (prior to everolimus dosage), (+/- 7 days).

At week 4 visit and at week 8 visit, patients enrolled to the pharmacokinetics substudy will be asked to complete a questionnaire (see Appendix VIII), which will provide information

about the prior 48-hour dosing of everolimus (details of dose, time and relationship to food). A de-identified copy of the form must be included along with the blood samples, and shipped to the address listed at the end of this section. Questionnaire responses are to be entered into Rave by site staff.

Collect 5 mL of peripheral venous blood in an EDTA (lavender) tube. The tubes should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the University of Pittsburgh. The samples should be shipped the same day that the blood is drawn per Section 6.2.1.

Label samples with the following identification:

1) Procurement date/time of collection
2) Alliance patient number
3) Patient initials
4) Alliance study number (i.e., A221701- PP1)
5) Specimen type (i.e., whole blood)

Samples should be shipped Monday-Thursday for next day delivery. DO NOT SHIP SAMPLES ON A FRIDAY OR A WEEKEND OR BEFORE A HOLIDAY.

Send samples and copies of the completed Pharmacokinetics questionnaires to the following address:

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration. **Protocol treatment must be initiated on the same day as the first dose of everolimus.**

For questions regarding treatment, please see the study contacts page.

From the start of the study, all patients will be provided information to perform good oral care. This consists of brushing teeth twice a day with a soft brill toothbrush and continuing to floss (if the patient was flossing).

A dexamethasone prescription will be provided to all participants following registration. This will be intended for individual patients to obtain from their local pharmacy if mouth pain related to stomatitis develops at any time during the 8 week study period. Treating physicians should provide a prescription for dexamethasone mouthwash with the same concentration as the study drug mouthwash described in Section 10.1.

Agent	Dose	Route
Everolimus	10 mg once daily for 8 weeks	p.o.
Dexamethasone/placebo	10 mL four times daily for 8 weeks*	Oral swish for 2 minutes then spit

* Patients who develop any mouth pain related to mouth sores should fill the prescription for dexamethasone oral solution, and 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.

7.1 Everolimus

Everolimus should be taken once per day, preferably swallowed with food.

7.2 Initial Dexamethasone/Placebo

Dexamethasone/placebo 10 mL will be swished in the mouth for two minutes, four times per day. The patient should take nothing by mouth for thirty minutes before swishing the mouthwash, and for at least an hour after each mouthwash. Except patients may take Nystatin® if the patient develops any evidence of thrush.

7.3 Open label dexamethasone

Patients should be instructed that if they develop any mouth pain related to mouth sores, they should fill the prescription for oral dexamethasone solution, and initiate swish-and-spit use of this four times daily for 2 minutes each time. If the patient determines that they should fill their prescription, they should contact the study nurse as soon as is feasible.

Patients will be instructed to stop taking the initially provided study medication if they start taking the prescription dexamethasone. Patients will not be unblinded at this time and will continue with all study procedures (such as questionnaires, phone calls and physical exams) until eight weeks from start of protocol treatment.

Patients should also be instructed that if they develop moderate or greater mouth pain that somewhat or greater interferes with their usual daily activities, they should call their treating physician to discuss holding and/or reducing the dose of the everolimus (per provider discretion).

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other agent to attempt to prevent mucositis/stomatitis at the start of the study; if mouth pain develops, clinicians will be allowed to treat this with additional agents if needed per their discretion. All topical (not ingested) topical anesthetics are allowed. Examples of such medicines include: Lidocaine, magic mouthwash, and biotene.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Antiemetics may be used with the exception of oral steroids, at the discretion of the attending physician.

8.1.4 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

- Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.2 Dose Modifications

There will be no dose modifications to the dexamethasone mouthwash on this study. Everolimus dose modifications will be left to the discretion of the treating physician.

However, the patient will be allowed to hold the study mouthwash during everolimus dose holds according to the treating physician's discretion, and allowed to resume the study mouthwash once the patient resumes everolimus.

If a CTCAE grade 3-4 toxicity develops that is probably or definitely attributable to dexamethasone mouth rinse or everolimus, study therapy will stop but follow-up assessments will continue until the end of the eight week study period.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency or at the end of protocol treatment. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

8.3.1 Emergency Unblinding Procedures

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling [redacted], pressing 1 to speak

- with an operator, and then asking for pager ID 8625 to return the call.
- The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., “A221701”)
- Alliance patient ID number (e.g., “999999”)
- Patient initials (e.g., “L,FM”)
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding
- Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted]. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

NOTE: PRO-CTCAE data should not be used for determining attribution, or reporting of adverse events.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Event Solicited form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and weekly throughout the eight weeks of treatment by CTCAE, PRO-CTCAE or both.

CTCAE v5.0 Term	PRO-CTCAE v1.0 Term	CTCAE v5.0 System Organ Class (SOC)
Mucositis oral	Mouth/throat sore	Gastrointestinal Disorders
Oral pain	Mouth/throat sore	Gastrointestinal Disorders
Insomnia	Sleep	Psychiatric Disorders
Fatigue	Fatigue	General Disorders and administration site conditions
Mucosal infection	N/A	Infections and Infestations
Hyperglycemia	N/A	Metabolism and Nutrition Disorders
Irritability	N/A	Psychiatric Disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted]
All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

PRO-CTCAE data should not be used for determining attribution, or reporting of serious adverse events.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using study Form, Notice of New Primary.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 diarrhea/constipation and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) with hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted] The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

Pregnancy loss

• Pregnancy loss is defined in CTCAE as "Death in utero."

• Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.

• A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.

10.0 DRUG INFORMATION

10.1 Dexamethasone Oral Solution

Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response.

IND Exempt: Dexamethasone is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for dexamethasone; this investigation will use an approved route of administration and dosage of dexamethasone and has no factors that increase the risk of the product; this investigation will be in compliance with 21CFR parts 56, 50, and 312.7; and neither the investigator nor sponsor will promote or represent that dexamethasone is safe or effective for the context that is under investigation in this study.

Procurement

Dexamethasone 0.5mg/5 mL oral solution (240 mL) and ORA-Sweet® Solution (480 mL) stock bottles will be provided and shipped by Fisher Clinical Services to sites.

After receiving IRB approval for this study, each participating institution will order a starter supply of twenty bottles of dexamethasone oral solution and ten bottles of ORA-Sweet® solution from Fisher Clinical Services, Inc. by faxing or emailing the Drug Order/Return Form to:

[redacted]

The A221701 Dexamethasone/Placebo Order Form can be found on the A221701 study page of the Alliance and CTSU websites.

Each site is responsible for monitoring their inventory and ordering additional bottles as needed. Each site will provide their own 16 oz. amber bottles.

Main member institutions will be provided a per patient reimbursement by the Alliance for their rebottling services and supplies.

Within ninety days after the last patient is treated at the institution, any expired or remaining supplies should be destroyed according to institutional procedure.

Preparation

The designated unblinded person at each institution will transfer either dexamethasone 0.5 mg/5 mL oral solution or ORA-Sweet® solution into five – 16 oz amber bottles based on the patient's treatment assignment. A total of 480 mL should be added to each bottle. This should be a sufficient supply for the entire 8 weeks of treatment. The five bottles (480 mL each) will be labeled "dexamethasone 0.5 mg/5 mL or placebo solution". Assign an expiration date of one year. If the expiration date of the stock bottle is less than one year, use the expiration date listed on the stock bottle.

Drug Accountability

Drug accountability logs must be kept for the dexamethasone 0.5 mg/5 mL oral solution and the ORA-Sweet® oral solution.

Formulation

Dexamethasone oral solution 0.5 mg/5mL is a dye-free, sugar-free solution with a cherry brandy flavor. The solution contains citric acid, disodium edetate, flavoring, glycerin, methylparaben, propylene glycol, propylparaben, sorbitol and water.

Administration

Dexamethasone/placebo will be administered at a dosage of 10 mL four times daily. Patients should be instructed to swish the solution in their mouth for two minutes. They should not eat or drink anything for thirty minutes before each mouthwash and at least one hour after each mouthwash.

Pharmacokinetics

Onset of action: Prompt

Duration of metabolic effect: 72 hours

Metabolism: Hepatic

Half-life elimination: Normal renal function: 4 ± 0.9 hours; Biological half-life: 36-54 hours

Time to peak, serum: Oral: 1-2 hours

Excretion: Urine (~10%)

Drug Interactions

Substrate of CYP3A4 (major), P-glycoprotein/ABCB1; Induces CYP2A6 (weak/moderate), 2C9 (weak/moderate), 3A4 (weak), UGT1A1

Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.

Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.

Ethanol/Nutrition/Herb Interactions:

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Dexamethasone interferes with calcium absorption. Limit caffeine.

Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)

Adverse Events

Known potential adverse events: Consult the package insert for the most current and complete information.

Common known potential toxicities, frequency not defined:

Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

Storage and Stability

Store at Controlled Room Temperature, 20- 25°C (68°-77°F); excursions permitted to 15–30°C (59–86°F).

10.1.1 Nursing Guidelines

1. For this protocol dose to be used is 10cc which converts to two teaspoons for patients.
2. Instruct patients to shake solution well before use.
3. Patients should have a clean mouth before using the rinse, no eating for 30 min prior to use.
4. Two teaspoons should be swished in the mouth for two minutes then spit out; do not swallow.
5. Patients should refrain from eating or drinking for one hour after rinsing.
6. Patients should refrain from eating foods with high acid content, and limit alcohol and caffeine intake, as these food items can irritate the mouth further.
7. Monitor regularly for hypertension, CHF and other evidence of fluid retention.
8. Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.
9. Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.
10. Evaluate for signs and symptoms of throat candida infection (thrush), and treat appropriately.
11. Monitor blood glucose frequently especially if diabetic.
12. Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.
13. Advise patient that easy bruising is a side effect.

10.2 Placebo Oral Solution

The placebo for this study will be ORA-Sweet®. This is a berry citrus flavored (contains FD&C Red #40) inert syrup vehicle. The ORA-Sweet® contains purified water, sucrose, glycerin, and sorbitol. It is buffered with citric acid and sodium phosphate, and preserved with methylparaben and potassium sorbate.

11.0 MEASURES

We plan to collect all of the data elements from the SWISH trial (Clinician grading of mucositis, patient reported pain, normalcy of diet scale), obtained in the same manner as in the SWISH study, in addition to other data elements. We will use daily logs to collect a numerical analogue mouth pain score, as shown in Appendix II. This was used effectively to assess patient-reported mouth pain in the SWISH study[2]. Once a week, patients will also be asked to respond to a numerical analogue single-item overall quality of life (QOL) self-assessment (Appendix III), two NCI-developed PRO-CTCAE items regarding mouth sores (as shown in Appendix IV)[21,22,23,24], two NCI-developed PRO-CTCAE items regarding insomnia, and two regarding fatigue (possible side effects of dexamethasone), as shown in Appendix III, PRO measures are believed to be more accurate than clinicians' CTCAE reporting for many toxicities.[17,18] For example, in a prospective study including lung cancer patients, PRO measurements of toxicities better reflected patients' underlying state and functional status than clinicians' evaluations.[18] As in multiple previous Alliance legacy trials,[19,20,21] patient questionnaires will be utilized to obtain outcome data.

11.1 Numerical Analogue Mouth Pain Scale (Appendix II)

This patient-reported mouth pain tool utilizes a numerical analogue scale methodology, which we have validated in numerous trials.[29] Completion of the Numerical Analogue Mouth Pain Scale will take less than one minute.

11.2 Numerical Analogue Self-Assessment (Appendix III)

The single-item Numerical Analogue Scale for quality of life (QOL) has been widely used in a variety of clinical trials for many years,[15,30,31] including in patients with advanced cancer,[25,26,27,28], and is routinely included in most Alliance trials. When administered prior to initiation of therapy, better scores on this measure may be prognostic for survival in cancer patients, independent of performance status.[32] This measure will be included to assess how the study medication impacts overall quality of life during treatment with everolimus. Completion of this single-item will take less than one minute.

11.3 PRO-CTCAE items (Mouth/throat sores, Sleep and Fatigue items) (Appendix IV)

The three 2-item PRO-CTCAE assessments regarding mouth/throat sores, sleep, and fatigue (Appendix IV) were recently developed and validated for use in cooperative group clinical trials.[21,22,23] PRO-CTCAE is a library of questions asking patients about specific symptomatic adverse events associated with cancer therapy. Completion of the six total PRO-CTCAE items will take less than one minute to complete.

11.4 Patient reported Mouthwash Use frequency (Appendix V)

This measure was created specifically for use in this study so that we could collect data regarding how much mouthwash was actually used by the participants (how many of the recommended 28 doses per week were taken), as well as data regarding whether or not (and when) the optional prescription dexamethasone was initiated. It also includes two questions regarding everolimus to allow us to assess what proportion of patients are able to stay on the full 10 mg starting dose of that drug on each study arm. This measure will take less than one minute to complete.

11.5 Nurse\Research coordinator weekly phone call assessments (Appendix VI)

Although patient-reported study data will be collected by daily patient logs and weekly questionnaires, there will also be weekly nurse phone calls to remind patients to fill out the patient booklets and to collect additional information (Appendix VI). During these approximately 5-minute weekly calls, nurses will remind participants to:

- Fill out the daily mouth pain form
- Fill out the weekly questionnaires (including PRO-CTCAE) and a mouthwash use questionnaire (as shown in Appendix V).

The nurse or research coordinator will also collect information on:

- Everolimus dose (and reasons for any dose reductions)
- Study mouthwash use frequency
- If and when the patient obtained the prescription mouthwash
- CTCAEs; and
- Normalcy of Diet Scale data (See Section 11.6)

Items about frequency of use of study and prescription mouthwashes (Appendix V) were adapted from multiple previous Alliance symptom control clinical trials, as was the nurse telephone assessment form (Appendix VI).

CTCAE assessments will be performed during these calls to collect mouth symptoms and to assess for toxicities of dexamethasone (i.e., thrush, hyperglycemia, irritability, fatigue, and insomnia) weekly during the study period (during the nurse phone calls if a patient is not scheduled to be seen in the clinic that week).

11.6 Normalcy of Diet Scale (Appendix VII)

The Normalcy of Diet Scale is part of the Performance Status Scale for Head and Neck Cancer Patients[33], and was chosen for use here primarily because this was used in the SWISH study[12] and will allow us to assess the same composite endpoint that was the primary endpoint in that study. This measure will be administered over the phone by a study nurse, who will begin by asking the patient what kinds of foods (s) he has been eating, and then ask what foods are difficult to eat. The nurse will then ask about specific examples of foods, working up from the bottom of the scale (or from the middle if the patient says he/she can eat everything), stopping at the item the patient cannot eat (and giving the patient the score below that item). This allows us to assess how stomatitis related to everolimus reduces a patient's ability to eat a normal diet on both arms of the study.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue until 8 weeks after start of everolimus treatment. Please see the study calendar (Section 5) and the treatment section (Section 7) for treatment and follow up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

Treatment will continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Pregnancy

- All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

- Termination of the study

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

There will be no follow up after the eight week treatment period.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

When patients stop protocol treatment early, they should be encouraged to complete QOL submissions but can stop if they prefer.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), baseline and off-treatment notice data submission is required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This trial is designed as a multi-center, randomized, double-blind, placebo-controlled phase III study where patients will be randomly assigned to receive either dexamethasone mouth rinse or placebo mouth rinse. The respective research hypotheses for the co-primary objectives 2.1.1 and 2.1.2 are:

1) Pain will be less common in patients who take dexamethasone preventatively (dexamethasone group) compared with those who initiate dexamethasone at the onset of mouth pain (placebo group). The research hypothesis for this first co-primary objective is: Dexamethasone taken preventively will substantially decrease the number of patients who develop mIAS.

2) The research hypothesis for this second co-primary objective is: The average severity of mIAS-associated pain over the eight week treatment period will be greater in those who initiate dexamethasone at the onset of mouth pain (placebo group) compared to those who take dexamethasone preventatively (dexamethasone group).

13.2 Sample Size, Accrual time and Study Duration

To account for 10% ineligible patients and cancelations, the targeted sample size is 279 patients (evaluable patients for data analysis are 254). Under a constant accrual rate of 10-15 patients per month, the study will last 28 months from initiation until the final patient is accrued, and another 2 months until the final patient completes treatment.

13.3 Primary objectives and endpoints

There are two co-primary endpoints in this study. Patient-reported mouth pain is 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" (Appendix II), and obtained at baseline (within seven days prior to the start of treatment) and then daily for 8-weeks.

13.3.1 First co-primary endpoint

The objective is to compare the incidence rate of mIAS-associated mouth pain between the two arms using a Chi-square test. The first co-primary endpoint is 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 eight-week study period.

13.3.2 Second co-primary endpoint

The objective is to compare the average AUC of the serially measured mIAS-associated mouth pain scores between the two arms using a two-sample t-test. The second co-primary endpoint is 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 is scaled according to the number of assessable patient-reported mouth pain scores to obtain a transformed AUC score on a scale of 0-100.

13.4 Secondary objectives and endpoints

13.4.1 (Objective 2.2.1) Using the same measurement method that was reported in the SWISH trial, we will generate an endpoint that consists of a combination of a patient reported pain scale, data from a normalcy of diet questionnaire, and CTCAE grading of stomatitis/mucositis to determine the incidence of $\geq$ grade 2 mIAS. Grade $\geq$ 2 mIAS is defined as having at least one of the following criteria:

1) Oral intake assessed at <50 on the Normalcy of Diet Scale

2) Patient's reported oral pain (using visual analogue scale 0-10) that meets one of the following:

- rating of 7 on two consecutive days
- rating of 8, 9, or 10 on any one day

Our hypothesis is that dexamethasone will substantially decrease the number of patients who develop grade ≥ 2 mIAS.

13.4.2 (Objective 2.2.2) We will determine if the initiation of dexamethasone at the start of everolimus increases time to development of mouth pain. Our hypothesis is that daily numerical analogue scale data will reveal longer time to the development of at least mild, at least moderate, and severe mouth pain in the upfront dexamethasone arm compared to the placebo arm.

13.4.3. (Objective 2.2.3) We will assess if quality of life and adverse related domains are better, as we hypothesize that it will be, when dexamethasone mouth rinse use starts at the same time as everolimus use versus at the time when mouth pain begins by comparing numerical analogue scale scores (Appendix III) and PRO-CTCAE mouth/throat and sleep items regarding level of interference with daily activities (Appendix IV).

13.4.4. (Objective 2.2.4) We will investigate if starting dexamethasone mouth rinse concurrent with starting everolimus improves patients' ability to adhere to everolimus therapy by comparing mean daily dose of everolimus between the arms, as well as the number of patients who stopped everolimus early and the number who reduced the dose of everolimus per arm between the groups.

13.4.5. (Objective 2.2.5) We will compare dexamethasone prescription fill rates and time to these fills between patients who received placebo versus study drug at the initiation of everolimus**.**

13.5 Analysis Plan and Sample Size Justification

The primary analyses will be based on the intent-to-treat (ITT) population, defined as all patients randomized who completed the numerical analogue mouth pain scale at least once during the study. For the co-primary endpoints, a fixed-sequence statistical strategy will be used to control the Type I error rate at 0.05. The first co-primary endpoint will be tested, followed by the second co-primary endpoint, both at the same significance level of 0.05, such that the second co-primary endpoint is only tested if statistical significance was achieved on the first co-primary endpoint. Although both co-primary endpoints are clinically relevant, the testing sequence was ordered largely by the likelihood of success.

13.5.1 First co-primary endpoint

The sample size was determined based on the between arm comparison of the incidence rate of mIAS-associated mouth pain using a Chi-square test. The incidence rate for each arm is defined as the proportion of patients reporting any pain score greater than zero during the eight week study period, based on the single item numerical analogue mouth pain scale (Appendix II). Based on prior studies (Section 13.7), we assumed that the incidence rate of mIAS-associated mouth pain in the placebo group is 50%, and hypothesized that the incidence rate of mIAS-associated mouth pain in the dexamethasone group will be 32%. To detect this difference in the incidence rate of mIAS-associated mouth pain with 80% power, 127 patients are needed per group or 254 patients total. The

sample size calculation was based on a Chi-square test with a 5% Type I error rate under two-sided alternative.

13.5.2 Second co-primary endpoint:

With 127 patients per group (254 total), the study is adequately powered to detect a moderate effect size for the second co-primary endpoint. Specifically, 127 patients per group will provide 97% power to detect a moderate effect size of 0.5 (equivalent to 10 points on the transformed AUC score scaled from 0-100 divided by an assumed standard deviation of 20 points). We assumed that the placebo group would have a higher transformed mean area under the curve (AUC, equivalent to increased mIAS-associated mouth pain) than dexamethasone group. This power calculation was based on a two-sample t-test with a two-sided 5% Type I error rate.

13.5.3 Secondary endpoints:

The SWISH trial approach incidence rate of grade 2 or higher stomatitis for each treatment group will also be compared by a Chi-square test.

The planned tests for the other secondary endpoints are detailed in the table below:

Study item	Measurement method	Statistical test
Time to develop at least mild mouth sores per study arm.	PRO-CTCAE Mouth/throat sore items (Appendix IV)	Kaplan-Meier and cumulative incidence curves
Time to develop at least moderate mouth sores per study arm.	PRO-CTCAE Mouth/throat sore items (Appendix IV)	Kaplan-Meier and cumulative incidence curves
Time to develop at least severe mouth sores per study arm.	PRO-CTCAE Mouth/throat sore items (Appendix IV)	Kaplan-Meier and cumulative incidence curves
Mean and median degrees of patient-reported mouth sores per study arm.	Numerical analogue mouth pain scale (Appendix II)	Independent samples T-tests
Incidence and time to develop at least mild mouth pain (pain scores of 1-3/10) per study arm.	Numerical analogue mouth pain scale (Appendix II)	Chi-squared tests and cumulative incidence curves, respectively
Incidence and time to develop at least moderate mouth pain (pain scores of 4-6/10) per study arm.	Numerical analogue mouth pain scale (Appendix II)	Chi-squared tests and cumulative incidence curves, respectively
Incidence and time to develop at least severe mouth pain (pain scores of 7-10/10) per study arm.	Numerical analogue mouth pain scale (Appendix II)	Chi-squared tests and cumulative incidence curves, respectively
Quality of life over time per study arm.	Linear Analogue Self-Assessment (Appendix III)	Independent samples t-tests

Study item	Measurement method	Statistical test
Level of activity interference with daily activities	PRO-CTCAE Mouth/throat sore items (Appendix IV) and PRO-CTCAE Sleep Items (Appendix IV)	Independent samples t-tests
Mean daily dose of everolimus over 8 weeks	Appendix VI	Independent samples t-tests
Number of patients who stopped everolimus per arm	Appendix VI	Chi-square tests
Number of patients who reduced the dose of everolimus per arm	Appendix VI	Chi-square tests
Proportion of patients who experience grade 2 stomatitis	Clinician-reported stomatitis performed at 1 and 2 months	Chi-squared tests
Number of patients who chose to fill their dexamethasone prescription per study arm and mean time until this happened	This information will be collected by patient questionnaire (Appendix V) and also will be nurse delineated (Appendix VI). Conflicts will be adjudicated by an investigator who is blinded to study arm.	Chi-squared tests and cumulative incidence curves respectively

13.6 Interim data analysis and stopping rule

No interim data analysis was planned for this trial.

Note: The statement regarding the interim analysis in previous Section 13.8 of the protocol was inadvertently carried over from another protocol. It was not meant to be included.

13.7 Primary Endpoint Justification: CTCAE items

One option for our primary analysis would be to use the identical endpoint measurement criterion that was developed and used de novo in the SWISH trial. This composite endpoint required that grade 2 or higher stomatitis needed to be confirmed by the investigator or treating physician and at least one of the following: 1) an oral pain score of greater than 8/10 on 1 occasion or 7/10 for 2 days, or 2) that patients could only eat soft chewable foods (or less, like liquids alone) as determined by a Normalcy of Diet Scale score less than or equal to 50/100. With this rule, a patient with classic CTCAE determination of grade 2 stomatitis could have been downgraded to grade 1 stomatitis if they did not meet the pain or diet criteria to keep them at grade 2 stomatitis (noting that this only happened for 2 patients in the SWISH trial—unpublished data provided to us). The main reason to consider choosing this measurement method is that it was used in the previously published SWISH trial. However, the downsides of utilizing this novel measurement is that this composite CTCAE clinician-determined measurement is not well validated psychometrically by itself, or by adding the 2 criteria noted above.

Additionally, data that can be collected daily by patient questionnaires will allow us to more accurately see daily changes on the days before and after patient actually took prescription dexamethasone (which they would have started because they developed mouth pain); we may not be able to collect CTCAE data at that exact time, if we used the SWISH measurement method.

Further supporting the use of a PRO measure of mouth sore related pain is that the definition of grade 2 or 3 CTCAE-determined mucositis is primarily based on pain, as is illustrated in the table below (thus the mouth pain that patients developed would have been the predominant factor to determine their CTCAE score).

Grade:	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Thus, we propose to use the PRO pain score as our primary measurement tool, while using the SWISH trial method as a secondary endpoint for both concurrent validation of the SWISH approach and comparison of the two results. This primary measurement tool will be used both to determine if initial dexamethasone is superior in preventing the development of any mouth sores-related pain compared to initial placebo, and to determine if the average severity of mIAS-associated pain over the eight week study period is greater in those who initiate dexamethasone at the onset of mouth pain compared to those who take dexamethasone preventatively, corresponding to the first and second co-primary objectives, respectively.

13.8 Sample Size and Power Considerations

13.8.1 Co-primary endpoint original consideration

The effect size estimates from the preliminary trials are profound, exceeding one standard deviation for multiple primary and secondary endpoints. For example, by 8 weeks, the incidence of **grade 2 or worse** stomatitis was two (2%) of 85 patients (95% CI 0·29–8·24), versus 159 (33%) of 482 patients (95% CI 28·8–37·4) for the duration of the BOLERO-2 study. This represents an effect size in excess of 5 standard deviations and would require only 29 patients per group, an impractically small sample size. Hence, we will use established norms for reasonable clinically meaningful effect sizes established by our group over fifteen years ago and used in numerous clinical trials by ourselves and others for the purposes of power calculations[35,36]. Our clinical colleagues' expert opinions as to what constitutes a clinically significant effect size were used as a confirmatory check on our effect size estimates.

For the first co-primary endpoint, a Chi-square test with 77 patients per group will have 99% power to detect a difference in the rate of mIAS pain (>50% in the placebo versus <15% in the dexamethasone treatment group) with a two-sided alternative and a 5% Type I error rate. These estimates are based on the SWISH and Bolero trial data.

For the second co-primary endpoint, the independent samples t-test using the simple summary AUC measure will have 87% power to detect a difference in the first co-primary endpoint of AUC for the 8-week period for the severity of mIAS-associated pain as assessed by the single item measure of 50% times the standard deviation (a moderate effect size equivalent to 10 points on the transformed AUC score scaled from 0-100, assuming a

standard deviation of 20 points in the AUC) among the two arms of 77 patients each, 154 patients total (type I error rate set at 5% and a two-tailed alternative). This effect size is considered clinically non-ignorable [37] and is a conservative estimate of efficacy given the profound results of the pilot test results.

13.8.2 Re-design co-primary endpoint consideration as a result of NCI CIRB review

Questions were raised regarding the sample size by the NCI CIRB regarding:

1) Calculation of initial effect size
2) Potential for patients to use the treatment more because they have ready access to what they believe is a pain ameliorating intervention.

Consideration of effect size: As indicated above in the introduction (section 1.2), the multiple phase II trials that have used this treatment have indicated effect sizes of more than five standard deviations in assessing reduction of the incidence of pain reported by patients or assessed by clinicians. The table below illustrates this point in using incidence rates for any stomatitis and grade 2+ stomatitis from the two pilot studies and historical control data from the Bolero study. More specifically, the effect sizes are all well above one standard deviation and require as few as 22 patients per group for a chi-square test for equality of proportions to achieve 80% power with a 5% Type I error rate. The sample size could be as large as 71 per group if we consider the San Antonio study and grade 2+ stomatitis. This is still less than the 77 patients per group required to detect a moderate effect size as described above as a non-ignorable clinically meaningful effect [38]

Source	Clinician-reported stomatitis incidence	Effect Size	Sample size to detect effect size (per group) with 80% power and 5% type I error
Historical Control (Bolero)	67% (any),		
SWISH	21% (any)	46%	22
San Antonio study	29%, 27.5% (any)	38%, 39.5%	31, 29
Historical Control (Bolero)	33% (gr 2+)		
Bolero-2	2% (gr 2+)	31%	29
San Antonio study	12%, 8% (gr 2+)	21%, 25%	71, 48

We consider the possibility that some patients fill the dexamethasone prescription when they really do not actually have pain, because they think it will prevent them from getting pain. One could assert that the likelihood of doing this should be equivalent between the treatment and placebo preparations and dismiss potential effect size confounder. However, in case that is not the case, in the extreme case that 1 out of every 6 patients in the treatment arm reports pain in the absence of pain, in order to gain permission to fill the dexamethasone script, compared to none in the placebo group (personal communication, CIRB), this would reduce our initially estimated effect size by 16.7%.

Recall that since the preliminary effect sizes were so large, we used a conservative estimate of effect size of ½ standard deviation to come up with our sample size of 71 per group to have 80% power. Our original power calculation was based on an incidence rate of pain in the control and treatment groups of >50% and <15% respectively. This provided the chi-square test a sample size of 33 patients per group to detect this difference with 80% power, or more than 99% power with 71 patients per group. If we modify the efficacy rate in the treatment group by 17% (rounding from 16.7%), then we would be comparing a stomatitis pain incidence of at least 50% in the control group with a rate of 32% (15+17 percent). For the chi-square test to have 80% power to detect this reduced efficacy rate, we would need 127 patients per group.

The table below provides required sample size for various assumed percentages of patients unnecessarily taking medication. It indicates that our conservative sample size of 71 patients per group can accommodate just over 10% of the patients taking medication when unnecessary. To ensure we cover the proposed estimate of 16.7% of "contamination" rate, we recommend increasing the sample size to 127 patients per group.

Estimated rate of medication taken when not needed	Resultant effect size in treatment group	Effect size in control group	Required sample size per group for 80% power
0%	15%	50%	33
5%	20%	50%	45
10%	25%	50%	66
16.7%	32%	50%	127
25%	40%	50%	408

In summary, then, taking these two issues under consideration, the ultimate sample size will be 279 patients in total (127 per group plus 10% for ineligibles and cancelations).

The revised sample size of 127 patients per group will provide at least as much power specified for the AUC co-primary t-test specified for the original sample size in section 13.7.1. More specifically, however, 127 patients per group will provide over 95% power to detect a non-ignorable clinically meaningful difference in average AUC of 50% times the standard deviation (a moderate effect size equivalent to 10 points on the transformed AUC score scaled from 0-100, assuming a standard deviation of 20 points in the AUC, type I error rate set at 5% and a two-tailed alternative). Further, there will be 80% power for the t-test to detect a difference of 35% of the standard deviation (equivalent to 7 points on the 0-100 point transformed AUC score between average AUC in the two groups. In summary, the expanded sample size will provide sufficient power for both co-primary endpoints to detect small to moderate effect sizes.

13.9 Study Monitoring

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.10 Missing Data and sensitivity analysis

As a further sensitivity analysis of our primary results, we will employ a further method due to Fairclough et al to producing the area under the curve (AUC) estimates based on using estimated parameters from a repeated-measures (means) mixed model with a random intercept[34]. The

outcome measures used in the repeated-measures (means) mixed model are the serially measured patient-reported mouth pain scores obtained at baseline and daily during the eight week study period. The covariates included in the model are indicator variables for all assessment time points, an indicator for the treatment approach (initial dexamethasone; initial placebo), and the corresponding two-way interaction terms. This macro will rerun the primary analyses with each alternative approach to imputation to demonstrate the veracity of the results in the presence of missing data. This analytic approach to compare the prevention approach vs early treatment approach will maintain the ITT principle and allow for missing data (i.e. under the reasonable assumption of missing at random). Furthermore, it has been shown that this analytic approach is superior to a simple AUC summary measure in terms of both bias and precision in the presence of missing data[34]. In this supplemental analysis, we will also account for the two stratification factors in the model, as well as potentially other baseline covariates. To maintain the 5% significance level, this statistical test will only be performed if the first primary endpoint is met.

13.11 Inclusion of Women and Minorities

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	1	1	4
Asian	1	1	1	1	4
Native Hawaiian or Other Pacific Islander	1	1	1	1	4
Black or African American	20	5	3	1	29
White	177	41	13	3	234
More Than One Race	1	1	1	1	4
Total	201	50	20	8	279

Ethnic Categories:

- Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- Not Hispanic or Latino

Racial Categories

- American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
- Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 2 substudies and all patients are encouraged to participate.

14.1 Pharmacogenomics and Everolimus induced stomatitis A221701-ST1

14.1.1 Background

The increased toxicity that has accompanied the everolimus plus exemestane therapy has been the primary reason for patients' discontinuation of treatment. While some patients experience severe oral mTOR inhibitor-associated stomatitis (mIAS), others do not; this is possibly due in part to genetic variability in genes that biotransform everolimus.

Everolimus is metabolized by CYP3A4, CYP3A5 and transported by p-glycoprotein. It binds with high affinity to FK506 binding protein -12 to form a complex that inhibits mTOR activation and reduces activity of effectors downstream, blocking cell cycle progression from G1 to S phase and leading to cell growth arrest and apoptosis. These proteins are encoded by genes that are genetically polymorphic and whose activities result in variability in the extent of metabolism of everolimus and variability in signaling associated with the mTOR pathway—all of which might lead to variations in everolimus sensitivity.

A recent next-generation sequencing study of tumor samples from patients identified somatic mutations as genetic markers in mTOR signaling pathway (TSC1, TSC2, MTOR alterations) to be associated with everolimus sensitivity [58] On the other hand, studies have reported single nucleotide polymorphisms (SNPs) in genes involved in everolimus pharmacokinetics and pharmacodynamics to be associated with everolimus clinical outcomes with varying results. For example in two studies examining FGFR4 rs351855 SNP in neuroendocrine tumors, one reported no association with everolimus efficacy [44]and the other reported reduced sensitivity to everolimus and increased tumor progression [45] . A recent review covering pharmacogenetics of mTOR inhibitors' role in the pharmacodynamics of immunosuppressive drugs,[46] it was highly recommended that 3 MTOR SNPs namely rs2024627, rs2295080, rs1883965 be investigated in studies as these were associated with decreases in hemoglobin levels in solid organ transplantation.

In the only study to date exploring the impact of germline variation on exemestane-everolimus outcome in 90 women with metastatic breast cancer, Pascual et al. (2017)[47] reported that CYP3A4 rs35599367 was associated with higher concentrations of everolimus in blood. The global minor allele frequency of the CYP3A4 rs35599367 SNP is low, 0.015, however in Caucasians the frequency ranges from 0.03-0.05. In this study by Pascual et al (2017), they found 4 patients with rs35599367 genotype out of 37 patients who had PK data on day 14 of the first everolimus cycle and were able to associate the genotype with plasma everolimus concentration levels. We will not genotype for the *CYP3A4* rs35599367 SNP in this study because of its low allele frequency. Polymorphisms in *CYP3A5 and CYP2C8* (everolimus metabolism) and in *ABCB1* (everolimus transport), and also in genes belonging to the PI3K/AKT/mTOR pathway *(FGFR4, PHLPP2, AKT2, PIK3R1, RAPTOR, AKT)* have also been evaluated for their association with everolimus sensitivity. While SNPs in *FGFR4, RAPTOR and PIK3R1* were associated with toxicities such as leucopenia, hyperglycemia and lymphopenia, only *ABCB1* rs1045642 SNP was associated with mucositis[47].

Furthermore in a GWAS study evaluating everolimus sensitivity in lymphoblastic cell lines,[48] showed that 10 SNPs (rs218869, rs7694207, rs10987149, rs12932018, rs2702449, rs16887552, rs2832270, rs1460196, rs4148330, rs13272072) were highly associated with everolimus sensitivity ($p=10^{-6}$) even though they did not reach the expected genome-wide

significance of $p<10^{-8}$ (**Table 1**). Six other SNPs that showed some association with everolimus after functional studies were reported in the same study (**Table 1**). The most significant gene whose expression has been reported to associate with everolimus sensitivity is *FBXW7*, $p=4x10^{-7}$.[48] This FBXW7 gene encodes a member of the F-box protein family and functions by binding directly to multiple substrates including cyclin E and targeting cyclin E for ubiquitin-mediated degradation [49,50]. Other substrates include c-Myc, c-Jun, Notch, Mcl-1 and mammalian target of rapamycin (mTOR)[51], all of which are involved in cell division, growth, survival and differentiation [50,52,53] *FBXW7* also functions as a tumor suppressor and inactivation of the protein is associated with deregulation of well ‐known oncoproteins some of which are indicated above [51,52] and is also one of the most frequently mutated genes in human cancers.[49,51] *FBXW7* is genetically polymorphic although no SNP was observed in the GWAS study[48] . However, polymorphisms in this gene have been reported in relation to blood pressure [55]and epilepsy[56]. As such, we will derive tagSNPs for *FBXW7* and explore correlations of the polymorphisms with stomatitis.

Given that the SNPs mentioned here (see also Table 1 : SNPs1-16, 22- 26) have previously been associated with everolimus and everolimus sensitivity (indicated above) and that oral mIAS results from sensitivity to everolimus intake, we will investigate these SNPs in this study to determine if they appear to predispose patients to different levels of stomatitis severity. In addition, we will explore any correlations that the *FBXW7* tagSNPs we derive will have on stomatitis severity. Moreover since the study proposes the use of dexamethasone to substantially decrease severity in mIAS-associated pain in the patients on treatment, we will evaluate if the use of dexamethasone changes any observed mIAS-SNP associations in the study.

Therefore, we will **validate** SNPs that have been associated with everolimus sensitivity by associating them with severity of stomatitis. TagSNPs for *FBXW7* will be explore for their associations with stomatitis severity. We propose to do this by following the objectives below:

14.1.2 Objectives

1) To derive tagSNPs for *FBXW7* and together with SNPs reported (**Table 1**), genotype all patient samples for those SNPs

2) To explore the association of the genotypes with severity of everolimus-related stomatitis (mIAS- associated pain) within the patients who initially received placebo at the start of everolimus treatment.

3) To explore the association of the genotypes with severity of everolimus-related stomatitis (mIAS- associated pain) within the patients who initially received dexamethasone at the start of everolimus treatment.

14.1.3 Methods

DNA Isolation, SNP selection and Genotyping:

Whole blood sample will be collected in 1 x10 mL EDTA vacutainer tube (purple top) from patients at start of study for germline DNA isolation. Blood samples will be sent to the Alliance Biorepository at Mayo Clinic and DNA will be isolated in the Biospecimen Accessioning and Processing (BAP) laboratory.

SNP selection for *FBXW7*: Genotype data from the National Center for Biotechnology Information (NCBI) dbSNP database will be used with programs in National Institute of environmental Health Sciences [redacted] and Genome variation

server [redacted] to derive tagged SNPs for *FBXW7* with allele frequencies of at least 10% and r2 ≥ 0.80 (Table 1, SNP # 17-21).

Genotyping: The acquired tagSNPs and the rest of the SNPs in Table 1 will be genotyped in the Genotyping Core of the Mayo Clinic Medical Genome Facility (MGF).

Table 1

SNP #	SNP ID	Allele	Chr	Reported/Mapped Gene	Context	Global MA	Global MAF
1	**rs218869**	A>T	8	*Intergenic/LOC107986930*	Intron variant	T	0.33
2	**rs7694207**	C>T	4	*MGC46496/COX7A2P2 - STPG2-AS1*	Flanking, 3UTR	T	0.29
3	**rs10987149**	A>G	9	*PBX3*	Flanking, 3UTR	G	0.35
4	**rs12932018**	A>G	16	*USP10*	Synonymous, exon variant	G	0.26
5	**rs2702449**	G>A	4	*AGA*	Flanking, 5UTR	A	0.36
6	**rs16887552**	A>C	4	*LOC107986181 - LOC105374493*	Intergenic variant	C	0.27
7	**rs2832270**	G>A	***21***	*C21orf7*	Flanking, 3UTR	A	0.14
8	**rs1460196**	C>T	18	*DCC*	Intron variant	T	0.10
9	**rs4148330**	A>G	16	*ABCC1*	Flanking, 5UTR	G	0.47
10	**rs13272072**	C>T	***8***	*STC1*	Flanking, 3UTR	T	0.10
11	rs17664713	C>T	15	*MCTP2*	Flanking, 3UTR	T	0.12
12	rs10870177	C>T	9	*MAN1B1*	Intron variant	T	0.18
13	rs7543260	T>C	1	*JUN*	Flanking, 5UTR	C	0.19
14	rs10780752	T>C	9	*C9orf153*	Flanking, 3UTR	C	0.32
15	rs17732246	G>A	15	*MCTP2*	Flanking, 3UTR	A	0.10
16	rs11075286	C>A	16	*ABCC1*	Flanking, 5UTR	A	0.45
17	rs6535847	T>C	4	*FBXW7*	Intergenic upstream variant	C	0.46
18	rs17361782	T>G	4	*FBXW7*	Intron variant	G	0.13
19	rs2255137	T>C	4	*FBXW7*	Intron variant	C	0.34
20	rs2714804	A>G	4	*FBXW7*	Intron variant	G	0.11
21	rs2714805	C>T	4	*FBXW7*	Intron variant	T	0.44
22	rs1045642	G>A	7	*ABCB1*	synonymous variant, exon	A	0.40
23	rs351855	G>A	5	*FGFR4*	Missense variant, exon	A	0.30
24	rs2024627	C>T	1	*MTOR*	Intron variant	T	0.2991
25	rs2295080	T>G	1	*MTOR*	Intergenic upstream variant	G	0.4623
26	rs1883965	G>A	1	*MTOR*	Intron variant	A	0.3063

SNP # 1-16: The most significant SNPs observed in the everolimus sensitivity GWAS study (bold font) and SNPs with functional implications from the same study.[48]

SNP #17-21: derived tagSNPs for FBXW7; SNP # 22-23: Reported everolimus associated SNPs.[44,47]

Abbreviations: SNP: single nucleotide polymorphism; UTR: untranslated region; MA: minor allele; MAF: minor allele frequency

14.1.4 Analyses

The MAF will be summarized for each of the SNPs listed in Table 1 of section 14.1.3 for objective 1 in section 14.1.2. The primary analysis for objectives 2 and 3 of this correlative

study will mirror that of the main study. For the purpose of the correlative, we will compare the difference in average PRO pain score within each arm separately and use each candidate SNP that meets the threshold of the cutoff (as defined in section 14.1.3) as the primary covariate of interest. The Bonferroni method will be applied to control the Type I error rate at 5% for each of the different models. Markers that do not meet the threshold of the cutoff will be summarized descriptively.

14.2 Population Pharmacokinetics (PK) of Everolimus A221701-PP1

14.2.1 Background

In transplantation settings, where therapeutic drug monitoring (TDM) aided dose-adjustment is common, everolimus should be generally targeted to a trough concentration (C_0) of 3–8 ng/mL when used in combination with other immunosuppressive drugs (calcineurin inhibitors and glucocorticoids); in calcineurin inhibitor-free regimens, the everolimus target C_0 range should be 6–10 ng/mL. Further studies are required to determine the clinical utility of TDM in nontransplantation settings[59]. In oncology settings, 10 mg/day seems to be the maximum tolerated dose. At this dose, everolimus C_0 of up to 17.0 ng/mL have been observed, with large interindividual differences. In patients with metastatic renal cell carcinoma (n = 42), the median everolimus C_0 was 14.1 ng/mL (range, 2.6–91.5 ng/mL). Fourteen (67%) versus 8 (38%) patients with median everolimus C_0 above or below 14.1 ng/ mL, respectively, were progression-free at 6 months (P =0.06); median progression-free survival was 13.3 versus 3.9 months, respectively [hazard ratio (HR), 0.66; 95% CI, 0.33–1.31; P = 0.23], and median overall survival was 26.2 versus 9.9 months, respectively (HR, 0.62; 95% CI, 0.28–1.37; P =0.24).[59]

Everolimus is orally active, with linear (dose-proportional) PK. Absorption is rapid, with peak concentration reached within 1.5–2 hours. The free fraction of everolimus (EVR) in plasma is approximately 0.26. There is a good correlation between predose or C_0 and area under the concentration–time curve (AUC) at steady state. In blood, everolimus is highly incorporated into erythrocytes, and there is evidence that this binding is concentration dependent, justifying the use of whole blood rather than plasma for EVR quantification. Everolimus has a long half-life of approximately 30 hours. Steady-state concentrations are, therefore, generally achieved within 4–7 days.

Everolimus is a substrate of both the efflux pump known as the ATP-binding cassette subfamily B member 1 (ABCB1; P-glycoprotein) and the CYP metabolic enzyme (particularly CYP3A4, with CYP3A5 and CYP2C8 playing minor roles). Everolimus is prone to substantial PK variability and numerous drug-drug interactions because of the involvement of ABCB1 and CYP3A4 in its PKs. Data regarding the effect of *CYP3A4* genetic variations on EVR PK (or pharmacodynamics) are still scarce. The *CYP3A4*1B* allele (rs2740574; c.-392G.A) showed no association with EVR dose-normalized concentrations in lung transplant recipients. No significant influence on everolimus PK was observed in relation to the *CYP3A4*22* (rs35599367; c.522191C.T) variant, which was found in 9 of 97 patients; 8 were heterozygous carriers and 1 was a homozygous carrier of the *CYP3A4*22* allele. Six studies have been reported to date, showing no association between the common *CYP3A5*3* allele (rs776746; c.219-237G.A) and everolimus blood concentrations, dose requirement, or PK parameters estimated using population PK approaches. No studies found a significant relationship between everolimus dosing or blood concentrations and *CYP2C8* genotype, which denotes 2 highly linked variants, rs11572080 (c.416G.A; p.R139K) and rs10509681 (c.1196A.G; p.K399R), occurring at relatively high frequency in whites (11%–14%), but rarely in Asians and Africans. This is consistent with its minor role in everolimus metabolism. A study in lung transplant recipients failed to demonstrate any association with *CYP2C8*2* (rs11572103: c.805A.T; p.Ile199Phe) and *CYP2C8*4* alleles (rs1058930: c.792C.G; p.Ile264Met), and a study in heart transplant recipients found no association between *CYP2C8*3* and everolimus adverse effects. Three pharmacogenetic studies also investigated the effects of *ABCB1* genetic polymorphisms on everolimus PK in solid organ transplantation and none reported significant associations.

Population PK models of everolimus have been developed. A model in heart transplant recipients reported an apparent clearance and distribution volume of 3.33 ± 0.20 L/h and 146 ± 33 L, respectively, and a significant influence of bilirubin concentration on clearance. In kidney transplant recipients, using a 2-compartment structural model with first-order absorption with lag time, ideal body weight was found to be significantly related to the volume of distribution.

The intrapatient PK variability of everolimus is reported to be high (45% for C_0, 27% for the AUC in *de novo* kidney transplant recipients administered CsA), as is interindividual variability (55% for C_0, 31% for the AUC).

In a multiple-dose study in kidney transplant recipients, a high-fat meal delayed t_{max} by a median of 1.75 hours and reduced C_{max} by 53% and AUC by 21%. Everolimus C_0 showed no food effect, suggesting that although overall exposure is prone to a food effect, this does not translate into C_0 variations.

We believe we will find in this study that the interpatient variability in everolimus exposure (C_0) exceeds 50% and that there is a correlation between everolimus exposure (C_0) and its toxicity and the use of dexamethasone.

14.2.2 Objectives

1. To determine the intrapatient and interpatient variability of everolimus exposure (C_0) in cancer patients being treated with everolimus.
2. To explore the association of everolimus exposure (C_0) with toxicity

14.2.3 Methods

Venous blood samples for everolimus trough concentrations (C_0) will be obtained at baseline, and at the 8 weeks scheduled follow-up clinic visit (and optional at 4 weeks) while still receiving study drug therapy. These samples will have the time of day they were obtained documented. At these follow up visits a patient questionnaire will be filled in which will request information about the timing of prior dosing of everolimus (See Appendix VIII). This will detail the time of day the last dose of study drug was taken.

Drug concentrations will be measured in whole blood using an Liquid Chromatography Tandem-Mass Spectrometry (LC-MS-MS) assay to be implemented in the Alliance Pharmacology/Pharmacokinetic core lab at the University of Pittsburgh using a modification of e.g. the assay published by Tszyrsznic, W et al.[60]

Frequentist approaches will be used for correlation, and if data permits, population modeling approaches may also be employed.

14.2.4 Analyses

Objective 1: We will calculate C_0 variability at 8 weeks as a metric of interpatient variability; while the inclusion of data from 4 week samples will allow calculation of intrapatient variability. We will approach this using a frequentist approach.

Objective 2: We will explore relationships between C_0 and mucosal toxicity, and dexamethasone use.

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16.0 MODEL CONSENT FORM

Study Title for Participants: Testing the use of dexamethasone mouthwash to prevent or treat painful mouth sores in patients being treated with everolimus

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol Alliance A221701, "Phase III placebo-controlled trial to evaluate dexamethasone use for everolimus-induced oral stomatitis: prevention versus early treatment approaches: MIST (My Individualized Stomatitis Treatment)", (NCT03839940)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer; to reduce side effects from cancer and cancer treatment and to improve the quality of life of cancer patients.

We are asking you to take part in this study because you have been diagnosed with cancer and you will be receiving a drug called everolimus as part of your usual care. It is known that this drug can cause painful mouth sores, which can interfere with activities of daily living, including eating and drinking. Patients who are not in this study are usually treated for these sores with rinses (or mouthwashes) containing different drugs such as lidocaine to numb the pain. Previous small studies have shown that dexamethasone can help with treating mouth sores. This study is being done to see if dexamethasone can help prevent getting the mouth sores.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute (NCI). The Alliance is made up of cancer doctors, health professionals, patient advocates and laboratory researchers, whose goal is

to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

Why is this study being done?

This study is being done to answer the following question:

Can we lower the chance of getting painful mouth sores by treating you with a dexamethasone mouthwash at the start of your cancer treatment?

We are doing this study to find out if this approach is better or worse than the usual approach for preventing painful mouth sores. The usual approach is defined as care most people get for painful mouth sores.

What is the usual approach to preventing painful mouth sores?

The usual approach is to wait until mouth sores develop before they are treated with medications that have been approved by the Food and Drug Administration (FDA).

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose to not get treated.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get dexamethasone mouthwash for up to eight weeks, or you will get placebo for up to eight weeks, or until you develop mouth pain at which time you will be asked to fill a prescription to start a dexamethasone mouthwash.

During the eight week study period, your doctor will watch you for side effects.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the mouth pain will be worse than it would have been otherwise.

There is also a risk that you could have side effects from the dexamethasone mouthwash. These side effects may be worse and may be different than you would get with the usual approach for treating mouth sores.

Some of the most common side effects that the study doctors know about are:

- Increased blood sugars
- Insomnia
- Change in energy level
- Stomach Upset

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that dexamethasone mouthwash is effective in treating mouth sores, so taking it before mouth sores start may help prevent you from developing mouth pain. It is not possible to know if the mouthwash will prevent your mouth sores as compared to the usual approach. This study will help the study doctors learn things that will help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NCI). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

You have cancer and will be receiving everolimus, which may cause painful mouth sores. The purpose of this study is to test whether a mouthwash made with a drug called dexamethasone can prevent or reduce the pain caused by mouth sores resulting from everolimus treatment. The effects of a dexamethasone mouthwash will be compared to a placebo. A placebo is a liquid that looks like the study drug but contains no medication.

Dexamethasone has already been approved by the Food and Drug Administration (FDA) to treat other disorders. The dexamethasone used in this study is considered investigational, which means it has not been approved by the FDA for the use described in this study. There will be about 279 people taking part in this study.

What are the study groups?

This study has 2 study groups. You will not be told which group you are in.

- **Group 1**
  If you are in this group, you will get dexamethasone mouthwash, which you will swish about 2 teaspoons for two minutes in your mouth and spit, four times per day, for eight weeks. You should take nothing by mouth for thirty minutes before each mouthwash and at least an hour after each mouthwash. However, you may take nystatin for treatment of thrush (a fungal infection of the mouth). You will also be asked to complete a daily pain log and weekly questionnaires. It should take about one minute to complete the daily log and about five minutes to complete the weekly questionnaire.

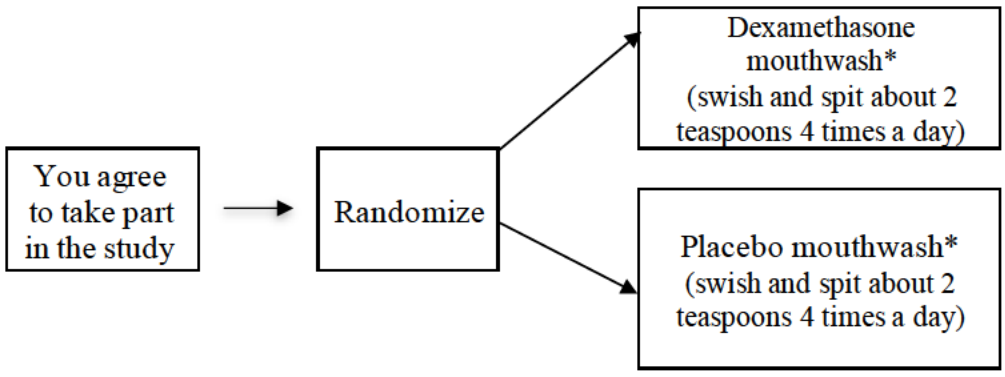
  There will be about 140 people in this group.

- **Group 2**
  If you are in Group 2, you will get the placebo mouthwash, which you will swish about 2 teaspoons for two minutes in your mouth and spit, four times per day for eight weeks. A placebo is a liquid that looks like the study drug but contains no medication. You should take nothing by mouth for thirty minutes before each mouthwash and at least an hour after each mouthwash. However, you may take nystatin for treatment of thrush (a fungal infection of the mouth). You will also be asked to complete a daily pain log and weekly questionnaires. It should take about one minute to complete the daily log and about five minutes to complete the weekly questionnaire.

  There will be about 140 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2. Regardless of which group you are in, you will be provided a prescription for dexamethasone at the start of treatment. If you develop any mouth pain related to mouth sores, you should fill the prescription for dexamethasone, and start swishing this in your mouth for two minutes, four times per day, instead of the study mouthwash. If you decide to fill your prescription, please inform your study nurse beforehand.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



* If you develop mouth pain, you may fill a prescription for dexamethasone mouthwash at the pharmacy, and use that instead of the study mouthwash

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.
As part of this study, a nurse will call you every week to remind you to complete your forms, check on your condition, to follow the effects of study treatment, including managing side effects.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

If you speak English, and choose to take part in this study, you will be asked to fill forms with questions about mouth pain and sores, sleep, fatigue and your general quality of life. Researchers will use this information to learn more about how cancer treatment affects people.

Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out forms,

- before you start treatment
- every day while you are using the mouthwash you will be asked about your mouth pain
- every week while you are using the mouthwash and after 8 weeks of using the mouthwash you will be asked questions about mouth sores, sleep, fatigue, and your general quality of life.
- You will also receive weekly phone call reminders from your nurse to use your mouthwash and complete the forms. The nurse will ask you some additional questions about your mouthwash use, your everolimus use, and about the types of food you are eating, as well.

The daily pain log will take less than a minute to complete and the weekly forms will take about five minutes to complete. Each phone call will take about five minutes. You don't have to answer any question that makes you feel uncomfortable.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach at preventing or treating your painful mouth sores.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.

- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The medications used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study.

Side Effect Risks

The drug used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drug.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

The table below shows the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of DEXAMETHASONE Mouthwash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving DEXAMETHASONE, from 4 to 20 may have:
• Fungal infection (termed thrush when it is in the mouth or throat) • Irritability • Insomnia • Changes in energy • High blood sugars • Stomach Upset

Additional Drug Risks

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Fill out forms

For women: Do not get pregnant or breastfeed while taking part in this study. Tell your study doctor right away if you think that you have become pregnant during the study.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for taking everolimus. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You or your insurance provider will not have to pay for the study medication that is provided as part of the study. However, if you develop painful mouth sores and fill the prescription for dexamethasone mouthwash, this will be billed to you and your insurance company.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The Alliance for Clinical Trials in Oncology
- The IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this study. There is no penalty for saying "no." You and your insurance company will not be billed for this optional study. If you sign up for, but cannot complete this study for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for the following study.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

If you choose to take part in the optional studies, researchers will collect two teaspoons of blood before you start study treatment, for research on why people have different side effects from the treatment. For this study, your blood will be sent to the Alliance biorepository at Mayo Clinic with your initials and collection date on it. These initials will be removed along with other identifiers before the researchers analyze the samples. Please see the "How will information about me be kept private" section below.

In addition, one teaspoon of blood will also be collected before you start study treatment, at your 4 week clinic visit and at your 8 week clinic visit for research on how the study drug changes in your body over time and if that can change your side effects. If you are not scheduled to come back for a 4 week visit, you don't need to provide this sample. You will also complete a form every time blood is collected for this research. It will take less than five minutes to complete this form. For this study, your blood will be sent to researchers at the University of Pittsburgh Cancer Center with your initials and collection date on it.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About a total of five teaspoons of blood will be collected from a vein in your arm.
2. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance.

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory study described above.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

APPENDIX I PATIENT QUESTIONNAIRE

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet (Baseline)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed day 1 during your clinic visit prior to treatment.

2. The booklet contains 2 set of questions:
    a. PRO-CTCAE
    b. Numerical Analogue Mouth Pain Scale

3. Directions on how to complete this set of questions are written on the top of the page.

4. Please return your booklet when you are finished.

Thank you for taking the time to help

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet (Weekly)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed every day for one week, starting on the first day of study treatment. You will be asked to record your mouth pain every day and to complete a questionnaire at the end of the week. Please answer the mouth pain question at the same time each day, preferably in the evening.

2. The booklet contains 2 groups of questions:
   TO BE COMPLETED DAILY:
   a. Numerical Analogue Mouth Pain Scale

   TO BE COMPLETED AT THE END OF THE WEEK:
   b. Numerical Analogue Self-Assessment
   c. PRO-CTCAE
   d. Patient Reported Mouthwash Use Frequency

3. Directions on how to complete this set of questions are written on the top of the page.

4. You may call a member of the study team to answer any questions you might have. You will be given a name and telephone number. You can call anytime with any concerns or questions. A nurse/research coordinator will also call you once a week and they can answer questions you might have.

5. It is very important that you return the booklet to us, whether you finish the study or not.

6. Please mail your completed booklet at the end of the week in the stamped pre-addressed envelope.

Thank you for taking the time to help

APPENDIX II NUMERICAL ANALOGUE MOUTH PAIN SCALE

Please circle the number that best reflects your response to the following question during the past 24 hours.

Which number represents the worst severity of your mouth pain over the past 24 hours that you think was caused by your cancer medication?

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

Day ______

0 1 2 3 4 5 6 7 8 9 10

(No pain) (pain as bad as it can be)

APPENDIX III NUMERICAL ANALOGUE SELF-ASSESSMENT

Directions: Please circle the number (0-10) best reflecting your response to the following question that describes your feelings **during the past week, including today**.

1. During the past week, including today, how would you describe your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX IV PRO-CTCAE

PRO-CTCAE Mouth/throat sore items:

1. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST:

   None / Mild / Moderate / Severe / Very severe

2. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities:

   Not at all / A little bit / Somewhat / Quite a bit / Very much

PRO-CTCAE- Sleep Items

1. In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST:

   None / Mild / Moderate / Severe / Very severe

2. In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities:

   Not at all / A little bit / Somewhat / Quite a bit / Very much

PRO-CTCAE Fatigue items:

1. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST:

   None / Mild / Moderate / Severe / Very severe

2. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities:

   Not at all / A little bit / Somewhat/ Quite a bit / Very much

APPENDIX V PATIENT REPORTED MOUTHWASH USE FREQUENCY

The first question below relates to how often you took the original study mouthwash that you were assigned when you started this study. Please skip this question if you are no longer taking the original study mouthwash that you were assigned when you started this study.

1. If you are still taking the study mouthwash, how many doses did you take over the last week, understanding that you would have taken 28 doses if you did not miss any doses:

   A.__28

   B.__21-27

   C.__14-20

   D.__<14

2. Did you fill the optional dexamethasone prescription at a pharmacy and start using it?

   No

   Yes—if yes, what date did you first use this: __/___/_____

3. If you are using the optional dexamethasone, are you using it every day or as needed?
   _____

4. If you are using the optional dexamethasone, how many times a day are you using it?
   _____

5. Are you still taking the everolimus? Y/N

6. If yes, how many milligrams per day (understanding that all patients started at 10 mg/day)? __ mg

If less than 10mg/day, why was the dose decreased?

_____

APPENDIX VI NURSE WEEKLY PHONE CALL ASSESSMENT SCRIPT

Hello, this is _____ , a nurse from the _____study.

How are you?

Do you have any questions about this study?

Are you still filling out your forms every day? Did you mail last week's booklet to your clinic?

Are you still taking the everolimus? Y/N ; If yes, how many milligrams per day? ___MG;__If less than 10mg, why did you decrease the dose? _____

Are you still taking the study mouthwash? Y/N ;If yes, approximately how many times per day? ___ ; Approximately how many doses did you take in the last week? (prompting with the total number of expected doses being 28) ___

Did you fill the optional additional dexamethasone prescription at the pharmacy? Y/N ;If so, have you started to take it? Y/N ;What date did you take your first dose? DATE ;If you are using the optional dexamethasone, are you using it every day or as needed. How many times a day? ___ ; Remind the patient that, if she/he is now taking the prescription dexamethasone, she/he should not be taking the study mouthwash any more.

Information to inform clinician-grading: Are you having any trouble with any of the following (asking follow-up questions to grade):
A white coating on your tongue or throat; 2) high blood sugars; 3) irritability; 4) fatigue; 5) difficulty sleeping; 6) mouth or throat sores or pain

If the nurse has suspicion for thrush, have patient evaluated and/or start an antifungal medication.

APPENDIX VII NORMALCY OF DIET SCALE

What kind of foods have you been eating? What foods are difficult to eat? (Nurse will ask about the specific options below. If the patient initially reports that s/he is eating everything, nurse will start with those scored 50 and move up until the patient cannot eat a category of food, and then will select the highest score of the category of food the patient can eat from the below options):

100: Full diet (no restrictions)
90: Full diet (liquid assist)
80: All meat
70: Raw carrots, celery
60: Dry bread and crackers
50: Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40: Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
30: Pureed foods (in blended)
20: Warm liquids
10: Cold liquids
0 Non-oral feeding (tube fed)

APPENDIX VIII PHARMACOKINETICS PATIENT QUESTIONNAIRE

Please advise patient not take their Everolimus dose prior to the clinic visit at Week 4 and Week 8.

Note: This form is to be completed for the following blood draw time points associated with the pharmacokinetic sub study A221701-PP1: Week 4 and Week 8.

Date:

The following questions refer to the day before yesterday (2 days ago):

What time did you take your study medication (*everolimus*)? _ _ : _ _ AM / PM

What time did you last eat before taking your study medication (*everolimus*)? _ _ : _ _ AM / PM

What time did you first eat after taking your study medication (*everolimus*)? _ _ : _ _ AM / PM

The following questions refer to yesterday (1 day ago):

What time did you take your study medication (*everolimus*)? _ _ : _ _ AM / PM

What time did you last eat before taking your study medication (*everolimus*)? _ _ : _ _ AM / PM

What time did you first eat after taking your study medication (*everolimus*)? _ _ : _ _ AM / PM

The following questions refer to today (ONLY APPLIES IF YOU HAVE TAKEN YOUR STUDY MEDICATION BEFORE BEING SEEN IN THE CLINIC TODAY):

What time did you take your study medication (*everolimus*)? _ _ : _ _ AM / PM

What time did you last eat before taking your study medication (*everolimus*)? _ _ : _ _ AM / PM

What time did you first eat after taking your study medication (*everolimus*)? _ _ : _ _ AM / PM

APPENDIX IX PATIENT INSTRUCTION SHEET

Dexamethasone

(dex-a-METH-a-sone)

How to take the mouthwash:

- Shake solution well before use.
- Swish about 2 teaspoons (10 cc) in your mouth and spit, four times a day, for eight weeks. Do not swallow.
- You should take nothing by mouth for thirty minutes before each mouthwash and at least an hour after each mouthwash. However, you may take nystatin for treatment of thrush (a fungal infection of the mouth).

Where to store your medication:

- Store the medication in a closed container at room temperature, away from heat, moisture, and direct light. The expiration date will be printed on the bottle. Please do not use the medication after this date.
- Keep medication out of the reach of children.

Foods to avoid:

- Please avoid eating foods with high acid content, limit alcohol and caffeine intake as these food items can irritate the mouth further.

Possible side effects:

- Increased blood sugars
- Insomnia
- Change in energy level
- Stomach Upset

When to call your doctor:

- If you experience mood or behavioral changes (i.e. depression, euphoria, insomnia, psychosis)
- If you experience frequent, unrelenting headaches or visual changes
- If you experience symptoms of a gastric ulcer
    - You may use antacids for symptoms of symptoms of gastric ulcer, heartburn or gastritis. If the antacids don't control these symptoms, call your doctor.
- If you experience easy bruising

If you notice other side effects that you think are caused by this medication, tell your doctor.